INTRAMOLECULAR CYCLIZATION OF STEROIDAL DIKETO ALDEHYDES TO ACETALS

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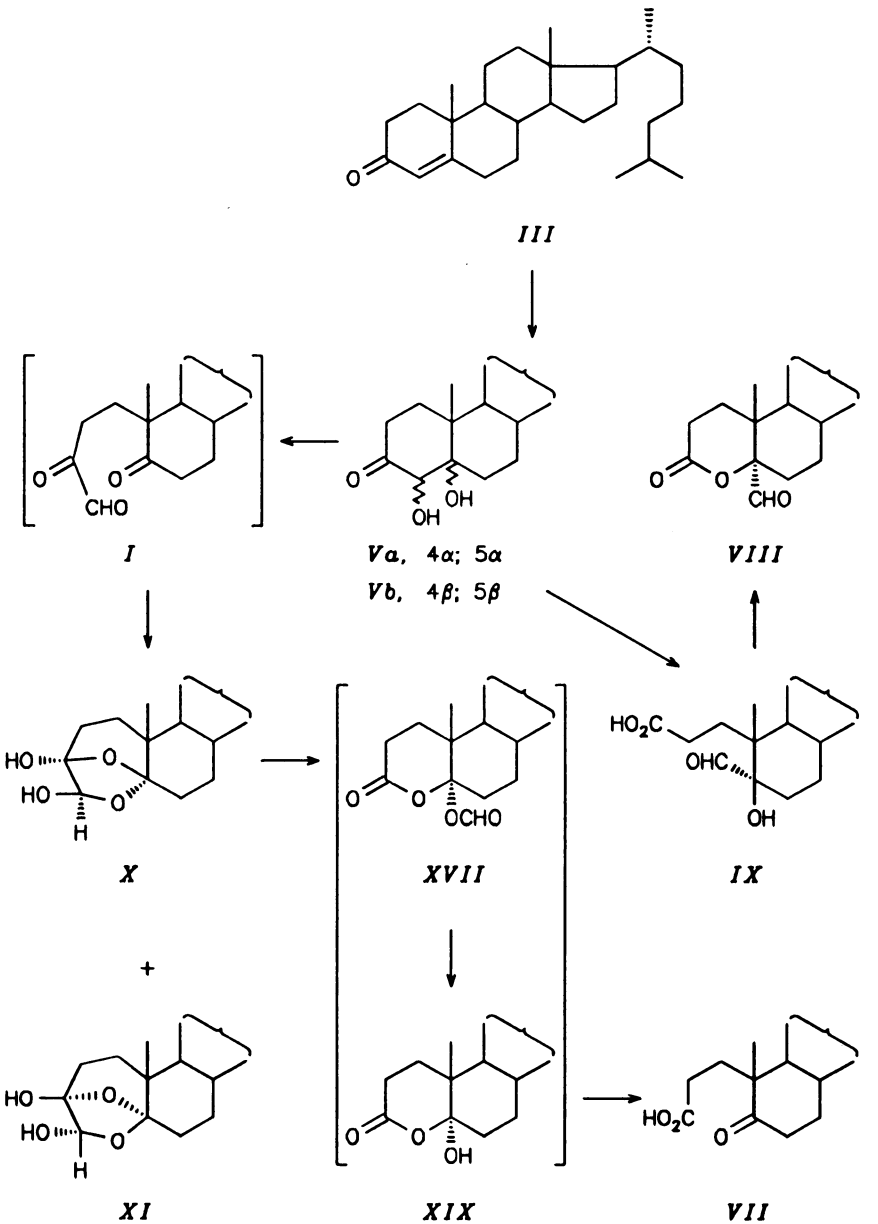
As an attempt to prepare diketo aldehydes *I* and *II* conjugated ketones *III* and *IV* were converted to the respective keto diols *V* and *VI*, which were treated with periodic acid and independently with lead tetraacetate. However, instead of desired diketo aldehydes *I* and *II*, unexpected and interesting cyclized acetals *X*, *XI*, and *XII* were obtained. The structures and some of their chemistry are described in this paper.

During our investigation on the oxidation of the conjugated steroidal ketones with the potassium permanganate–sodium periodate mixture we observed that, depending on the position of the double bonds, various amount of cyclized products were formed. We also established that the formation of the cyclized products predominates, when double bonds were hindered (e.g. Δ^5 or Δ^7 in the ring B of the steroid system[1]). On the assumption that the formation of the cyclized products involved the intermediate formation of a diketo aldehydes such as *I* and *II* we attempted to synthesize such compounds to learn more of their chemistry. This paper describes the attempts the synthesis of cholestane derivatives *I* and *II* and their cyclization with some stereochemical consideration.

As an attempt to prepare the diketo aldehydes *I* and *II* conjugated ketones *III* and *IV* were converted to the respective keto diols[2,3] *V* and *VI*.

Treatment of the mixture of isomeric keto diols *V* with periodic acid in methanol gave two known compounds: keto acid[4] *VII* (85%) and lactone aldehyde[5] *VIII* (10%). It is most likely that lactone aldehyde *VIII* could arise by the cyclization of the intermediate hydroxy aldehyde acid *IX* which was formed by cleavage of C(3)–C(4) bond in one of the isomeric keto diols *V*. Trans-fusion of the six-membered lactone and B ring strongly supports that lactone aldehyde *VIII* could be formed from the keto diol *Vb* with 4β and 5β hydroxyl groups (see Scheme 1).

When keto diols *V* were oxidized with lead tetraacetate in benzene in the presence of glacial acetic acid for 3 h three products were obtained: keto acid *VII* (10%), acetal



SCHEME 1

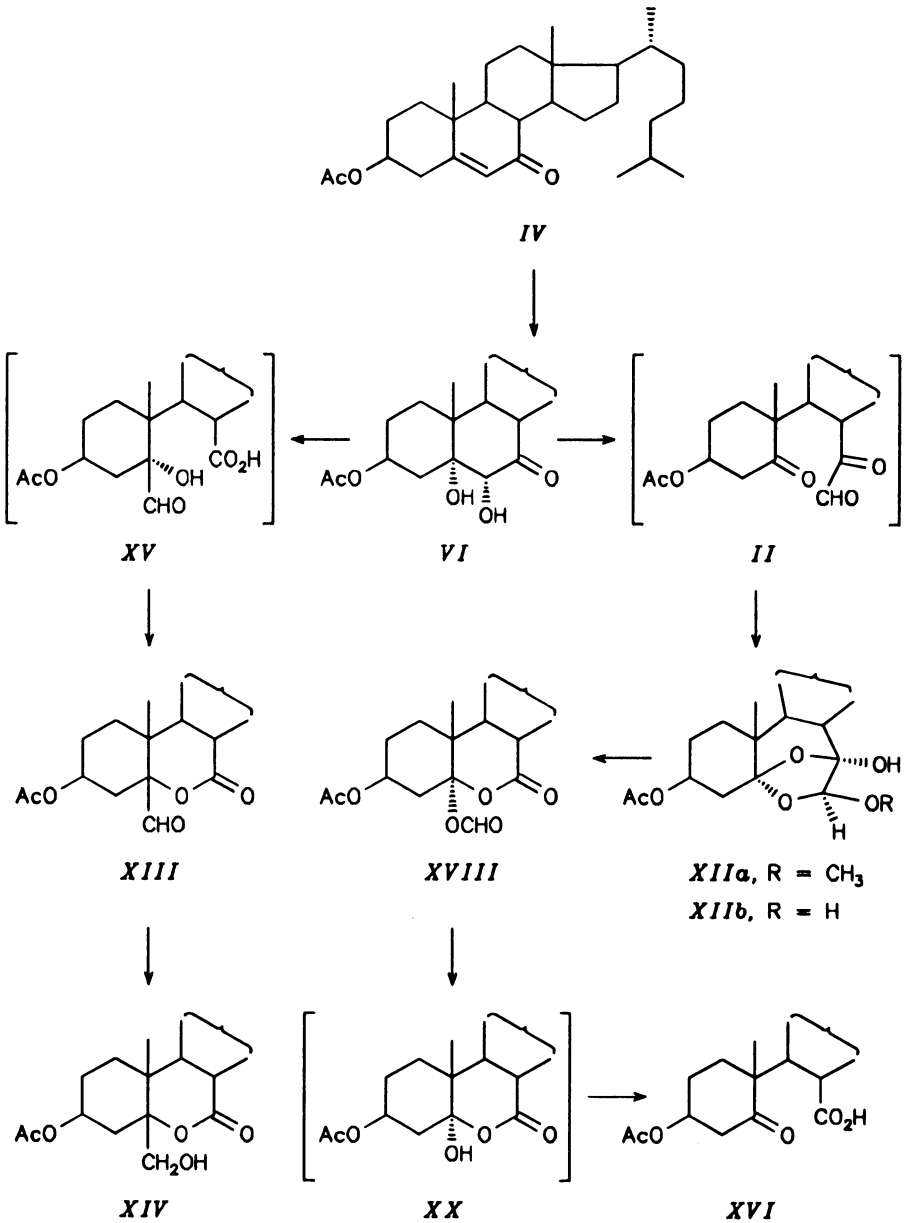
X (70%), and acetal *XI* (2.3%). Reactions were also carried out in other solvents in order to examine solvent effect on the products distributions (cf. Table I).

When the oxidation was conducted in chloroform or dichloromethane the same products were obtained with no significant variation in the yields indicating that no solvent effect was involved. When the reaction was carried out for 3 h in methanol the keto acid *VII* was the only product. This may be result from the fact that lead tetraacetate will cleave 1,2-dicarbonyl compounds (such as *I* and *II*) in the presence of protic solvents (water or methanol) which can add to the carbonyl group[6]. Structures of compounds *X* and *XI* followed from their elemental analysis, IR, ^{1}H NMR and ^{13}C NMR spectra. However, on the basis of NMR evidence alone it was not possible to establish unequivocally the configuration at C-3 an C-4 as well as a fusion of the acetal and B rings in the cyclized products *X* and *XI*. In ^{13}C NMR spectrum of *X* the chemical shift of C-19 at δ 15.44 suggested trans-fusion of the acetal and B rings, whereas the chemical shift of C-19 in minor product *XI* (δ 20.41) indicated cis-fusion of those rings[7]. Using proton NMR nuclear Overhauser enhancement difference technique (NOEDS), the trans-fusion of the acetal and B rings in the compounds *X* was readily established. Irradiation of H-4 proton of *X*, located at δ 4.91 in ^{1}H NMR spectrum, produced intense enhancement of the H-2α proton located at δ 1.67. This experiment also proved the configurations at C-3 and C-4.

Treatment of the keto diol *VI* with periodic acid in methanol gave a mixture of methoxy acetal *XIIa* (11%) and 3β-acetoxy lactone aldehyde *XIII* (79%). In ^{1}H NMR spectrum of the lactone aldehyde *XIII* the signal due to H-3 appeared as one-proton multiplet at δ 5.15 with half width $W_{1/2}$ = 12 Hz indicated an equatorial position of 3α-hydrogen and cis-fusion of six-membered lactone and A ring[8]. The singlet at δ 9.65 was characteristic for the proton of aldehyde group and its presence was confirmed when the reduction of *XIII* with lithium aluminum tri-tert-butoxyhydride afforded 3β-acetoxyhydroxy lactone *XIV*. 3α-Acetoxy lactone aldehyde *XIII* could arise by a cyclization of the hydroxy acid aldehyde *XV*, which was formed (in the similar way as compound *IX*) by a cleavage of C(6)–C(7) bond in the keto diol *VI* (see Scheme 2).

TABLE I
Effect of solvent on product distribution (in %) in oxidation of keto diols *V* and *VI* with $Pb(OAc)_4$. All reactions were carried out at 25 °C for 3 h with $Pb(OAc)_4$ containing 15% glacial acetic acid

Solvent	*V*			*VI*		
	VII	*X*	*XI*	*XIIa*	*XIIb*	*XVI*
Benzene	10	70	2.3	0	75	6
Dichloromethane	12	69	2.5	0	72	4
Chloroform	10	70	2.0	0	70	5
Methanol	92	0	0	69	5	15


AcO
O
IV
AcO
OH
CO2H
CHO
XV
AcO
OH
OH
O
VI
AcO
O
O
CHO
II
AcO
O
O
CHO
XIII
AcO
O
OCHO
XVIII
AcO
O
OH
OR
H
XIIa, R = CH3
XIIb, R = H
AcO
O
CH2OH
XIV
AcO
O
OH
XX
AcO
O
CO2H
XVI

SCHEME 2

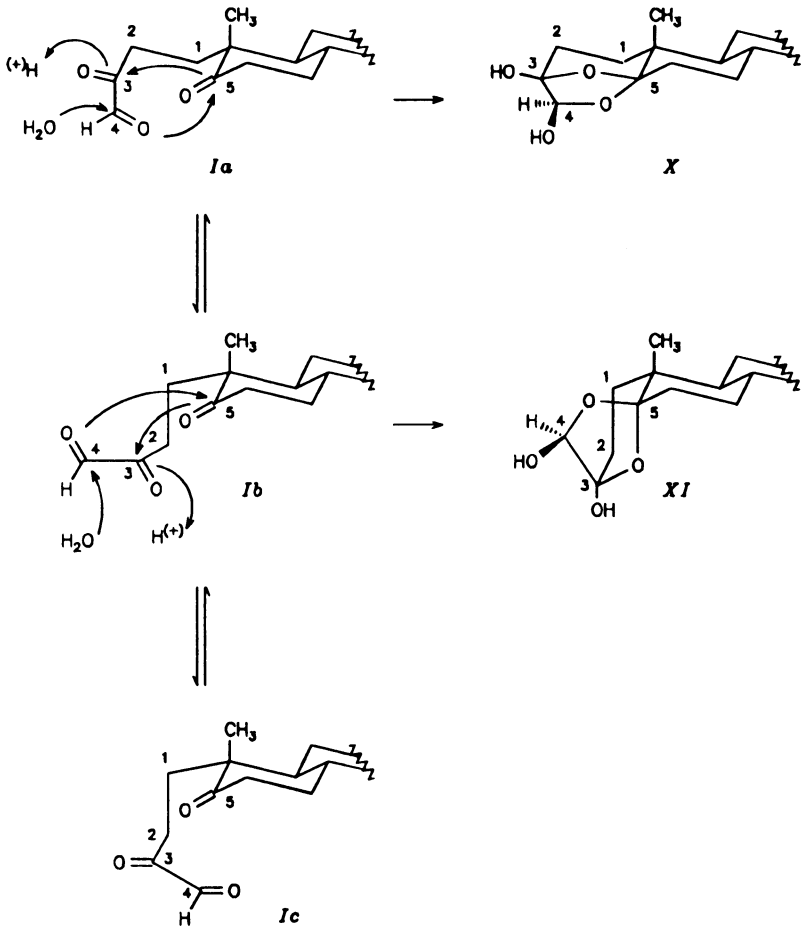
When keto diol *VI* was treated with lead tetraacetate in benzene with glacial acetic acid for 3 h two products were obtained: acetal *XIIb* (75%) and the known keto acid[9] *XVI* (6%). Reactions were also carried out in other solvents to examine solvent effect on the products distribution. The major product obtained in dichloromethane and chloroform was identified as the acetal *XIIb*. The major product obtained with methanol as solvent was formulated as the methoxy acetal *XIIa* (see Table I). The structure of *XIIb* was based upon its IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis. However, on the basis of ^{1}H NMR two possible structure *XIIb* and *XIIc* could be considered. The structure of *XIIc* was ruled out by NOEDS technique. The locations of H-6 (δ 5.01), H-9 (δ 1.10) and H-8 (δ 1.92) were assigned on the basis of ^{1}H–^{13}C 2D-COSY spectrum. The irradiation of the H-6 signal gave strong enhancement of the H-9 signal. Since no enhancement was observed between H-6 and H-8 this NOE interaction is consistent with the structure *XIIb*. The structure of *XIIa* was confirmed by comparison of the ^{1}H NMR spectra *XIIa* and *XIIb*. It should be noted that the structure of the acetal *XIIb* is analogical to that for acetal *XIIa*.

In order to obtain evidence for the formation of keto acids *VII* and *XVI* further oxidations of acetals *X* and *XIIb* were carried out. The progress of the reactions was monitored by TLC analysis to determine the sequence of the reactions and whether other intermediates might be detected. In both cases the TLC analysis showed presence two unidentified products: polar and non-polar. It was clearly observed that non-polar disappeared first followed by the polar product. Attempts of isolation of those intermediates failed due to instability of those compounds on silica gel and only keto acids *VII* and *XVI* were obtained. The IR spectra of the mixtures obtained by the oxidation of *X* and *XIIb* showed the presence of OH group. In the ^{1}H NMR spectra of these mixtures the formate proton appeared at δ 8.06. These results suggested that the oxidation gave lactonoformates *XVII* and *XVIII*, which after hydrolysis afforded keto acids *VII* and *XVI* via lactols *XIX* and *XX*, respectively. It also proved that the formation of keto acids *VII* and *XVI* during the reactions of the respective keto diols *V* and *VI* with lead tetraacetate could arise not directly but via cyclized acetals *X* and *XIIb*.

In order to obtain more information about cyclization reactions isolation of diketo aldehydes *I* and *II* were tried. When keto diols *V* were oxidized with lead tetraacetate without glacial acetic acid the same products as in the previous experiments were obtained. Inspection of the course of the reaction by TLC analysis showed the presence of non-polar product in the reaction mixture. However, attempts of the isolation these compounds failed and only acetals *X* and *XI* were isolated. When keto diol *VI* was treated in a similar manner the non-polar product was isolated in 40% yield. The IR and ^{1}H NMR spectrum suggested that this product could be a lactonoformate *XVIII*. The signal due to 3α-proton appeared as septete at δ 4.70 and the singlet at δ 8.24 coresponded to formate. The compound *XVIII* was very unstable and easily hydrolyzed to the keto acid *XVI*.

In order to explain regio- and stereochemistry of the intramolecular cyclization of diketo aldehydes *I* and *II* molecular mechanics calculations using Alchemy II program[10] have been performed to compute the steric energy of the possible intermediates.

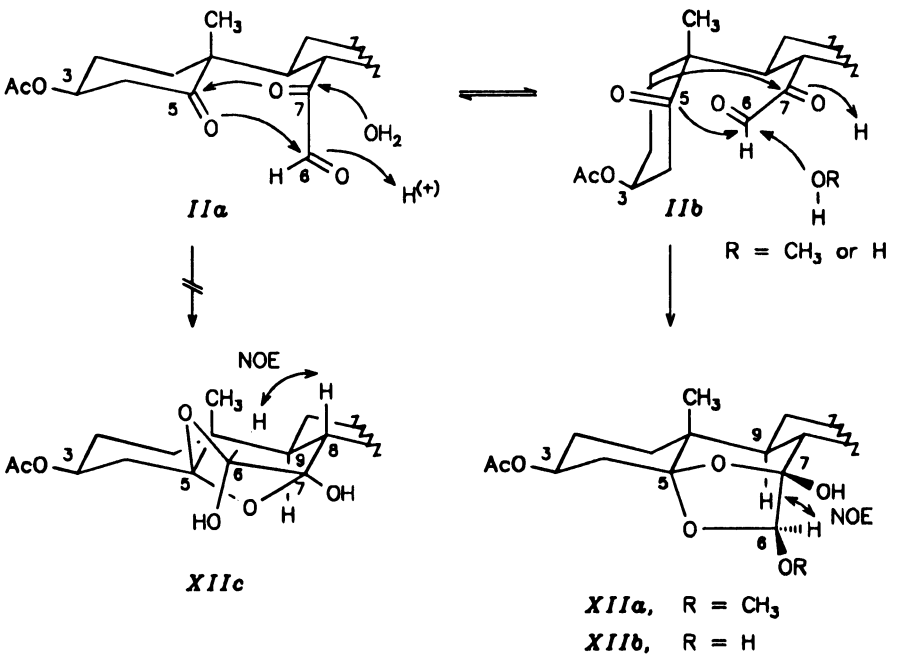
Three conformers *Ia*, *Ib* and *Ic* as possible intermediates for the cyclization of diketo aldehyde *I* could be considered. The conformer *Ia* is related to product *X*, the conformers *Ib* and *Ic* could lead to product *XI*. The calculated conformational energy difference favors the conformer *Ia* which is 8 kJ/mol lower in energy than the



SCHEME 3

conformer *Ib*. This difference is due to non-bonded interaction of the carbonyl group at C-5 with peri hydrogen at C-1 in *Ib*. The conformer *Ic* close to optimum arrangement to cyclization to acetal *XI* did not stabilize and reverted to *Ib* on minimalization. The experimentally obtained yields of acetals (96% of *X* and 4% of *XI*) are in a good correlation with theoretically calculated conformers *Ia* and *Ib* distribution (97% of *Ia* and 3% of *Ib*) (in calculations we consider the fact that the part of acetals *X* and *XI* undergoes further oxidation to keto acid *VII*). Furthermore, the strain energies calculated for the products of the cyclization indicated that product *X* with trans-fused acetal and B rings is more stable. Because that product is a major in the reaction mixture we could conclude that cyclization proceeds preferentially via conformer *Ia* as an intermediate (see Scheme 3).

An examination of molecular models representative cyclization of the diketo aldehyde *II* shown that this compound had two possible conformers *IIa* and *IIb*. The stereoselectivity for the formation of the acetals *XIIa* or *XIIb* required conformer *IIb* as an intermediate, whereas the conformer *IIa* could lead to the alternative structure *XIIc*. Since the formation of *XIIc* was not observed, we could conclude that the reaction proceeds exclusively via conformer *IIb*. This was rationalized by molecular mechanics calculations carried out on the two conformers *IIa* and *IIb* of diketo aldehyde *II*. It was found that the most stable conformation *IIb* is preferred by 33 kJ/mol over the conformation of *IIa* (see Scheme 4).



SCHEME 4

In the presence of methanol the cyclization of *II* to *XIIa* is in competition with the cleavage C(6)–C(7) bond (by lead tetraacetate) which lead to keto acid *XVI* (see Scheme 2).

EXPERIMENTAL

All melting points were determined on a Boetius hot stage microscope and were uncorrected. Thin layer chromatography (TLC) was carried out with DC-alufolien plates (Merck) precoated with 0.25 mm of silica gel GF-254. The plates were eluted with various solvents system and visualized with 50% sulfuric acid after heating at 150 °C. Flash column chromatography was performed as described by Still, Kahn and Mitra[11] on silica gel (Kieselgel 60, 230 – 400 mesh, Merck) packed in benzene, and the samples were put on the column in benzene. The IR spectra were recorded on UR-20 (Jena) spectrometer; wavenumbers in cm^{-1}. ^1H NMR spectra were obtained on Bruker WP-100 SY (100 MHz, FT-mode), ^{13}C NMR on JEOL FX 90 Q (22.5 MHz) spectrometers in deuteriochloroform with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in ppm (δ-scale), half witdh ($W_{1/2}$) in H_2. ^1H NMR NOE difference spectra (NOEDS) were obtained on the Bruker WP 500 (500 MHz) spectrometer. Optical rotations were measured on Perkin–Elmer 241 polarimeter in $CHCl_3$ (*c* 1.0). Analytical samples were dried in vacuo at 133 Pa over phosphorus pentoxide at room temperature.

The starting compounds were prepared according to the following references: *III* (ref.[12]), *IV* (ref.[13]), *V* (ref.[2]), *VI* (ref.[3]).

Oxidation of 4ζ,5ζ-Dihydroxycholestan-3-one (*V*) with Periodic Acid

To a solution of keto diols *V* (0.836 g, 2.0 mmol) in methanol (100 ml) periodic acid (5.01 g, 2.2 mmol, $HIO_4 . H_2O$) in water (40 ml) was added and the resulting mixture was stirred for 3 h at 25 °C under nitrogen. The reaction was terminated with 40% sodium bisulfite solution (30 ml), then extracted thoroughly with dichloromethane, washed with water, 50% bicarbonate solution, with water and dried (Na_2SO_4). The solvent was evaporated to give 0.072 g of the solid neutral fraction. The sodium bicarbonate wash was acidified with 10% hydrochloric acid and extracted with dichloromethane. The extract was washed with water, dried (Na_2SO_4) and solvent was evaporated to give 0.688 g (85%) of keto acid *VII*, which after crystallization with hexane–dichloromethane, was found identical in all respects with that of an authentic sample.

The neutral fraction was purified by flash chromatography on silica gel (10 g). Elution with 20% ethyl acetate in hexane afforded 0.067 g (10%) of lactone aldehyde *VIII*: m.p. 129 – 133 °C, $[\alpha]_D^{24}$ +11.5° (literature[6] gives m.p. 131 °C, $[\alpha]_D^{21}$ +11.2°).

Oxidation of 4ζ,5ζ-Dihydroxycholestan-3-one (*V*) with Lead Tetraacetate

To a solution of keto diols *V* (0.418 g, 1.0 mmol) in dry benzene (15 ml) lead tetraacetate (0.500 g, 1.12 mmol, 80% moistened with glacial acetic acid) was added. The mixture was stirred 3 h at 25 °C under nitrogen. The reaction was terminated with 40% sodium bicarbonate solution (10 ml), then extracted thoroughly with dichloromethane. The extract was washed with water, 50% bicarbonate solution, again with water and dried (Na_2SO_4). Dichloromethane was evaporated to give 0.324 g of solid neutral fraction. The sodium bicarbonate wash was acidified with 10% hydrochloric acid and extracted with dichloromethane. The extract was washed with water, dried (Na_2SO_4) and solvent was evaporated to give 44.5 mg (10%) of keto acid *VII*. The product, after crystallization with hexane–dichloromethane was found identical in all respects with that described in the previous experiment.

The neutral fraction was chromatographed on silica gel (15 g) and the elution with 10% ethyl acetate in benzene gave 10 mg (2.3%) of acetal *XI* and 304 mg (70%) of acetal *X*. The samples of acetals *X* and *XI* were recrystallized twice from hexane.

3β,5-*Epoxy-A-homo-4a-oxa-5β-cholestan-3α,4β-diol* (X): M.p. 165 – 167 °C, $[\alpha]_D^{24}$ +5.1°. IR spectrum (KBr): 3 390 (OH); 1 140 (C–O). ^{1}H NMR spectrum: 0.65 (s, 3 H, 3 × H-18); 1.04 (s, 3 H, 3 × H-19); 4.25 (m, 1 H, OH, disappears on the addition of D_2O); 4.96 (s, 1 H, H-4). ^{13}C NMR spectrum: 111.20 (C-5); 102.62 (C-3), 92.6 (C-4); 15.44 (C-19). For $C_{27}H_{46}O_4$ (434.6) calculated: 74.61% C, 10.67% H; found: 74.59% C, 10.72% H.

3α,5-*Epoxy-A-homo-4a-oxa-5α-cholestan-3β,4α-diol* (XI). M.p. 142 – 144 °C, $[\alpha]_D^{24}$ +2.9°. IR spectrum (KBr): 3 350 (OH); 1 135 (C–O). ^{1}H NMR spectrum: 0.72 (s, 3 H, 3 × H-18); 1.1 (s, 3 H, 3 × H-19); 4.15 (m, 1 H, OH, disappears on the addition of D_2O); 5.05 (s, 1 H, H-4). ^{13}C NMR spectrum: 112.05 (C-5); 101.75 (C-3); 93.37 (C-4); 20.42 (C-19). For $C_{27}H_{46}O_4$ (434.6) calculated: 74.61% C, 10.67% H; found: 74.81% C, 10.72% H.

The Attempt of Synthesis of 4,5-Secocholestan-3,5-dione-4-al (*I*)

To a solution of keto diols *V* (0.839 g, 2.0 mmol) in dry benzene (30 ml) lead tetraacetate (0.879 g, 2.2 mmol, dried over sodium hydroxide for 3 h). The mixture was stirred at 25 °C under nitrogen and the progress of the reaction was monitored by TLC analysis. After 0.5 h the TLC (benzene–ethyl acetate 8 : 2) indicated the presence of the starrting material R_F 0.25 and four products: acetals *X* and *XI* (R_F 0.35 and 0.36, respectively), keto acid *VII* (R_F 0.16) and non-polar product (R_F 0.62). The products were extracted with dichloromethane. The extract was washed with water and dried (Na_2SO_4). The solvent was evaporated in vacuum at 25 °C. The ^{1}H NMR spectrum in $CDCl_3$ of the crude reaction mixture showed singlet at δ 8.20 which disappeared after 10 min. Purification of the residue by chromatography on Florisil with 20% pentane in ether as eluent afforded mixtures of acetals *X* and *XI* (0.425 g) and 0.105 g of the starting material. Elution with ether gave keto acid *VI*.

Oxidation of 3β-Acetoxy-5α,6α-dihydroxycholestan-7-one (*VI*) with Periodic Acid

To a solution of keto diol *VI* (4.767 g, 10 mmol) in methanol (100 ml) a solution of periodic acid (2.51 g, 11 mmol, $HIO_4 . 2 H_2O$) in water (30 ml) was added. The progress of the reaction was monitored by TLC. After 20 h the mixture was extracted with ether (3 × 150 ml). The combined organic layers were washed with saturated sodium bicarbonate solution in order to remove keto acid *XVI* and were dried (Na_2SO_4). Evaporation of the solvent and purification of the residue by flash chromatography on 50 g of silica gel with 300 ml portion of 20% ethyl acetate in hexane as eluant afforded, in order of elution, 3.75 g (79%) of lactone aldehyde *XIII* and 0.56 g (11%) of methoxy acetal *XIIa*. The analytical sample of *XIII* was obtained by two recrystallization from hexane, m.p. 158 – 160 °C, $[\alpha]_D^{25}$ +2.7°. IR spectrum (KBr): 1 720, 1 735, 1 740. ^{1}H NMR spectrum: 0.69 (s, 3 H, 3 × H-18); 1.22 (s, 3 H, 3 × H-19); 2.02 (s, 3 H, CH_3COO); 5.15 (m, 1 H, $W_{1/2}$ = 12, H-3α); 9.65 (s, 1 H, CHO). For $C_{29}H_{46}O_5$ (474.7) calculated: 73.38% C, 9.77% H; found: 73.40% C, 9.80% H.

The methoxy acetal *XIIa* was obtained as a foam, $[\alpha]_D^{23}$ +5.0°. IR spectrum ($CHCl_3$): 3 420 (OH); 1 735 (C=O); 1 010 (C–O). ^{1}H NMR spectrum: 0.71 (s, 3 H, 3 × H-18); 1.00 (s, 3 H, 3 × H-19); 2.04 (s, 3 H, CH_3COO); 3.48 (s, 3 H CH_3O); 3.90 (s, 1 H, OH), disappears on the addition of D_2O); 4.60 (s, 1 H, H-6); 4.94 (m, 1 H, $W_{1/2}$ = 22.5, H-3α). ^{13}C NMR spectrum: 170.07 (carbonyl of acetate); 109.66 (C-5); 104.89 (C-7); 96.16 (C-6); 70.65 (C-3); 54.78 (CH_3O). For $C_{30}H_{50}O_6$ (506.7) calculated: 71.11% C, 9.95% H; found: 71.19% C, 10.18 %H.

The sodium bicarbonate layer (see above) was acidified with 10% hydrochloric acid and extracted with ether (3 × 150 ml). The combined organic extracts were washed with water and dried (Na_2SO_4). Evapo-

ration of the solvents gave 0.071 g (1.5%) of keto acid *XVI*, which after crystallization with hexane–dichloromethane was identical in all respects with that of an authentic sample.

3β-Acetoxy-5β-hydroxymethyl-6-oxacholestan-7-one (*XIV*)

A solution of lactone aldehyde *XIII* (2.388 g, 5.0 mmol) and lithium aluminum tri-tert-butoxyhydrode (3.81 g, 15 mmol) in tetrahydrofuran (40 ml) was stirred under reflux under nitrogen. After 20 h the mixture was cooled (ice bath) and 10 ml of 10% hydrochloric acid was added. The combined extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent afforded crude hydroxy lactone *XIV* (2.204 g, 92.5%), m.p. 192 – 193 °C. The analytical sample was obtained by two crystallization from hexane–dichloromethane, m.p. 198 – 199 °C, $[\alpha]_D^{24}$ +10.2°. IR spectrum (KBr): 3 385 (OH); 1 740 (C=O); 1 735 (C=O). ^{1}H NMR spectrum: 0.67 (s, 3 H, 3 × H-18); 0.71 (s, 3 H, 3 × H-19); 3.80 (s, 2 H, CH_2OH); 6.01 (m, 1 H, $W_{1/2}$ = 6, H-3α). For $C_{29}H_{48}O_5$ (476.7) calculated: 73.07% C, 10.15% H; found 73.10% C, 10.17% H.

Oxidation of 3β-Acetoxy-5α,6α-dihydroxycholestan-7-one (*VI*) with Lead Tetraacetate

A solution of keto diol *VI* (4.767 g, 10 mmol) and lead tetraacetate (5.856 g, 11 mmol, moistened with glacial acetic acid) in dry benzene (10 ml) was stirred under nitrogen for 3 h. The work-up as in the previous experiment gave 3.920 g of neutral material and 0.285 g of acidic material. Neutral material was purified by flash column chromatography on silica gel (30 g). Elution with 20% ethyl acetate in hexane afforded 3.695 g (75%) of crystalline acetal *XIIb*, which upon crystallization with ether–hexane gave an analytical sample, m.p. 168 – 169 °C, $[\alpha]_D^{24}$ +3.9°. IR spectrum (KBr): 3 400 (OH); 1 735 (C=O); 1 010 (C–O). ^{1}H NMR spectrum: 0.71 (s, 3 H, 3 × H-18); 1.00 (s, 3 H, 3 × H-19); 2.07 (s, 3 H, CH_3COO); 2.45 (m, 1 H, $W_{1/2}$ = 15, OH, disappears on the addition of D_2O); 4.91 (m, 1 H, $W_{1/2}$ = 22.5, H-3α, 5.01 (s, 1 H, H-6). ^{13}C NMR spectrum: (170.67 carbonyl of acetate'; 109.50 (C-5); 106.16 (C-7); 90.37 (C-6); 70.98 (C-3); 16.14 (C-19). For $C_{29}H_{48}O_6$ (492.7) calculated: 70.69% C, 9.82% H; found: 70.71% C, 9.91% H.

Crystallization of crude acidic material with hexane–dichloromethane gave 0.275 g (6%) of keto acid *XVI* identical with that obtained in the previous experiment.

3β-Acetoxy-5α-formyloxy-6-oxacholestan-7-one (*XVIII*)

A solution of lead tetraacetate (0.467 g, 1 mmol, dried over sodium hydroxide for 3 h in vacuo at 650 Pa) in dry benzene (10 ml) was stirred at 25 °C under nitrogen for 45 min. The reaction mixture was cooled at 5 °C and 40% sodium bicarbonate (5 ml) was added. The product was extracted with dichloromethane. The extract was washed with water and dried (Na_2SO_4). Evaporation of the solvent amd purification of the residue by chromatography on Florisil with 10% pentane in ether as eluant afforded 0.192 g (40%) lactone formate *XVIII* as colorless oil homogeneous by TLC analysis. IR spectrum ($CHCl_3$): 2 9000 (C–H); 1 730 (C=O of formate); 1 750 (C=O of lactone and acetate); 1 225 (C–O). ^{1}H NMR spectrum: 0.68 (s, 3 H, 3 × H-18); 1.15 (s, 3 H, 3 × H-19); 1.98 (s, 3 H, CH_3COO); 4.70 (m, 3 H, $W_{1/2}$ = 30, H-3α); 8.24 (s, 1 H, OCHO).

The lactone formate *XVIII* was found to hydrolyze to the keto acid *XVI* with almost quantitative yield during chromatography on silica gel.

Examination of the Oxidation Reaction of Acetals *X* and *XIIb* with Lead Tetraacetate

A) Oxidation of acetal X. A solution of acetal *X* (0.485 g, 1 mmol) in dry benzene (25 ml) was stirred at 25 °C with lead tetraacetate (0.487 g, 1.1 mml, dried over sodium hydroxide for 3 h in vacuo at 650 Pa).

The progress of the reaction was monitored by TLC analysis. After 0.5 h TLC (benzene with 20% ethyl acetate) indicated the presence of starting material (R_F 0.35) and two products (R_F 0.44 and 0.64, respectively) as well as keto acid *VII* (R_F 0.16). The reaction was terminated by the addition of water (1 ml) and

the products were extracted with ether (3 × 25 ml). After drying (Na_2SO_4) the solvent was evaporated in vacuo at 25 °C. The IR spectrum of the crude reaction mixture showed the presence of the hydroxyl group (3 350 cm^{-1}). The ^1H NMR spectrum showed singlet at δ 8.05 ppm which disappeared after 15 min. These two products were found to rearrange to the keto acid *VII* as indicated TLC analysis. Flash column chromatography on 6 g of silica gel with 20% ethyl acetate in benzene as eluant gave 0.150 g of keto acid *VII* and 0.210 g of the starting material.

B) *Oxidation of acetal* XIIb. A solution of acetal *XIIb* (0.492 g, 1.0 mmol) in dry benzene (25 ml) was stirred at 25 °C with lead tetraacetate (0.487 g, 1.1 mmol). The progress of the reaction was monitored by TLC analysis using benzene with 20% ethyl acetate as eluant. After 0.5 h it showed four components in the reaction mixture: starting material (R_F 0.33), keto acid *XVI* (R_F 0.16) and two products (R_F 0.44 and 0.62, respectively). The products were isolated in the manner previously described for the oxidation of acetal *X*. The ^1H NMR spectrum of the crude reaction mixture showed a singlet at δ 8.09 ppm. Two products were found to rearrange to keto acid *XVI* (0.215 g) and the starting material *XIIb* (0.223 g) were isolated by flash column chromatography using 30% ethyl acetate in benzene.

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