Studies Directed toward Synthesis of Quassinoids. 2.[1] D-Ring Cleavage of Cholic Acid Derivatives

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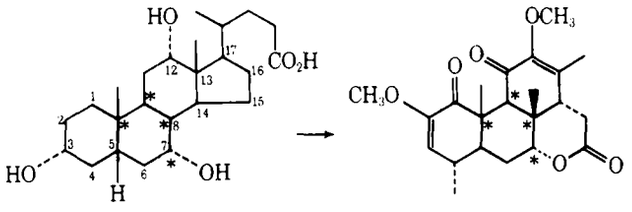
Important results directed toward the conversion of a triterpene derivative, cholic acid, to a diterpene skeleton related to quassin are presented. A useful D-ring cleavage of 17-en-20-one steroids to 16,17-secodioic acids by ozone or permanganate is described, and selective esterification of the least hindered carboxyl group of a glutaric acid anhydride analogue (8) was demonstrated.

A long-term goal of our work is to develop general methods for the eventual synthesis of simaroubaceous lactones[3] related to quassin starting, principally, from cholic acid. The rationale for this approach revolves around the already existing stereochemical attributes common to both cholic acid and quassin (starred positions below). Although positions 5



cholic acid quassin

and 14 will need to be isomerized at some appropriate point in the synthetic sequence, leaving these asymmetric sites unaltered would generate abnormal analogues which would be of interest for biological evaluation. An opposite approach involves building up quassinoids from simpler molecules; this will necessarily require one or more resolution steps involving two or more asymmetric carbons and is under investigation.[4]

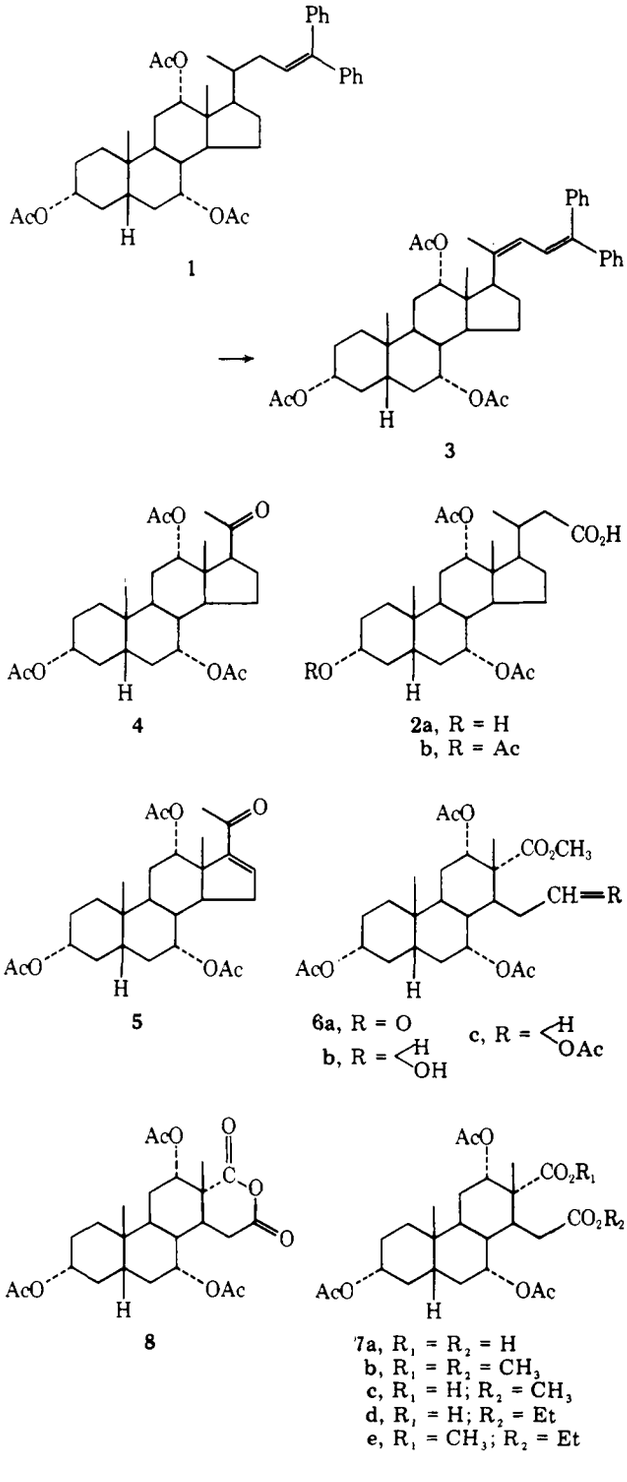
Critical to our approach is 17-side chain degradation and D-ring cleavage. Both transformations are vital areas requiring thorough investigation and development of more improved methods. These developments will have general application beyond our work. This paper describes some of our results in D-ring cleavage.

Results

The 17-side chain degradation starts with the Barbier–Wieland sequence.[5] Grignard reaction of methyl cholate with excess phenylmagnesium bromide in THF afforded 3α,7α,12α,24-tetrahydroxy-24,24-diphenyl-5β-cholane, which was acetylated and dehydrated with refluxing acetic anhydride–acetic acid to give monoene **1** (Scheme I); trace amounts of the apo analogue to **1** were observed as a higher R_f component by TLC. Allylic bromination of monoene **1** with NBS followed by dehydrobromination with dimethylaniline[6] resulted in diene **3**. This diene generally contained small amounts of monoene **1** and was used without further purification. Chromium trioxide oxidation of this olefinic mixture yielded mainly ketone **4** and some hydroxy acid **2a** after base extraction and acidification; acetylation of **2a** yielded **2b** which was identical with the acid obtained by oxidation of monoene **1**.

In this work, ketone **4** was converted to enone **5** by bromination with 1 equiv of bromine in glacial acetic acid[7] followed by dehydrobromination in hot HMPA[8] or with lithium carbonate in DMF. Ozonolysis of enone **5** and treatment of the ozonide with 30% H_2O_2 in glacial acetic acid afforded a mixture of acids consisting of mainly diacid **7a**; treatment of this

Scheme I

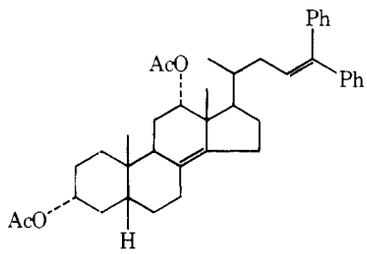


1 **3** **4** **2a**, R = H; **b**, R = Ac **5** **6a**, R = O; **b**, R = H, OH; **c**, R = H, OAc **8** **7a**, $R_1 = R_2 = H$; **b**, $R_1 = R_2 = CH_3$; **c**, $R_1 = H$; $R_2 = CH_3$; **d**, $R_1 = H$; $R_2 = Et$; **e**, $R_1 = CH_3$; $R_2 = Et$

acid mixture with diazomethane yielded aldehyde **6a** and dimethyl ester **7b**. If the acid mixture was first treated with acetic anhydride and pyridine, acid anhydride 8 was the principal product. Reaction of acid anhydride 8 with hot absolute methanol generated acid ester **7c**. Alternatively, acid anhydride 8 could be treated with absolute ethanol containing pyridine to yield acid ester **7d** which in turn is converted to diester **7e** by reaction with diazomethane. Aldehyde **6a** can be reduced with sodium borohydride to give alcohol **6b** which may be acetylated to yield **6c**. Oxidation of enone **5** with potassium permanganate followed by esterification produced diester **7b** and an unidentified seco monoester.

Discussion

In the acetylation–dehydration of 3α,7α,12α,24-tetrahydroxy-24,24-diphenyl-5β-cholane minor amounts of a higher R_f by-product were observed, and it was deduced to be the apo analogue of 1 from the NMR, which exhibited only two acetate



apo analogue of monoene 1, 3α,12α-diacetoxy-24,24-diphenyl-5β-chola-8(14),23-diene

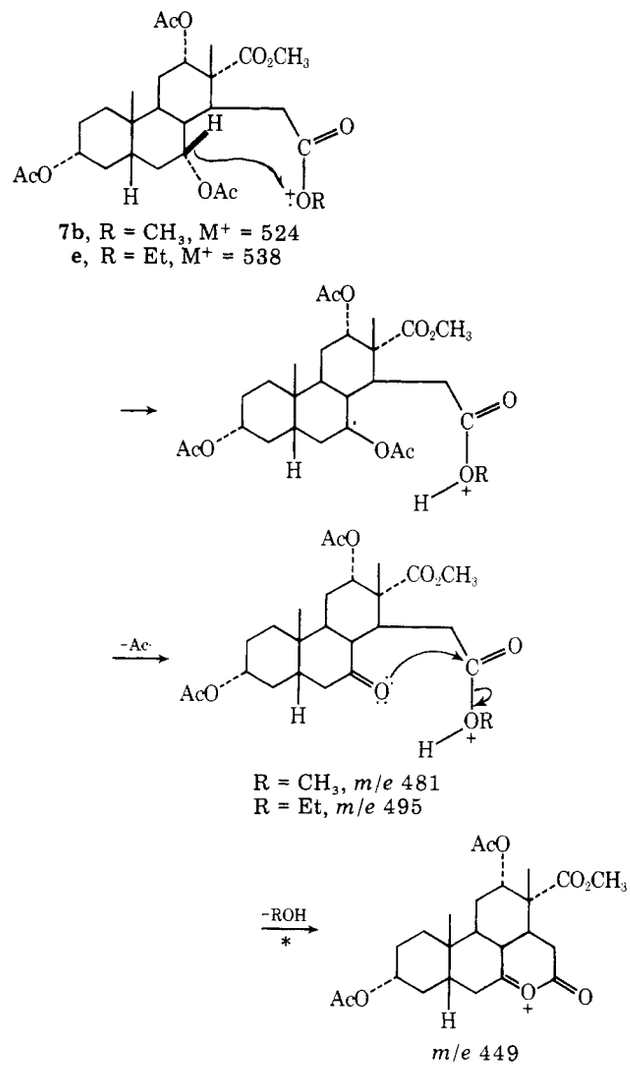
peaks around δ 2.0, and the mass spectrum, which gave a molecular ion of *m/e* 594. Formation of this apo analogue of 1 was minimized by thorough removal of trace strong acid from the workup of the precursor diphenylcarbinol or by prior acetylation in acetic anhydride–pyridine before dehydration in acetic anhydride–acetic acid. Other methods for more expeditious degradation of the 17-side chain are currently underway.

Ketone **4** serves as the pivot point in our efforts for D-ring cleavage studies. In bromination and dehydrobromination of ketone **4**, a slight excess of bromine gave 21-bromo-3α,7α,12α-triacetoxy-5β-pregn-16-en-20-one as a by-product, which exhibited a UV bathochromic shift ($\Delta\lambda_{max}$ 9 nm) in the π to π* transition as compared to enone **5**, and it was found more convenient to perform ozonolysis on the unpurified product from the dehydrobromination step. The mass spectrum of enone **5** exhibited an M − 43 base peak which emanates from the migration of the C-18 methyl to position C-17 followed by ejection of the acetyl radical generating an allylic carbonium ion.[9] Formation of aldehyde **6a** was variable, and it may well be that acid-al formation is responsible for its survival in the peracetic acid treatment under the conditions we employed. The alternate structure for aldehyde **6a** where the aldehyde and ester functional groups are interchanged is ruled out by the absence of a significant chemical shift for the C-18 methyl ^{1}H NMR signal upon reduction of **6a** to **6b**. As anticipated the less sterically hindered acid ester **7c** or **7d** can be made by treatment of acid anhydride 8 with either methanol or ethanol, respectively, the bulkier ethanol requiring base catalysis with pyridine. Presence of *m/e* 449 ion peak in the mass spectra of both **7b** and **7e** (Scheme II) substantiates that it is the least sterically hindered carboxyl group that is esterified upon reaction of acid anhydride 8 with either methanol or ethanol.

Experimental Section

General. All melting points were determined with a Fisher-Johns apparatus and are corrected. Infrared data ($\bar{\nu}_{max}$) were obtained on a Perkin-Elmer 710 spectrophotometer; ^{1}H NMR data, reported in parts per million (δ) from internal Me_4Si, were determined in $CDCl_3$ on a Varian A-60 or T-60 NMR; and mass spectra were obtained at an ionization voltage of 70 eV with a Nuclide 12-90-G single focusing instrument having a resolution of 10 000. C, H microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Scheme II



Column chromatography was performed using silica gel (MCB grade 62), and TLC was done on silica gel HF_{254} (E. Merck). Column elution was performed with benzene–EtOAc, and TLC development was done with hexane–EtOAc. Visualization of analytical TLC was achieved by spraying with 2% ceric sulfate in 2 N H_2SO_4 solution followed by brief heating; **4**, **5**, and esters of **7** gave characteristic green colors.

3α,7α,12α-Triacetoxy-24,24-diphenyl-5β-chol-23-ene (1). Methyl cholate (50 g) was reacted with phenylmagnesium bromide in THF to yield 3α,7α,12α,24-tetrahydroxy-24,24-diphenylcholane of mp 225–227 °C (lit.[5a] 220–230 °C). This total product was heated at reflux for 1 h in a mixture of HOAc (300 mL) and acetic anhydride (150 mL). Most of this solvent was removed by distillation, and the residue was poured into H_2O. Column chromatography yielded 65 g of **1**: mp 95–99 °C; $\bar{\nu}_{max}$ 1730, and 1250 (OAc), and 1600 cm^{-1} (C=C); ^{1}H NMR δ 7.22 (s, 10H, C-24 phenyl protons), 6.08 (t, 1H, C-23), 5.08 (peak, 1H, 12β-H), 4.87 (peak, 1H, 7β-H), 4.53 (hump, 1H, 3β-H), 2.10, 2.05, and 2.02 (s, 3H each, 3α,7α,12α-OAc's), 0.92 (s, 3H, C-19), and 0.73 (s, 3H, C-18); λ_{max} 250 nm (log ϵ_{max} 4.3).

A higher R_f product of 3α,12α-diacetoxy-24,24-diphenyl-5β-chola-8(14),23-diene was obtained: $\bar{\nu}_{max}$ 1730 and 1250 (OAc) and 1600 cm^{-1} (C=C); ^{1}H NMR δ 7.20 (s, 10H, phenyl H's), 6.07 (m, 1H, C-23), 5.10 (peak, 1H, 12β-H), 4.60 (hump, 1H, 3β-H), 2.03 (s, 6H, OAc's), 0.87 (s, 3H, C-19), and 0.86 (s, 3H, C-18); *m/e* 594, 534 (M − HOAc), 519 (M − HOAc − CH_3), 474 (M − 2HOAc), 459 (M − 2HOAc − CH_3), 341, 281 (100), and 220.

3α,7α,12α-Triacetoxy-24,24-diphenyl-5β-chola-20(22),23-diene

(3). A mixture of monoene 1 (60 g), CCl_4 (1.2 L), and NBS (23 g) was irradiated with a sun lamp for 25 min while heating at reflux. *N,N*-Dimethylaniline (96 mL) was added to the cool, filtered solution, and CCl_4 was subsequently distilled off. The residue was column chromatographed with benzene to yield 39 g of diene **3** contaminated with some monoene **1**: $\bar{\nu}_{max}$ 1730 (OAc), 1600, 970, 950, 890, and 770 cm^{-1}; ^1H NMR δ 7.25 (s, 10H, C-24 phenyl protons), 6.88 (d, J = 11 Hz, 1H, C-23), 5.90 (d, J = 11 Hz, 1H, C-22), 4.88 (peak, 1H, 7β-H), 4.80 (peak, 1H, 12β-H), 4.56 (hump, 1H, 3β-H), 2.67 (m, 1H, C-17), 2.06 and 2.03 (s, 3H each, 3α,7α-OAc's), 1.94 (s, 3H, 12α-OAc), 1.83 (s, 3H, C-21), 0.92 (s, 3H, C-19), and 0.63 (s, 3H, C-18); λ_{max} 306 nm (log ϵ_{max} 4.4).

3α,7α,12α-Triacetoxy-5β-pregnan-20-one (4). A solution made by dissolving CrO_3 (20 g) in H_2O (20 mL) and adding to glacial HOAc (100 mL) was added to a solution of diene **3** (30 g) in $CHCl_3$ (30 mL) and glacial HOAc (150 mL) while maintaining the temperatures between 45 and 50 °C. After stirring the reaction solution at 50 °C for 1 h, the reaction mixture was cooled and quenched with CH_3OH (20 mL). This mixture was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ layer was concentrated on a rotary evaporator and the residue dissolved in ether which was successively washed with H_2O, dilute HCl, and H_2O again. The ether layer was extracted with 3% KOH solution. Removal of the ether yielded neutral product that was column chromatographed through silica gel. Eluting with benzene–EtOAc (9:1) yielded 11 g of ketone **4**: mp 151–153 °C (crystals from hexane–Et_2O); $\bar{\nu}_{max}$ 1740 (OAc) and 1715 cm^{-1} (ketone); ^1H NMR 5.14 (peak, 1H, 12β-H), 4.93 (peak, 1H, 7β-H), 4.57 (hump, 1H, 3β-H), 3.00 (t, 1H, C-17), 2.18 (s, 3H, C-21), 2.07 (s, 3H, OAc), 2.04 (s, 6H, 2O-Ac's), 0.93 (s, 3H, C-19), and 0.70 (s, 3H, C-18); *m/e* 433 (M − 43), 373, 356 (100), 313, 296, 281, and 253.

Anal. Calcd for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 67.71; H, 8.24.

The KOH layer was acidified with dilute HCl and extracted with ether. Removal of the ether and recrystallization of the residue yielded 3 g of acid **2a**: mp 210–211 °C (needles from hexane–acetone); $\bar{\nu}_{max}$ 3475 (OH stretch), 1740 (OAc), and 1710 cm^{-1} (CO_2H); ^1H NMR δ 6.53 (peak, 2H, 3α-OH and CO_2H, exchanges with D_2O), 5.08 (peak, 1H, 12β-H), 4.90 (peak, 1H, 7β-H), 3.47 (hump, 1H, 3β-H), 2.5 (m, 2H, C-22), 2.12 and 2.08 (s, 3H each, 7α,12α-OAc's), 0.92 (s, 3H, C-19), and 0.78 (s, 3H, C-18).

3α,7α,12α-Triacetoxy-5β-cholan-24-oic Acid (2b). Oxidation of monoene **1** or acetylating acid **2a** gave **2b**: mp 105–107 °C (lit.[5] 106–107 °C, needles from hexane–acetone); ^1H NMR δ 9.9 (hump, 1H, CO_2H), 5.11 (peak, 1H, 12β-H), 4.93 (peak, 1H, 7β-H), 4.57 (hump, 1H, 3β-H), 2.5 (m, 2H, C-22), 2.15, 2.10, and 2.06 (s, 3H each, 3α,7α,12α-OAc's), 0.93 (s, 3H, C-19), and 0.78 (s, 3H, C-18).

3α,7α,12α-Triacetoxy-5β-pregn-16-en-20-one (5). To a solution of ketone **4** (6.0 g) in glacial HOAc (120 mL) containing 40% HBr (2 drops) was added Br_2 in glacial HOAc (13 mL of 1.0 M). After this mixture was stirred at room temperature for 10 min, it was poured into ice water which was subsequently extracted with ether. The ether solution was washed successively with H_2O, $NaHCO_3$ solution, and H_2O again. The ether was evaporated on a rotary evaporator, and the residue was dissolved in HMPA (60 mL) and heated at 120 °C with stirring under a N_2 atmosphere for 1 h. The cooled HMPA solution was diluted with H_2O and extracted with EtOAc which was subsequently concentrated. Column chromatography of the residue thus obtained through silica gel afforded 3.6 g of enone **5** upon elution with benzene–EtOAc (95:5): mp 185–187 °C (granular crystals from hexane–Et_2O); $\bar{\nu}_{max}$ 1740 (OAc) and 1670 and 1600 cm^{-1} (C=C–C=O); ^1H NMR δ 6.67 (peak, 1H, C-16), 5.49 (peak, 1H, 12β-H), 5.02 (peak, 1H, 7β-H), 4.56 (hump, 1H, 3β-H), 2.7 (m, 2H, C-15), 2.24 (s, 3H, C-21), 2.10, 2.03, and 1.98 (s, 3H each, 3α,7α,12α-OAc's), and 0.97 (s, 6H, C-18 and C-19); λ_{max} 236 nm (log ϵ_{max} 3.88).

Anal. Calcd for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07; O, 23.60. Found: C, 68.04; H, 8.02; O, 23.94.

Also, a higher R_f product of 21-bromo-3α,7α,12α-triacetoxy-5β-pregn-16-en-20-one was obtained: $\bar{\nu}_{max}$ 1730 and 1250 (OAc) and 1665 and 1595 cm^{-1} (C=C–C=O); ^1H NMR 6.73 δ(peak, 1H, C-16), 5.45 (peak, 1H, 12β-H), 5.00 (peak, 1H, 7β-H), 4.55 (hump, 1H, 3β-H), 4.23 and 3.88 (d, J = 11 Hz, 1H each C-21), 2.10 (s, 3H, OAc), 2.02 (s, 6H, OAc's), and 0.96 (s, 6H, C-18 and C-19); λ_{max} 245 nm (log ϵ_{max} 3.78).

Methyl 3α,7α,12α-Triacetoxy-16,17-seco-5β-androstane-16,17-dioate (7b) and Methyl 3α,7α,12α-Triacetoxy-16,17-seco-16-oxo-5β-androstan-17-oate (6a). Ozone was passed through a solution of enone **5** (0.4 g) in dry EtOAc (40 mL) for 5 min (solution becomes deep blue) at dry ice–acetone temperature. After allowing the solution to warm to room temperature (blue color fades), the solvent was removed in vacuo, the residue was redissolved in glacial HOAc (40 mL) and 30% H_2O_2 (10 mL) was added. After stirring overnight, the HOAc was removed on a rotary evaporator with the aid of a hot water bath. The residue was dissolved in EtOAc which was washed with water (discarded) and then extracted with 5% KOH solution. Acidification of the KOH layer followed by extraction with EtOAc yielded 0.32 g of acidic products. This was dissolved in CH_2Cl_2 and treated with diazomethane prepared from *N*-nitrosomethylurea. Chromatography through silica gel yielded 50 mg of aldehyde **6a** upon elution with benzene–EtOAc (95:5): mp 185–187 °C (needles from hexane–benzene); $\bar{\nu}_{max}$ 1745 (OAc) and 1720 cm^{-1} (aldehyde C=O); ^1H NMR δ 9.88 (m, 1H, C-16), 5.13 (peak, 1H, 12β-H), 4.93 (peak, 1H, 7β-H), 4.56 (hump, 1H, 3β-H), 3.66 (s, 3H, OCH_3), 2.4 (m, 2H, C-15), 2.11, 2.08, and 2.04 (s, 3H, each, 3α,7α,12α-OAc's), 1.24 (s, 3H, C-18), and 0.94 (s, 3H, C-19); *m/e* 434 (M − HOAc), 392, 360, 332, 300, 272, 257, and 213 (100).

Anal. Calcd for $C_{26}H_{38}O_9$: C, 63.14; H, 7.74; O, 29.12. Found: C, 63.11; H, 7.70; O, 29.19.

Further elution with benzene–EtOAc (9:1) afforded 0.25 g of diester **7b** as a glassy solid: $\bar{\nu}_{max}$ 1730 cm^{-1} (broad); ^1H NMR δ 5.13 (peak, 1H, 12β-H), 4.87 (peak, 1H, 7β-H), 4.57 (hump, 1H, 3β-H), 3.62 (s, 3H, OCH_3), 2.3 (m, 2H, C-15), 2.10, 2.07, and 2.03 (s, 3H each, 3α,7α,12α-OAc's), 1.18 (s, 3H, C-18), and 0.93 (s, 3H, C-19); *m/e* 524 (M^+), 493 (M − OCH_3), 481 (M − 43), 464 (M − HOAc), 449 (M − 43 − 32), 404 (M − 2HOAc), 344 (M − 3HOAc), and 285 (M − 3HOAc − 59).

Methyl 3α,7α,12α-Triacetoxy-16,17-seco-5β-androstane-16,17-dioate (7b) from Permanganate Oxidation of Enone 5. A solution of enone **5** (400 mg) in benzene (20 mL) containing dicyclohexyl-18-crown-6 (100 mg) and pulverized $KMnO_4$ (600 mg) was stirred at room temperature for 20 h. The brown reaction mixture was treated with $NaHSO_3$ solution (2 g in 10 mL of H_2O), the benzene layer was separated, and the acidified aqueous layer was extracted with EtOAc. The combined organic layers was extracted with 5% NaOH solution. The alkali extract was acidified, concentrated in vacuo, and extracted with EtOAc. Removal of the solvent yielded 150 mg of acid which was treated with diazomethane followed by acetic anhydride–pyridine. Thin layer chromatography yielded 90 mg of diester **7b**. Also, 50 mg of an unidentified lower R_f, secomonoester was obtained, mp 104–106 °C (needles from benzene–hexane).

3α,7α,12α-Triacetoxy-16,17-seco-5β-androstane-16,17-dioic Acid 16-Methyl Ester (7c). The acid (0.30 g) obtained by ozonolysis of enone **5** was heated at reflux with a mixture of pyridine (5 mL) and acetic anhydride (5 mL) for 2 h. This cooled reaction mixture was poured into ice water which was extracted with EtOAc; the EtOAc layer was washed with H_2O, dilute HCl solution, and H_2O again. Removal of the solvent afforded 0.28 g of anhydride **8** containing very little impurity: $\bar{\nu}_{max}$ 1810 and 1770 (anhydride C=O) and 1730 cm^{-1} (OAc); ^1H NMR δ 5.38 (peak, 1H, 12β-H), 5.00 (peak, 1H, 7β-H), 4.57 (hump, 1H, 3β-H), 2.6 (m, 2H, C-15), 2.10 (s, 6H, 7α,12α-OAc's), 2.04 (s, 3H, 3β-OAc), 1.27 (s, 3H, C-18), and 0.94 (s, 3H, C-19). Reaction of this anhydride with dry CH_3OH (10 mL) at 50 °C for 3 h followed by removal of the solvent and chromatography of the residue yielded 0.20 g of acid methyl ester **7c**: mp 106–108 °C (crystal from hexane–EtOAc); $\bar{\nu}_{max}$ 3000 (broad), 1700 (CO_2H), 1745 (OAc), and 1730 cm^{-1} (CO_2CH_3); ^1H NMR δ 8.4 (peak, 1H, CO_2H, exchanges with D_2O), 5.14 (peak, 1H, 12β-H), 4.86 (peak, 1H, 7β-H), 4.53 (hump, 1H, 3β-H), 3.58 (s, 3H, OCH_3), 3.0 (m, 2H, C-15), 2.10 (s, 6H, 7α,12α-OAc's), 2.03 (s, 3H, 3α-OAc), 1.20 (s, 3H, C-18), and 0.93 (s, 3H, C-19).

Anal. Calcd for $C_{26}H_{38}O_{10}$: C, 61.16; H, 7.50. Found: C, 61.26; H, 7.81.

Treatment of this acid ester (**7c**) with diazomethane produced a product which was in every way identical with diester **7b**.

3α,7α,12α-Triacetoxy-16,17-seco-5β-androstane-16,17-dioic Acid 16-Ethyl Ester (7d) and 16-Ethyl-17-methyl 3α,7α,12α-Triacetoxy-16,17-seco-5β-androstane-16,17-dioate (7e). Anhydride **8** (0.30 g) was treated with absolute EtOH (10 mL) and pyridine (2 mL) at 50 °C for 4 h with stirring. The reaction mixture was diluted with H_2O which was extracted with EtOAc. After washing the EtOAc extractrate with dilute HCl and then H_2O, the organic solvent was evaporated off and the residue chromatographed to yield 0.15 g of acid ester **7d**: ^1H NMR δ 8.5 (peak, 1H, CO_2H, exchanges with D_2O), 5.14 (peak, 1H, 12-β-H), 4.86 (peak, 1H, 7β-H), 4.53 (hump, 1H, 3β-H), 4.04 (q, J = 7 Hz, 2H, OEt), 3.0 (m, 2H, C-15), 2.10 (s, 6H, 7α,12α-OAc's), 2.03 (s, 3H, 3α-OAc), 1.22 (t, J = 7 Hz, 3H, OEt), 1.20 (s, 3H, C-18), and 0.93 (s, 3H, C-19). Reaction of this with diazomethane followed by chromatography afforded 0.10 g of diester **7e**: ^1H NMR δ 5.12 (peak, 1H, 12β-H), 4.87 (peak, 1H, 7β-H), 4.53 (hump, 1H, 3β-H), 4.03 (q, J = 7 Hz, 2H, OEt), 3.59 (s, 3H, OCH_3), 3.0 (m, 2H, C-15), 2.09, 2.08, and 2.03 (s, 3H each, 3α,7α,12α-OAc's), 1.23 (t, J = 7 Hz, OEt), 1.17 (s, 3H, C-18), and 0.92 (s, 3H, C-19); *m/e* 538 (M^+), 507 (M −

OCH_3), 495 (M − 43), 478 (M − HOAc), 449 (M − 43 − 46), 418 (M − 2HOAc), 358 (M − 3HOAc), and 299 (M − 3HOAc − 59).

Methyl 3α,7α,12α-Triacetoxy-16-hydroxy-16,17-seco-5β-androstan-17-oate (6b). A solution of aldehyde **7a** (30 mg) and $NaBH_4$ (20 mg) in CH_3OH (5 mL) was stirred at room temperature for 0.5 h. The reaction mixture was poured into ice water and extracted with EtOAc. After washing the EtOAc layer with dilute HCl solution and then H_2O, the organic solvent was evaporated. Recrystallization of the residue from hexane–EtOAc afforded 20 mg of **6b:** mp 193–195 °C; ^1H NMR δ 5.19 (peak, 2H, 7β,12β-H's), 4.57 (hump, 1H, 3β-H), 3.62 (s, 3H, OCH_3), 3.61 (peak, 2H, C-16), 2.10, 2.07, and 2.03 (s, 3H each 3α,7α,12α-OAc's), 1.25 (s, 3H, C-18), and 0.93 (s, 3H, C-19); *m/e* 436 (M − HOAc), 394, 362, 334, 302, 274 (100), and 213 (100).

Anal. Calcd for $C_{26}H_{40}O_9$: C, 62.89; H, 8.12. Found: C, 62.78; H, 7.88.

Acetylation of **6b** with pyridine–Ac_2O yielded tetraacetate **6c:** ^1H NMR δ 4.97 (peak, 2H, 7β,12β-H's), 4.54 (hump, 1H, 3β-H), 3.93 (peak, 2H, C-16), 3.60 (s, 3H, OCH_3), 2.10, 2.05, 2.02, and 1.96 (s, 3H, each, OAc's), 1.17 (s, 3H, C-18), and 0.93 (s, 3H, C-19).

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Registry No.—**1,** 51102-05-7; **2a,** 61543-86-0; **2b,** 52840-09-2; **3,** 61543-87-1; **4,** 61543-88-2; **5,** 61543-89-3; **6a,** 61543-90-6; **6b,** 61543-91-7; **6c,** 61543-92-8; **7b,** 61543-93-9; **7c,** 61543-94-0; **7d,** 61543-95-1; **7e,** 61543-96-2; **8,** 61543-97-3; methyl cholate, 1448-36-8; phenyl bromide, 108-86-1; 3α,12α-diacetoxy-24,24-diphenyl-5β-chola-8(14),23-diene, 61543-98-4; NBS, 128-08-5; 21-bromo-3α,7α,12α-triacetoxy-5β-pregn-16-en-20-one, 61543-99-5; ozone, 10028-15-6; diazomethane, 334-88-3.

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Terpenes and Terpenoids. 5. The Four Isomeric Thujanols. Their Preparative Chemistry, Conformation, and Reactivity. A Comprehensive Study

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The preparative chemistry (50–100-g scale) of (−)-3-isothujone (**1**), (+)-3-thujone (**2**), (−)-3-neoisothujanol (**3**), (−)-3-isothujanol (**4**), (+)-3-thujanol (**5**), and (+)-3-neothujanol (**6**) was developed. As starting material was utilized western red cedar (*Thuja plicata Don*) leaf oil containing 80–90% of **1**. Conformation and reactivity of alcohols **3–6** were studied by three probes: lanthanide shift reagent (LSR) induced ^1H NMR chemical shifts and their conformational interpretation, rate of chromium trioxide oxidation, and rate of acetic anhydride–pyridine acetylation. Shifts induced by $Eu(thd)_3$ indicated a slightly developed boatlike conformation (**3a–6a**) with a dihedral angle of 14 ± 4° between C2–C3 and/or C3–C4. Positionally analogous protons in *trans-* and *cis*-2-methycyclopentanol (**9, 10**) showed shifts very similar to those in **3–6.** Rates of chromium trioxide oxidation of alcohols **3–6, 9,** and **10** in AcOH at 25.0 ± 0.1 °C follow (alcohol, $k_2 \times 10^2$ L mol^{-1} s^{-1}, relative rate of cyclopentanol = 1): **3,** 36.3, 6.91; **4,** 27.9, 5.31; **5,** 17.7, 3.37; **6,** 55.3, 10.5; **9,** 7.36, 1.40; **10,** 15.4, 2.93. Rates of acetic anhydride–pyridine acetylation follow (alcohol, $k_2 \times 10^5$ L mol^{-1} s^{-1}, relative rate of cyclopentanol = 1): **3,** 14.3, 1.36; **4,** 4.49, 0.42; **5,** 19.4, 1.84; **6,** 0.912, 0.086; **9,** 16.2, 1.54; **10,** 5.22, 0.49. Oxidation and acetylation rates were adequately rationalized by comparison with rates of 2- and 3-substituted cyclopentanols. They supported results observed in the LSR–NMR study. LSR-induced shifts in thujones **1** and **2** indicated a flat, five-membered ring, i.e., an overall L-shaped conformation of these two ketones.

The two isomeric thujones (**1, 2**) and the four isomeric thujanols **3–6** (Scheme I) form a unique group of monoterpenes derived from bicyclo[3.1.0]hexane.[2,3] The ketones are fairly common in nature, whereas the alcohols are relatively rare. The recent review by Whittaker and Banthorpe[4] covering the past 25 years has shown that despite considerable work carried out on various aspects of the chemistry of **1–6** the overall picture remains rather fragmented. In particular, with regard to alcohols **3–6** a systematic study correlating quantitatively their reactivity and exploring their conformation was notably absent. One reason for this may have been the tedious preparation of pure alcohols **3–6** in larger quantities.[5,6,7a]

The present paper deals with two subjects. The first is an extension and conclusion of our work[8,9] concerning the preparation of alcohols **3–6.** Simple procedures have now been developed, which make them easily accessible starting with a single abundant source, viz., western red cedar (*Thuja plicata Don*) leaf oil.[10]

The second subject is the study of conformation and reactivity of these alcohols. As probes we applied the ^1H NMR–LSR technique using $Eu(thd)_3$, rate of chromium trioxide oxidation, and rate of acetylation. The overall conformation of the bicyclohexane skeleton of the thujanols may be boatlike (**3a–6a**), L-shaped with a flat five-membered ring (**3–6**), or chairlike (**3b–6b**). Bergqvist and Norin[6] and Tori[11] proposed on the basis of NMR coupling constants a well-developed boatlike conformation (**1a–6a**) in thujanols as well as in thujones.[12] However, limitations to the conformational interpretation of *J* constants in bicyclo[*n*.1.0] compounds were voiced.[4,13] Later Norin et al.[7b] utilized the $Eu(thd)_3$ LSR reagent to study 3-neoisothujanol (**3**) and 3-thujanol (**5**) and confirmed the suggested boatlike conformation. We found[9] by IR that under conditions of extreme dilution in nonpolar solvents **3** and **5** may exist in a chairlike conformation (**3b, 5b**) due to the intramolecular hydrogen bond between OH and the edge of the cyclopropane ring. As suggested by one referee of