A New Approach to 3β,11α,15α-Trihydroxy-5α-cholestan-7-one, a Key Intermediate in the Synthesis of the Steroidal Moiety of Oogoniols

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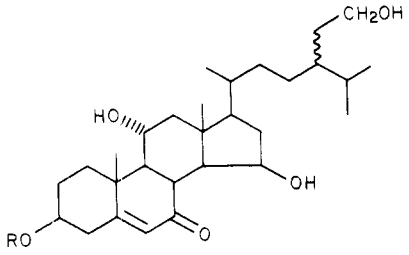
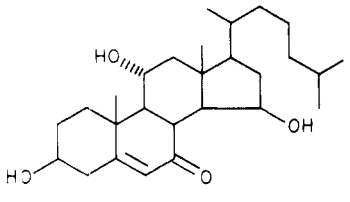
The oogoniols are a group of closely related steroidal sex hormones which induce the formation of oogonia, or female sex organs, in the water mold *Achlya*. Isolation and structure elucidation of these steroids were reported by McMorris et al.[1] They have named these compounds oogoniol-1, -2, and -3 and have proposed structures **1a–c**,



1a, R = $(CH_3)_2CHC{=}O$
b, R = $CH_3CH_2C{=}O$
c, R = Ac
d, R = H

respectively, for these compounds. The parent tetrol **1d** was simply named oogoniol. Because of the very small amount of hormone which was available, the structures were determined mainly by analysis of spectral data. No confirmation of the structure assignment by synthesis is so far available. Recently, Taylor and Djerassi[2] reported the synthesis of 3β,11α,15β-trihydroxycholest-5-en-7-one (**2**), a compound containing the nuclear functionalities of



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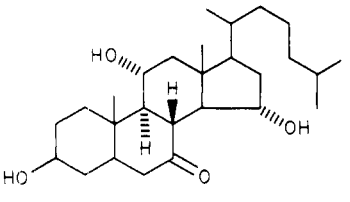

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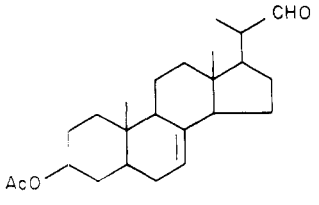

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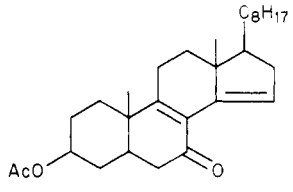
oogoniol (**1d**). Such work was directed to achieve a route to the introduction of the correct oxygenated functionalities into the sterol nucleus of oogoniols. The key intermediate of the synthesis is 3β,11α,15α-trihydroxy-5α-cholestan-7-one (**3**). We now report a new approach to this compound starting from 5α-cholest-7-en-3β-ol. This starting material was chosen in connection with our search for a method for the stereospecific synthesis from aldehyde **4** of (24*R*)- and (24*S*)-3β,29-dihydroxy-5α-stigmast-7-ene. One of them contains the right side chain and the C-24 chirality of **1d** and a Δ^7 double bond which should allow us to introduce the nuclear functionalities of oogoniol.

In a previous work[4] we developed a method for the synthesis of 15-oxygenated steroids from ring D unsubstituted precursors. It was shown that action of chromic acid on 5α-cholesta-8,14-dien-3β-ol acetate gave rise to 3β-(acetyloxy)-9α-hydroxy-5α-cholest-8(14)-en-15-one. The formation of the last compound was rationalized with the intermediary formation of a 14α,15α-oxide ring (Scheme I).

These results suggested that the formation of 14α,15α-oxide on 3β-(acetyloxy)-5α-cholesta-8,14-dien-7-one (**5**),



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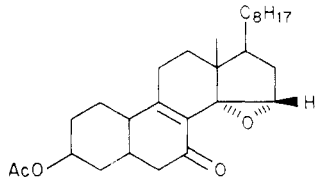

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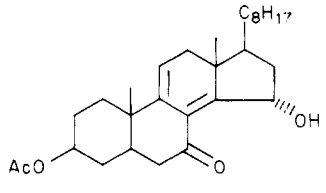

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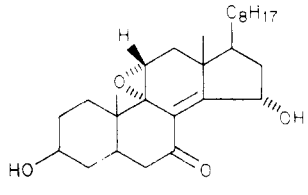

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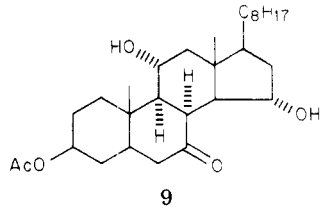

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obtainable[5] from 5α-cholest-7-en-3β-ol, followed by acidic treatment, should produce a $\Delta^{8(14)}$-9α,15α-dihydroxy system and eventually a $\Delta^{9(11),8(14)}$-diene-15α-ol, by elimination of the elements of water from the 9α- and 11-positions. The dienone should be hydroxylated at the 11α-position by selective epoxidation of the more nucleophilic 9(11) double bond followed by hydrogenolysis of the allylic 9α-position. Saturation of the double bond followed by base equilibration of C-8 should produce 3β,11α,15α-trihydroxy-5-cholestan-7-one (**3**). With this in mind we examined the reaction of dienone **5** with 3-chloroperbenzoic acid[6] (MCPBA) (1.2 molar equiv) and were able to obtain

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(1) T. C. McMorris, S. R. Schow, and G. R. Weine, *Tetrahedron Lett.*, 335 (1978), and references cited therein.
(2) E. J. Taylor and C. Djerassi, *J. Org. Chem.*, **42**, 3571 (1977).
(3) K. Sakai and K. Tsuda, *Chem. Pharm. Bull.*, 11, 529 (1963).
(4) M. Anastasia, A. Fiecchi, and A. Scala, *J. Chem. Soc., Perkin Trans. 1*, in press.
(5) L. F. Fieser, K. Nakanishi, and W. Y. Huang, *J. Am. Chem. Soc.*, **75**, 4720 (1953).
(6) The reaction of dienone **5** with perbenzoic acid was first reported by Fieser et al.[5] to yield two unidentified products. The main product isolated by these authors arises from methanol addition to the epoxide **6**, probably during crystallization as demonstrated by mass spectral (*m/e* 488, M^+) and NMR data [δ 3.2 (s, 3 H, OMe)]. The minor product isolated by Fieser is identical with compound **7**.

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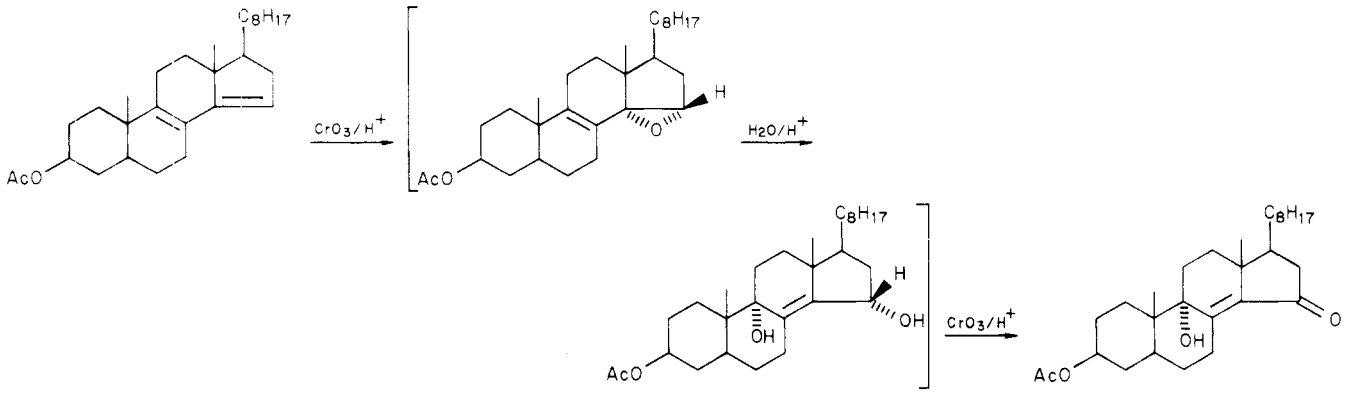
Scheme I



in 65% yield 3β-(acetyloxy)-14α,15α-epoxy-5a-cholest-8-en-7-one (**6**).

The assignment of structure **6** to this epoxy ketone is based on the expected addition of the peroxyacid to the α face of the Δ^{14} double bond and on spectral evidence. The compound shows the appropriate carbonyl absorptions in IR and UV spectra. The ^{1}H NMR spectrum exhibits a signal at δ 4.65, assigned to the 15β proton, which undergoes a deshielding effect by the 7-keto group. A similar effect can be observed in the parent dienone **5** where the 15-vinylic proton resonates at δ 6.5. The chemical shifts observed for C-18 and C-19 angular methyl groups show good agreement with the calculated[7] values for **6**. Compound **6** was accompanied by minor amounts (ca. 20%) of a more polar compound to which the structure of 3β-(acetyloxy)-15α-hydroxy-5α-cholesta-8(14),9(11)-dien-7-one (**7**) was assigned on the basis of its origin, spectral properties, and reactivity. The compound **7** was the main product after 2 days' standing of the reaction mixture at 0 °C.

The elemental analysis and mass spectrum of **7** are in keeping with the molecular formula $C_{29}H_{44}O_4$. The IR and UV spectra show the presence of a strongly conjugated chromophore in the molecule. The ^{1}H NMR information is consistent with the assigned structure, showing a signal at δ 5.54 for the vinyl proton at C-11 and signals at δ 4.83 and 4.7 for the 3α and 15β protons, respectively. Finally, the positions of C-18 and C-19 methyl signals are in agreement with the calculated[7] values for **7**.

The dienone **7** contains a cross-conjugated system as does the dienone **5**; the $\Delta^{9(11)}$ double bond of **7** can react with peroxyacids to give a 9α,11α-epoxide. In fact, treatment of **7** with MCPBA afforded in 60% yield a product shown to be the desired 3β,15α-dihydroxy-9α,11α-epoxy-5α-cholest-8(14)-en-7-one (**8**).

The spectral properties of **8**, notably those associated with the presence of a $\Delta^{8(14)}$-7-ketone, establish the identity of this compound. Strong supporting evidence for this structure is provided by the ^{1}H NMR spectrum which exhibits a signal at δ 3.42 for the epoxydic proton at C-11 and signals at δ 4.65 and 4.53, assigned to the 3α and 15β protons, respectively. The chemical shifts observed for the C-18 and C-19 angular methyl groups also show good agreement with the values calculated[7] for **8**. A further proof of structure **8** is offered by subsequent chemical transformations.

Compound **8** can be obtained in 65% yield by a one-pot reaction of the dienone **5** with MCPBA (2 molar equiv). This oxidation represents a ready route to functionalize rings C and D of **5**.

The final stage of the synthesis is the formation of the 11α-hydroxy group by hydrogenolysis of the 9α,11α-epoxy ring of **8**. Hydrogenolysis of an epoxide gives different products when either nickel or palladium are used as catalysts. It was suggested[8] that hydrogenolysis with inversion mainly occurs in the case of palladium-on-charcoal. On the contrary, hydrogenolysis with retention occurs if Raney nickel is used. Retention occurs when the oxygen atom of the epoxide ring is located upon the surface of the catalyst during the hydrogenation. Because an α attack of the compound **8** by catalyst is the only expectable one with either catalyst, formation of an 11α-hydroxy-9α-H-steroid is predictable in the reaction. In fact, catalytic hydrogenation of allylic epoxide **8** with palladium-on-charcoal produced 3β-(acetyloxy)-11α,15α-dihydroxy-5α,8α-cholestan-7-one (**9**).

The saturated ketone **9** probably possesses the "unnatural" 8α-H,9α-H configuration, as it can be expected by the catalyst attack on the double bond from the α face of the molecule. This is in accordance with the results of Taylor and Djerassi[2] in the reduction of 3β,11α,15α-trihydroxy-5α-cholest-8-en-7-one. The product **9** can be isolated by crystallization in nearly pure form. The mass spectrum as well as the IR spectrum are in accord with the proposed structure. As a result of the conformational changes induced in rings B and C by the 8α-H,9α-H junction, Zürcher additivity rules are no longer applicable to check the proposed structure. The product **9** appeared to equilibrate slowly to a less polar compound on standing in solution or upon TLC. Complete equilibration at C-8 of **9** was achieved in methanolic potassium hydroxide to give a quantitative yield of 3β,11α,15α-trihydroxy-5α-cholestan-7-one (**3**), thus providing independent chemical confirmation of the structure **9**. The spectral properties of **3** are in agreement with the assigned structure and with those reported by Taylor and Djerassi.[2] Because (*Djerassi et al.*) have been able to transform **3** into a compound containing the nuclear functionalities of oogoniol, the present synthesis of **3** represents an alternative route to the oogoniol nucleus. Our own approach has the merit of relative brevity.

Experimental Section

All melting points are uncorrected. Infrared (IR) spectra were recorded for solutions in chloroform. Optical rotations were measured for solutions in chloroform. Ultraviolet (UV) spectra were recorded for solutions in ethanol.

Nuclear magnetic resonance (NMR) spectra were recorded on Varian HA-100 and Varian XL 100 spectrometers as chloroform-*d*

(7) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964, Chapter 2; W. Arnold, W. Meister, and G. Englet, *Helv. Chim. Acta*, 57, 1559 (1974).

(8) A. Suzuki, M. Miki, and M. I. Toh, *Tetrahedron*, 3621 (1967).

solutions and are reported in δ units relative to Me_4Si. Mass spectra were recorded on a Varian 112 S spectrometer by direct inlet.

The progress of all reactions and column chromatographs (silica gel G–Celite, 50:50 (v/v)) was monitored by TLC on E. Merck silica gel HF_{254} plates, visualized by spraying with 70% sulfuric acid followed by heating.

3-(Acetyloxy)-14α,15α-epoxy-5α-cholest-8-en-7-one (6). MCPBA (0.12 g) in dichloromethane (3 mL) was added to a solution of 3β-(acetyloxy)-5α-cholesta-8,14-dien-7-one (**5**) (0.3 g) in the same solvent (10 mL) dropwise over 30 min at 0 °C. The solution was washed with water, saturated $NaHCO_3$, and finally water, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed. Elution with 3% diethyl ether–hexane gave 3β-(acetyloxy)-14α,15α-epoxy-5α-cholest-8-en-7-one (**6**) (0.19 g). When crystallized from diisopropyl ether, **6** had the following properties: mp 122–123 °C; UV λ_{max} 246 nm (log ε 4.00); IR 1743, 1660, 1590 cm^{-1}; ^1H NMR δ 0.71 (s, 3 H, 18-CH_3; calcd[7] δ 0.73), 1.18 (s, 3 H, 19-φCH_3; calcd[7] δ 1.19), 2.00 (s, 3 H, OAc), 4.63 (m, 1 H, 15β-H; $w_{1/2}$ ca. 4 Hz), 4.75 (m, 1 H, 3α-H, $w_{1/2}$ ca. 20 Hz); mass spectrum *m/e* 456 (35%, M^+), 441 (100, M – CH_3).

Anal. Calcd for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: C, 76.21; H, 9.88.

Elution with 5% diethyl ether–hexane gave 3β-(acetyloxy)-15α-hydroxy-5α-cholesta-8(14),9(11)-dien-7-one (**7**): 0.06 g; mp 154 °C (from methanol); $[\alpha]^{23}_D$ +85°; UV λ_{max} 226, 318 nm (log ε 4.04, 3.41); IR 3485, 1740, 1670, 1628, 1580 cm^{-1}; ^1H NMR δ 0.82 (s, 3 H, 18-CH_3; calcd[7] δ 0.80), 1.06 (s, 3 H, 19-CH_3; calcd[7] δ 1.07), 2.04 (s, 3 H, OAc), 4.65 (m, 1 H, OH, $w_{1/2}$ ca. 7 Hz), 4.70 (m, 1 H, 3α-H, $w_{1/2}$ ca. 20 Hz), 4.83 (m, 1 H, 15β-H, $w_{1/2}$ ca. 12 Hz), 5.54 (dd, 1 H, 11β-H, J_{AX} = 3 Hz, J_{BX} = 7 Hz); mass spectrum *m/e* 456 (46%, M^+), 441 (100, M – CH_3).

Anal. Calcd for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: C, 76.50; H, 9.51.

When the reaction was worked up after standing for 24 h at 0 °C, dienone **7** was obtained in 65% yield.

3β,15α-Dihydroxy-9α,11α-epoxy-5α-cholest-8(14)-en-7-one (8). (a) From 3β-(Acetyloxy)-15α-hydroxy-5α-cholesta-8-(14),9(11)-dien-7-one (7). MCPBA (170 mg) in dichloromethane (4 mL) was added to a solution of **7** (300 mg) in the same solvent (20 mL) at 0 °C. After 2 h at room temperature, the usual workup yielded a pale yellow solid (300 mg), which, after chromatography, gave (eluted with 3% diethyl ether–hexane) pure epoxy ketone **8**: mp 140 °C; $[\alpha]^{23}_D$ +57°; UV λ_{max} 253 nm (log ε 3.97); IR 3430, 1725, 1680, 1610 cm^{-1}; ^1H NMR δ 1.01 (s, 3 H, 18-CH_3; calcd[7] 0.97), 1.15 (s, 3 H, 19-CH_3; calcd[7] δ 1.13), 3.42 (dd, 1 H, 11β-H, J_{AX} = 2 Hz, J_{BX} = 6 Hz), 4.45 (bs, 1 H, 15α-OH), 4.53 (m, 1 H, 15β-H, $w_{1/2}$ ca. 10 Hz), 4.65 (m, 1 H, 3α-H, $w_{1/2}$ ca. 20 Hz); mass spectrum *m/e* 472 (20%, M^+), 287 (100).

Anal. Calcd for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.75; H, 9.60.

(b) From 3β-(Acetyloxy)-5α-cholesta-8,14-dien-7-one (5). Treatment of **5** (600 mg) in dichloromethane (20 mL) with MCPBA (590 mg) at 0 °C for 24 h gave, after the usual workup, the epoxy ketone **8** (0.4 g), identical with that described above.

3β,11α,15α-Trihydroxy-5α-cholestan-7-one (3). Catalytic hydrogenation of the epoxy ketone **8** (300 mg) with 10% Pd/C (150 mg) in ethanol (20 mL) plus pyridine (50 μL) at 25 °C and 1 atm was complete after 4 h. The catalyst was removed by filtration, and the solution was concentrated to give a residue (300 mg) which, after crystallization from methanol, was slightly impure on TLC: mp 103–105 °C; IR 3530, 3380, 1730 cm^{-1}; ^1H NMR δ 0.84 (s, 6 H), 0.92 (s, 6 H), 0.98 (d, 3 H), 2.02 (s, 3 H, OAc), 3.1–4.0 (2 m (overlapping), 2 H, 11β-H, 15β-H), 4.7 (m, 1 H, 3α-H); mass spectrum *m/e* 476 (4%, M^+), 458 (10, M – H_2O), 443 (5, M – H_2O – CH_3), 398 (11, M – H_2O – OAc), 345 (21, M – H_2O – side chain), 249 (100), 209 (64).

The product was dissolved in 5% methanolic potassium hydroxide and heated under reflux for 3 h. After the usual workup and crystallization from diethyl ether the triolone **3** was obtained (100% yield): mp 134 °C $[\alpha]^{23}_D$ +5°; IR 3610, 3450, 1695 cm^{-1}; ^1H NMR δ 0.72 (s, 3 H, 18-CH_3; calcd[7] δ 0.72), 1.21 (s, 3 H, 19-CH_3; calcd[7] δ 1.21), 3.60, 3.80, 4.00 (3 m (overlapping), 3 H, 3α-H, 11β-H, and 15β-H); mass spectrum *m/e* 434 (6%, M^+), 416 (9, M – H_2O), 398 (13, M – $2H_2O$), 303 (24, M – H_2O – side chain), 285 (11, M – $2H_2O$ – side chain), 209, (78), 208 (38), 207 (100); lit.[2] mp 117–120 °C; $[\alpha]^{23}_D$ +4.5°; all the other chemicophysical characteristics are identical.

Anal. Calcd for $C_{27}H_{46}O_4$: C, 74.59; H, 10.67. Found: C, 74.39; H, 10.50.

Acetylation of **3** (200 mg) in pyridine (5 mL) by treatment with acetic anhydride (2.5 mL) at room temperature for 10 h gave 3β,11α-bis(acetyloxy)-15α-hydroxy-5α-cholestan-7-one, which, when crystallized from acetone–hexane, was identical (melting point, optical rotation, NMR spectrum, and mass spectrum) with the compound described by Taylor and Djerassi.[2]

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Registry No. **3**, 71116-97-7; **5**, 63115-68-4; **6**, 71076-39-6; **7**, 71076-40-9; **8**, 71129-43-6; **9**, 71076-41-0; 3β,11α-bis(acetyloxy)-15α-hydroxy-5α-cholestan-7-one, 71116-98-8.

Stereoselective Synthesis of *cis*- and *trans*-2-(3,4-Dihydroxyphenyl)cyclobutylamine. Conformationally Restrained Analogues of Dopamine

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Due to our interest in the pharmacological activity of substituted 2-arylcylobutylamines, we have investigated methods of producing such compounds.[1] The report of a facile preparation of cyclobutanones[2,3] from aldehydes offered an attractive starting point for the preparation of 2-substituted cyclobutanone oximes and the conversion of such materials to *cis*- and *trans*-2-substituted cyclobutylamines. The conversion of 2-phenylcyclobutanone oxime to *trans*-2-phenylcyclobutylamine has been reported;[4] however, no successful method was found for the preparation of the cis isomer from the oxime. The cis isomer of 2-phenylcyclobutylamine was prepared by an alternate route.[4]

In this report, we present the synthesis of 2-(3′,4′-methylenedioxyphenyl)cyclobutanone oxime (**1**) and its stereoselective conversion to *cis*- and *trans*-2-(3′,4′-methylenedioxyphenyl)cyclobutylamine (**2** and **3**) (see Scheme I). The latter two compounds were transformed readily into conformationally restricted analogues of dopamine **4** and **5** and the ability of these compounds to bind to dopamine receptors has been previously reported.[5,6]

Results and Discussion

Our initial step in the synthetic scheme was the preparation of ketone **6** from piperonal (**7**). We first utilized the method of Trost and Bogdanowicz,[2,3] since it has been

(1) D. D. Miller, F. L. Hsu, K. N. Salman, and P. N. Patil, *J. Med. Chem.*, **19**, 180 (1976).
(2) B. M. Trost, R. LaRochelle, and M. J. Bogdanowicz, *Tetrahedron Lett.*, 3449 (1970).
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(5) H. L. Komiskey, J. F. Bossart, D. D. Miller, and P. N. Patil, *Proc. Natl. Acad. Sci. U.S.A.*, **75**, 2641 (1978).
(6) D. D. Miller, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **37**, 2394 (1978).

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