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MECHANISM AND STRUCTURAL EFFECTS IN BROMOLACTONIZATION†

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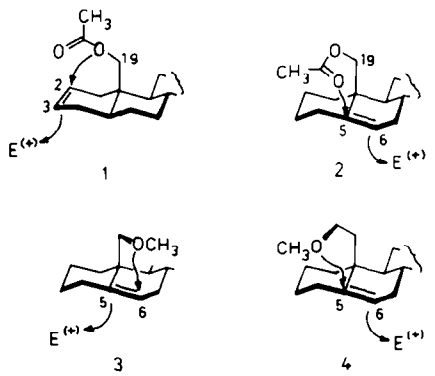
Abstract—Hypobromous acid addition to unsaturated steroid C-19 acids **5** and **7** involves intramolecular participation of the carboxyl group and affords bromolactones **21** and **25**. The C-19 ester group in methyl esters **6** and **8** shows no participation and the addition proceeds with external nucleophile attack yielding bromohydrins **22** and **26**. By contrast, homologous C-19a methyl esters **10**, **12**, as well as acids **9**, **11**, afford bromolactones. ^{18}O-Labeling proved that the bromolactonization in **10** and **12** took place with participation by the carbonyl oxygen. The different reactivity of the ester groups in **6**, **8** and **10**, **12** is due to stereoelectronic factors. Mechanistic aspects of bromolactonization in acids and esters are discussed.

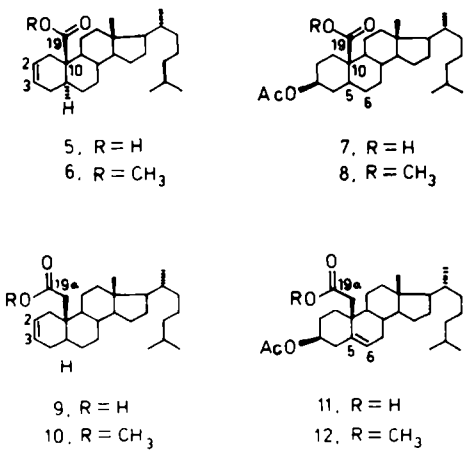
Neighboring group participation[1-3] is an established tool for reactivity control. It has been used for stereoselective introduction of functional groups,[4-6] selective protection[6,7] and double bond transposition.[8,9] Other tactics have employed participating groups for conformational changes in the substrate molecule in order to control the direction and selectivity of subsequent synthetic steps.[4,10-12] In previous papers[13-18] we have investigated intramolecular participation of mono and bidentate oxygen groups at C-19 or C-19a in electrophilic additions to double bonds located in the A or B ring of the steroid skeleton (Scheme 1). If the participating group is an acetate, there are, *a priori*, two different O atoms capable of interaction with the electron-deficient center. For instance, hypobromous acid addition to 19-acetoxy-5α-cholest-2-ene **1** proceeds with participation of the ether O (5(O)^n process; for notation *cf* Ref. 14), while the competing 7(O)$^{\pi,n}$ reaction involving the carbonyl O is disfavored.[18] On the other hand, a transposition of the double bond as in 19-acetoxycholest-5-ene **2** alters the mechanism in that the participation by the carbonyl O (6(O)$^{\pi,n}$ process) is favored over the 5(O)^n reaction.[18] In these cases the reaction course depends on both the participation propensity of the O (such as the electron density, polarizability and stereoelectronic factors) and the ring size in the intermediates (5-, 6- or 7-membered rings). In order to eliminate the latter (i.e. entropy factors), in the present paper we have examined bromolactonization in 10β and 19-carboxyl cholestenes **5**, **7**, **9**, **11** and in the corresponding methylesters **6**, **8**, **10** and **12** (Scheme 2). Bromolactonization,[19,20] together with iodo[21,22] and selenolactonization,[23] are important synthetic reactions, so a detailed information on the mechanism was of interest.



Scheme 1.

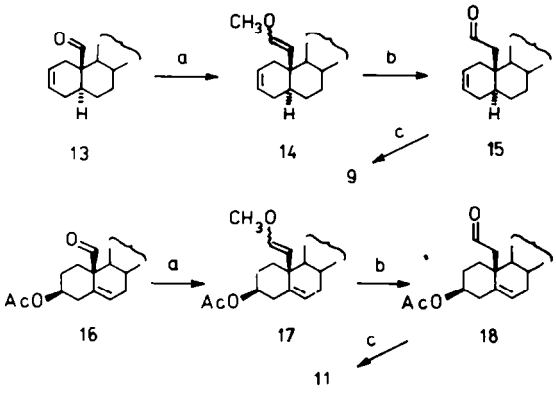
Reactions and products

The preparation of acids **5** and **7** was described earlier.[16] The corresponding methyl esters **6** and **8** were

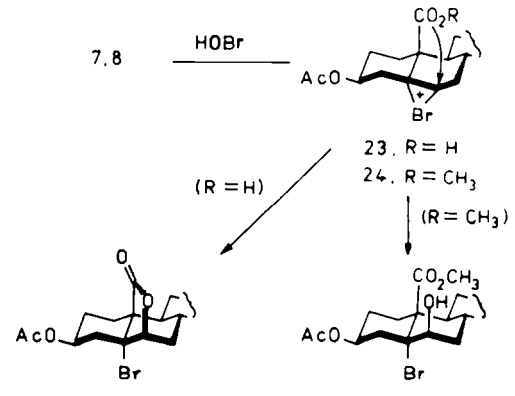


Scheme 2.

†Dedicated to the memory of Professor František Šorm. Part 290 in the Series on Steroids.



Scheme 3.



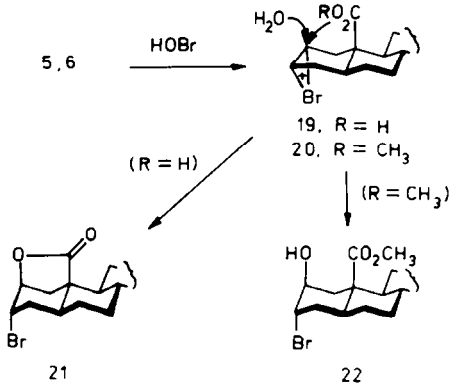
Scheme 5.

obtained by esterification with diazomethane. The homologous acids **9** and **11** were prepared as follows (Scheme 3). 19-Oxoderivatives **13** and **16**[24] were coupled with triphenylmethoxymethylenephosphorane[25] to give 19-methoxy methylidene cholestenes **14** and **17**, respectively. It is noteworthy that the ylide had to be generated with n-BuLi[26] to be sufficiently reactive towards the aldehydes **13** and **16**, while Na-salt of dimethyl sulfoxide failed.[27] On hydrolysis **14** and **17** were converted to aldehydes **15** and **18**, respectively, which were oxidized to acids **9** and **11**. Methylation of the latter compounds afforded the methyl esters **10** and **12**.

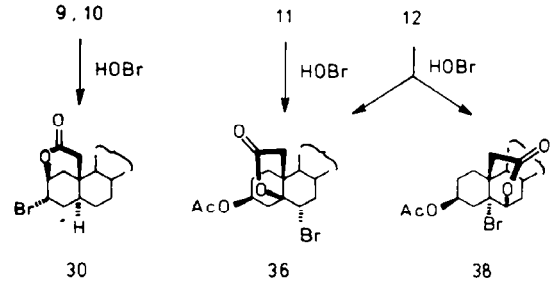
The model compounds **5–12** were treated with hypobromous acid prepared *in situ*. As postulated earlier,[16] in **5** the addition proceeds via a 2α, 3α-bromonium ion (**19**) which is then cleaved by an O of the carboxylic group to give bromolactone **21** (Scheme 4). The acid **7** reacted similarly, yielding the lactone[16] **25** (Scheme 5). By contrast, the 19-ester group in **6** and **8** showed no participation. The intermediary α-bromonium ions (**20**, **24**; Schemes 4 and 5) were cleaved externally by water, giving rise to diaxial bromohydrins **22** and **26**, respectively. Structures for the latter products followed from the spectral data. The NMR spectrum of **22** displayed two one-proton multiplets at 4.16 and 4.37 ppm which corresponded to equatorial CH–O and CH–Br methines. The signal of the ester Me group appeared as a singlet at 3.76 ppm. The IR spectrum of **22** showed an ester group (ν(C=O) = 1728 cm^{-1}) and a H-bridged OH (ν(OH) = 3525 cm^{-1}). Similarly, the IR spectrum of **26** confirmed the presence of an intramolecular H-bond (ν(OH) = 3447 cm^{-1}) and the NMR spectrum exhibited a CH–O multiplet at 3.72 ppm, the width of which (W = 11 Hz) confirmed the axial orientation of 6β-OH. *trans*-Annulation of AB rings is consistent with the width of the 3α-H multiplet (W = 30 Hz).

The homologous acids **9** and **11** reacted with hypobromous acid with formation of bromolactones **30** and **36**, respectively (Scheme 6). While the former lactone arose as a single product, the latter was accompanied by minor amount of unidentified by-products. The structures of **30** and **36** were inferred from the spectra. The mass spectrum of **30** showed abundant molecular ions $C_{28}H_{45}BrO_2$ and fragments $(M-CH_2COOH)^+$, $(M-Br)^+$, $(M-C_{11}H_{23})^+$ and $(M-Br-C_{11}H_{22})^+$. The IR spectrum displayed a δ-lactone band (ν(C=O) = 1742 cm^{-1}). The NMR spectrum showed two methine multiplets (CH–Br, δ = 4.42 ppm and CH–O, δ = 4.72 ppm), the widths of which (12 and 15 Hz, respectively) gave evidence for diaxial arrangement of the substituents at C-2 and C-3. The mass spectrum of **35** contained low intensity molecular ions *m/z* 550,552 and fragments $(M-AcOH)^+$, $(M-Br)^+$, $(M-Br-CH_2CO)^+$ and $(M-AcOH-Br)^+$. The presence of a γ-lactone ring in **35** followed from the IR spectrum (ν(C=O) = 1775 cm^{-1}) which was consistent with a *cis*-junction of AB rings, as also deduced from the NMR spectrum (3α–H: δ = 5.12 ppm, W = 15 Hz, 6β–H: δ = 4.20 dd, J = 12 and 5 Hz).

The methyl esters **10** and **12** behaved similarly as the corresponding acids **9** and **11**, giving bromolactones **30** (a single product from **10**) and **36** (67%) and **38** (21%) from **12**. The structure for **38** was confirmed by spectral data.



Scheme 4.



Scheme 6.

The IR spectrum showed the presence of a δ-lactone (ν(C=O) = 1730 cm^{-1}, overlapped with the acetate CO band). The NMR spectrum was consistent with *trans* AB junction (3α-H, δ = 5.35 ppm, W = 30 Hz) and 6β-oxygen bridge (6α-H, δ = 4.52 m).

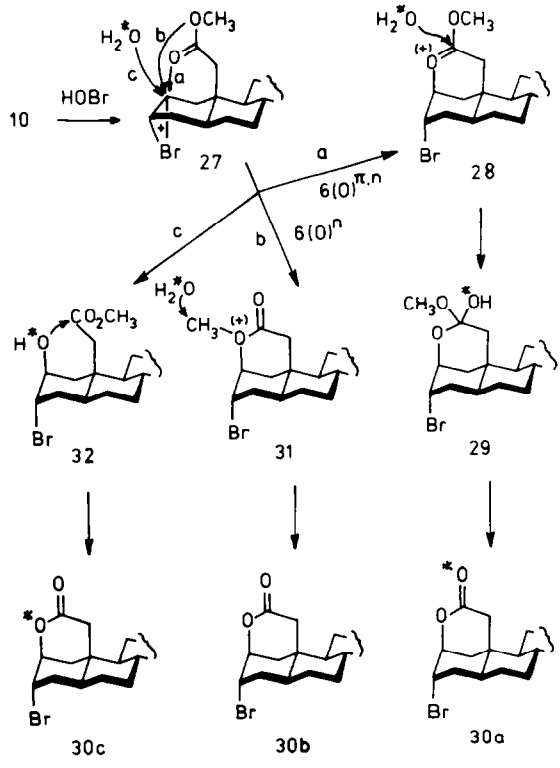
Mechanism

The bidentate character of both the carboxyl and ester groups raised a question as to the relative reactivity of the CO *vs* OH or ether O atoms in bromolactonization. Since the O atoms of the carboxyl group cannot be distinguished due to rapid proton migration,[31] we have examined the behavior of the methyl esters **10** and **12**. The bromolactonization in **10** can be visualized as proceeding via three different mechanisms (Scheme 7):

(a) The originally formed 2α, 3α-bromonium ion **27** is cleaved by the carbonyl O in a 6(O)$^{\pi,n}$ process (Path a). The transient oxonium ion **28** is then quenched externally by water to give ortho-ester **29** which eventually eliminates methanol yielding the bromolactone **30a**.

(b) Ion **27** is cleaved by the ether O (6(O)^{n} process; Path b) and the transient oxonium ion **31** undergoes nucleophilic attack by water at the Me group to produce lactone **30b**. A similar (O)^{n} mechanism was found to be effective in participation of alkoxy groups[13-16] (*cf* also Scheme 1).

(c) The addition of hypobromous acid leads to bromohydrin **32** (Path c) which then undergoes lactonization to **30c**.



Scheme 7.

The actual role of these potential routes was elucidated by a labeling experiment. The ester **10** was treated with hypobromous acid enriched in ^{18}O isotope (27% $H_2{}^{18}O$). The ^{18}O content in the purified bromolactone was determined from the mass spectra which showed complete incorporation of the label (Table 1). This definitely excluded route (b) for which complete absence of label would have been expected instead. To distinguish between routes (a) and (c) it was necessary to localize the label within the lactone moiety (Scheme 7). The IR spectrum of the labeled lactone **30** showed, beside the original ν(C=O) band at 1744 cm^{-1}, a new band (1711 cm^{-1}) corresponding to ν(C=^{18}O). The ratio of integral intensities A(C=^{16}O)/A(C=^{18}O) was found to be 3-4:1 which is close to that expected from the total label content (2.7:1 for 27% ^{18}O). A conclusive evidence for ^{18}O distribution in **30** was obtained from ^{13}C NMR spectra. The labeled lactone **30** displayed two ^{13}C signals at δ = 171.373 and 171.319, corresponding to ^{16}O and ^{18}O carbonyl groups, respectively. The upfield shift (Δδ = 0.054 ppm) due to the ^{18}O-isotope effect is slightly higher than that observed for other esters.[32] On the other hand, the signal of $C_{(2)}$ (δ = 77.19) was not accompanied by any isotope satellite. From the signal-to-noise ratio (S/N = 40 for the $C_{(2)}$ line) it followed that the content of $C_{(2)}$-^{18}O species did not exceed 2%. With regard to the total ^{18}O content in **30** it means that more than 92% of the label entered the CO group. Blank experiments, carried out under the same conditions as the bromolactonization,

Table 1. ^{18}O Content and distribution in **30**, **36** and **38**

Compound	Label Content (%)	Location
30 [a]	27.0 ± 0.4 [b]	C-19a
30 [c]	<0.2	
36 [a]	26.7 ± 1.4 [d]	C-19a
36 [c]	8.0 ± 1.6	CH_3CO_2 (7.2 %)[b]; C-19a (0.8 %)[e]
38 [a]	25.5 ± 1.7 [d]	C-19a

[a]Labeling experiment; [b]determined from the ^{18}O abundance in M^+ and $(M-Br)^+$; [c]blank experiment; [d]from M^+, $(M-Br)^+$, $(M-CH_3CO_2H)^+$, $(M-CH_3CO_2H-CH_3)^+$ and $(M-Br-CH_3CO_2H)^+$; [e]from $(M-CH_3CO_2H)^+$.

proved that O exchange between $H_2{}^{18}O$ and the lactone CO in **30** was negligible. Hence it follows that $6(O)^{\pi,n}$ participation (Path a) is a predominating mechanism in bromolactonization of **10**, while the competing routes (b) and (c) are either ineffective or absent.

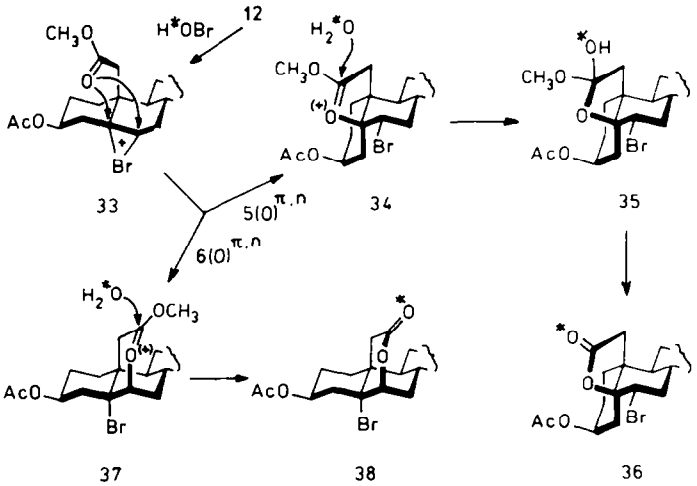
Similar results were obtained with ester **12**. The transient bromonium ion **33** (Scheme 8) is cleaved by the carbonyl O which attacks both C-5 and C-6. The $5(O)^{\pi,n}$ participation at C-5 which contradicts the Fürst–Plattner rule is the main reaction path proceeding via oxonium ion **34** and ortho ester **35** to give 5-membered lactone **36**. The evidence for this mechanism followed from the content (26.7% ^{18}O, Table 1) and location of label in **36**. The IR spectrum of the unlabeled lactone **36** contained two $\nu(C{=}O)$ bands corresponding to the acetate (1730 cm^{-1}) and δ-lactone (1775 cm^{-1}). In the labeled lactone **36** the relative intensity of both bands was changed by contribution of 20–30% of $\nu(C{=}{}^{18}O)$ lactone band at 1730 cm^{-1} in agreement with the expected isotope effect. The ^{13}C NMR spectrum of the labeled lactone **36** confirmed that, beside the expected incorporation into the lactone CO group (δ = 170.241 and 170.187 for $C{=}{}^{16}O$ and $C{=}{}^{18}O$, respectively), the label did not enter the $C_{(5)}$–O ether group. Based on the S/N ratio, the ^{18}O content in the latter group does not exceed 5% which proves again that the majority of the label was incorporated into the lactone CO. The minor product **38** was found to contain 25.5% ^{18}O (Table 1) located mainly in the lactone CO. This was evident from the IR spectrum of the labeled lactone **38** in which a new $\nu(C{=}{}^{18}O)$ band appeared at 1712 cm^{-1} in addition to the overlapping acetate and δ-^{16}O-lactone bands at 1742 cm^{-1}. In line with this finding, the ^{13}C NMR spectrum confirmed that **38** did not contain ^{18}O label in the $C_{(6)}$–O group (a single signal at δ = 81.62) in an amount of exceeding the noise level (10%). The content of ^{18}O in the lactone CO could not be proved directly through the ^{13}C NMR spectrum, due to close spacing of the lactone and acetate lines (δ = 170.24 and 170.19, respectively). Blank experiments again confirmed that exchange between $H_2{}^{18}O$ and the lactone CO in **38** did not occur, though some incorporation into the acetate group was detected by mass spectrometry (Table 1). The above results gave conclusive evidence for the dominant role of the ester CO participation, i.e. $(O)^{\pi,n}$ process, in formation of both **36** and **38**.

The preferential reactivity of the CO group in **10**, **12** can be in part ascribed to a greater polarizability of the ester π-orbitals when compared with the p_z orbital of the ether O. This π-polarization of the ester group that increases the net charge at the carbonyl O[32] favors the interaction of the latter with the carbon electron-deficient center. It should be noted that stereoelectronic factors such as the distance and angle of approach[18,34] of O orbitals are favorable for both types of participation due to relative flexibility of the 6-membered ring in the intermediates **28** and **31**. On the other hand, the $(O)^n$ participation by the ether O may be slowed down by S_N2 removal of the ester Me group in the oxonium intermediate **31**. This effect may also account for the different behavior of 10β acids **5**, **7** and methyl esters **6** and **8** (*vide supra*). In **5–8** the participation at C-2 or C-6 by the C-19 ester π-orbitals is impaired by unfavorable geometry of the system resulting in a large distance and angle of approach. Similar conclusions have been recently arrived at with 10β-vinyl derivatives.[35] In the acids **5** and **7** the intramolecular participation by the OH p_z orbital competes well with the external nucleophile attack due to rapid quenching of the intermediate oxonium ions by proton abstraction. On the other hand, the formation of lactones from esters **6** and **8** requires that the ester Me group be removed by S_N2 attack of the external nucleophile.

From the above results it follows that the carboxyl group is capable of participation via 5- or 6-membered ring, while the participating propensity of the ester group is more sensitive to structural variations. This is in general agreement with the slower rate of halolactonization in unsaturated esters, reported earlier.[5,19,28–30]

EXPERIMENTAL

M.ps were determined on a Kofler block. Analytical samples were dried at 50°/26 Pa (0.2 Torr). Optical rotations were measured in $CHCl_3$ with an error of ±3°. The IR spectra were recorded on a Zeiss UR 20 spectrometer in CCl_4 unless otherwise stated. The ^1H NMR spectra were recorded on a Varian XL-200 apparatus (FT-mode) and on a Tesla BS 476 instrument



Scheme 8.

(60 MHz) in $CDCl_3$ at 30° with TMS as internal reference. Chemical shifts were given in ppm. Apparent coupling constants were obtained from the first order analysis. The ^{13}C NMR spectra were measured on a Varian XL-200 instrument (50.309 MHz, FT-mode, pulse width 8 μs, square wave broad-band decoupling) in $CDCl_3$ and with TMS as an internal reference. The degree of carbon protonation in **36** was obtained from single frequency off-resonance decoupling. The mass spectra were recorded on a Joel JMS D-100 spectrometer operating at 14–75 eV. The samples were introduced using a direct inlet at lowest temp. enabling evaporation. The elemental compositions of ions were determined by accurate mass measurements. The identity of the samples prepared by different routes was checked by mixture m.p. determination, by TLC and by IR and ^1H NMR spectra. Usual work up of an ethereal soln means washing the soln with 5% HClaq, water, a 5% $KHCO_3$ aq, water, drying with $NaSO_4$ and evaporation of the solvent *in vacuo*.

3β-Acetoxy-cholest-5-en-19-oic acid methyl ester (**8**). The acid **7** (250 mg) was dissolved in ether (5 ml) and treated with an ethereal soln of diazomethane at room tempe for 5 min. The excess reagent was quenched with AcOH, the mixture was diluted with ether, washed successively with water, 5% $KHCO_3$aq, water, dried with Na_2SO_4 and the solvent was evaporated. The residue was dissolved in a mixture of light petroleum and benzene (4:1) and filtered through a column of aluminum oxide. The eluate was evaporated and the residue was crystallized from aqueous acetone to yield **8** (165 mg), m.p. 151–152°. ^1H NMR spectrum: 0.62 (3H, s, 18-H), 2.00 (3H, s, CH_3CO_2), 3.72 (3H, s, CO_2CH_3), 4.63 (1H, m, W = 30 Hz, 3α-H), 5.72 (1H, m, W = 13 Hz, 6-H). (Found: C, 76.01; H, 10.26. $C_{30}H_{48}O_4$ requires: C, 76.23; H, 10.24%.)

5α-Cholest-2-ene-19-carboxylic acid (**9**). The alcohol **15** (350 mg) was dissolved in acetone (8 ml) and treated with Jones' reagent at room tempe. for 30 min. The excess reagent was decomposed with MeOH, the mixture was treated with ether and water, the ethereal layer was washed several times with water, dried with Na_2SO_4 and evaporated. The residue was dissolved in a mixture of benzene and light petroleum (1:4) and filtered through a column of aluminium oxide. The filtrate was evaporated to furnish **9** (210 mg), $[\alpha]_D^2 + 61°$ (*c* 1.7). IR spectrum: 1652, 1700, 3000 cm^{-1}. (Found: C, 80.85; H, 11.32. $C_{28}H_{46}O_2$ requires: C, 81.10; H, 11.18%.)

19-Carboxymethyl-5α-cholest-2-ene (**10**). The acid **9** (220 mg) in ether (10 ml) was treated with an ethereal soln of diazomethane and then worked up as given for **8** to afford oily **10** (195 mg), $[\alpha]_D^{20} + 78°$ (*c* 2.3). ^1H NMR spectrum: 0.67 (3H, s, 18-H), 2.28 (2H, brd s, 19-H), 3.58 (3H, s, CO_2CH_3), 5.63 (2H, m, W = 10 Hz, 2-H and 3-H). (Found: C, 81.07; H, 11.10. $C_{29}H_{48}O_2$ requires: C, 81.25; H, 11.29%.)

3β-Acetoxy-cholest-5-ene-10-carboxylic acid (**11**). The aldehyde **18** (500 mg) was dissolved in acetone (15 ml) and treated with Jones' reagent at room tempe. for 15 min. The excess reagent was decomposed with MeOH and the mixture was worked up as given for **9**. The crude product was crystallized from aqueous acetone to yield **11** (280 mg), m.p. 164–165°, $[\alpha]_D^{20} - 50°$ (*c* 1.7). IR spectrum ($CHCl_3$): 1235, 1704, 1726, 3000 cm^{-1}. (Found: C, 76.09; H, 10.30. $C_{30}H_{48}O_4$ requires: C, 76.23; H, 10.24%.)

19-Carboxymethyl-cholest-5-en-3β-ol 3-acetate (**12**). The acid **11** (300 mg) in ether (15 ml) was treated with an ethereal soln of diazomethane and then worked up as for **8** to give oily **12** (275 mg), $[\alpha]_D^{20} - 48°$ (*c* 3.2). ^1H NMR spectrum: 0.68 (3H, s, 18-H), 2.00 (3H, s, CH_3CO_2), 3.58 (3H, s, CO_2CH_3), 4.67 (1H, m, W = 30 Hz, 3α-H), 5.55 (1H, m, W = 15 Hz, 6-H). IR spectrum: 1242, 1735 cm^{-1}. (Found: C, 76.38; H, 10.46. $C_{31}H_{50}O_4$ requires: C, 76.50; H, 10.35%.)

5α-Cholest-2-ene-19-carbaldehyde (**15**). A 1.5 M soln of n-BuLi in hexane (1 ml, 1.5 mmol) was added to a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (513 mg, 1.5 mmol) in THF (5 ml) at 0° in the course of 10 min and the mixture was then stirred at room tempe for 15 min. A soln of **13** (500 mg, 1.3 mmol) in THF (5 ml) was then added at 0° in the course of 5 min, the mixture was stirred at room tempe for 5 min and then refluxed for 3 hr. The mixture was then cooled, decomposed by pouring into NH_4Cl, the product was extracted with ether, the etheral soln was successively washed with water, a 5% $KHCO_3$aq, water, dried with Na_2SO_4 and evaporated. The residue was dissolved in a mixture of benzene and light petroluem (1:4) and filtered through a column of aluminium oxide. The filtrate was evaporated to yield the mixture of *E*- and *Z*-isomers of **14**. Its ^1H NMR spectrum contains two signals of Me at δ = 3.43 and δ = 3.50 ppm in *ca* 3:1 ratio. This product was refluxed in a mixture of AcOH (10 ml), water (3 ml) and dioxane (5 ml) for 1 hr, then the volume of the soln was reduced to about one-fifth by evaporation *in vacuo*. The residue was treated with CH_2Cl_2 and water, the organic phase was successively washed with NaClaq, water, a 5% $KHCO_3$aq, water, dried and evaporated. The residue was dissolved in a mixture of benzene and light petroleum (1:5) and filtered through a column of aluminum oxide. The filtrate was evaporated to yield oily **15** (380 mg), $[\alpha]_D^{20} + 65°$ (*c* 2.0). ^1H NMR spectrum: 0.63 (3H, s, 18-H), 5.68 (2H, m, W = 9 Hz, 2-H and 3-H), 9.80 (1H, m, W = 17 Hz, CH=O). IR spectrum: 1655, 1714, 2735 cm^{-1}. (Found: C, 84.15; H, 11.47. $C_{28}H_{46}O$ requires: C, 84.36; H, 11.63%.)

3β-Acetoxy-cholest-5-ene-19-carbaldehyde (**18**). A 1.5 M soln of n-BuLi in hexane (10 ml, 15 mmol) was added to stirred suspension of (methoxymethyl)triphenylphosphonium chloride (5.13 g, 15 mmol) in THF (30 ml) at 0° in the course of 10 min and the mixture was then stirred at room temp for 30 min. A soln of **16** (4.5 g, 10.2 mmol) in THF (20 ml) was then added at 0° in the course of 3 min, the mixture was stirred at room tempe for 5 min and then refluxed while stirring for 3 hr. The mixture was then cooled and worked up as given in the previous experiment to yield a mixture of *E*- and *Z*-isomers of **17**. Its ^1H NMR spectrum contains two OMe singlets at δ = 3.48 and δ = 3.52 ppm in *ca* 3:2 ratio. This product was refluxed in a mixture of AcOH (40 ml) and water (10 ml) for 2 hr, the volume of the soln was reduced to about one fifth by evaporation *in vacuo* and then worked up as given for **15** to yield after crystallization from aqueous acetone **18** (3.1 g), m.p. 81–83°, $[\alpha]_D^{20} - 28°$ (*c* 2.1). ^1H NMR spectrum: 0.62 (3H, s, 18-H), 2.03 (3H, s, $MeCO_2$), 4.70 (1H, m, W = 30 Hz, 3α-H), 5.65 (1H, m, W = 11 Hz, 6-H), 9.77 (1H, m, W = 10 Hz, CH=O). IR spectrum: 1240, 1718, 1732, 2727 cm^{-1}. (Found: C, 78.72; 10.63. $C_{30}H_{48}O_3$ requires: C, 78.90; H, 10.59%.)

Addition of hypobromous acid to compounds **5–12**. The unsaturated compound (0.5 mmol) was dissolved in dioxane (5 ml) and treated with 10% perchloric acid (0.5 ml) and N-bromoacetamide (80 mg, 0.6 mmol) at room tempe for 15 min. The mixture was then diluted with ether and washed successively with water, a 5% $KHCO_3$aq, a 5% Na_2SO_3, water, dried with Na_2SO_4 and the solvent was evaporated. The residue was chromatographed on three preparative silica gel plates (20 × 20 cm) using a mixture of light petroleum, ether and acetone (90:5:5) or (80:10:10) as eluent. Zones containing the desired compound were collected, eluted with ether and evaporated. The yields are given in the text.

Addition of labeled hypobromous acid to **10** *and* **12**. The unsaturated compound (100 mg) was dissolved in dry dioxane (2 ml), water (0.2 ml) containing 27% $H_2{}^{18}O$ was added and the mixture was treated with 70% aqueous perchloric acid (*c.* 0.01 ml) and N-bromoacetamide (40 mg) at room tempe for 15 min. The mixture was worked up and chromatographed as given in the previous experiment. MS data of the products are given in the Table 1.

2β-Hydroxy-3α-bromo-5α-cholestan-19-oic Acid methyl ester (**22**). M.p. 156–157°, $[\alpha]_D^{20} + 55°$ (*c* 1.9). ^1H NMR spectrum: 0.58 (3H, s, 18-H), 3.76 (3H, s, CO_2Me), 4.16 (1H, m, W = 12 Hz, 2α-H), 4.37 (1H, m, W = 12 Hz, 3β-H). IR spectrum. 1201, 1215, 1698, 1728, 3460, 3525, 3604 cm^{-1}. (Found: C, 65.58; H, 9.37; Br, 15.74. $C_{28}H_{47}BrO_3$ requires: C, 65.74; H, 9.26; Br, 15.62%.)

3β-Acetoxy-5-bromo-6β-hydroxy-5α-cholestan-19-oic acid methyl ester (**26**). M.p. 138–140°, $[\alpha]_D^{20} - 36°$ (*c* 1.6). ^1H NMR spectrum: 0.58 (3H, s, 18-H), 2.00 (3H, s, CH_3CO_2), 3.72 (1H, m, W = 11 Hz, 6α-H), 3.82 (3H, s, $MeCO_2$), 5.42 (1H, m, W = 30 Hz, 3α-H). IR spectrum: 1239, 1736, 3447, 3602 cm^{-1}. (Found: C, 63.47; H, 8.65; Br, 14.19. $C_{30}H_{49}BrO_5$ requires: C, 63.26; H, 8.67; Br, 14.03%.)

3α-Bromo-19-homo-5α-cholestan-19a→2β-olide (**30**). M.p.

148–149°, $[\alpha]_D^{20}$ + 32° (*c* 2.8). ^{1}H NMR spectrum: 0.62 (3H, s, 18-H), 2.55 (2H, brd s, 19-H), 4.42 (1H, m, W = 12 Hz, 3β-H), 4.72 (1H, m, W = 15 Hz, 2α-H). ^{13}C NMR spectrum: 171.37, 77.19, 56.18, 56.12, 50.70, 48.04, 42.12, 39.45, 39.22, 39.14, 36.08, 35.95, 35.68, 34.50, 32.68, 31.37, 31.27, 29.70, 28.07, 27.97, 27.68, 24.10, 23.78, 22.70, 22.53, 20.58, 18.65, 11.81. IR spectrum: 1742 cm^{-1}. (Found: C, 67.92; H, 9.15; Br, 16.31. $C_{28}H_{45}BrO_2$ requires: C, 68.14; H, 9.19; Br, 16.19%.)

3β-*Acetoxy*-6α-*bromo*-19-*homo*-5β-*cholestan*-19*a*→5-*olide* (**36**). M.p. 143–144°, $[\alpha]_D^{20}$ − 26° (*c* 4.7). ^{1}H NMR spectrum: 0.67 (3H, s, 18-H), 2.03 (3H, s, CH_3CO_2), 2.03 (1H, d, J = 17 Hz, 19-H), 2.83 (1H, d, J = 17 Hz, 19-H), 4.20 (1H, dd, J = 5 and 12 Hz, 6β-H), 5.12 (1H, m, W = 15 Hz, 3α-H). ^{13}C NMR spectrum: 174.64s, 170.67s, 86.11s, 67.04d, 58.74d, 56.15d, 54.78d, 47.02d, 42.80s, 41.71d, 39.44t, 39.09t, 37.77d, 36.01t, 35.65d, 29.80t (2C), 28.07 d + t (2C), 27.98t, 25.57t, 23.95t, 23.78t, 23.72t, 22.79q, 22.54q, 21.38q, 18.57q, 12.01q. IR spectrum: 1245, 1730, 1775 cm^{-1}. (Found: C, 65.19; H, 8.41; Br, 14.60. $C_{30}H_{47}BrO_4$ requires: C, 65.32; H, 8.59; Br, 14.49%.)

3β-*Acetoxy*-5-*bromo*-19-*homo*-5α-*cholestan*-19*a*→6β-*olide* (**38**). M.p. 148–149°, $[\alpha]_D^{20}$ − 36° (*c* 1.6). ^{1}H NMR spectrum: 0.36 (3H, s, 18-H), 2.02 (3H, s, $MeCO_2$), 2.58 (1H, d, J = 14 Hz, 19-H), 2.88 (1H, d, J = 14 Hz, 19-H), 4.52 (1H, m, W = 10 Hz, 6α-H), 5.35 (1H, m, W = 30 Hz, 3α-H). ^{13}C NMR spectrum: 170.24, 170.19, 81.62, 73.47, 69.91, 55.96, 54.79, 48.00, 42.59, 39.45, 39.18, 39.09, 39.03, 36.06, 35.65, 33.66, 32.71, 31.01, 29.21, 28.05, 28.00, 26.13, 23.76, 23.54, 22.79, 22.54, 21.33, 21.21, 18.62, 12.13. IR spectrum: 1249, 1730 cm^{-1}. (Found: C, 65.21; H, 8.67; Br, 14.33. $C_{30}H_{47}BrO_4$ requires: C, 65.32; H, 8.59; Br, 14.49%.)

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