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Synthesis of the ABC Ring System of Batrachotoxin and Several Related Highly Functionalized Cholane Derivatives[1]

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The objective of this work is the synthesis of the ABC ring system of the powerful neuropoison batrachotoxin (1) from cholic acid (2), utilizing intermediates which permit subsequent elaboration to the entire toxin molecule. Thus, stereoselective routes to a series of highly functionalized cholane derivatives are described, culminating with an efficient synthesis of **58** as follows: **2** → **5** → **38** → **51** → **53** → **58**. It was also shown that earlier established side-chain degradation procedures are applicable in this series, **7** → **22** and **40** → **45**, as potential entries to the D,E ring system of **1**. Unsuccessful approaches to the ABC ring system of **1** included the synthesis from **2** of epoxides **8** and **9**. Whereas earlier the oxidative cyclization of **18** → **20** had been described, epoxides **8** and **9** afforded ketones **12** and **13** under the cyclization conditions without formation of the desired **21**. In another approach, rather than 3α,9α-oxide **24**, dione **23** was obtained in high yield by treatment of epoxide **17** with methoxide ion. While **23** was convertible into ketone **25**, this last substance afforded neither hydrazone **28** nor epoxide **34**, two key intermediates required for a fragmentation approach to the ABC ring system. In another attempt **25** was reduced to an epimeric mixture **29** of C-7 alcohols. Mild MeOH–acid treatment of **29** led to a mixture of unsaturated keto steroids rather than to the desired 3α,9α-oxido ketal **33**.

Batrachotoxin (1) is one of four rare, powerfully toxic steroid alkaloids found in the skin of a small, brightly colored Colombian frog of the genus *Phyllobates*.[3] The molecule has proven important as a tool for the study of ion movements in electrogenic membranes.[4] Following the elegant structural elucidation studies of Witkop,[3] batrachotoxin has been the target of synthetic studies, those of Wehrli culminating in the formal total synthesis of the molecule from other steroids.[5] We have already described in preliminary form the synthesis of the ABC ring system of **1** from the readily available cholic acid (**2**).[1] We now present the details of this work together with the stereoselective synthesis and some reactions of several highly functionalized cholane derivatives which have proven useful in our initial evaluation of practical synthetic routes to the ABC ring system of batrachotoxin.

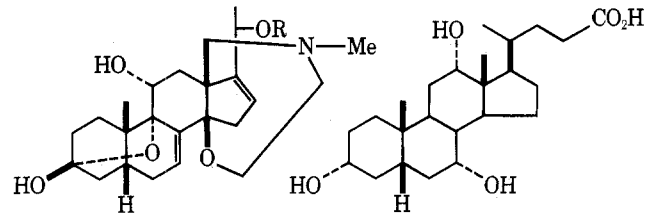
Our initial plan called for the synthesis of an intermediate possessing functional groups in the ABC portion of the molecule which would be relatively inert toward reagents required for the elaboration of the DE portion of the molecule, yet be readily convertible into the ABC system after the DE synthetic operations were completed. Methyl 3α,7α-diacetoxy-9α,11α-oxidocholanate (**6**) seemed ideal in view of the remarkable chemical stability exhibited by the 9α,11α-oxido grouping in several AB-cis steroids.[6] Moreover, Fieser[7] showed that the closely related alcohol **18** could be converted directly into the 11-oxo-3β-hydroxy 3α,9α-oxide **20** by oxidation with CrO_3.

Accordingly, epoxide **6** was synthesized from cholic acid as follows. Cholic acid (**2**) was converted into enone **3** by the method of Fieser.[8] Desulfurization of the corresponding dithioketal **4** afforded olefin **5**, epoxidation of which with *m*-chloroperoxybenzoic acid (MCPA) led to the desired epoxide **6**. The oxide ring was assigned the α orientation in accordance with the rule of rear attack,[9] the distinctive NMR splitting pattern of the C_{11} axial proton,[10] and the chemical shifts of the protons attached to C-18 and 19.[11] The overall process afforded 50 g of **6** starting with 200 g of cholic acid.

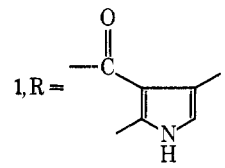
As a first step toward construction of the DE ring system of batrachotoxin, the acid **7** was prepared from epoxide **6** by selective hydrolysis of **6** with aqueous K_2CO_3–MeOH, affording acid alcohol **8** in 96% yield. Acetylation of **8** produced **7**. Treatment of **7** with $Pb(OAc)_4$[12] gave olefin **22** in high yield. Δ^{22}-Steroids have been employed by others[13] for efficient production of either bisnor acids or C-20 ketones.

Before proceeding further with the DE ring elaboration it seemed prudent to demonstrate the synthesis of the ABC system from epoxide **6** using Fieser's[7] oxidative cyclization procedure (**18** → **20**). Unfortunately, all attempts to oxidize acid **8** or its methyl ester **9** employing variations of Fieser's method uniformly led in near-quantitative yield to keto epoxides **12** and **13** with no hint of the desired oxide **21**. At the time it seemed likely that in **8** the 7α (axial) acetoxy group sterically prevented formation of the 3α,9α-oxide linkage present in **20**. In the light of our synthesis of ester **54** by an-

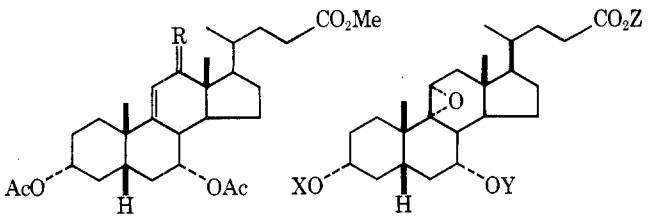
Chart I



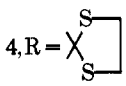
2 (cholic acid)



1, R =

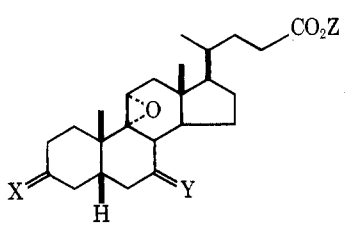


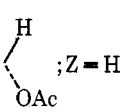
3, R = O

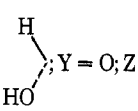
4, R = 

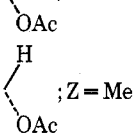
5, R = H, H

6, X = Y = Ac; Z = Me
7, X = Y = Ac; Z = H
8, X = H; Y = Ac; Z = H
9, X = H; Y = Ac; Z = Me
10, X = Y = H; Z = Me
11, X = Ac; Y = H; Z = Me

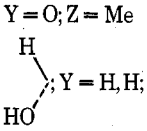


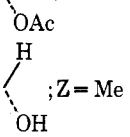
12, X = O; Y =  ; Z = H

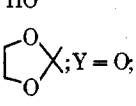
16, X =  ; Y = O; Z = Me

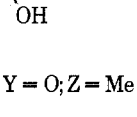
13, X = O; Y =  ; Z = Me

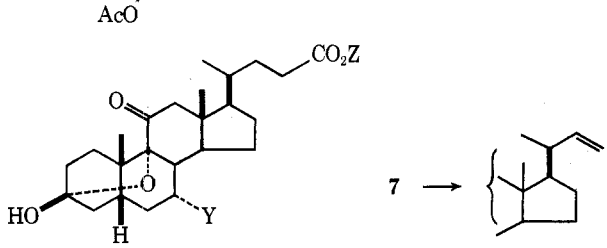
17, X = Y = O; Z = Me

18, X =  ; Y = H, H; Z = Me

14, X = O; Y =  ; Z = Me

19, X =  ; Y = O; Z = Me

15, X =  ; Y = O; Z = Me



20, Y = H; Z = Me
21, Y = OAc; Z = H

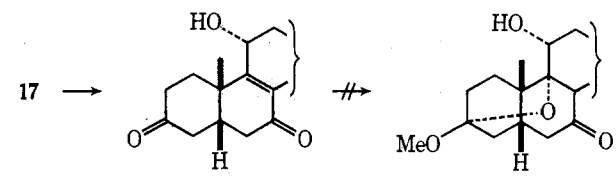
7 →

22

other route (see below) this explanation seems tenuous. Epoxide **12** was characterized as its ester **13**, which on treatment with methoxide ion in methanol gave alcohol **14**.

These results required that the ABC ring system be assembled in a multistep manner from one of the above intermediates. The following exploratory chemistry was carried out. Treatment of diacetate **6** with methoxide ion afforded diol **10** in 93% yield. Reacetylation of **10** led to alcohol **11**, oxidation of which gave the 7-ketone **15**. Earlier,[14] a compound provisionally assigned the structure **15** was obtained as a by-product from the oxidation of a $\Delta^{7,9(11)}$-steroid. Its properties differed somewhat from those we have observed for **15** and are inconsistent with that structure (see Experimental Section).

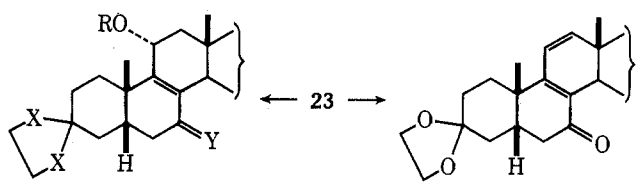
Gentle methoxide treatment of **15** afforded alcohol **16**. Finally, dichromate oxidation of diol **10** produced diketone **17**. With this latter substance in hand we had hoped to go directly to 3α,9α-oxide **24** by reaction with methoxide ion in methanol. Instead, dione **23** was obtained in greater than 90% yield. This substance could not be made to undergo cyclization to **24** under a variety of either acidic or basic conditions.



23 **24**

A second attempt to produce the 3α,9α-oxide linkage also proceeded from epoxide **17**. Thus, while Fieser[7] was able to effect a near-quantitative conversion of 3-oxo-9α,11α-oxido-5β-steroids into 11β-chloro-3α,9α-hemiacetals using HCl, our 3,7-dioxo-α-epoxide **17** failed to react with HCl under Fieser's conditions.

At this point we formulated a new plan toward the ABC ring system of batrachotoxin (see Scheme I) which required the synthesis of intermediates selectively ketalized at C-3. Exchange ketalization of dione **23** with TsOH and 2-methyl-2-



25, R = H; X = Y = O
26, R = Ac; X = Y = O
27, R = Ac; X = S; Y = O

28, R = H; X = O; Y = N—
29, R = H; X = O; Y = H, OH
30, R = Ac; X = O; Y = H, OH

31

ethyldioxolane led to a complex mixture from which ketal **25** could be isolated in only 7% yield. Moreover, the highly selective[15,16] reagent, DMF ethylene acetal, and **23** under mild conditions led to dienone **31** (tentative assignment) in 30% yield. Formation of **31** is remarkable since the hydroxy group in **23** is a vinylogous α-hydroxy ketone.

An alternative synthesis of ketal **25** in good overall yield resulted from the selective ketalization of dione epoxide **17** with DMF ethylene acetal to produce ketal **19**, followed by treatment with methoxide ion. Efforts to execute the plan of Scheme I which envisaged a novel methoxide ion induced fragmentation (**32** → **33**) of the tosylhydrazone **28** were thwarted by our inability to prepare **28** in acceptable yield from ketone **25**. Similarly, an intended use of the Wharton reaction[17] in the conversion of epoxy ketone **34** to olefin **35** was prevented by the extreme resistance of the double bond of **25** toward a variety of epoxidizing agents, including MCPA and alkaline H_2O_2. With the aim of removing the C-7 ketone

Scheme I

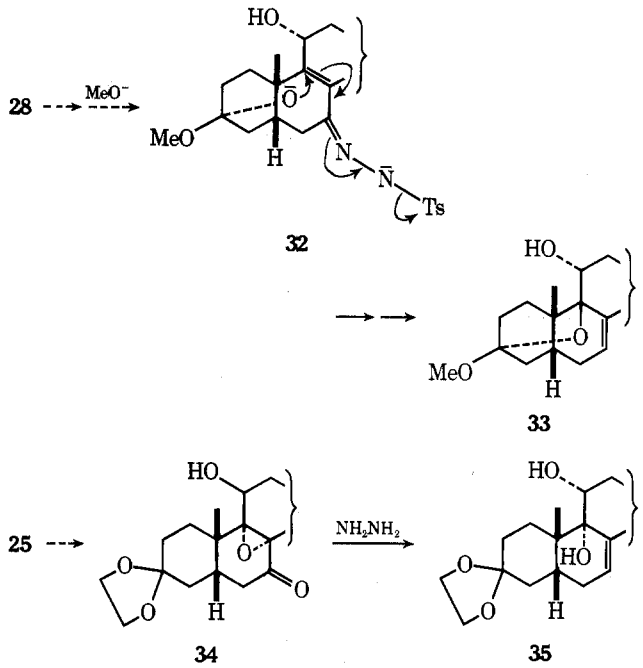
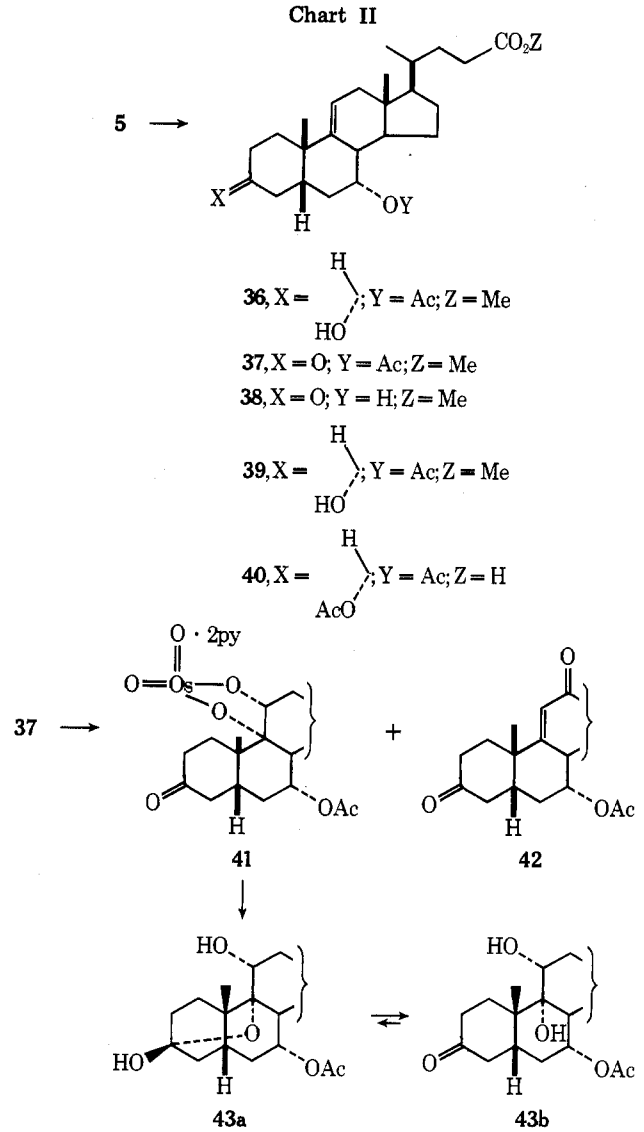


Chart II



function of **25** for another series of experiments, this substance was converted into acetate **26** and then treated with ethanedithiol. Rather than formation of the C-7 thioketal, we observed complete exchange at C-3, producing dithioketal **27**.

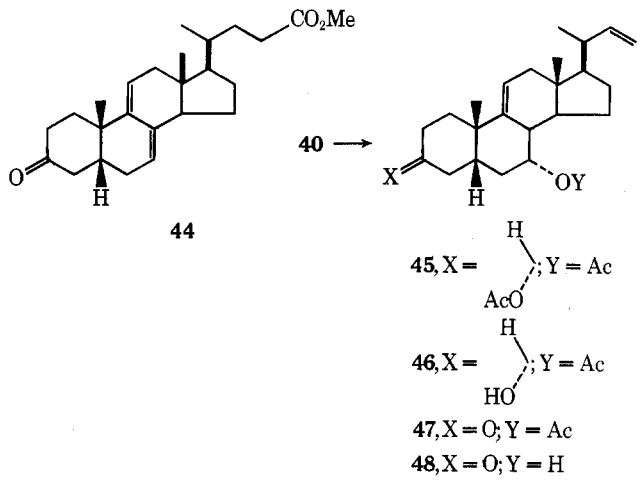
Our final efforts toward utilization of these substances for batrachotoxin-oriented synthetic work involved $NaBH_4$ reduction of ketone **25** to a crystalline epimeric mixture **29** of alcohols at C-7. Witkop[3] indicated that the ring system produced by $NaBH_4$ reduction of batrachotoxinin A underwent facile acid-catalyzed rearrangements to a mixture of enediols involving C-7, 8, 9, and 11. We therefore treated intermediate enediol **29** with very dilute HCl in MeOH with the hope of trapping the correct isomer as the $3\alpha,9\alpha$-oxide **33**. Even under very mild conditions we observed a clean conversion to what appeared to be a mixture of Δ^8-3,7-dione and Δ^8-3,11-dione steroids. Similarly, acetate **30**, prepared by $NaBH_4$ reduction of **26**, failed to afford the desired ring system present in **33**.

During the course of the above experiments there appeared a report from the Wehrli laboratory[18] of a successful osmylation of a 3-oxo-$\Delta^{9(11)}$-5β-steroid. Whereas in Fieser's[6] account of the inertness of the 5β-$\Delta^{9(11)}$-steroids toward OsO_4 reaction conditions were not given, Wehrli[18] achieved osmylation in pyridine at 25 °C over 7 days. An ideal candidate for the osmylation and subsequent introduction of the ring B double bond in our series was keto acetate **37**. This substance was obtained in high overall yield from diacetate **5** via selective hydrolysis to alcohol **36** followed by esterification to **39** and subsequent oxidation.

In keto acetate **37** the axial 7α-acetate group was expected to retard still further reaction with the bulky osmium reagent. In the event the reaction required 8 days (followed by TLC). Chromatography afforded crystalline osmate ester **41** in 50% yield together with starting **37** (34%) and a crystalline byproduct, enone **42**, in 15% yield. Formation of this latter product is interesting in that to our knowledge, allylic oxidation during osmylation is without precedent, although Cross[19] observed the oxidation of secondary alcohols during osmylation. Cleavage of osmate **41** proceeded well with H_2S–NH_4Cl, producing hemiacetal **43** (see below for a discussion of hemiacetal vs. ring open equilibria) in 93% yield.

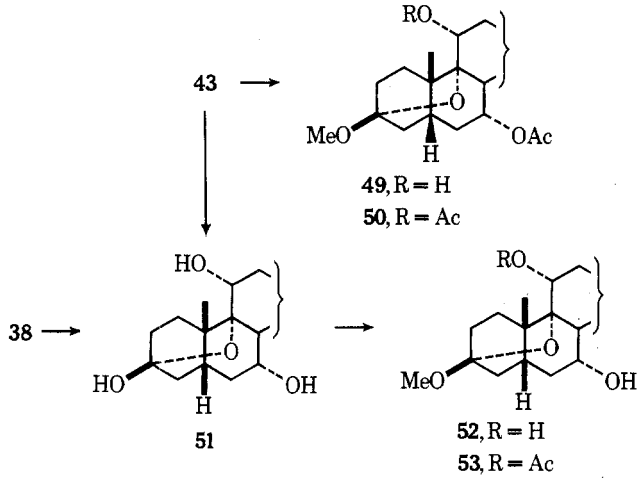
Our synthetic series at this point was linked to earlier work through the conversion of acetate **37** into alcohol **38** followed by dehydration with $POCl_3$ in pyridine to the known[14] $\Delta^{7,9(11)}$-ketone **44**.

A series of $\Delta^{9(11),22}$-dienes were also prepared at this stage as potential candidates for osmylation studies. Thus, acetylation of **36** gave acid **40**, oxidative decarboxylation of which with $Pb(OAc)_4$ afforded crystalline diene **45** in 90% yield. Ketones **47** and **48** were then prepared from intermediate alcohol **46** by oxidation followed by deacetylation as in the previous preparations of the corresponding C-24 esters **37** and **38**. Preliminary studies indicated that the presence of an



unprotected hydroxyl group in the 7α position greatly facilitated the reaction of the 9(11) double bond with OsO_4. We were thus led to the discovery of the facile reaction of alcohol ester **38** with OsO_4 in which hemiacetal **51** was obtained after 1 day reaction in 98% yield.

Originally we had prepared **51** by deacetylation of **43**. Acetate **43** was at first converted into acetal **49** by treatment with acidic MeOH and thence to diacetate **50** by acetylation. To our surprise, prolonged reflux of **49** with methoxide ion in



49, R = H
50, R = Ac

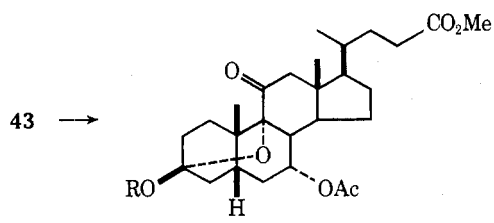
51

52, R = H
53, R = Ac

MeOH did not effect deacetylation at C-7 to give diol **52**. This suggested that, once formed, diol acetal **52** might undergo selective acetylation at C-11, producing 11α-acetate acetal **53**. Accordingly, diol hemiacetate **51** was converted into acetal **52** and treated with acetic anhydride–pyridine, affording **53** in near-quantitative yield.

Thus far we have indicated the structure of steroids **43** and **51** as hemiacetals although equilibrium with the ring-opened isomer is possible. Indeed, inspection of the NMR spectra (see Experimental Section) of the well-characterized crystalline steroids **43** and **51** shows quite clearly that 7α-acetate **43** exists (at 25 °C in $CDCl_3$) primarily in the ring-opened 3-keto 9α-alcohol form **43b**, whereas **51** appears to be a slowly (NMR time scale) equilibrating mixture of closed and open forms. These conclusions follow by noting the position of the C-19 methyl resonance in the ring-closed acetal form as compared with that of its "hemiacetal" precursor.

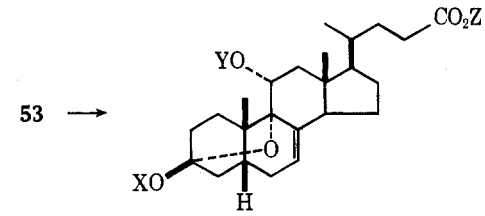
It is worth noting here that 7α-acetate **43** is structurally similar to the intermediate which would have likely been formed during the attempted oxidative fission of alcohol epoxides **8** or **9** to **21** under Fieser's conditions (see above). Since acetate **43** did not assume the closed form postulated for that



54, R = H
55, R = Me

intermediate, some support is lent to the steric argument advanced above to explain the failure of 3α,9α-oxide formation from **8** or **9**. We further examined this process by oxidizing **43** to the 11-keto hemiacetal **54**, purified as the acetal **55**. Interestingly, however, the angular methyl resonances of keto acetate **54**, when compared with those for acetal **55**, indicated that when a C-11 keto group was present, the ring closed form is dominant at equilibrium (cf. **43** above).

Returning to the completion of the synthesis of the toxin's ABC ring system, dehydration of 11α-acetate **53** with $POCl_3$



56, X = Me, Y = Ac; Z = Me
57, X = H; Y = Ac; Z = Me
58, X = Y = Z = H
59, X = Y = H; Z = Me

in pyridine afforded Δ^7-acetal **56** as a colorless oil. The protective methyl acetal of **56** was then hydrolyzed with dilute perchloric acid, giving crystalline Δ^7-hemiacetal **57**. Finally, alkaline hydrolysis of **57** afforded the ABC ring system of batrachotoxin as contained in 3β,11α-dihydroxy-3α,9α-oxido-5β-chol-7-enic acid (**58**), mp 172–174 °C, and its methyl ester **59**.

Experimental Section[20]

Methyl 3α,7α-Diacetoxy-5β-chol-9(11)-enate (5). To a solution of methyl 3α,7α-diacetoxy-12-oxo-5β-chol-9(11)-enate (**3**,[8] 50.2 g, 0.10 mol, mp 154–156 °C) in $CHCl_3$ (50 ml) was added 1,2-ethanedithiol (42 ml) and the solution was cooled to −15 °C. (N_2). Anhydrous HCl (ca. 2 l.) was then passed through the solution after which the temperature was raised and maintained at 0 °C for 20 h. The usual workup gave 50.5 g of crude **4** (87%) suitable for further reaction, *m/e* 578 (M^+). To a solution of crude **4** (10.0 g) in absolute EtOH (200 ml) was added Raney nickel (ca. 65 g) and the mixture was refluxed (N_2) for 8 h. The usual workup afforded 8.10 g of foam. Crystallization from hexane gave **5** (7.16 g, 85%, mp 104–108 °C) as colorless needles suitable for further reaction. Two additional crystallizations from hexane gave the analytical sample as colorless needles: mp 114–115 °C; NMR δ 0.62 (s, 3, C-18 H), 1.10 (s, 3, C-19 H), 2.04 (s, 6, $COCH_3$), 3.72 (s, 3, CO_2CH_3), 4.62 (m, 1, C-3 H), 5.12 (m, 1, C-7 H), 5.51 (m, 1, C-11 H); *m/e* 428 (M − AcOH), 413, 368, 353. Anal. Calcd. for $C_{29}H_{44}O_6$: C, 71.28; H, 9.08. Found: C, 71.63; H, 9.26.

Methyl 3α,7α-Diacetoxy-9α,11α-oxido-5β-cholanate (6). To a solution of **5** (15.0 g, 30.7 mmol) in $CHCl_3$ (80 ml) was added MCPA (6.0 g). The mixture was stirred at 45 °C overnight. The usual workup followed by crystallization from hexane and then MeOH gave **6** (12.0 g, 77%, mp 123–126 °C) as colorless prisms. Preparative TLC afforded the analytical sample: mp 125.5–127 °C; NMR δ 0.67 (s, 3, C-18 H), 1.16 (s, 3, C-19 H), 2.05 (s, 3, C-7 $COCH_3$), 2.11 (s, 3, C-3 $COCH_3$), 3.15 (m, 1, C-11 H), 3.73 (s, 3, CO_2CH_3), 4.70 (m, 1, C-3 H), 5.21 (m, 1, C-7 H); *m/e* 504 (M^+), 462, 444, 402, 384. Anal. Calcd for $C_{29}H_{44}O_7$: C, 69.02; H, 8.79. Found: C, 69.25; H, 8.88.

3α-Hydroxy-7α-acetoxy-9α,11α-oxido-5β-cholanic Acid (8). A mixture of **6** (500 mg), K_2CO_3 (700 mg), MeOH (10 ml), and water (4 ml) was heated briefly on the steam bath until a clear solution was obtained. The temperature of the solution was then maintained at 40–45 °C for 6 h. The usual workup produced a colorless oil which was crystallized from MeOH–water, affording pure **8** (430 mg, 96%) as long, colorless needles: mp 177–179 °C; *m/e* 448 (M^+), 446, 416, 388, 294, 280. Anal. Calcd for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.83; H, 9.12.

3α,7α-Diacetoxy-9α,11α-oxido-5β-cholanic Acid (7). A solution of **8** (225 mg), pyridine (0.75 ml), and Ac_2O (0.4 ml) was heated (N_2) at 100 °C for 0.5 h. The usual workup gave a light yellow oil which was crystallized from acetone–hexane to yield **7** (218 mg, 89%, mp 175–180 °C) suitable for further reaction. Recrystallization from acetone–hexane gave the analytical sample: mp 182–183 °C; *m/e* 490 (M^+), 448, 430, 388, 370. Anal. Calcd for $C_{28}H_{42}O_7$: C, 68.55; H, 8.63. Found: C, 68.47; H, 8.74.

3α,7α-Diacetoxy-9α,11α-oxido-5β-24-norchol-22-ene (22). To **7** (188 mg) was added benzene (2.75 ml), $Pb(OAc)_4$ (330 mg), $Cu(OAc)_2$ (16 mg), and pyridine (0.15 ml). This mixture was heated (N_2) on the steam bath for 0.5 h. Filtration and removal of the solvent gave a green oil (246 mg). Chromatography over silica gel (4 g) gave **22** (54 mg) as a colorless oil. Yields approaching 90% have been obtained with longer reaction periods (4–6 h). Crystallization occurred on slow evaporation of a hexane solution giving **22** as small, colorless needles: mp (liquid transition at 80 °C) 103–106 °C; *m/e* 444 (M^+),

402, 384, 368, 342. Anal. Calcd for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07. Found: C, 72.85; H, 9.24.

Methyl 3α-Hydroxy-7α-acetoxy-9α,11α-oxido-5β-cholanate (9). An ethereal solution of **8** (50 mg) was treated with excess CH_2N_2. The ether was then removed to afford **9** as an oil which crystallized from hexane as long, colorless needles (49 mg, 95%): mp 114–114.5 °C; *m/e* 462 (M^+). Anal. Calcd for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15. Found: C, 70.31; H, 9.37.

3-Oxo-7α-acetoxy-9α,11α-oxido-5β-cholanic Acid (12) and Methyl 3-Oxo-7α-acetoxy-9α,11α-oxido-5β-cholanate (13). Following the method of Fieser,[8] alcohol **8** (33 mg) was dissolved in HOAc (0.75 ml) and cooled to 9 °C at which point a solution of chromic acid (35 mg) in water (0.06 ml) was added. After the solution had stood at 4 °C for 16 h, the usual workup gave **12** (30 mg, 91%) as a waxy, white solid: NMR δ 0.71 (s, 3, C-18 H), 1.28 (s, 3, C-19 H), 2.06 (s, 3, $COCH_3$), 3.17 (m, 1, C-11 H), 5.21 (m, 1, C-7 H), 9.67 (1, CO_2H). Crude **12** (28 mg) was taken up in MeOH (1 ml) and a trace of 48% HBr added. The mixture was allowed to stand overnight. Removal of the solvent gave **13** (28 mg, 97%) as a colorless oil. Two recrystallizations from hexane gave the analytical sample: mp 132–133 °C; *m/e* 460 (M^+), 418, 400. Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.41; H, 8.75. Found: C, 70.39; H, 9.17. The keto acid **12** was also obtained when this chromate oxidation procedure was carried out at 25 °C. At 40 °C a complex mixture of products was produced. Methyl ester **9** also afforded ketone **13** when oxidized with chromic acid at 9 °C or with sodium dichromate in acetic acid at 25 °C.

Methyl 3-Oxo-7α-hydroxy-9α,11α-oxido-5β-cholanate (14). To **13** (20 mg) was added excess NaOMe–MeOH solution. After a 2-h reflux (N_2), the usual workup afforded **14** (16 mg, 88%) (acetone–hexane) as long, colorless needles: mp 137–138 °C; *m/e* 418 (M^+), 400, 385, 382. Anal. Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.78; H, 9.47.

Methyl 3α,7α-Dihydroxy-9α,11α-oxido-5β-cholanate (10). To **6** (9.80 g) was added a solution formed from Na (1.2 g) added to MeOH (80 ml) and the reaction mixture was refluxed (N_2) for 2 h. The usual workup afforded **10** as white needle clusters (7.6 g, 93%, mp 114–120 °C) (aqueous EtOH) suitable for further reaction. Chromatography and then recrystallization from methylcyclohexane afforded the analytical sample of **10** as long, colorless needles: mp 126–126.5 °C; *m/e* 420 (M^+), 402, 384. Anal. Calcd for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.42; H, 9.67.

Methyl 3α-Acetoxy-7α-hydroxy-9α,11α-oxido-5β-cholanate (11). To **10** (50 mg) was added (N_2) at 0 °C a solution of Ac_2O in pyridine (16:1, 2 ml). The resulting solution was stirred at 25 °C for 5 h. The usual workup yielded 59 mg of crude, partly crystalline material. Chromatography over silica gel (2 g) gave pure **11** (44 mg, 80%) as small, colorless needles: mp 129–130 °C; *m/e* 462 (M^+), 444, 402, 384. Anal. Calcd for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15. Found: C, 70.04; H, 9.22.

Methyl 3α-Acetoxy-7-oxo-9α,11α-oxido-5β-cholanate (15). To **11** (26 mg) in HOAc (0.5 ml) was added a solution of sodium dichromate dihydrate (9 mg) in HOAc (0.1 ml) and the dark solution was left at 25 °C for 3 h. Pouring the solution over ice and dilution with water gave a precipitate which was filtered to yield 25.0 mg of a white powder. Recrystallization from hexane afforded pure **15** (20.0 mg, 76%) as colorless needles: mp 147–147.5 °C; NMR δ 0.69 (s, 3, C-18 H), 1.38 (s, 3, C-19 H), 2.00 (s, 3, $COCH_3$), 3.12 (m, 1, C-11 H), 3.68 (s, 3, CO_2CH_3), 4.80 (m, 1, C-3 H); *m/e* 460 (M^+), 432, 416, 400, 189. Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.41; H, 8.75. Found: C, 70.29; H, 8.75.

Fieser[14] had provisionally assigned the same structure **15** to a by-product isolated after perbenzoic acid oxidation of methyl 3α-acetoxychola-7,9(11)-dienate. He found for **15** mp 152–153.5 °C. Found: C, 70.81; H, 8.91. His material crystallized from cold $CHCl_3$–MeOH, a solvent system too polar for recrystallization of **15**.

Methyl 3α-Hydroxy-7-oxo-9α,11α-oxido-5β-cholanate (16). To **15** (15 mg) was added excess NaOMe–MeOH solution. The resulting solution was refluxed for 0.5 h (N_2). The usual workup followed by chromatography over silica gel (0.5 g) afforded **16** (8 mg, 50%) as small needles. Recrystallization from acetone–hexane gave the analytical sample, mp 145–145.5 °C. Anal. Calcd for $C_{25}H_{38}O_5$; *m/e* 418.272. Found: *m/e* 418.271.

Methyl 3,7-Dioxo-9α,11α-oxido-5β-cholanate (17). To **10** (6.00 g) dissolved in HOAc (80 ml) was added a solution of sodium dichromate dihydrate (3.4 g) in HOAc (30 ml). The resulting dark solution was stirred overnight at 25 °C and then poured into water (3.5 l.). The usual workup followed by crystallization from acetone–hexane gave slightly dark **17** (4.50 g, 76%, mp 165–170 °C). An analytical sample was prepared by chromatography over silica gel: mp 171–173 °C; *m/e* 416 (M^+), 401, 398, 388, 372; ORD Φ_{302}[22] −133°, Φ_{266}[22] +3100°. Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71; *m/e* 416.256. Found: C, 71.67; H, 8.53; *m/e* 416.253. Treatment of **17** with a saturated solution of HCl in $CHCl_3$ after the method of Fieser[15] gave after workup complete recovery of **17**.

Methyl 3,7-Dioxo-11α-hydroxy-5β-chol-8-enate (23) and 3,7-Dioxo-11α-hydroxy-5β-chol-8-enic Acid. To **17** (1.00 g) was added a solution of NaOMe prepared from MeOH (25 ml) and Na (0.1 g). The reaction mixture was then heated briefly on a steam bath to give a clear solution which was cooled and stirred at 25 °C for 0.5 h. White needles of enone **23** began to separate out during this period. The mixture was cooled to 0 °C and neutralized with HOAc, and the product was precipitated with water (800 ml). Filtration gave crude **23** (890 mg, 89%, mp 195–198 °C). Recrystallization from MeOH afforded long, colorless needles (765 mg, 76.5%): mp 200–201 °C; NMR δ 0.65 (s, 3, C-18 H), 1.64 (s, 3, C-19 H), 3.66 (s, 3, CO_2CH_3), 4.82 (m, 1, C-11 H); ir 3595 (w), 3450 (w), 2945 (s), 1710 (s), 1668 cm^{-1} (s, enone); *m/e* 416 (M^+), 414, 412, 398, 383; uv max EtOH) 252 nm (log ε 3.95). Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.77; H, 8.69.

The corresponding C-24 acid of **23** was obtained as colorless needles by treatment of **17** with KOH in MeOH. This acid, which readily gave **23** on reaction with diazomethane, analyzed as the monohydrate (mp 189–191 °C). Anal. Calcd for $C_{24}H_{34}O_5 \cdot H_2O$: C, 68.55; H, 8.63. Found: C, 68.43; H, 8.36.

Methyl 3-Ethylenedioxy-7-oxo-5β-chola-8,11-dienate (31). To a solution of **23** (700 mg) in CH_2Cl_2 (25 ml) were added dimethylformamide ethylene acetal (2.5 ml) and HOAc (2.5 ml). This solution was refluxed (N_2) for 3 h. The usual workup followed by chromatography over silica gel (10 g) afforded 31 (213 mg, 30%) as light yellow needles. Recrystallization from hexane gave the analytical sample: mp 144–146 °C; NMR δ 0.67 (s, 3, C-18 H), 1.27 (s, 3, C-19 H), 3.67 (s, 3, CO_2CH_3), 3.90 (s, 4, OCH_2–), 6.03 (d, J = 10 Hz, 1, C-11 H), 6.78 (d, J = 10 Hz, 1, C-12 H); ir 2950 (s), 1726 (s), 1644 cm^{-1} (s, dienone); *m/e* 442 (M^+), 427, 411, 397, 327, 300; uv max (EtOH) 310 nm (log ε 3.88). Anal. Calcd for $C_{27}H_{38}O_5$: C, 73.27; H, 8.65. Found: C, 73.23; H, 8.77.

Methyl 3-Ethylenedioxy-7-oxo-9α,11α-oxido-5β-cholanate (19) and 3-Ethylenedioxy-7-oxo-9α,11α-oxido-5β-cholanic Acid. To a solution of **17** (2.00 g) in CH_2Cl_2 (55 ml) were added dimethylformamide ethylene acetal (6 ml) and HOAc (6 ml). The resulting light yellow solution was refluxed (N_2) for 3 h. The usual workup afforded 3.5 g of a yellow solid wet with high-boiling liquids. Extraction of this material into hot heptane (4 × 50 ml) left a dark yellow residue (350 mg). On cooling to 0 °C the heptane solution yielded **19** (529 mg, mp 162–166 °C) as hard white crystals. Chromatography of the mother liquor over silica gel (30 g) (benzene) afforded an additional 889 mg of **19**. The combined portions of **19** (1.42 g, 64%, mp 162–166 °C) were suitable for further reaction. The analytical sample was obtained by recrystallization from heptane: mp 169–171 °C; *m/e* 460 (M^+), 445, 442, 432, 416. Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.41; H, 8.75. Found: C, 70.55; H, 8.75.

Several attempts were made to prepare epoxide **34** by treatment of **19** in *t*-BuOH/water/NaOH, with 30% H_2O_2.[21] In all cases saponified **19** was isolated in near-quantitative yield as small, colorless needles: mp 189–190 °C; *m/e* 446 (M^+), 444, 428, 413; uv max (EtOH) 250 nm (log ε 3.93). The elemental analysis showed fractional retention of water. Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 69.54; H, 8.99.

Methyl 3-Ethylenedioxy-7-oxo-11α-hydroxy-5β-chol-8-enate (25). To **19** (200 mg) was added a solution of NaOMe prepared from MeOH (20 ml) and Na (100 mg). The mixture was briefly heated (N_2), forming a light yellow solution which was cooled to 25 °C and stirred for 0.5 h. The usual workup followed by crystallization from acetone–hexane afforded **25** as colorless plates (174 mg, 87%): mp 140–141 °C; NMR δ 0.58 (s, 3, C-18 H), 1.35 (s, 3, C-19 H), 3.63 (s, 3, CO_2CH_3), 3.87 (s, 4, OCH_2–), 4.58 (m, 1, C-11 H); ir 2487 (w), 2947 (s), 1727 (s), 1666 cm^{-1} (s, enone); *m/e* 460 (m^+), 442, 427, 411, 328; uv max (EtOH) 250 nm (log ε 3.93). Anal. Calcd. for $C_{27}H_{40}O_6$: C, 70.41; H, 8.75; *m/e* 460.282. Found: C, 70.41; H, 9.21; *m/e* 460.280.

Methyl 3-Ethylenedioxy-7-oxo-11α-acetoxy-5β-chol-8-enate (26) and Methyl 3-Ethylenedithio-7-oxo-11α-acetoxy-5β-chol-8-enate (27). To **25** (100 mg) was added pyridine (3 ml) and Ac_2O (0.5 ml) and the solution was heated (N_2) at reflux for 3 h. The usual workup followed by chromatography over silica gel (2 g) afforded acetate **26** (110 mg) as a colorless oil which would not crystallize: NMR δ 0.62 (s, 3, C-18 H), 1.32 (s, 3, C-19 H), 2.02 (s, 3, $COCH_3$), 3.63 (s, 3, CO_2CH_3), 3.88 (s, 4, OCH_2–), 5.63 (dd, J = 7, 4.5 Hz, 1, C-11 H).

To a solution of crude **26** (130 mg) in $CHCl_3$ (2 ml) was added 1,2-ethanedithiol (0.025 ml). After cooling to −15 °C (N_2), dry HCl was bubbled through the solution for 1 min. After 20 h at 5 °C, the bright red solution was basified with solid Na_2CO_3, diluted with ether,

and filtered. The ether solution was washed successively with cold 5 N NaOH, water, 2 N HCl, water, and brine. After drying (Na_2SO_4) the solvent was removed, affording 101 mg of a yellow oil. Chromatography over silica gel gave **27** as a light yellow oil. Dissolving this oil in methanol and allowing the solvent to evaporate overnight provided long, thin, yellow needles of **27** (89.5 mg, 65%): mp 105 °C dec; NMR δ 0.58 (s, 3, C-18 H), 1.33 (s, 3, C-19 H). 2.03 (s, 3, $COCH_3$), 3.28 (s, 4, SCH_2–), 3.67 (s, 3, CO_2CH_3), 5.60 (m, 1, C-11 H); ir 2960 (m), 1729 (s), 1676 cm^{-1} (m, enone); *m/e* 534 (M^+), 492, 474, 459, 443, 416, 414, 359, 328, 305; uv max (EtOH) 248 nm (log ϵ 4). Anal. Calcd for $C_{29}H_{42}O_5S_2$: C, 65.13; H, 7.92. Found: C, 65.17; H, 8.03.

Isomerization of Intermediates 30 and 29. To a solution of crude **26** (148 mg) in MeOH (2 ml) was added $NaBH_4$ (100 mg). The mixture was stirred (N_2) for 3 h at 25 °C. The usual workup afforded 142 mg of a white powder. Extraction into hot hexane and removal of the solvent gave **30** (130 mg, 88%) as a white powder (mixture of C-7 epimers): NMR δ 0.60 (s, 3, C-18 H), 1.67 (s, 3, C-19 H), 2.01 (s, 3, $COCH_3$), 3.67 (s, 3, CO_2CH_3), 3.92 (s, 4, OCH_2–), 4.13 (m, 1, C-7 H), 5.63 (m, 1, C-11 H); *m/e* 444 (M − AcOH), 442, 426, 411, 395, 364, 312. Attempts to isomerize **30** to the Δ^7-9-ol with aqueous oxalic acid/dioxane, HCl/MeOH/water, or THF/water/$HClO_4$ led to products spectrally identified as diones and enones. Alcohol **29** (prepared as above from **25** and $NaBH_4$) gave mixtures of enones [uv max (EtOH) 253 nm] upon treatment with aqueous acid.

3α-Hydroxy-7α-acetoxy-5β-chol-9(11)-enic Acid (36). A mixture of 5 (8.10 g), K_2CO_3 (11.5 g), MeOH (160 ml), and water (65 ml) was heated briefly on the steam bath and then maintained at 40–45 °C for 6 h. Concentration under vacuum, dilution with water, and addition of HOAc (9 ml) gave a flocculent white precipitate. Filtration and drying gave crude **36** (7.15 g, 99%) as a white powder: NMR δ 0.58 (s, 3, C-18 H), 1.05 (s, 3, C-19 H), 2.00 (s, 3, $COCH_3$), 3.50 (m, 1, C-3 H), 5.00 (m, 1, C-7 H), 5.43 (m, 1, C-11 H), 7.10 (CO_2H); *m/e* 432 (M^+), 417, 372, 357, 354, 339, 300. The crude product resisted all attempts at crystallization and was used without further purification. Anal. Calcd for $C_{26}H_{40}O_5$: *m/e* 432.288. Found: *m/e* 432.290.

Methyl 3α-Hydroxy-7α-acetoxy-5β-chol-9(11)-enate (39) and Methyl 3-Oxo-7α-acetoxy-5β-chol-9(11)-enate (37). To the crude acid **36** (6.94 g) dissolved in dioxane (50 ml) was added to solution of diazomethane in ether until the yellow color persisted. Removal of the volatiles under vacuum gave **39** (7.00 G, 98%) as an essentially pure colorless oil: *m/e* 446 (M^+), 386, 371, 368, 353. Anal. Calcd for $C_{27}H_{42}O_5$: *m/e* 446.303. Found: *m/e* 446.307.

To crude ester alcohol **39** (6.90 g) in HOAc (65 ml) was added a solution of sodium dichromate dihydrate (1.95 g) in HOAc (20 ml). After 10 h at 25 °C, the usual workup followed by chromatography over silica gel (20 g) gave pure **37** (6.34 g, 92%) as a colorless oil: NMR δ 0.64 (s, 3, C-18 H), 0.96 (d, J = 5.0 Hz, 3, C-21 H), 1.18 (s, 3, C-19 H), 2.10 (s, 3, $COCH_3$), 3.68 (s, 3, CO_2CH_3), 5.15 (m, 1, C-7 H), 5.66 (m, 1, C-11 H); *m/e* 444 (M^+), 412, 384, 369, 353. Anal. Calcd for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07. Found: C, 72.51; H, 9.15.

Methyl 3-Oxo-7α-acetoxy-9α,11α-dihydroxy-5β-cholanate Osmate Ester (41) and Methyl 3,12-Dioxo-7α-acetoxy-5β-chol-9(11)-enate (42). To a solution of **37** (1.00 g) in pyridine (7 ml) was added osmium tetroxide (0.5 g) and the solution kept in the dark (N_2) for 8 days. The reaction was monitored by TLC and exhibited maximum formation of **41** between 5 and 7 days and a slow, steady increase of by-product **42**. The pyridine was removed under vacuum and the dark brown residue was extracted with benzene.

The benzene-soluble portion was chromatographed over silica gel (10 g) giving recovered **37** (340 mg, 34%), crystalline **42** (160 mg, 15%), and the crude dark crystalline osmate ester **41** (960 mg, 50%). Crude **41** could be recrystallized from ether as small, white needles of the dipyridine adduct, mp 168 °C dec. Enone **42** was recrystallized from hexane as long, colorless needles: mp 150–150.5 °C; NMR δ 0.99 (s, 3, C-18 H), 1.03 (d, J = 6 Hz, 3, C-21 H), 1.34 (s, 3, C-19 H), 2.00 (s, 3, $COCH_3$), 3.68 (s, 3, CO_2CH_3), 5.26 (m, 1, C-7 H), 5.97 (d, J = 2.4 Hz, 1, C-11 H); ir 2946 (m), 1722 (s), 1679 cm^{-1} (s, enone); *m/e* 458 (M^+), 427, 398, 328, 257, 243; uv max (EtOH) 236 nm (log ϵ 4.03). Anal. Calcd for $C_{27}H_{38}O_6$: C, 70.72; H, 8.35. Found: C, 70.84; H, 8.46.

Methyl 3β,11α-Dihydroxy-3α,9α-oxido-7α-acetoxy-5β-cholanate (43). To the crude osmate **41** (869 mg) were added dioxane (20 ml) and saturated aqueous NH_4Cl (20 ml). H_2S was bubbled through this mixture for 1 h after which it was heated to 65 °C for 1 h. The cooled mixture was filtered through Celite with EtOAc washings. The solvents were removed and the crude product crystallized from acetone–hexane to provide **43** (450 mg, 93%, mp 112–116 °C) as light yellow crystals which contained a trace amount of osmate **41**. The analytical sample was obtained by chromatography over silica gel: mp 117–119 °C; NMR δ 0.72 (s, 3, C-18 H), 0.95 (d, J = 6 Hz, 3, C-21 H), 1.20 (s, 3, C-19 H), 2.10 (s, 3, $COCH_3$), 3.68 (s, 3, CO_2CH_3), 3.94 (m, 1, C-11 H), 5.08 (m, 1, C-7 H); ir 3491 (w), 2956 (s), 1726 cm^{-1} (s); *m/e* 478 (M^+), 460, 418, 400, 147. Anal. Calcd for $C_{27}H_{42}O_7$: C, 67.76; H, 8.84. Found: C, 67.87; H, 8.97.

Methyl 3-Oxo-7α-hydroxy-5β-chol-9(11)-enate (38). To **37** (436 mg) dissolved in MeOH (3 ml) was added a solution of MeONa prepared from MeOH (2 ml) and Na (ca. 100 mg) and the resulting solution was refluxed for 3 h. The usual workup gave a colorless oil which afforded **38** (364 mg, 88%, mp 123–126 °C) as white needles on crystallization from hexane. Chromatography over silica gel (6 g) gave the analytical sample: mp 127–128 °C; NMR δ 0.66 (s, 3, C-18 H), 0.95 (d, J = 5 Hz, 3, C-21 H), 1.16 (s, 3, C-19 H), 3.68 (3, s, CO_2CH_3), 4.07 (m, 1, C-7 H), 5.65 (m, 1, C-11 H); ir 3605 (w), 2945 (s), 1710 cm^{-1} (s); *m/e* 402 (M^+), 400, 384, 369, 332, 314. Anal. Calcd for $C_{25}H_{38}O_4$: *m/e* 402.277. Found: *m/e* 402.276.

Methyl 3-Oxo-5β-chola-7,9(11)-dienate (44). To **38** (100 mg) dissolved in pyridine (5 ml) was added $POCl_3$ (0.5 ml) and the resulting solution was stirred (N_2) at 25 °C overnight. The usual workup followed by crystallization from acetone–hexane gave **44** (88 mg, 92%) as small, white needles, mp 140–142 °C (lit.[14] 143.5–144 °C).

3α,7α-Diacetoxy-5β-chol-9(11)-enic Acid (40). To **36** (1.00 g) were added pyridine (4 ml) and Ac_2O (2 ml) and the resulting solution was heated at 100 °C (N_2) for 0.5 h. The usual workup gave a colorless oil which formed long needles of **40** (920 mg, 84%, mp 198 °C) on crystallization from acetone–hexane. Recrystallization from acetone–hexane gave the analytical sample: mp 205 °C; *m/e* 474 (M^+), 414, 399, 354. 339. Anal. Calcd for $C_{28}H_{42}O_6$: C, 70.86; H, 8.92. Found: C, 70.94; H, 8.80.

3α,7α-Diacetoxy-24-nor-5β-chola-9(11),22-diene (45). To **40** (500 mg) were added benzene (7.5 ml), $Pb(OAc)_4$ (900 mg), $Cu(OAc)_2$ (44 mg), and pyridine (0.4 ml). This mixture was heated at 100 °C (N_2) for 2.5 h. After cooling, the mixture was filtered and the filtrate was evaporated, giving a green oil which was chromatographed on silica gel (5 g) to give pure **45** (405 mg, 90%, mp 101–103 °C) as small, white needle clusters: *m/e* 428 (M^+), 413, 368, 353, 308. Anal. Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41; *m/e* 428.293. Found: C, 75.26; H, 9.56; *m/e* 428.288.

3α-Hydroxy-7α-acetoxy-24-nor-5β-chol-9(11),22-diene (46) and 3-Oxo-7α-acetoxy-24-nor-5β-chola-9(11),22-diene (47). A mixture of **45** (200 mg), K_2CO_3 (280 mg), MeOH (4 ml), and water (1.6 ml) was heated briefly at 100 °C to form a clear solution and then stirred at 45 °C for 6 h. Removal of most of the methanol under vacuum, dilution with water, and extraction with $CHCl_3$ gave crude **46** as a light yellow oil (180 mg): NMR δ 0.62 (s, 3, C-18 H), 1.07 (s, 3, C-19 H), 2.00 (s, 3, $COCH_3$), 3.48 (m, 1, C-3 H), 4.80 and 4.96 (m, 2, C-23 H), 5.00 (m, 1, C-7 H), 5.48 (m, 1, C-11 H), 5.60 (m, 1, C-22 H). Alcohol **46** (180 mg) was oxidized without further purification by dissolving in HOAc (2 ml), adding solid sodium dichromate dihydrate (50 mg), and allowing the solution to stand at 25 °C for 12 h. Dilution with water and extraction with $CHCl_3$ gave crude **47** which was chromatorgaphed over silica gel (4 g) to afford pure **47** (131 mg, 73% from **45**) as a colorless oil: NMR δ 0.68 (s, 3, C-18 H), 1.06 (d, J = 6 Hz, 3, C-21 H), 1.18 (s, 3, C-19 H), 2.00 (s, 3, $COCH_3$), 4.84 (dd, J = 2 and 5 Hz, 1, C-23 H), 4.96 (dd, J = 12 and 2 Hz, 1, C-23 H), 5.17 (m, 1, C-7 H), 5.70 (m, 2, C-11 H and C-22 H); *m/e* 384 (M^+), 340, 324, 309. Anal. Calcd for $C_{25}H_{36}O_3$: *m/e* 384.266. Found: *m/e* 384.268.

3-Oxo-7α-hydroxy-24-nor-5β-chola-9(11),22-diene (48). To **47** (100 mg) was added excess MeONa solution. The resulting solution was refluxed (N_2) for 2 h. The usual workup followed by crystallization from hexane afforded pure **48** (74 mg, 83%): mp 109–110 °C; *m/e* 324 (M^+), 327, 324, 314, 313. Anal. Calcd for $C_{23}H_{34}O_2$: *m/e* 342.256. Found: *m/e* 342.256.

Methyl 3β,7α,11α-Trihydroxy-3α,9α-oxido-5β-cholanate (51). A. From 43. To **43** (120 mg, mp 112–116 °C) was added a MeONa solution prepared from MeOH (5 ml) and Na (ca. 100 mg). The resulting solution was refluxed (N_2) for 2 h. The usual workup followed by two recrystallizations from methylcyclohexane gave pure **51** (79 mg, 82%) as long, colorless needles: mp 185–185.5 °C; NMR δ 0.71 (s, 3, C-18 H), 0.96 (d, J = 5 Hz, 3, C-21 H), 1.18 (s, temperature sensitive, C19 H), 3.67 (s, 3, CO_2CH_3), 4.04 (m, 2, C-7 H and C-11 H), 4.16–4.34 (1, variable, OH); ir 3940 (very broad), 2945 (s), 1705 cm^{-1} (s, sh); *m/e* 436 (M^+), 418, 400. Anal. Calcd for $C_{25}H_{40}O_6$: C, 68.78; H, 9.23. Found: C, 68.45; H, 9.42.

B. From 38. To **38** (71 mg) was added pyridine (1.5 ml) containing 75 mg of OsO_4. After 1 h the reaction was complete. Chromatography yielded the osmate ester dipyridine adduct (145 mg, 100%) as a brown solid which gave on osmate cleavage (see **43**) crude diol hemiacetal **51** (76 mg, 98%) identified by its NMR spectrum and melting point.

Methyl 3β-Methoxy-3α,9α-oxido-7α-acetoxy-11α-hydroxy-5β-cholanate (49). To a solution of **43** (50 mg) in MeOH (5 ml) was

added a drop of 48% HBr. After 0.5 h at 25 °C, the solution was neutralized by addition of solid $NaHCO_3$. The usual workup gave crude **49** as a colorless oil which was chromatographed over silica gel (1 g), affording **49** (41 mg, 79%) as a pure oil which would not crystallize: NMR δ 0.70 (s, 3, C-18 H), 0.96 (d, J = 5 Hz, 3, C-21 H), 1.00 (s, 3, C-19 H), 2.07 (s, 3, $COCH_3$), 3.47 (s, 3, OCH_3), 3.67 (m, 1, C-11 H), 4.98 (m, 1, C-7 H); ir 3578 (w), 2950 (s), 1725 cm^{-1} (s); *m/e* 492 (M^+), 432, 400, 390, 279. Anal. Calcd for $C_{28}H_{44}O_7$: C, 68.26; H, 9.00; *m/e* 492.309. Found: C, 67.81; H, 8.96; *m/e* 492.305.

Methyl 3β-Methoxy-3α,9α-oxido-7α,11α-diacetoxy-5β-cholanate (50). A solution of **49** (20 mg) in pyridine (1.5 ml) and Ac_2O (0.25 ml) was heated at 40 °C for 6 h (N_2). Evaporation of the solvent gave an oily residue which was dissolved in EtOAc and filtered through alumina. Removal of the solvent gave a colorless oil which crystallized from hexane at −10 °C, affording white crystals of **50** (15 mg, 71%) which liquefied to a pure oil: NMR δ 0.78 (s, 3, C-18 H), 0.95 (s, 3, C-19 H), 2.08 (s, 6, $COCH_3$), 3.50 (s, 3, OCH_3), 3.67 (s, 3, CO_2CH_3), 5.00 (m, 2, C-7 and C-11 H); ir 2956 (m), 1727 cm^{-1} (s); *m/e* 534, 492, 432, 414. Anal. Calcd for $C_{30}H_{46}O_8$: *m/e* 534.319. Found: *m/e* 534.319.

Methyl 3β-Methoxy-3α,9α-oxido-7α,11α-dihydroxy-5β-cholanate (52). To a solution of **51** (22 mg) in MeOH (2 ml) was added a trace of 48% HBr. After 0.5 h, the usual workup followed by chromatography over silica gel gave pure **52** (19 mg, 85%) which crystallized from hexane as long, colorless needles: mp 155–156 °C; NMR δ 0.70 (s, 3, C-18 H), 0.96 (d, J = 5 Hz, 3, C21 H), 1.00 (s, 3, C-19 H), 3.30 (s, 3, OCH_3), 3.67 (s, 3, CO_2CH_3), 3.5–4.0 (m, 2, C-7 H and C-11 H); ir 3580 (w), 3500 (s), 2945 (s), 1726 cm^{-1} (s); *m/e* 450 (M^+), 432, 364, 302, 293. Anal. Calcd for $C_{26}H_{42}O_6$: C, 69.30; H, 9.39; *m/e* 450.298. Found: C, 69.31; H, 9.86; *m/e* 450.296.

Methyl 3β-Methoxy-3α,9α-oxido-7α-hydroxy-11α-acetoxy-5β-cholanate (53). A solution of **52** (50 mg) in pyridine (1.5 ml) and Ac_2O (0.25 ml) was heated to 40 °C for 6 h (N_2). The usual workup gave **53** (55 mg, 100%) as a pure, colorless oil which would not crystallize: NMR δ 0.80 (s, 3, C-18 H), 0.95)d, J = 5 Hz, 3, C-21 H), 0.96 (s, 3, C-19 H), 3.40 (s, 3, OCH_3), 3.68 (s, 3, CO_2CH_3), 3.74 (m, 1, C-7 H), 5.10 (dd, J = 11 and 5 Hz, 1, C-11 H); ir 3505 (w), 2945 (s), 1676 cm^{-1} (s); *m/e* 492 (M^+), 461, 432, 346, 302. Anal. Calcd for $C_{28}H_{44}O_7$: *m/e* 492.309. Found: *m/e* 492.308.

Methyl 3β-Hydroxy-3α,9α-oxido-7α-acetoxy-11-oxo-5β-cholanate (54) and Methyl 3β-Methoxy-3α,9α-oxido-7α-acetoxy-11-oxo-5β-cholanate (55). To a solution of 43 (45 mg) in CH_2Cl_2 (1 ml) was added 6 equiv of a 5% CH_2Cl_2 solution of CrO_3–pyridine complex[22] at 10 °C. After 0.5 h the solvent was removed under vacuum and the organic material was taken up in benzene and chromatographed over silica gel to afford hemiacetal **54** (27 mg, 60%) as a tacky, colorless oil: NMR δ 0.61 (s, 3, C-18 H), 1.10 (s, 3, C-19 H), 2.13 (s, 3, $COCH_3$), 3.67 (s, 3, CO_2CH_3), 5.06 (m, 1, C-7 H), Acetal **55** was immediately prepared from **54** (27 mg) by treatment with HBr in methanol (1 ml) (see **49**). Chromatography over silica gel gave pure **55** (18 mg, 64%) as a clear oil: NMR δ 0.62 (s, 3, C-18 H), 1.10 (s, 3, C-19 H), 2.10 (s, 3, $COCH_3$), 3.42 (s, 3, OCH_3), 3.67 (s, 3, CO_2CH_3), 5.09 (m, 1, C-7 H); ir 2960 (s), 1712 cm^{-1} (s); *m/e* 490 (M^+), 472, 420, 402. Anal. Calcd for $C_{28}H_{42}O_7$: *m/e* 490.293. Found: *m/e* 490.293.

Methyl 3β-Methoxy-3α,9α-oxido-11α-acetoxy-5β-chol-7-enate (56). To a solution of **53** (50 mg) in pyridine (2.5 ml) was added $POCl_3$ (0.25 ml) and the solution was stirred overnight (N_2) at 25 °C. The usual workup gave **56** (47 mg, 100%) as a pure, colorless oil which would not crystallize. Chromatography over silica gel provided the analytical sample: NMR δ 0.66 (s, 3, C-18 H), 0.88 (s, 3, C-19 H), 0.91 (d, J = 5 Hz, 3, C-21 H), 2.09 (s, 3, $COCH_3$), 3.32 (s, 3, OCH_3), 3.67 (s, 3, OCH_3), 3.67 (s, 3, CO_2CH_3), 5.09 (dd, J = 11 and 5 Hz, 1, C-11 H), 5.21 (m, 1, C-7 H); ir 2946 (s), 1725 cm^{-1} (s); *m/e* 474 (M^+), 432, 414, 399, 367, 328, 299, 149. Anal. Calcd for $C_{28}H_{42}O_6$: *m/e* 474.298. Found: *m/e* 474.295.

Methyl 3β-Hydroxy-3α,9α-oxido-11α-acetoxy-5β-chol-7-enate (57). To a solution of **56** (40 mg) in HOAc (0.5 ml) and water (0.5 ml) was added 60% $HClO_4$ (0.02 ml). After 12 h at 25 °C, the usual workup gave crude **57** (33 mg) which contained some of the corresponding acid. Treatment with CH_2N_2 and then chromatography over silica gel gave pure **57** (30 mg, 77%) which crystallized from acetone–hexane as small needles: mp 100–103 °C; NMR δ 0.66 (s, 3, C-18 H), 0.88 (s, 3, C-19 H), 0.92 (d, J = 5 Hz, 3, C-21 H), 2.10 (s, 3, $COCH_3$), 3.68)s, 3, CO_2CH_3), 5.09 (dd, J = 11 and 5 Hz, 1 C-11 H), 5.21 (m, 1, C-7 H); ir 3576 (w), 2946 (s), 1732 cm^{-1} (s); *m/e* 460 (M^+), 419, 412, 400, 385, 382, 371, 327. Anal. Calcd for $C_{27}H_{40}O_6$: *m/e* 460.282. Found: *m/e* 460.281.

3β,11α-Dihydroxy-3α,9α-oxido-5β-chol-7-enic Acid (58) and Methyl 3β,11α-Dihydroxy-3α,9α-oxido-5β-chol-7-enate (59). To a solution of **57** (24 mg) in EtOH (2 ml) was added 0.2 N NaOH (2 ml) and the mixture was boiled for 1 h. The EtOH was removed under vacuum and the mixture was poured into dilute HOAc. The white precipitate was crystallized twice from acetone–hexane to give **58** (14.7 mg, 70%, mp 170–173 °C). Recrystallization from CH_3CN gave the analytical example: mp 172–174 °C; NMR δ 0.56 (s, 3, C-18 H), 0.94 (s, 3, C-19 H), 0.96 (d, J = 5 Hz, 3, C-21 H), 3.84 (dd, J = 12 and 5 Hz, 1, C-11 H), 5.26 (m, 1, C-7 H); ir 3571 (w), 2942 (s), 1710 mm^{-1} (s); *m/e* 404 (M^+), 386, 371, 368, 353, 316. Anal. Calcd for $C_{24}H_{36}O_5 \cdot \frac{1}{3}H_2O$: C, 70.22; H, 9.00; *m/e* 460.256. Found: C, 70.21; H, 8.98; *m/e* 460.256.

The methyl ester **59** was prepared by treating **58** (8 mg) with excess CH_2N_2 in ether. Chromatography of the crude product over silica gel gave **33** (6 mg, 72%) as an amorphous white solid which formed gels on attempted crystallization from acetone–hexane or methylcyclohexane: NMR δ 0.56 (s, 3, C-18 H), 0.94 (s, 3, C-19 H), 3.68 (s, 3, CO_2CH_3), 3.84 (m, 1, C-11 H), 5.26 (m, 1, C-7 H); ir 3586 (w), 2945 (s), 1731 cm^{-1} (s); *m/e* 418 (M^+), 400, 385, 382, 367, 346, 313, 285. Anal. Calcd for $C_{25}H_{38}O_5$: *m/e* 418.272. Found: *m/e* 418.268.

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