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Synthesis of Cholest-5-ene-3β,11α,15β-triol-7-one. A Model for the Steroid Nucleus of Oogoniol, a Sex Hormone of the Water Mold *Achlya*

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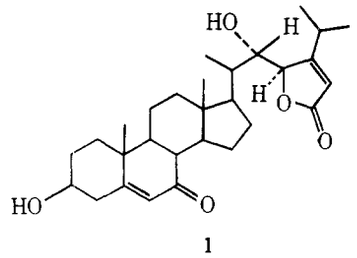
The synthesis of cholest-5-ene-3β,11α,15β-triol-7-one (**4**), a compound containing the nuclear functionalities of oogoniol, is described. Starting from a relatively unfunctionalized steroid, 7-dehydrocholesterol benzoate, oxygen functions were introduced into rings B, C, and D. The first stage of the synthesis was the oxygenation of C-15 through the hydroboration of cholesta-7,14-dien-3β-ol (**7b**) to give cholest-7-ene-3β,15α-diol (**8**). Then the 11α-alcohol and C-7 ketone functions were introduced via the Δ^7 double bond by a series of reactions first developed in the early 1950s to oxygenate C-11 of ring C unsubstituted steroids for corticosteroid syntheses. The resulting cholestane-3β,11α,15α-triol-7-one (**12a**) was selectively acetylated at C-3 and C-11 and the Δ^5 double bond was introduced through a bromination–dehydrobromination sequence. The final stage of the synthesis was the inversion of the C-15 alcohol to generate the desired β configuration. The 15α-alcohol was oxidized to the ketone and subsequent hydride reduction yielded predominantly the 15β-alcohol. This reduction also reduced the unsaturated C-7 ketone which was then oxidized with manganese dioxide. Saponification of the 3β- and 11α-acetates produced the desired cholest-5-ene-3β,11α,15β-triol-7-one (**4**), which proved to be biologically inactive.

Sexual reproduction in the water mold *Achlya* has been thoroughly studied and the involvement of sex hormones regulating this process has been conclusively demonstrated.[2] Sexual reproduction in *Achlya bisexualis* is initiated by the secretion of antheridiol (**1**) by the female strain which induces the formation of antheridial branches in the male strain. Antheridiol, isolated as a crystalline compound[3] and shown to have structure **1**,[4] was the first steroidal sex hormone to be identified in the plant kingdom and several syntheses have been reported.[5] After stimulation by anteridiol, the sexually activated male strain releases a second hormone, hormone B, which causes the female strain to develop oogonial branches. From a hermaphroditic strain of *Achlya heterosexualis* which produces hormone B without prior stimulation by anteridiol, McMorris and co-workers have recently isolated and characterized two crystalline compounds having hormone B activity.[6] They have named these compounds oogoniol-1 and -2 and have proposed structures **2a, 2b,** and **2c,** respectively, for these two compounds plus a third closely related compound, oogoniol-3, which was obtained as part of a noncrystalline mixture.



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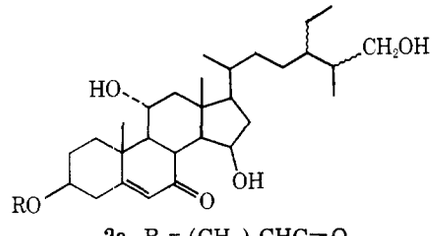


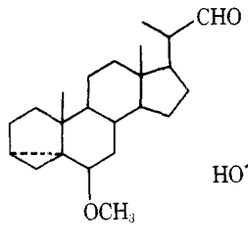
2a, R = $(CH_3)_2CHC{=}O$
2b, R = $CH_3CH_2C{=}O$
2c, R = Ac
2d, R = H

The oogoniols are therefore the second example of steroidal plant sex hormones to be identified, and confirmation of the structure assignment by synthesis is desirable. Even more importantly, structural modification would permit an evaluation of the structural specificity of the biological activity associated with the different functionalities of structure **2.** Oogoniol-1, -2, and -3 (**2a, 2b,** and **2c**) differ only in the kind of ester group present at C-3. The parent tetraol **2d,** which will be referred to here simply as oogoniol, has been shown to be even slightly more biologically active than **2a** and **2b.**[6] It was therefore decided to devise a synthesis of oogoniol (**2d**) rather than any of the C-3 esterified compounds **2a, 2b,** and **2c.**

Any synthesis of oogoniol utilizing a steroidal starting material can be logically divided into two parts. One part is the construction of the side chain, which ideally should be stereospecific so that the stereochemistry and absolute configuration at C-24 and C-25 can be determined. The other part

of the synthesis is the introduction of the correct functionalities into the steroid nucleus. This was the synthetic approach that was decided upon in this laboratory.

Specifically, the aldehyde **3**, which is derived from stigmasterol[7] was chosen as a convenient starting material for the elaboration of the side chain. The main skeleton functionalities of oogoniol can then be introduced by means of the regenerated 5-en-3β-ol moiety. Since both parts of this synthesis were expected to be multistep and to involve selective manipulations of several functionalities, it was decided to devise the route for the introduction of the functional groups into the steroid nucleus using a model system, i.e., starting with a compound containing the cholesterol side chain. The synthesis of this model compound cholest-5-ene-3β,11α,15β-triol-7-one (**4**) is described here. Compound **4** is also of intrinsic interest,



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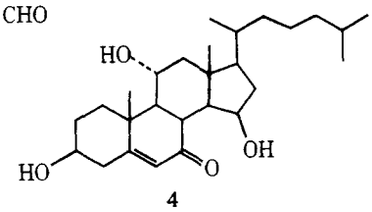

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since it provides an opportunity to determine the importance of the substituents at C-24 and C-26 of **2** for biological activity.

Discussion

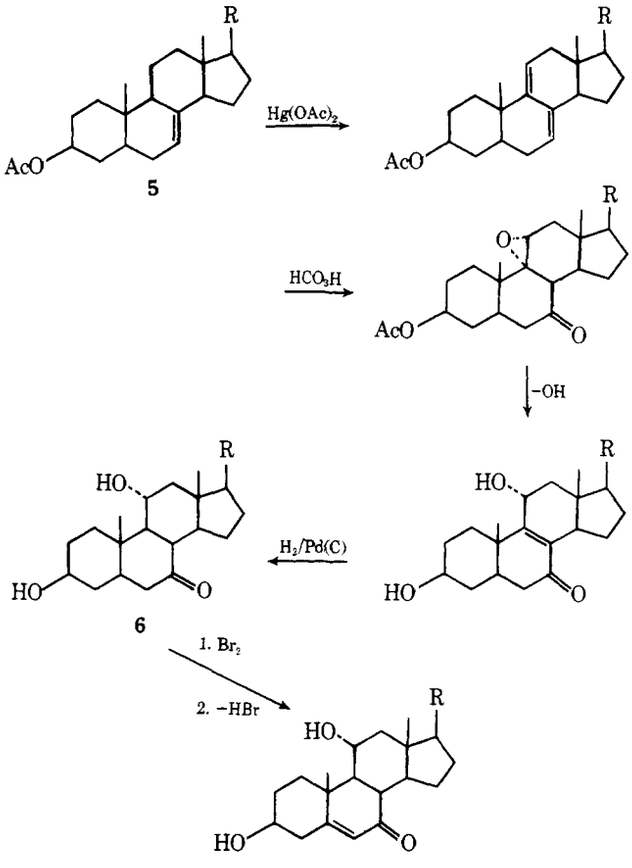
The synthetic scheme proposed above for oogoniol requires that the oxygen functions in rings B, C, and D of **4** be introduced starting from the 5-en-3β-ol group of cholesterol. As part of the work done in the early 1950s to develop methods for synthesizing 11-oxygenated steroids from ring C unsubstituted precursors, it was shown that the 11α-ol-7-one compound **6** can be produced in several steps from the Δ^7-steroid **5**.[8] Bromination at C-6 followed by dehydrobromination to the 5-en-7-one would then give the correct functionality for **4** in rings A, B, and C (Scheme I).

This leaves the problem of introducing the 15β-alcohol into the molecule. One standard method of oxygenating C-15 is the hydroboration of a Δ^{14} double bond to give a 15α-alcohol.[9] Subsequent oxidation of this alcohol and stereospecific reduction should then produce the desired 15β-alcohol configuration (Scheme II).

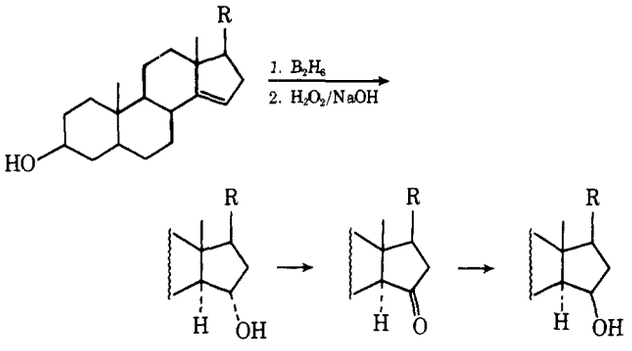
With these two schemes in mind, the starting material chosen for the synthesis of **4** was cholesta-7,14-dien-3β-ol benzoate (**7a**),[10] obtained from the acid-catalyzed double-bond isomerization of 7-dehydrocholesterol benzoate.[11] Sondheimer and co-workers have reported that the hydroboration of steroidal 7,9(11)-dienes produces Δ^7-11α-alcohols in good yield.[12] The selectivity and stereospecificity of this reaction was accounted for by their observation that Δ^7 double bonds are unreactive and $\Delta^{9(11)}$ steroids yield the 11α-hydroxy compounds in the hydroboration reaction. These results suggested that the hydroboration of a 7,14-diene should produce the Δ^7-15α-alcohol. This reaction would then serve to link Schemes I and II by oxygenating C-15 while leaving the Δ^7 double bond for functionalizing ring C.[13]

Hydroboration of cholesta-7,14-dien-3β-ol (**7b**), obtained from the saponification of the benzoate **7a**, followed by oxidation with alkaline peroxide did, in fact, afford in 78% yield a product shown to be the desired 14α-cholest-7-ene-3β,15α-diol (**8**). The assignment of structure **8** to this enediol is based on the analogy to the 7,9(11)-diene system and the expected overall *cis* addition of water to the α side of the Δ^{14} double bond.[9] Strong supporting evidence for this structure is provided by the NMR spectrum which exhibits a signal at

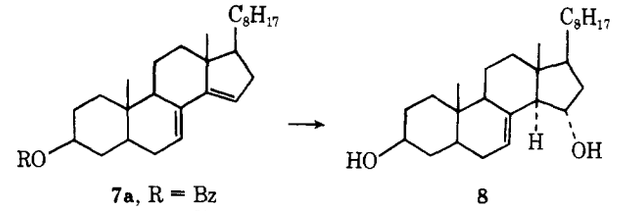
Scheme I



Scheme II



δ 5.44 ppm for the vinyl proton at C-7 and signals at δ 3.57 and 4.20 ppm assigned to the 3α- and 15β-protons, respectively. The signal at 4.20 ppm is consistent with a 15β-proton which has an expected chemical shift at ca. 4.13 ppm, rather than a 15α proton which resonates further upfield at ca. 3.95 ppm.[14a] The chemical shifts observed for the C-18 and C-19 angular methyl groups also show good agreement with the values calculated for **8**.[14,15]



7a, R = Bz
7b, R = H

8

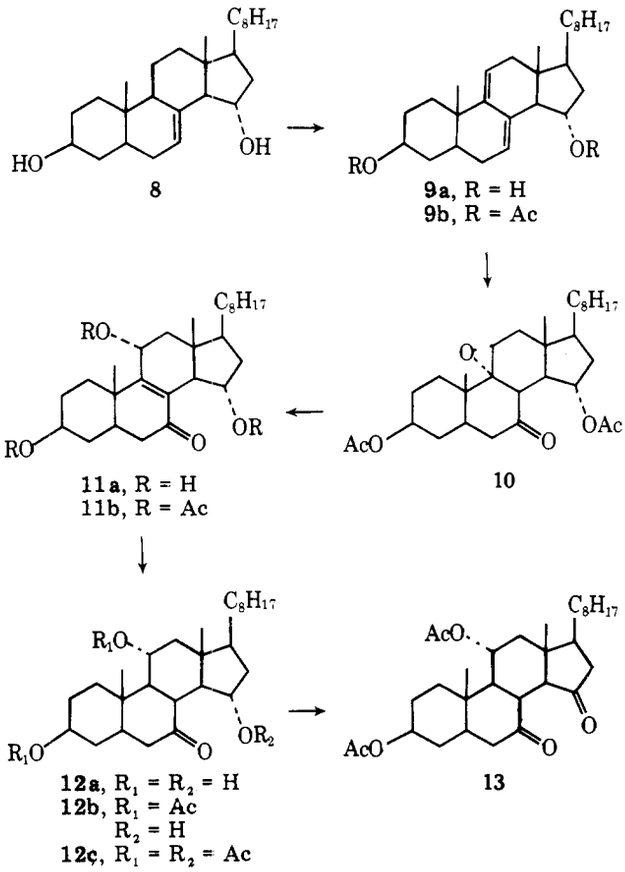
Additional confirmation of the α configuration of the C-15 alcohol in compound **8** is furnished by a consideration of the molecular rotation contribution of this alcohol. The $\Delta[M]_D$ value going from cholest-7-en-3β-ol to **8** is +172°. This value

is in accord with the positive $\Delta[M]_D$ contribution expected for a 15α-hydroxyl group, rather than the negative value associated with a 15β-alcohol.[9,14] Further proof of structure **8** is offered by subsequent chemical transformations.[16]

Attempts to oxidize **8** to the corresponding diketone using either Jones or Collins reagent led to mixtures of products presumably due to allylic oxidation of the double bond and also isomerization to the conjugated 8(14)-en-15-one. The desired cholest-7-ene-3,15-dione could not be isolated from this mixture. It had been hoped that the 15β-alcohol configuration could be obtained by hydride reduction of this diketone to cholest-7-ene-3α,15β-diol. In light of these unpromising results, however, it was decided to delay this C-15 configurational inversion until later in the synthesis. This decision to carry through the 15α-alcohol proved to have some interesting consequences as will be discussed later.

The next few steps in the synthesis (Scheme III) are concerned with the formation of the desired 11α-hydroxy-7-one **12a** from the Δ^7 precursor **8**, based on the earlier work of Djerassi and co-workers (see Scheme I).[8] The mercuric acetate dehydrogenation[17] of **8** proceeded smoothly to give the 7,9(11)-diene **9a** which was directly acetylated with acetic anhydride in pyridine. After purification by column chromatography on silica and recrystallization from methanol, a 62% yield of cholesta-7,9(11)-diene-3β,15α-diol diacetate (**9b**) was obtained. This product exhibited spectral properties consistent with the structure **9b.**

Scheme III

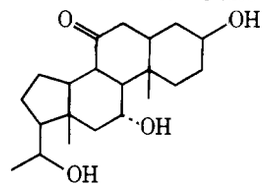


The treatment of the 7,9(11)-diene **9b** with performic acid as described in the literature[8] led to a complex mixture of products from which a 30% yield of pure 9α,11α-epoxycholestane-3β,15α-diol-7-one diacetate (**10**) could be isolated. The physical and spectral properties of this compound outlined in the Experimental Section are completely consistent with the assigned structure. Subsequent rearrangement of **10** in dilute methanolic potassium hydroxide produced a nearly quantitative yield of cholest-8(9)-ene-3β,11α,15α-triol-7-one (**11a**), thus providing independent chemical confirmation of the epoxyketone structure **10.** The spectral properties of **11a,** notably those associated with the presence of an α,β-unsaturated ketone, establish the identity of this compound.

Attempted selective diacetylation of the 3β- and 11α-alcohols of **11a** using 2 equiv of acetic anhydride led to a mixture of products in which the di- and triacetates could not be separated by chromatography. Therefore, the configuration of the C-15 alcohol could not be inverted at this stage of the synthesis. The triacetate **11b** was prepared by acetylation of **11a** with an excess of acetic anhydride in pyridine.

The next step in the synthetic scheme is the reduction of the $\Delta^{8(9)}$ double bond. The catalytic hydrogenation of the triolenone **11a** with palladium on carbon did not produce directly the saturated ketone **12a** with the normal 8β-H,9α-H trans configuration that was expected from the literature report.[8] Instead, two products were observed by TLC. The major product appeared to equilibrate slowly to the minor product on standing in solution or upon chromatography. Complete conversion of the hydrogenation product to the more stable isomer was achieved by heating under reflux in 5% methanolic potassium hydroxide. This afforded a 90% yield of cholestane-3β,11α,15α-triol-7-one (**12a**) as white crystals. If the catalytic hydrogenation of **11a** occurs from the α side of the molecule, the initial product must possess the unstable 8α-H,9α-H cis configuration. Base treatment causes equilibration at C-8 (α to the ketone) to give the normal all trans steroid configuration for the triolone **12a.** The spectral properties of this compound are in agreement with the assigned structure.

However, the CD curve of **12a** is extremely interesting because of the positive Cotton effect, $[\theta]_{290}$ +1770 (dioxane), that it displays. This is in contrast to the negative value expected for a C-7 ketone[18] and shown by the related ketone, pregnane-3β,11α-20β-triol-7-one (**14**),[19] $[\theta]_{298}$ −2250 (dioxane).



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Also, the magnitude of the Cotton effect for **12a** is solvent dependent, showing a considerable decrease in methanol, $[\theta]_{288}$ +922, compared to dioxane, $[\theta]_{290}$ +1770. The results can be explained in terms of a large positive front octant contribution of the 15α-alcohol.

Kirk and Klyne[20] have found that there is a definite front octant effect of ring D in the CD spectra of 5α-androstan-7-one and D-homo-5α-androstan-7-one, which is caused mostly by the interaction of C-15 with the carbonyl group. These authors suggested that this interaction falls off rapidly with distance, which explains the observed large positive contribution to the Cotton effect for the six-membered ring D of the D homocompound compared to the much smaller positive contribution for the normal five-membered ring D in which C-15 is farther from the C-7 ketone. This being the case, the 15α-alcohol of **12a,** which has a strong interaction with the C-7 ketone, would be expected to make a large front octant contribution. Apparently, this front octant effect is large enough to reverse the normal sign of the Cotton effect and give a positive CD curve. The decrease in magnitude of the Cotton effect in methanol solvent as compared to dioxane can be attributed to the ability of methanol to disrupt the internal hydrogen bonding between the alcohol and the ketone and thus increase the distance between these two functionalities.

Table I. ^{13}C NMR Chemical Shifts (ppm Relative to Me_4Si) for Cholesta-3β,11α,15α-triol-7-one (12a), the 3β,11α-Diacetate (12b), and the Triacetate (12c)

Carbon	12a[a]	12b[a]	12c[a]
1	37.6	36.0	35.8
2	31.5	27.5	27.5
3	70.0	71.9	72.0
4	38.5	34.3	34.3
5	46.1	45.4	45.0
6	46.2	45.7	47.1
7	214.6	212.9	208.1
8	49.6	49.4	48.5
9	61.0	56.4	56.4
10	37.6	37.5	38.2
11	68.0	70.2	69.8
12	50.8	45.4	46.2
13	45.0	44.6	43.4
14	57.8	57.2	52.8
15	72.1	71.9	74.3
16	39.1	39.1	36.5
17	53.7	53.4	50.6
18	14.2	13.9	14.0
19	12.4	12.3	12.5
20	35.1	34.9	35.2
21	18.7	18.7	18.7
22	36.1	36.0	36.0
23	24.0	23.8	23.8
24	39.5	39.5	39.5
25	28.0	28.0	28.0
26	22.5	22.5	22.5
27	22.7	22.7	22.7
CH_3 (acetate)		21.6, 21.1	21.6, 21.4, 21.1
C=O (acetate)		169.9, 169.6	171.5, 169.8, 169.6

[a] Registry no.: **12a**, 63324-80-1; **12b**, 63324-81-2; **12c**, 63324-82-3.

Acetylation of the triolone **12a**, in contrast to the results for the unsaturated precursor **11a**, proved to be selective for the 3β- and 11α-alcohols even using an excess of acetic anhydride in pyridine. Trace amounts of the triacetate **12c** were separated from the diacetate **12b** by careful column chromatography on silica affording a 92% yield of cholestane-3β,11α,15α-triol-7-one 3β,11α-diacetate (**12b**). The location of the free alcohol in **12b** was ascertained by a specific mass spectral fragmentation process (see Experimental Section) as well as by infrared spectral evidence. The latter showed carbonyl absorptions at 1720 and 1700 cm^{-1} for the acetates and the saturated ketone of **12b**, compared with the carbonyl absorption at 1695 cm^{-1} for the triolone **12a**. The triacetate **12c** shows only one carbonyl peak at 1720 cm^{-1}. Thus, it appears that the diacetate **12b** still retains the hydrogen bonding interaction between the 15α-alcohol and the C-7 ketone which lowers the frequency of the carbonyl absorption.

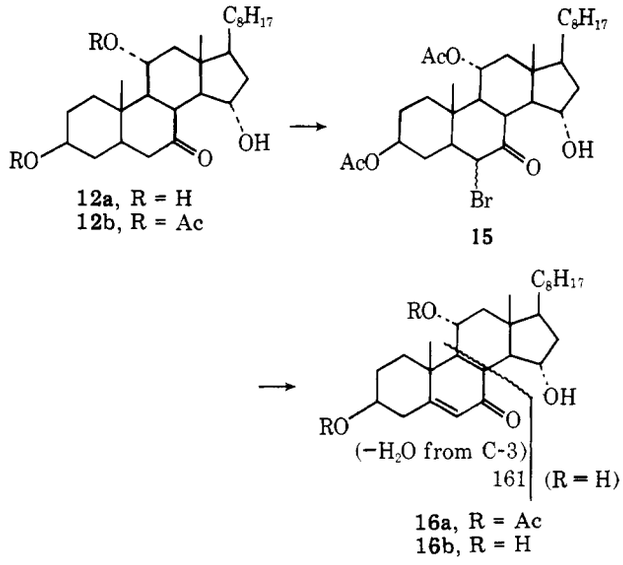
The ^{13}C NMR spectra of compounds **12a**, **12b**, and **12c** provide further supporting evidence for locating the free hydroxyl group of **12b** at C-15 (Table I). The assignments of the chemical-shift values to specific carbon atoms is based on previous work done in this laboratory on the ^{13}C NMR spectra of keto and hydroxy steroids.[21] The data for the diacetate **12b** show that the resonances for C-3 and C-11 have shifted the appropriate 2 ppm downfield upon acetylation, whereas the C-15 signal has not changed. The resonances for the carbon atoms adjacent to the acetoxy carbons, C-2, C-4, C-9, and C-12, also show the characteristic 4–5 ppm upfield shift compared with the triol **12a**.[21a] The chemical shifts for C-14 and C-16 are unchanged in the spectrum of **12b**, but they do shift upfield in the spectrum of the triacetate **12c**. It can be concluded from these data that the 15α-alcohol is not acetylated in the diacetate **12b**.

The CD curves for **12b** and **12c** are very similar to that of **12a** both in shape and in showing a positive Cotton effect. The presence of an acetate at C-15 as opposed to an alcohol does not appear to have much effect on the magnitude of the Cotton effect, $[\theta]_{290}$ +2510 for **12b** and $[\theta]_{295}$ +2070 for **12c**; however, there is a slight shift in wavelength.

Additional proof for locating the free hydroxyl group of **12b** at C-15 was obtained by chemical transformation. Jones oxidation of **12b** produced a quantitative yield of cholestane-3β,11α-diol-7,15-dione diacetate (**13**) with the expected carbonyl absorption at 1740 cm^{-1} characteristic of a five-membered ring ketone, as well as the absorption at 1720 cm^{-1} for the acetates and the C-7 ketone. The CD curve of the diketone **13** displays a very large positive Cotton effect, $[\theta]_{295}$ +9680 (compared to $[\theta]_{290}$ +2510 for **12b**), which would be expected for the contribution of a C-15 ketone.[18] The mass spectral fragmentation of **13** also locates the new ketone at C-15.[22]

The introduction of the Δ^5 double bond is the next step in the synthetic sequence (Scheme IV). Enone **16b** is the C-15

Scheme IV



epimer of **4**, the model compound for the steroid nucleus of oogoniol, and the diacetylated enone **16a** is suitably functionalized to accomplish the inversion of the C-15 alcohol. The most general method for synthesizing α,β-unsaturated ketones is through the dehydrobromination of the α-bromo ketone. It has been reported that cholestan-3β-ol-7-one acetate is not brominated at an appreciable rate in acetic acid at room temperature; however, bromination in chloroform proceeds rapidly to give a mixture of the 6α- and 6β-bromo isomers with no detectable 8-bromo ketone.[23] Dehydrobromination of this mixture should then produce only the desired 5-en-7-one.

However, the attempted bromination in chloroform of either **12a** or **12b** resulted only in recovery of starting material. The bromination of **12b** to give the 6α- and 6β-bromo ketone mixture **15** was eventually achieved by treatment with pyridinium hydrobromide perbromide[24] in acetic acid at 70–75 °C. These reaction conditions also caused a slight amount of acetylation at C-15 of **12b**. Because of the acetylation side reaction of these bromination conditions, the triolenone **16b** could not be synthesized directly from the corresponding triolone **12a**. Compound **16b** was obtained instead by saponification of the diacetate **16a**.

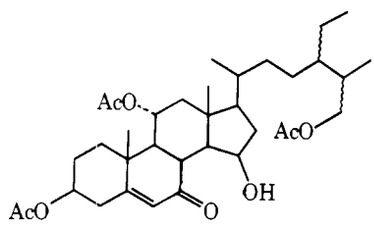
After partial purification by column chromatography, the crude α-bromo ketone mixture **15** was dehydrobrominated by treatment with calcium carbonate in boiling dimethylacetamide to give the enone **16a** plus some 3,5-dien-7-one side product (UV 283 nm). Column chromatography on silica af-

Table II. Chemical Shifts of Proton Signals in a Series of Steroids Related to Oogoniol (2d)

Compd	Registry no.	18-CH_3	19-CH_3	3α-H	11β-H	15β-H	15α-H	6-H	15α-OH
12b		0.76	1.22	4.64	5.25	3.80			5.07
16a	63324-83-4	0.79	1.35	4.70	5.32	3.94		5.87	5.64
18	63324-84-5	0.80	1.34	4.68	5.32			5.90	
17	63358-17-8	1.01	1.32	4.73	5.32		4.73	5.84	
20	63324-85-6	1.02	1.32	4.69	5.32		4.69	5.84	
16b	63340-13-6	0.75	1.36	~3.65	~4.15	~3.95		5.84	5.81
4	63324-86-7	0.99	1.36	3.72	4.15		4.70	5.83	
2d	63358-18-9	0.96	1.34	Not given	4.14		4.68	5.80	

forded a 71% yield (from **12b**) of cholest-5-ene-3β,11α,15α-triol-7-one 3β,11α-diacetate (**16a**). The mass spectrum of **16a** shows slight traces of the saturated ketone **12b,** but the spectral properties are in accord with the assigned structure.

The presence of the unsaturated ketone is confirmed by the appropriate carbonyl absorptions in the IR and UV spectra, and the CD curve of **16a** is almost identical to that of cholest-5-en-3β-ol-7-one acetate. The NMR spectrum shows a vinyl proton signal as well as a sharp singlet at δ 5.64 ppm which is assigned to the alcohol proton on the basis of its ability to exchange with D_2O. Compound **12b** shows a similar alcohol proton resonance at 5.07 ppm and the presence of these signals probably is due to the previously demonstrated hydrogen-bonding interaction of the 15α-alcohol and the C-7 ketone. The signals in the NMR spectrum of the enone **16a** for the 3α, 11β, and 15β protons appear at approximately the same chemical shifts as for the saturated ketone **12b** (see Table II). However, the 15α proton of the related 15β alcohol **17**[6] in the oogoniol series resonates at 4.73 ppm, compared to



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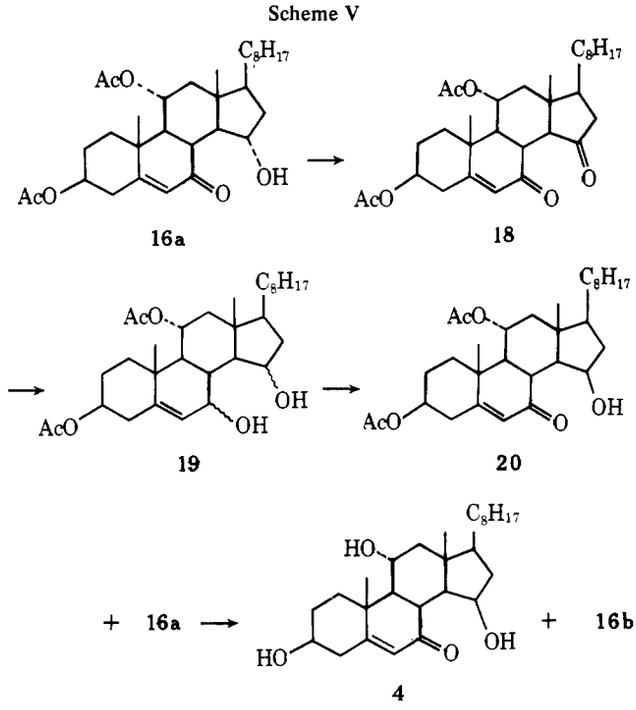
3.94 ppm for the 15β-H of **16a,** which proves that these two compounds have different C-15 alcohol configurations. The 15α-H of **17** is strongly deshielded by the C-7 ketone.[25]

The triolenone **16b,** the C-15 epimer of cholest-5-ene-3β,11α,15β-triol-7-one (**4**), obtained by treatment of the diacetate **16a** with potassium carbonate in aqueous methanol had spectral properties which were completely consistent with the proposed structure. The CD curve is similar to that of the diacetate precursor **16a** and the NMR chemical shifts are listed in Table II for comparison with those of oogoniol (**2d**).[6] Again, these NMR data show the obvious C-15 stereochemical difference between the 15β-H of **16b** at ca. δ 3.95 ppm and the 15α-H of **2d** at 4.68 ppm.

The high-resolution mass spectrum of **16b** establishes a molecular weight of 432.3225 compared with calculated value of 432.3239 for $C_{27}H_{44}O_4$. The *m/e* 414 ion, which corresponds to loss of water, is quite pronounced, but the base peak appears at *m/e* 161. The *m/e* 161 ion is also responsible for the base peak in the mass spectrum of oogoniol (**2d**)[6] and is an intense ion in the mass spectrum of 7-keto-β-sitosterol,[26] another compound containing the 3β-ol-5-en-7-one moiety. Thus, this *m/e* 161 ion probably results from cleavage through ring C and loss of water from C-3 as indicated by the wavy line in structure **16.**

The final stage of the synthesis is the inversion of the C-15 alcohol to generate the required 15β configuration. This conversion was accomplished as depicted in Scheme V. Jones

Scheme V



oxidation of compound **16a** produced a 90% yield of cholest-5-ene-3β,11α-diol-7,15-dione diacetate (**18**) with the expected spectral properties (see Experimental Section and Table II).

A hydride reduction of the C-15 ketone of **18** was expected to produce predominantly the 15β-alcohol. Lithium tri-*tert*-butoxyaluminum hydride[27] was chosen as the reducing agent for two reasons. First, this reagent is generally more stereospecific than sodium borohydride or lithium aluminum hydride and it should therefore yield more of the desired 15β-alcohol.[27b] Second, it has been reported that a saturated ketone can be selectively reduced in the presence of an α,β-unsaturated ketone using lithium tri-*tert*-butoxyaluminum hydride.[27b] Thus, it should be possible to reduce the diketone **18** directly to the 15β-alcohol **20** in which the 5-en-7-one chromophore is still present.

However, an attempt to selectively reduce the C-15 ketone of **18** using this reducing agent was unsuccessful. The 5-en-7-one moiety appeared to be reduced at least as rapidly if not faster than the saturated ketone. This unexpected result is probably due to the sterically hindered nature of the C-15 ketone and the proximity of the two carbonyl groups.

Therefore, the diketone **18** was reduced completely to the diol mixture **19** using an excess of lithium tri-*tert*-butoxyaluminum hydride. The allylic alcohol of **19** was then directly oxidized with manganese dioxide in chloroform to give a 57% yield of a product which was predominantly the desired cho-

lest-5-ene-3β,11α,15β-triol-7-one 3β,11α-diacetate (**20**). Unfortunately, this reduction was not as stereospecific as had been anticipated and the product contained ca. 20–25% [as judged by the intensity of the C-18 methyl, C-15 proton, and 15α-OH signals in the NMR spectrum (see Table II)] of the 15α-alcohol **16** which could not be separated from the 15β-epimer **20** by TLC. Two recrystallizations of this mixture left the product ratio essentially unchanged.

The spectral properties of cholest-5-ene-3β,11α,15β-triol-7-one 3β,11α-diacetate (**20**) (which contained some **16a**), with the exception of the NMR spectrum, are very similar to those of the 15α epimer **16a.** Both the mass spectrum and the CD curve of **20** are almost identical to those of **16a.** The infrared and UV spectra of **20** show unsaturated carbonyl absorptions at 1655 cm^{-1} and 235 nm (log ε = 4.05) compared to 1660 cm^{-1} and 239 nm (log ε = 4.05) for **16a.** The NMR spectrum of the 15β-alcohol **20,** however, shows two major differences from that of the 15α-epimer **16a** (see Table II). The signal for the C-18 methyl group of **20** appears at δ 1.02 ppm, which is 0.23 ppm further downfield than the C-18 methyl resonance of **16a** at 0.79 ppm. This large downfield shift is expected for the change from a 15α-alcohol to a 15β-alcohol.[14,15] The 15α-H of the 15β-alcohol **20** is also strongly deshielded by the C-7 ketone[25] and appears at 4.69 ppm. This chemical shift is comparable to the 4.73 ppm resonance of the 15α-H of the analogous 15β-alcohol **17** in the oogoniol series[6] (see Table II), whereas the 15β-H of the 15α-alcohol **16a** appears at 3.94 ppm. The other NMR signals for the protons at C-3, C-11, and C-6 have similar chemical shifts to the corresponding protons in both **16a** and **17.**

To complete the synthetic scheme, the diacetate **22** was treated with potassium carbonate in aqueous methanol to yield cholest-5-ene-3β,11α,15β-triol-7-one (**4**), the target molecule of this synthesis. Again, with the exception of the NMR spectrum (see Table II), the spectral properties of the 15β-alcohol **4** (which contains some of the 15α-epimer **16b**) resemble those of the 15α-alcohol **16b.** As is the case for the diacetate precursor **20,** the NMR spectrum of **4** shows a 0.24 ppm downfield shift of the C-18 methyl group at δ 0.99 ppm compared to the C-18 methyl resonance of the 15α epimer **16b** at 0.75 ppm. Furthermore, the 15α-H of the 15β-alcohol **4,** which is deshielded by the C-7 ketone,[25] resonates at 4.70 ppm compared with a chemical shift of 4.68 ppm for the 15α-H of oogoniol (**2d**).[6]

Cholest-5-ene-3β,11α,15β-triol-7-one (**4**) and cholest-5-ene-3β,11α,15α-triol-7-one (**16b**) were submitted to Professor T. C. McMorris (University of California at San Diego) for hormone B bioassay in *Achlya.* Even at the highest doses tested (3.5 μg/mL for the 15α-isomer **16b** and 22.6 μg/mL for the 15β-isomer **4**) no biological activity was observed, whereas the natural oogoniol-1 was fully active at 1.8 μg/mL. Unless the small contaminant of the 15α epimer **16b** present in **4** had a hormone antagonist action, one can conclude that the intact nuclear skeleton is not sufficient for significant sex-hormone activity and that the hydroxylated side chain plays an essential role.

Experimental Section

General Notes. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared (IR) spectra were recorded for solutions in chloroform on a Perkin-Elmer Model 421 spectrometer. Optical rotations were measured for solutions in chloroform using a Perkin-Elmer Model 141 spectropolarimeter. Ultraviolet (UV) spectra were recorded on a Cary-14 spectrometer for solutions in ethanol. Nuclear magnetic resonance (NMR) spectra were recorded on Varian Model T-60 (^1H NMR) and Varian XLFT-100 (^1H and ^{13}C NMR) spectrometers using deuteriochloroform as solvent and tetramethylsilane as internal reference. The 100 MHz ^1H NMR spectra were determined by Ronald L. Elsenbaumer and Dr. L. J. Durham and the ^{13}C NMR spectra by Craig L. VanAntwerp. Circular dichroism (CD) curves were determined by Mrs.R. Records with a JASCO Model ORD/UV-5 spectrometer modified for CD for solutions in dioxane, unless otherwise specified. Low-resolution mass spectra were determined by Mr. R. G. Ross with an AEI MS-9 spectrometer operating at 70 eV using a direct inlet system. The mass spectra and CD curves are reproduced in the Ph.D. thesis of E. J. Taylor, Stanford University, 1977. High-resolution mass spectra and metastable defocussing were also obtained with the MS-9 instrument. Element analyses were determined by the Microanalytical Laboratory, Stanford University.

Column chromatography was done using E. Merck silica gel 60 (60–230 mesh ASTM). The progress of all reactions and column chromatographies was monitored by thin-layer chromatography on E. Merck silica gel $HF_{254+366}$ plates visualized by spraying with ceric sulfate solution (2% in 1 M sulfuric acid) followed by heating. Preparative thin-layer chromatography was done on 0.75-mm thick $HF_{254+366}$ silica gel plates and the bands were detected either visually or by viewing under ultraviolet light.

Cholesta-7,14-dien-3β-ol (7b). Cholesta-7,14-dien-3β-ol benzoate (**7a**)[10] (11.0 g) was saponified by heating under reflux in 5% methanolic potassium hydroxide (150 mL) for 3 h. The white crystalline material obtained after workup was recrystallized from methanol to yield 8.10 g (92%) of the alcohol **7b** as white needles: mp 103–105 °C (lit.[28] mp 104–105 °C); $[\alpha]^{20}_D$ −185° (*c* 1.41); IR 3610, 3450 (O–H), 1635 cm^{-1} (C=C); NMR δ 0.77 (s, 3 H, 18-CH_3), 0.80 (s, 3 H, 19-CH_3), 3.60 (m, 3α-H, $w_{1/2}$ ca. 16 Hz), 5.48, 5.75 (2 × m, 2 H, 7-H, and 15-H); mass spectrum *m/e* 384 (100%, M^+), 369 (25, M − CH_3), 351 (12, M − CH_3 + H_2O), 271 (94, M − side chain), 257 (29, M − C_9H_{19}), 253 (15, M − side chain + H_2O).

Cholest-7-ene-3β,15α-diol (8). Cholesta-7,14-dien-3β-ol (**7b**) was hydroborated using a modification of Sondheimer's procedure.[9] A stirred solution of dienol **7b** (7.50 g, 19.5 mmol) in 300 mL of anhydrous ether was cooled to 0 °C under nitrogen. To this solution was added 80 mL of a 1 M solution of BH_3 in THF dropwise over 1 h at 0 °C under nitrogen. Stirring was continued an additional hour at room temperature, and then the excess borane was decomposed by careful addition of water. This mixture was oxidized directly with alkaline peroxide by cooling to 0 °C and adding 80 mL of 10% aqueous sodium hydroxide. Then, 60 mL of 30% aqueous hydrogen peroxide was added dropwise and the mixture was stirred at 0 °C for 1 h. The organic layer was separated and washed with 10% sodium sulfite solution and brine. After drying over anhydrous Na_2SO_4, the solution was evaporated to give 7.57 g of white crystalline material. Column chromatography on 300 g of silica eluting with ether yielded 6.15 g (78%) of the enediol **8** as white crystals: mp 184.5–186 °C (acetone); $[\alpha]^{20}_D$ +45.6° (*c* 1.32); IR 3615, 3470 cm^{-1} (O–H); NMR δ 0.57 (s, 3 H, 18-CH_3; calcd[15] 0.57), 0.80 (s, 3 H, 19-CH_3; calcd[15] 0.81), 3.57 (m, 1 H, 3α-H, $w_{1/2}$ ca. 14 Hz), 4.20 (m, 1 H, 15β-H, $w_{1/2}$ ca. 14 Hz), 5.44 (m, 1 H, 7-H); mass spectrum *m/e* 402 (47%, M^+), 387 (39, M − CH_3), 384 (100, M − H_2O), 369 (36, M − H_2O + CH_3), 351 (15, M − 2H_2O + CH_3), 317 (11), 290 (20, M − $C_7H_{12}O$ (RDA from Δ^7 double bond)[29]), 289 (10, M − side chain), 271 (84, M − H_2O + side chain), 257 (22, M − H_2O + C_9H_{19}), 253 (13, M − 2H_2O + side chain), 247 (16), 235 (12), 112 (48, $C_7H_{12}O$(RDA)).

Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.64; H, 11.56.

Cholesta-7,9(11)-dien-3β,15α-diol Diacetate (9b). Mercuric acetate (10.0 g) was added to a solution of 5.00 g of cholest-7-ene-3β,15α-diol in 125 mL of chloroform and 200 mL of acetic acid, and the mixture was stirred vigorously for 18 h at room temperature.[17] The mixture was filtered, and the filtrate was concentrated to a small volume in vacuo, dissolved in ether, washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. The resulting orange crystalline material (5.78 g) containing the dienediol **9a** was acetylated directly with acetic anhydride in pyridine. The orange oil (6.36 g) obtained after workup was chromatographed on 250 g of silica eluting with 15% ether–hexane. Recrystallization of the product from methanol gave 3.74 g (62%) of the diene diacetate **9b:** mp 126–128 °C; $[\alpha]^{20}_D$ +107° (*c* 1.06); IR 1725 (C=O), 1604 cm^{-1} (C=C); NMR δ 0.57 (s, 3 H, 18-CH_3; calcd[15] 0.57), 0.90 (s, 3 H, 19-CH_3; calcd[15] 0.92), 2.00, 2.03 (2 × s, 6 H, –OAc), 4.70 (m, 1 H, 3α-H, $w_{1/2}$ ca. 14 Hz), 5.00 (m, 1 H, 15β-H, $w_{1/2}$ ca. 16 Hz), 5.45 (m, 2 H, 7-H and 11-H); UV λ_{max} 234, 242, 249 (log ε = 4.23, 4.29, 4.12); mass spectrum *m/e* 242 (32%, M − AcOH), 311 (100, M − AcOH + side chain), 251 (14, M − 2AcOH + side chain).

Anal. Calcd for $C_{31}H_{48}O_4$: C, 76.82; H, 9.98. Found: C, 76.64; H, 9.98.

9α,11α-Epoxycholesta-3β,15α-diol-7-one Diacetate (10). A suspension of cholesta-7,9(11)-diene-3β,15α-diol diacetate (**9b**) (7.30 g) in 200 mL of formic acid was treated with 5 mL of 30% hydrogen

peroxide and stirred at room temperature for 2 h.[8] (All the steroid had dissolved after 15 min.) The solution was poured into 1 L of ice–water, and the precipitate was filtered and dissolved in ether. The ether solution was washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to give 8.10 g of pale yellow oil. This oil consisted of a complex mixture of products by TLC. The major product was the crystalline epoxyketone **10** which was isolated by column chromatography on silica (350 g) eluting with 2:1 hexane–ether. Recrystallization from methanol afforded 2.34 g (30%) of pure epoxy ketone **10** as white needles: mp 195–197 °C; $[\alpha]^{20}_D$ −46.0° (*c* 1.02); IR 1720 cm^{-1} (C=O); NMR δ 0.79 (s, 3 H, 18-CH_3; calcd[15] 0.73) 1.38 (s, 3 H, 19-CH_3; calcd[15] 1.30), 2.02, 2.04 (2 × s, 6 H, -OAc), 3.17 (d, 1 H, 11β-H, *J* = 5 Hz), 3.23 (d, 1 H, 8β-H, *J* = 11 Hz), 4.62 (m, 1 H, 3α-H, $w_{1/2}$ ca. 18 Hz), 5.04 (m, 1 H, 15β-H, $w_{1/2}$ ca. 14 Hz); $CD^{30}[\theta]_{295}$ −1140; mass spectrum *m/e* 516 (8%, M^+), 474 (42, M − C_2H_2O), 473 (13, M − C_2H_3O), 456 (97, M − AcOH), 455 (13), 428.3280 (16, M − AcOH + CO; calcd for $C_{28}H_{44}O_3$: 428.3290), 413.3047 (48, M − AcOH + CO + CH_3; calcd for $C_{27}H_{41}O_3$: 413.3056), 412.2978 (53, M − AcOH + C_2H_4O; calcd for $C_{27}H_{40}O_3$: 412.2977), 368 (12, M − 2AcOH + CO), 343 (57, M − AcOH + side chain), 316.1673 (100, M − AcOH + $C_{10}H_{20}$; calcd for $C_{19}H_{24}O_4$: 316.1675), 299.1651 (33, M − AcOH + C_2H_4O + side chain; calcd for $C_{19}H_{23}O_3$: 299.1647), 288 (12), 283 (13, M − 2AcOH + side chain), 261.2218 (34, M − AcOH + $C_{11}H_{15}O_3$; calcd for $C_{18}H_{29}O$: 261.2218), 260.2218 (13, M − AcOH + $C_{11}H_{16}O_3$; calcd for $C_{18}H_{28}O$: 260.2135), 260.1412 (10, calcd for $C_{16}H_{20}O_3$: 260.1412), 247.1333 (18, calcd for $C_{15}H_{19}O_3$: 247.1334).

Anal. Calcd for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36. Found: C, 72.15; H, 9.56.

Cholest-8(9)-ene-3β,11α,15α-triol-7-one (11a). A solution of the epoxy ketone **10** (2.34 g) in 100 mL of 1% methanolic potassium hydroxide was allowed to stand overnight at room temperature. The solution was diluted with water, neutralized with dilute HCl, and extracted with ether, and the ether extracts were dried (Na_2SO_4) and evaporated to yield 2.13 g of pale yellow semicrystalline material. Chromatography on silica (60 g) eluting with 1:2 acetone–hexane gave 1.95 g (99%) of the triolenone **11a** as white crystals: mp 116–119 °C (EtOAc–hexane); $[\alpha]^{20}_D$ +112° (*c* 1.39); IR 3610, 3460 (O–H), 1655 (C=O), 1600 cm^{-1} (C=C); NMR δ 0.59 (s, 3 H, 18-CH_3; calcd[15,32] 0.65), 1.18 (s, 3 H, 19-CH_3; calcd[15,32] 1.30), 3.69 (m, 1 H, 3α-H, $w_{1/2}$ ca. 16 Hz), 4.21 (m, 1 H, 15β-H, $w_{1/2}$ ca. 15 Hz), 4.48 (m, 1 H, 11β-H, $w_{1/2}$ ca. Hz); UV λ_{max} 254 (log ε = 3.90); $CD^{33}[\theta]_{215}$ +2850, $[\theta]_{238}$ −4,440, $[\theta]_{267}$ +524, $[\theta]_{287}$ −207, $[\theta]_{347}$ +1490; mass spectrum *m/e* 432.3242 (2%, M^+, calcd for $C_{27}H_{44}O_4$: 432.3239), 414.3128 (100, M − H_2O; calcd for $C_{27}H_{42}O_3$: 414.3134), 399 (19, M − H_2O + CH_3), 301 (36, M − H_2O + side chain), 288 (10, M − H_2O + C_9H_{18}), 283 (26, M − $2H_2O$ + side chain), 245.1548 (M − H_2O + side chain + ring D − 1 H; calcd for $C_{16}H_{21}O_2$: 245.1542), 157.0656 (43, calcd. for $C_{11}H_9O$: 157.0633).

Cholest-8(9)-ene-3β,11α,15α-triol-7-one Triacetate (11b). Acetylation of the triolenone (**11a**) (50 mg) with excess acetic anhydride (0.5 mL) in pyridine (1 mL) at room temperature overnight yielded 62 mg of pale yellow crystals of the triacetate derivative **11b:** mp 160–162 °C (MeOH); $[\alpha]^{20}_D$ +140° (*c* 1.08); IR 1725, 1672 cm^{-1} (C=O); NMR δ 0.62 (s 3 H, 18-CH_3; calcd[15,32] 0.72), 1.14 (s, 3 H, 19-CH_3; calcd[15,32] 1.29), 2.05, 2.08, 2.10 (3 × s, 9 H, -OAc), 2.80 (d, 1 H, 14α-H, *J* = 10 Hz), 4.70 (m, 1 H, 3α-H, $w_{1/2}$ ca. 18 Hz), 5.72 (2 × m, 2 H, 11β-H and 15β-H); UV λ_{max} 249 (log ε = 4.00); CD^{34} $[\theta]_{218}$ −21 200, $[\theta]_{248}$ +47 600, $[\theta]_{285}$ −452, $[\theta]_{362}$ +2770; mass spectrum *m/e* 498 (7%, M − AcOH), 457.3311 (16, M − $C_4H_5O_3$; calcd for $C_{29}H_{45}O_4$: 457.3318), 456.3236 (26, M − $C_4H_6O_4$; calcd for $C_{29}H_{44}O_4$: 456.3239), 455.3165 (28, M − AcOH + C_2H_3O; calcd for $C_{29}H_{43}O_4$: 455.3161), 440.3287 (46, M − $C_4H_6O_4$; calcd for $C_{29}H_{44}O_3$: 440.3290), 438 (21, M − 2AcOH), 423 (12, M − 2AcOH + CH_3), 353 (11), 351.1967 (25; calcd for $C_{23}H_{27}O_3$: 351.1960), 338 (12), 327 (41, M − $C_4H_6O_4$ + side chain), 325 (32, M − 2AcOH + side chain), 311.1651 (63, M − 2AcOH + C_9H_{19}; calcd for $C_{20}H_{23}O_3$: 311.1647), 298.1574 (100, M − 2AcOH + $C_{10}H_{20}$; calcd for $C_{19}H_{22}O_3$: 298.1569), 287 (12), 284 (13).

Anal. Calcd. for $C_{33}H_{50}O_7$: C, 70.94; H, 9.02. Found: C, 71.05; H, 9.09.

Cholestane-3β,11α,15α-triol-7-one (12a). The catalytic hydrogenation of the triolenone **11a** (1.00 g) with 500 mg of 10% Pd on C in 50 mL of ethanol plus a couple of drops of pyridine at 20 °C and 1 atm was complete after 2 h. The catalyst was removed by filtration and the solution was concentrated to give 1.02 g of pale yellow oil which showed two spots on TLC. The oil was dissolved in 50 mL of 5% methanolic potassium hydroxide and heated under reflux for 3 h. TLC analysis of the reaction showed that the mixture had equilibrated to one product having the same R_f as the higher R_f compound (minor product) prior to base treatment. Chromatography of the resulting pale yellow crystalline material (1.03 g) on silica (30 g) eluting with 1:2 acetone–hexane afforded 905 mg (90%) of white crystals of the triolone **12a:** mp 117–120 °C (ether); $[\alpha]^{20}_D$ +4.7° (*c* 1.11); IR 3610, 3450 (O–H), 1695 cm^{-1} (C=O); ^1H NMR δ 0.72 (s, 3 H, 18-CH_3; calcd[15] 0.72), 1.21 (s, 3 H, 19-CH_3; calcd[15] 1.21), 3.60, 3.80, 4.00 (3× m (overlapping), 3 H, 3α-H, 15β-H, and 11β-H); ^{13}C NMR, see Table I; CD $[\theta]_{290}$ +1770 (dioxane), $[\theta]_{288}$ +922 (methanol), $[\theta]_{288}$ +931 (room temp EPA), $[\theta]_{289}$ +922 (low temp EPA); mass spectrum *m/e* 434.3394 (14%, M^+; calcd for $C_{27}H_{46}O_4$: 434.3396), 416 (9, M − H_2O), 398 (15, M − $2H_2O$), 303 (21, M − H_2O + side chain), 285 (8, M − $2H_2O$ + side chain), 209.1911 (60, calcd for $C_{14}H_{25}O$: 209.1905), 208.1456 (36, calcd for $C_{13}H_{20}O_2$: 208.1463), 207.1380 (100, calcd for $C_{13}H_{19}O_2$: 207.1385); metastable defocusing, parent ions of 209; 434.49 (M^+, ca. 30%), 253.39 (M − $C_{11}H_{17}O_2$ (rings A and B + 1 H), ca. 60%), also 417.01, 398.57, 380.77, 322.28, 266.98, 223.70 (all <2%): 208; 434.94 (M^+, ca. 75%), 417.23 (M − OH, ca. 23%), also 304.61, 251.55, 222.68 (all <1%): 207; 434.42 (M^+, ca. 56%), 416.48 (M − H_2O, ca. 37%), 303.14 (M − side chain + H_2O, ca. 5%), also 399.48, 265.68, 249.72, 236.29 (all <1%).

Cholestane-3β,11α,15α-triol-7-one 3β,11α-Diacetate (12b). The triolone **12a** (900 mg) was acetylated in pyridine (20 mL) by treatment with acetic anhydride (10 mL) at room temperature for 2.5 h. The pale yellow oil (1.09 g) obtained after standard workup was chromatographed on silica (70 g) eluting with 10% acetone–hexane to give first a colorless oil (36 mg) which was identified as the triacetylated derivative **12c** and then 989 mg (92%) of white crystals of the 3β,11α-diacetate **12b:** mp 126–127.5 °C (acetone–hexane); $[\alpha]^{20}_D$ −7.0° (*c* 1.51); IR 3455 (O–H), 1720 and 1700 cm^{-1} (C=O); ^1H NMR δ 0.76 (s, 3 H, 18-CH_3; calcd[15] 0.75), 1.22 (s, 3 H, 19-CH_3; calcd[15] 1.20), 2.00, 2.04 (2× s, 6 H, -OAc), 3.80 (m, 1 H, 15β-H, $w_{1/2}$ ca. 14 Hz), 4.64 (m, 1 H, 3α-H, $w_{1/2}$ ca. 18 Hz), 5.07 (s, 1 H, OH), 5.25 (m, 1 H, 11β-H, $w_{1/2}$ ca. 16 Hz); ^{13}C NMR, see Table I; CD $[\theta]_{290}$ +2510; mass spectrum *m/e* 518 (8%, M^+), 503 (7, M − CH_3), 458 (25, M − AcOH), 443 (12, M − AcOH + CH_3), 440 (52, M − AcOH + H_2O), 425 (8, M − AcOH + H_2O + CH_3), 405 (30, M − side chain), 380 (12, M − 2AcOH + H_2O), 365 (15, M − 2AcOH + H_2O + CH_3), 345 (33, M − AcOH + side chain), 327 (33, M − AcOH + H_2O + side chain), 267 (14, M − 2AcOH + H_2O + side chain), 250 (61, $C_{15}H_{22}O_3$), 249 (100, $C_{15}H_{21}O_3$), 211 (21), 209 (70, $C_{14}H_{25}O$).

Anal. Calcd for $C_{31}H_{50}O_6$: C, 71.78; H, 9.72. Found: C, 71.92; H, 9.84.

Cholestane-3β,11α,15α-triol-7-one Triacetate (12c). When the acetylation of the triolone **12a** was allowed to run for a longer period of time, i.e., overnight, larger amounts of the triacetate **12c** were obtained. Column chromatography separated this triacetate from the diacetate **12b,** but as a colorless oil which could not be crystallized: $[\alpha]^{20}_D$ −32.3° (*c* 1.16); IR 1720 cm^{-1} (C=O); ^1H NMR δ 0.81 (s, 3 H, 18-CH_3; calcd[15] 0.78), 1.23 (s, 3 H, 19-CH_3; calcd[15] 1.19), 1.97, 2.00 (3× s, 9 H, -OAc), 4.36–5.46 (3 m (overlapping), 3 H, 3α-H, 11β-H, and 15β-H); ^{13}C NMR, see Table I; CD $[\theta]_{295}$ +2070; mass spectrum *m/e* 517 [100%, M − 43 (C_2H_3O)], 457 (19, M − AcOH + 43), 440 (83, M − 2AcOH), 425 (10, M − 2AcOH + CH_3), 397 (9, M − 2AcOH + 43), 327 (42, M − 2AcOH + side chain).

Anal. Calcd for $C_{33}H_{52}O_7$: C, 70.68; H, 9.35. Found: C, 70.53; H, 9.29.

Cholestane-3β,11α-diol-7,15-dione Diacetate (13). A solution of cholestane-3β,11α,15α-triol-7-one 3β,11α-diacetate (**12b**) (50 mg) in 5 mL of acetone was treated with excess Jones reagent[36] (ca. 0.05 mL) and stirred 30 min at room temperature. The reaction mixture was diluted with water and extracted with ether. The ether extracts were washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to yield a colorless oil (49 mg, 98%) which crystallized on standing. Recrystallization from acetone–hexane gave fine white needles of the diketone (**13**): mp 179–181 °C; $[\alpha]^{20}_D$ −2.1° (*c* 0.52); IR 1740, 1720 cm^{-1} (C=O); NMR δ 0.76 (s, 3 H, 18-CH_3; calcd[15] 0.79), 1.22 (s, 3 H, 19-CH_3; calcd[15] 1.20), 2.01, 2.03 (2× s, 6 H, -OAc), 4.62 (m, 1 H, 3α-H, $w_{1/2}$ ca. 18 Hz), 5.21 (m, 1 H, 11β-H, $w_{1/2}$ ca. 17 Hz); CD $[\theta]_{295}$ +9680; mass spectrum *m/e* 516 (5%, M^+), 501 (25, M − CH_3), 457 (51), 456 (78, M − AcOH), 441 (71, M − AcOH + CH_3), 403 (100, M − side chain), 343 (34, M − AcOH + side chain), 288 (17, M − AcOH + side chain + ring D), 283 (23, M − 2AcOH + side chain), 273 (11, M − AcOH + side chain + ring D + CH_3), 228 (46, M − 2AcOH + side chain + ring D), 211 (28), 209 (13).

Anal. Calcd for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36. Found: C, 72.07; H, 9.48.

Cholest-5-ene-3β,11α,15α-triol-7-one 3β,11α-Diacetate (16a). A solution of cholestane-3β,11α,15α-triol-7-one 3β,11α-diacetate (**12b**) (250 mg, 0.483 mmol) in 5 mL of acetic acid was warmed to 70 °C. Pyridinium hydrobromide perbromide[24] (162 mg, 0.507 mmol) was added portionwise over 10 min and the solution was stirred an additional 20 min at 70–75 °C. The solution was poured into saturated $NaHCO_3$ and extracted with ether. The ether extracts were washed

with saturated sodium thiosulfate, saturated $NaHCO_3$, and brine and dried over anhydrous Na_2SO_4. Evaporation of the ether solution yielded 294 mg of yellow oil which was chromatographed on 25 g of silica eluting with 10% acetone–hexane to give a small amount (30 mg) of a yellow oil which was probably triacetylated material, then 235 mg of a crude mixture of the epimeric 6-bromo-7-ketones **15** as a yellow oil: NMR δ 4.21 [small signal, d, J = 2 Hz, 6α-H (6β-Br)], 4.68 [<1 H, d (superimposed on 3α-H signal at 4.61), J = 12 Hz, 6β-H(6α-Br)].

The α-bromo ketone **15** was directly dehydrobrominated with 120 mg of calcium carbonate in 4 mL of dry dimethylacetamide. The mixture was heated at the boiling point for 1 min and then poured into water. After neutralizing with dilute HCl, the mixture was extracted with ether. The ether extracts were washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated to yield 240 mg of pale yellow oil which contained the enone **16a** plus some of the 3,5-dien-7-one (λ_{max} 283 nm). Chromatography on 20 g of silica eluting with 10% acetone–hexane afforded 176 mg (71%) of white crystals of the enone **16a:** mp 149–151 °C (acetone–hexane), $[\alpha]^{20}_D$ −84.5° (c 1.14); IR 3440 (O–H), 1724, 1660 cm^{-1} (C=O); NMR δ 0.79 (s, 3 H, 18-CH_3; calcd[15] 0.78), 1.35 (s, 3 H, 19-CH_3; calcd[15] 1.28), 2.02, 2.04 (2× s, 6 H, -OAc), 3.94 (m, 1 H, 15β-H, $w_{1/2}$ ca. 14 Hz), 4.70 (m, 1 H, 3α-H, $w_{1/2}$ ca. 18 Hz), 5.32 (s, 1 H, 11β-H, $w_{1/2}$ ca. 14 Hz), 5.64 (s, 1 H, O–H), 5.87 (s, 1 H, 6-H); UV λ_{max} 239 (log ϵ = 4.05); CD[37] $[\theta]_{218}$ −46 700, $[\theta]_{321}$ +5230; mass spectrum m/e 516 (7%, M$^+$), 456 (100, M − AcOH), 396 (41, M − AcOH), 381 (16, M − 2AcOH + CH_3), 378 (24, M − 2AcOH + H_2O), 363 (11, M − 2AcOH + H_2O + CH_3), 325 (11, M − AcOH + H_2O + side chain), 283 (33, M − 2AcOH + side chain), 265 (24, M − 2AcOH + H_2O + side chain), 261 (14), 249 (11), 227 (26, M − 2AcOH + side chain + ring D − 1 H), 213 (48, M − 2AcOH + CH_3 + side chain + ring D), 209 (20, $C_{14}H_{25}O$).

Anal. Calcd for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36. Found: C, 72.06; H, 9.50.

Cholest-5-ene-3β,11α,15α-triol-7-one (16b). A solution of the diacetate **16a** (20 mg) in 5 mL of methanol and 0.5 mL of H_2O was treated with 50 mg of K_2CO_3 at room temperature overnight. The solution was diluted with H_2O, neutralized with dilute HCl, and extracted well with ether. The combined ether extracts were dried over anhydrous Na_2SO_4 and evaporated to yield 18 mg of white semicrystalline material which contained the triolenone **16b** plus some 3,5-dien-7-one (UV 283 nm). Purification by preparative TLC on silica and developing with 1:1 acetone–hexane afforded 13 mg (78%) of white crystals of the triolenone **16b:** mp 102–104 °C (EtOAc–hexane); $[\alpha]^{20}_D$ −65° (c 0.136); IR 3610, 3400 (O–H), 1653 cm^{-1} (C=O); NMR δ 0.75 (s, 3 H, 18-CH_3; calcd[15] 0.74), 1.36 (s, 3 H, 19-CH_3; calcd[15] 1.30); 3.5–4.3 [3× m (overlapping), 3 H, 3α-H, 11β-H, 15β-H], 5.81 (s, 1 H, O–H), 5.84 (s, 1 H, 6-H); UV λ_{max} 240 nm (log ϵ = 4.00); CD[37] $[\theta]_{224}$ −41 500, $[\theta]_{320}$ +6220; mass spectrum m/e 432.3255 (18%, M$^+$; calcd for $C_{27}H_{44}O_4$: 432.3239), 414.3128 (95, M − H_2O; calcd for $C_{27}H_{42}O_3$: 414.3134), 399 (11, M − H_2O + CH_3), 396 (18, M − 2H_2O), 381 (12, M − 2H_2O + CH_3), 301 (22, M − H_2O + side chain), 283 (40, M − 2H_2O + side chain), 265 (12, M − 3H_2O + side chain), 245 (11, M − H_2O + ring D + side chain − 1 H), 227 (16, M − 2H_2O + ring D + side chain − 1 H), 161 (100, $C_{11}H_{13}O$ (rings A + B − H_2O from C-3 + 1 H)).

Cholest-5-ene-3β,11α-diol-7,15-dione Diacetate (18). A solution of cholest-5-ene-3β,11α-15α-triol-7-one 3β,11α-diacetate (**16a**) (90 mg) in 10 mL of acetone was treated with excess Jones reagent[36] (ca. 0.1 mL) and stirred at room temperature for 20 min. The mixture was diluted with water and extracted with ether. The ether extracts were washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated to yield 89 mg of pale yellow semicrystalline material. Recrystallization from acetone–hexane afforded 80 mg (90%) of the diketone **18:** mp 173–176 °C; $[\alpha]^{20}_D$ −101° (c 0.133); IR 1740, 1725, 1684 (C=O); NMR δ 0.80 (s, 3 H, 18-CH_3; calcd[15] 0.82), 1.34 (s, 3 H, 19-CH_3; calcd[15] 1.28), 2.04, 2.06 (2× s, 6 H, -OAc), 4.68 (m, 1 H, 3α-H, $w_{1/2}$ ca. 18 Hz), 5.32 (m, 1 H, 11β-H, $w_{1/2}$ ca. 18 Hz), 5.90 (s, 1 H, 6-H); UV λ_{max} 235 (log ϵ = 4.10); CD $[\theta]_{233}$ −35 000, $[\theta]_{300}$ +12 600, $[\theta]_{330}$ +10 000; mass spectrum m/e 514 (1%, M$^+$), 454 (23, M − AcOH), 439 (95, M − AcOH + CH_3), 394 (42, M − 2AcOH), 379 (98, M − 2AcOH + CH_3), 341 (72, M − AcOH + side chain), 313 (14, M − AcOH + $C_{10}H_{21}$), 287 (12, M − AcOH + side chain + ring D), 281 (15, M − 2AcOH + side chain), 263 (M − 2AcOH + H_2O + side chain), 134 (100, $C_9H_{10}O$).

Anal. Calcd for $C_{31}H_{46}O_6$: C, 72.34; H, 9.01. Found: C, 72.06; H, 9.14.

Cholest-5-ene-3β,11α,15β-triol-7-one 3β,11α-Diacetate (20). A solution of the diketone **18** (70 mg) in 2 mL of dry THF was added to a stirred solution of LiAlH(O-t-Bu)$_3$[27] (140 mg) in 2 mL of dry THF and stirred overnight at room temperature. The excess hydride was decomposed by the addition of 15 mL of 5% AcOH and the solution was extracted with ether. The ether extracts were washed with saturated $NaHCO_3$ and water, dried over anhydrous Na_2SO_4, and evaporated to yield 67 mg of the alcohol mixture **19** as a colorless oil: IR 3370 (O–H), 1730 cm^{-1} (C=O); mass spectrum 518 (M$^+$).

The crude alcohol mixture **19** was oxidized directly with MnO_2 (670 mg) in 10 mL of $CHCl_3$ by stirring overnight at room temperature. The MnO_2 was filtered and the precipitate was washed well with chloroform. The filtrate and washings were evaporated to yield 65 mg of pale yellow oil which contained predominantly the desired cholest-5-ene-3β,11α,15β-triol-7-one 3β,11α-diacetate (**20**). Preparative TLC on silica eluting with 30% acetone–hexane afforded 52 mg of colorless oil which was recrystallized from acetone–hexane to give 40 mg (57%) of white crystals of **20,** which contained some of the 15α-alcohol **16a** by NMR. A second recrystallization yielded 23 mg of **20** which still contained ca. 20–25% of the 15α epimer **16a:** mp 115–119 °C; $[\alpha]^{20}_D$ −101° (c 1.35); IR 3480 (O–H), 1720, 1655 (C=O); NMR δ 1.02 (s, 3 H, 18-CH_3; calcd[15] 1.01), 1.32 (s, 3 H, 19-CH_3; calcd[15] 1.31), 2.02, 2.06 (2× s, 6 H, -OAc), 4.69 (2× m, 2 H, 3α-H and 15α-H), 5.32 (m, 1 H, 11β-H, $w_{1/2}$ ca. 18 Hz), 5.84 (s, 1 H, 6-H), plus small signals at 0.79 (18-CH_3), 3.96 (15β-H), and 5.64 (O–H) for the 15α-alcohol **16a;** UV λ_{max} 235 nm (log ϵ = 4.05); CD[37] $[\theta]_{215}$ −43 400, $[\theta]_{330}$ + 6950; mass spectrum m/e 516 (11%, M$^+$), 456 (100, M − AcOH), 396 (36, M − 2AcOH), 381 (19, M − 2AcOH + CH_3), 378 (24, M − 2AcOH + H_2O), 363 (11, M − 2 AcOH + H_2O + CH_3), 283 (30, M − 2AcOH + side chain), 265 (24, M − 2AcOH + H_2O + side chain), 261 (15), 227 (11, M − 2AcOH + side chain + ring D − 1H), 213 (32, M − 2AcOH + CH_3 + side chain + ring D), 211 (13) 209 (17).

Anal. Calcd for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36. Found: C, 71.96, H, 9.42.

Cholest-5-ene-3β,11α,15β-triol-7-one (4). The diacetate **20** (which contained ca. 20–25% **16a**) (20 mg) was dissolved in 5 mL of methanol and 0.5 mL of H_2O and treated with 50 mg of K_2CO_3 overnight at room temperature. Standard workup yielded 19 mg of colorless oil which contained some 3,5-dien-7-one (UV 283 nm). Preparative TLC yielded 12 mg (70%) of white semicrystalline material which was predominantly the desired triolenone **4** plus some (ca. 20–25%) of the 15α-alcohol epimer **16b** (by NMR) and could not be recrystallized: $[\alpha]^{20}_D$ −73° (c 0.15); IR 3610, 3440 (O–H), 1655 (C=O); NMR δ 0.99 (s, 3 H, 18-CH_3; calcd[15] 0.98), 1.36 (s, 3 H, 19-CH_3; calcd[15] 1.33), 3.72 (m, 1 H, 3α-H, $w_{1/2}$ ca. 18 Hz), 4.15 (m, 1 H, 11β-H, $w_{1/2}$ ca. 18 Hz), 4.70 (m, 1 H, 15α-H, $w_{1/2}$ ca. 16 Hz), 5.83 (s, 1 H, 6-H), plus small signals at 0.75 (18-CH_3), 3.90 (15β-H), and 5.96 (O–H) for the 15α-alcohol **16b;** UV λ_{max} 238 nm (log ϵ = 4.0); CD[37] $[\theta]_{214}$ −53 000, $[\theta]_{327}$ +5250; mass spectrum m/e 432.3242 (24%, M$^+$; calcd for $C_{27}H_{44}O_4$: 432.3239), 414 (86, M − H_2O), 399 (15, M − H_2O + CH_3), 396 (17, M − 2H_2O), 381 (11, M − 2H_2O + CH_3), 301 (31, M − H_2O + side chain), 283 (32, M −2H_2O + side chain), 245 (14, M − H_2O + ring D + side chain − 1 H), 227 (14, M − 2H_2O + ring D + side chain − 1 H), 161 (100, $C_{11}H_{13}O$, rings A + B − H_2O from C − 3 + 1 H).

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Registry No.—7a, 20748-22-5; **7b,** 27751-96-8; **8,** 63358-19-0; **9a,** 63358-81-6; **9b,** 63324-87-8; **10,** 63324-88-9; **11a,** 63324-89-0; **11b,** 63324-90-3; **13,** 63324-91-4; **6α-15,** 63324-92-5; **6β-15,** 63358-83-8; **19,** 63324-93-6.

References and Notes

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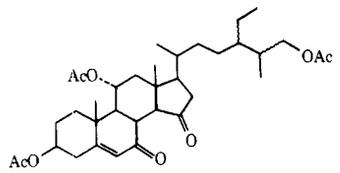
(22) The base peak in the mass spectrum of **13** at *m/e* 403 results from loss of the side chain from the molecular ion. This cleavage is readily rationalized for a C-15 ketone, but it would not be expected for a ketone at C-11.



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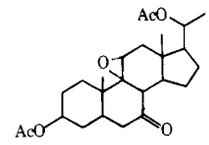
(30) The CD curve of a similar epoxy ketone, 9α,11α-epoxypregnane-3β,20β-diol-7-one diacetate (**21**),[31] also displays a negative Cotton effect,



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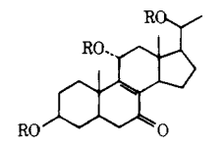
$[\theta]_{295}$ −2780. The magnitude of this Cotton effect is considerably more negative than that of epoxy ketone **10,** which may be due to a positive front octant contribution[20] of the 15α-acetate of **10.**
(31) A sample of this compound (see ref 8) was provided by Dr. L. Throop of Syntex Research, Palo Alto, Calif.
(32) The chemical shift value for the effect of the conjugated 8(9)-en-7-one chromophore was obtained from the observed chemical shifts of the angular methyl groups of cholest-8(9)-en-7-one. See I. Midgley and C. Djerassi, *J. Chem. Soc. Perkin Trans. 1,* 2771 (1972).
(33) The shape of the CD curve of **11a** $[\theta]_{245}$ −22 200, $[\theta]_{372}$ +1090 is similar to that of the related compound **22a**[31] (obtained by base treatment of epoxy



22a, R = H
22b, R = Ac

ketone **21**), but several differences are apparent. The major change is that the magnitude of the Cotton effect for **11a** in the $\pi \rightarrow \pi^*$ transition region $[\theta]_{288}$ −4440 is considerably less negative than that of **22a,** $[\theta]_{245}$ −22 000, and occurs at shorter wavelength. The differences may be due to the strong hydrogen-bonding interaction between the C-7 ketone and the 15α-alcohol of **11a.**
(34) There is a dramatic change in the shape of the CD curve upon acetylation of **11a** to yield the triacetate **11b.** The Cotton effect for **11b** in the $\pi \rightarrow \pi^*$ transition region has a large positive value $[\theta]_{248}$ +47 600, whereas **11a** shows a small negative value $[\theta]_{238}$ −4440. There must be a large conformational change around the unsaturated ketone upon acetylation of the alcohols which essentially results in a reversal of the chirality of this chromophore. See ref 18 and A. W. Burgstahler and R. C. Barkhurst, *J. Am. Chem. Soc.,* **92,** 7601 (1970). This conformational change is probably due mostly to the interaction of the 15α-acetate with the C-7 ketone; however, acetylation at C-11 may also have some effect, as seen from the CD curve of the triacetate **22b**[35], $[\theta]_{255}$ −6950, $[\theta]_{375}$ +2360, compared with that of the triolone **22a.**
(35) Compound **22b** was prepared by acetylation of a sample of **22a.**[31] See ref 8.
(36) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.,* 39 (1946).
(37) The CD curve of this compound is similar to that of 7-ketocholesterol acetate, $[\theta]_{214}$ −45 900, $[\theta]_{335}$ +3600.