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SYNTHESIS OF STEROID 24,20-LACTONES BY MEANS OF PHENYLSELENOLACTONIZATION

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Abstract—A synthesis of (20 *R*)- and (20 *S*)-3β-methoxy-5-cholen-24,20-lactones (**7a** and **7b**) from 3β-methoxy-5-androsten-17-one (**2**) is described. The 17-ketone **2** was treated with isopropenyllithium to give 3β-methoxy-17α-(prop-1′-en-2′-ylo)-5-androsten-17β-ol (**3**). Compound **3** on reaction with ethyl orthoacetate and Claisen rearrangement of intermediate 17β-orthoester furnished ethyl esters of (*E*)- and (*Z*)-3β-methoxy-chol-5,17(20)-diene-24-acids (**4b** and **4a**). Hydrolysis of ester groups in **4a** and **4b** and phenylselenolactonization afforded stereospecifically and regioselectively unsaturated (20 *R*)- and (20 *S*)-3β-methoxy-chol-5,16-diene-24,20-lactones (**6a** and **6b**), respectively. Reduction of double bond 16–17 in **6a** and **6b** gave the final products **7a** and **7b**. The phenylselenolactonization of (*E*)- and (*Z*)-3β-methoxy-chol-5,17(20)-diene-24-acids (**5b** and **5a**) and spontaneous elimination of phenylselenyl moiety was investigated and compared with iodolactonization of the same unsaturated acids.

As a part of studies on synthesis and the biological activity of steroid lactones,[1,2] (20 *R*)-3β-methoxy-5-cholen-24,20-lactone (**7a**) and (20 *S*)-3β-methoxy-5-cholen-24,20-lactone (**7b**) were synthesized. Shalon *et al.*[3] have prepared similar 24,20-lactones by oxidation of the side-chain of cholanic acid, and have then used them for construction of the bufadienolide ring system.[4,5] The present synthesis of lactones **7a** and **7b** involved utilization 3β-acetoxy-5-androsten-17-one (**1**) as starting material for construction of the side-chain to the androstane skeleton to obtain γ–δ unsaturated acids **5a** and **5b**, and their lactonization.

At first, compound **1** was transformed into 3β-methoxy-5-androsten-17-one (**2**)[6] which upon reaction with isopropenyllithium afforded alcohol **3** in a 76% yield. The 17β orientation of the OH group in this compound was assigned on the basis of known stereochemistry of addition of organometallic compounds to 17-oxosteroids.[7] Treatment of **3** with ethyl orthoacetate at 135–145° for 6 hr afforded two isomeric esters **4a** and **4b** in 65% total yield as a result of Claisen rearrangement of the intermediate 17β-orthoester. The products were separated on a silica gel column to give **4a** and **4b** in 5:2 ratio. Configuration *Z* at double bond 17–20 was assigned to more abundant **4a**, on the basis of its PMR spectrum in which the signal of protons of C-21 Me group occurred in the higher field (δ = 1.50 ppm) than in the PMR spectrum of minor isomer **4b** (δ = 1.66 ppm). Such relationship has been established for isomers *Z* and *E* of 17(20)-dehydrocholesterol.[8] In these isomers the chemical shifts of protons of C-21 Me groups are δ = 1.53 ppm and δ = 1.68 ppm, respectively.

The individual esters **4a** and **4b**, hydrolyzed with an aqueous-methanolic solution of KOH, yielded the acids **5a** and **5b**, respectively.

Lactonization of acids **5a** and **5b** was the next stage of the synthesis. Attempts to use H_2SO_4 as a cyclising agent[9] caused marked decomposition of the starting material. We concentrated on the application of phenylselenolactonization[10,11] followed by oxidative removal of the PhSe-group and hydrogenation of the double bond.

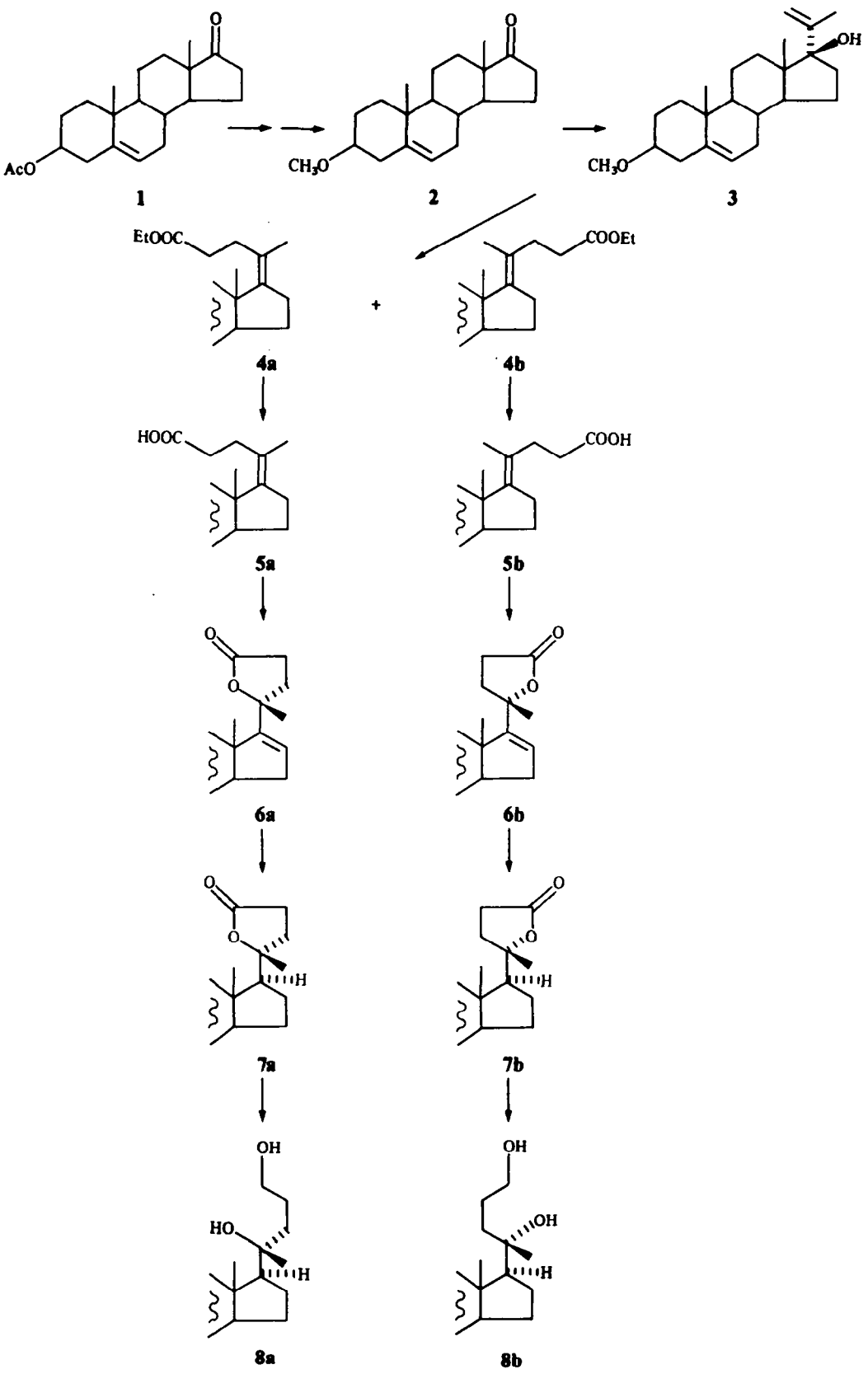
The reaction of acid **5a** with PhSeCl in the presence of triethylamine afforded in a 60% yield a product whose IR spectrum indicated the occurrence of a 5-membered lactone ring (band at 1760 cm^{-1}). However, the PMR spectrum of this product did not contain the aromatic proton signals, indicating the absence of the phenylseleno group in the molecule. On the other hand, in the spectrum a signal integrating for 1 proton δ = 5.60 ppm appeared; this signal was assigned to a proton on trisubstituted double bond. Above considerations indicated that phenylselenolactonization of acid **5a** directly yielded unsaturated lactone **6a**. The structure of **6a** was confirmed by other spectroscopic data and by elemental analysis.

Double bond 16–17 in lactone **6a** was reduced with diimide[12] generated *in situ* by oxidation of hydrazine hydrate with atmospheric O_2 in the presence of acid catalyst, lactone **7a** was obtained in a 58% yield. Alternatively, hydrogenation of **6a** on Pt catalyst gave **7a** (20%) accompanied by a more polar product structure of which was not elucidated.† The reaction of acid **5b** with PhSeCl carried out similarly as for acid **5a**, yielded unsaturated **6b** in a 55% yield. Reduction of **6b** with diimide afforded **7b**.

The described synthesis was complemented by determination of the absolute configuration at C-20 in lactones **7a** and **7b**. Comparison of the chemical shifts of protons of Me groups C-18 and C-21 in **7a** [δ(C-18) = 0.77 ppm; δ(C-21) = 1.43 ppm] and **7b** [δ(C-18) = 0.83 ppm; δ(C-21) = 1.45 ppm] with the corresponding PMR data for (20 *R*)-cholan-24,20-lactone and (20 *S*)-cholan-24,20-lactone, published by Shalon *et al.*,[3] suggested that **7a** and **7b** have the 20 *R* and 20 *S* configuration, respectively. However, due to the small difference between chemical shifts of C-21 protons in the epimers, it seemed advantageous to reduce lactones **7a** and **7b** to corresponding diols **8a** and **8b**, and to compare the PMR data of these compounds with those

† Deceased on 24 March 1980.

† It was assumed that the more polar product is an acid formed on hydrogenolysis of C—O bond.


AcO
O
1
CH3O
2
OH
3
EtOOC
COOEt
4a
4b
HOOC
COOH
5a
5b
6a
6b
7a
7b
HO
8a
8b

Scheme 1.

obtained for a known pair of epimers: (20 *R*)-cholan-20,24-diol and (20 *S*)-cholan-20,24-diol.[3] Lactones **7a** and **7b** were reduced with LAH to **8a** and **8b**. Comparison of the chemical shifts of protons of group C-21 in derivatives **8a** (δ = 1.16 ppm) and **8b** (δ = 1.28 ppm) with the corresponding PMR data for (20 *R*)-cholan-20,24-diol (δ = 1.15 ppm) and (20 *S*)-cholan-20,24-diol (δ = 1.30 ppm) confirmed the configuration assigned. Compounds **7a** and **7b** are the 20 *R* and 20 *S* isomers, respectively.

On the basis of the configuration of lactones **7a** and **7b**, the absolute configuration was assigned to unsaturated lactones **6a** (20 *R*) and **6b** (20 *S*).

Phenylselenoactonization of 17–20 unsaturated acids **5a** and **5b**, which proceeds *stereo*specifically and *regio*selectively, proved to be a convenient method for preparation of lactones **7a** and **7b**. The course of the reaction leading to 16–17 unsaturated compounds, though efficient in the synthesis was unexpected, since similar cases of lactonization proceeding concomitantly with elimination of phenylseleno group was, to our knowledge, not reported. Therefore it seemed of interest to gain insight into this reaction. The course of the reaction of acid **5a** with PhSeCl was studied under various conditions similar to those applied by Nicolaou *et al.*[10] It was found that:

(A) Treatment of acid **5a** with 1.1 eq. of PhSeCl in the presence of 1.1 eq. of $N(Et)_3$ failed to cause any evident changes in the substrate;

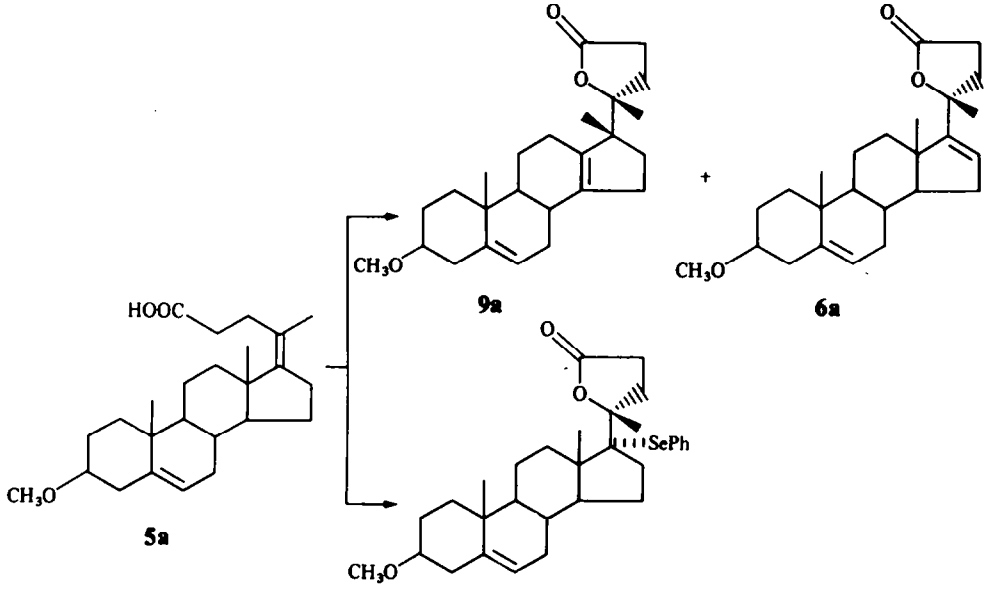
(B) Treatment of acid **5a** with 2 eq. of PhSeCl in the presence of 1.1 eq. $N(Et)_3$ afforded product **6a** in a 60% yield (Scheme 1);

(C) Treatment of acid **5a** with 1.5 eq. of PhSeCl in the presence of a 1.5 molar excess of anhyd K_2CO_3 gave lactone **6a** in a 38% yield (30% of substrate recovery);

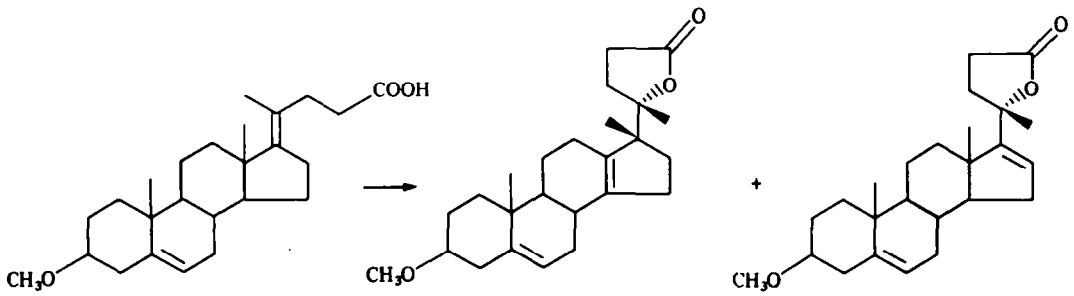
(D) Treatment of acid **5a** with 2 eq. of PhSeCl without $N(Et)_3$ yielded lactone **6a** (30%) and lactone **9a** (40%)—(Scheme 2).

The structure of **9a** was determined from the following data: the mass spectrum and elemental analysis corresponded to expected formula ($C_{25}H_{36}O_3$). The IR spectrum showed an absorption band at 1760 cm^{-1}, typical for 5-membered lactone. The PMR spectrum of **9a** comprised a signal of one olefinic proton, characteristic of proton C-6—H (multiplet at δ = 5.30 ppm), indicating that **9a** contains a tetrasubstituted double bond. Its presence and position were confirmed by the ^{13}C-NMR spectrum which within the range above 120 ppm exhibited 5 signals: at δ = 177.00; 141.60; 140.60; 137.97 and 121.27 ppm. The signal in the lowest field corresponded to the chemical shift of C atom of the CO group (C-24), and the remaining 4 signals of the ethylenic C atoms were assigned to atoms C-5, C-13, C-14 and C-6, respectively, according to calculation—in conformity with the rules of Smith[13]—of the chemical shifts of these C atoms. The *R* configuration at C-20 was assigned for **9a**, because migration of the C-18 group does not affect the *stereo*chemistry at C-20, and the reaction of **5a** with PhSeCl affords lactones 20 *R*, as previously shown.

(E) Treatment of acid **5a** with 1.1 eq. of PhSeCl in the presence of 10 molar excess of anhyd K_2CO_3 afforded selenolactone **10** in a 65% yield. Its PMR spectrum contained signals of aromatic protons (multiplets at 7.68 and 7.31 ppm), indicating to the presence of the phenylseleno group in the molecule. This compound is crystalline and stable, it can be stored for several months. Moreover, **10** was unaffected by treatment with triethylamine in a CH_2Cl_2 soln. The chromatographic properties of selenolactone **10** were identical with those of the intermediate product obtained in reactions A, B, C, D, however its isolation in preparative-scale amounts was unsuccessful. For confirmation of the assumption that selenolactone **10** is the intermediate product in reactions A, B, C, D, **10** was treated with PhSeCl:



Scheme 2.



5b **9b** **6b**

Scheme 3.

(a) in the presence of triethylamine—product **6a** was obtained in a 72% yield,
(b) in the absence of triethylamine within the temp. range from −78° (6 hr) to −18° (12 hr)—products **9a** and **6a** were obtained in a 4:1 ratio,
(c) in the absence of triethylamine within the temp. range from −78° (5 min) to +20° (2 hr)—compounds **9a** and **6a** were obtained in a 1:1 ratio.

It is evident that the ratio of products **9a** and **6a** depends on temperature. TLC of the mixture showed that in case (b), after 6 hr of the reaction at −78°, only **9a** was present, in addition to the substrate (about 50%).

Compound **10**—resisted any change on treatment with PhSeCl, in the presence of a 10 molar excess of powdered anhyd K_2CO_3. It was found that K_2CO_3 decomposed PhSeCl, at room temperature, this decomposition was immediate.

Selenolactone **10** was treated with 0.1 eq. of dry HCl (1.2×10^{-3} M HCl in CH_2Cl_2), yielding acid **5a** as the main reaction product; moreover, from the mixture **6a** and **9a** (formed in a 1–3% yield) were isolated and identified. "Retroselenolactonization" taking place in this case has a *stereo*specific course. It is noteworthy that Clive *et al.*[11] who have reacted 6-membered selenolactone with HCl, found no formation of the corresponding γ–δ unsaturated acid, in addition to the more stable 5-membered selenolactone, they obtained two isomeric chloroselenides with a free carboxyl group.

The above experiments seem to indicate that PhSeCl is the agent causing elimination of the −SePh group from the selenolactone **10** and inducing formation of **6a** and **9a**. The occurrence of typical Wagner–Meerwein product **9a** indicates that the reaction involves—at least partly—carbocation at C-17. The described course of phenylselenolactonization of acids **5a** and **5b** can be explained by steric strain of the intermediate selenolactones. In view of the unexpected course of selenolactonization, we attempted brief experiments on iodolactonization[14] of **5a** and **5b**.

Treatment of acid **5a** with I_2 in the presence of an aqueous solution of $NaHCO_3$ afforded lactone **9a** in a 87% yield. An analogous reaction of acid **5b** with I_2 yielded two products: **9b** (64%) and **6b** (23%). In this case I-containing intermediate was isolated which decomposed spontaneously at room temperature with formation of HI as well as of products **6b** and **9b** (Scheme 3).

The described course of iodolactonization of acids **5a** and **5b** confirms tendency for formation of unsaturated compounds which are less hindered sterically than seleno- or iodolactones.

EXPERIMENTAL

General. The PMR spectra were obtained in $CDCl_3$ on a Jeol YNM-4-H-100 spectrometer (100 MHz) and reported in δ (ppm) from Me_4Si. The ^{13}C-NMR spectrum was recorded in $CDCl_3$ and reported in δ (ppm) from Me_4Si, on a Jeol FX90Q spectrometer. The IR spectra were carried out with a Beckmann IR 4240 spectrophotometer. The mass spectra (MS) were obtained on a LKB 2091 spectrometer (at 70 eV, unless otherwise stated). High-resolution mass spectra (MS HR) were recorded on a Varian MAT 711 spectrometer. M.ps measured in a Kofler hot bench are uncorrected. Microanalyses were performed on Perkin–Elmer 240 and Hewlett–Packard 185 units. Symbols: s—singlet, d—doublet, t—triplet, q—quartet, m—multiplet, were applied in the description of the PMR spectra.

In the description of the IR and MS spectra, only the most intense and/or structurally most important peaks were given. For column chromatography silica gel (Merck 230–400 mesh or MN 100–200 mesh) was used. For HPLC, 5 preparative columns (internal dia. 8 mm, length 30 cm) packed with Lichrosorb Si 60 were used. TLC was performed on plates coated with a 0.25 mm layer of silica gel (Merck 60F-254). Chromatograms were developed by spraying with 50% H_2SO_4 and heating. Ethyl ether and THF were distilled from LAH. CH_2Cl_2 and Et_3N were distilled from CaH_2. Extracts were dried over $MgSO_4$ or Na_2SO_4, solvents were removed by distillation under reduced pressure.

All reactions with PhSeCl were carried out under argon, using dry, freshly distilled solvents. Commercial PhSeCl (Aldrich) or PhSeCl prepared according to Reich *et al.*[15] was used. Reaction temp were measured externally. The reported yields concern chromatographically homogeneous material.

3β-Methoxy-17α-(prop-1'-en-2'ylo)-5-androsten-17β-ol (**3**). To a suspension of Li (4.2 g, 0.6 gr.-at.) in dry ether (100 ml) under argon, at 0° several drops of freshly distilled isopropenyl chloride were added. After initiation of the reaction, slow drop-wise addition was made of an isopropenyl chloride soln (22.5 ml, 300 mmol) in ether (70 ml), with vigorous stirring. After dissolving of Li (2 hr), during 1.5 hr a soln of **2** (6.6 g, 21.8 mmol) in an ether/THF mixture 9:1 (100 ml) was added drop-wise. Stirring was continued for 2 hr at 0°, whereupon the mixture was left to stand for 12 hr at room temp and then was poured into ice. The product was extracted with ether and purified by crystallization from acetone: 5.7 g (76%) of alcohol **3** m.p. 135–136°, were obtained.

IR ($CHCl_3$) ν_{max}: 3610 (OH); 1640 ($R_2C{=}CH_2$); 1095 (C—O—C) cm^{-1}. PMR: 5.35 (m, 1H, C-6—H); 5.01 (m, 1H, C-22—H); 4.66 (m, 1H, C-22—H); 3.31 (s, 3H, OCH_3); 3.00 (m, 1H, C-3—H); 1.82 (s, 3H, C-21—H); 1.0 (s, 3H) and 0.92 (s, 3H)—protons of angular methyl groups. MS (*m/e*): 344 (M^+, 100%); 326 ($M^+ - H_2O$, 22%); 312 ($M^+ - CH_3OH$, 10%); 294 ($M^+ - H_2O - CH_3OH$, 10%). (Found: C, 79.58; H, 10.57. Calc for $C_{23}H_{36}O_2$: C, 80.16; H, 10.55%.)

Ethyl ester of 3β-methoxy-chol-5,17(20)-(Z)-diene-24-acid (**4a**) *and ethyl ester 3β-methoxy-chol-5,17(20)-(E)-diene-24-acid* (**4b**). A mixture of 3 (2.05 g, 5.96 mmol), ethyl orthoacetate (13 ml) and propionic acid (106 mg, 1.4 mmol) was heated under argon for 6 hr at 135–145°. From the mixture the volatile components were removed by distillation under reduced pressure, whereas the residue was dissolved in ether and washed with $NaHCO_3$ aq; after removal of the solvent, the residue was chromatographed on silica gel (hexane–ether, 92:8), yielding 1.56 g (65%) of a mixture of products and 470 mg (24%) of substrate **3**. The mixture of products was chromatographically separated on silica gel (hexane–ether, 98.5:1.5); 1.12 g of **4a** m.p. 87–89° (MeOH), was obtained:

IR (KBr) ν_{max}: 1730 (C=O); 1100 (C—O—C) cm^{-1}. PMR: 5.30 (m, 1H, C-6—H); 4.00 (q, J = 6 Hz, 2H, COO—$\underline{CH_2}$—CH_3); 3.30 (s, 3H, OCH_3); 3.00 (m, 1H, C-3—H); 1.50 (s, 3H, C-21—H); 1.20 (t, J = 6 Hz, 3H, COO—CH_2—$\underline{CH_3}$); 0.97 (s, 3H, C-19—H); 0.86 (s, 3H, C-18—H). MS (*m/e*): 414 (M^+, 12%); 399 ($M^+ - CH_3$, 14%); 367 ($M^+ - (CH_3)$—(CH_3OH), 15%); 285 ($M^+ - C_7H_{13}O_2$, 95%); 253 (285–CH_3OH, 36%). (Found: C, 78.20; H, 10.36. Calc for $C_{27}H_{42}O_3$: C, 78.26; H, 10.14%) and compound **4b** (450 mg), oil, was obtained: IR (KBr) ν_{max}: 1730 (C=O); 1100 (C—O—C) cm^{-1}. PMR: 5.28 (m, 1H, C-6—H); 4.00 (q, J = 6 Hz, 2H, COO—$\underline{CH_2}$—CH_3); 3.30 (s, 3H, OCH_3); 3.00 (m, 1H, C-3—H); 1.66 (s, 3H, C-21—H); 1.20 (t, J = 6 Hz, 3H, COO—CH_2—$\underline{CH_3}$); 0.96 (s, 3H, C-19—H); 0.83 (s, 3H, C-18—H). MS (*m/e*): 414 (M^+, 13%); 399 ($M^+ - CH_3$, 14%); 367 ($M^+ - (CH_3)$—(CH_3OH), 15%); 326 ($M^+ - CH_3COOEt$, 16%); 311 ($M^+ - (CH_3)$—(CH_3COOEt), 14%); 285 ($M^+ - C_7H_{13}O_2$, 100%); 279 ($M^+ - (CH_3)$—(CH_3COOEt)—(CH_3OH), 13%); 253 (285–CH_3OH, 36%). MS HR (*m/e*): Found: 414.3148. Calc for $C_{27}H_{42}O_3$: 414.3134.)

3β-Methoxy-chol-5,17(20)-(Z)-diene-24-acid (**5a**). A solution of the ester **4a** (414 mg, 1 mmol) in MeOH (20 ml), containing KOH (120 mg, 2.1 mmol) and water (0.5 ml), was heated for 2 hr (till disappearance of **4a** according to TLC). The postreaction mixture was acidified with 5% HCl and extracted with $CHCl_3$; 380 mg (99%) of acid **5a**, m.p. 67–69° (MeOH), were obtained.

IR ($CHCl_3$) ν_{max}: 3510 (COOH); 1710 (C=O); 1100 (C—O—C) cm^{-1}. PMR: 7.60 (m, 1H, COO—H); 5.33 (m, 1H, C-6—H); 3.35 (s, 3H, OCH_3); 3.00 (m, 1H, C-3—H); 1.55 (s, 3H, C-21—H); 1.00 (s, 3H, C-19—H); 0.87 (s, 3H, C-18—H). MS (*m/e*): 386 (M^+, 97%); 371 ($M^+ - CH_3$, 51%); 354 ($M^+ - CH_3OH$, 22%); 339 ($M^+ - (CH_3)$—(CH_3OH), 44%); 313 (47%); 285 ($M^+ - C_5H_9O_2$, 51%); 253 (285–CH_3OH, 37%).

3β-Methoxy-chol-5,17(20)-(E)-diene-24-acid (**5b**). A soln of **4b** (100 mg, 0.24 mmol) in MeOH (8 ml), containing KOH (30 mg, 0.54 mmol) and water (0.25 ml), was heated for 2 hr. The product was isolated similarly as **5a**; 90 mg (97%) of **5b**, m.p. 166–168° (MeOH), were obtained. IR ($CHCl_3$) ν_{max}: 3510 (COOH); 1710 (C=O); 1100 (C—O—C) cm^{-1}. PMR: 9.4 (m, 1H, COO—H); 5.33 (m, 1H, C-6—H); 3.33 (s, 3H, OCH_3); 3.00 (m, 1H, C-3—H); 1.66 (s, 3H, C-21—H); 1.00 (s, 3H, C-19—H); 0.82 (s, 3H, C-18—H). MS (*m/e*): 386 (M^+, 97%); 371 ($M^+ - CH_3$, 70%); 354 ($M^+ - CH_3OH$, 35%); 339 ($M^+ - (CH_3)$—(CH_3OH), 73%), 313 (19%), 285 ($M^+ - C_5H_9O_2$, 89%); 253 (285–CH_3OH, 47%).

(20R)-*3β-Methoxy-chol-5,16-diene-24,20-lactone* (**6a**). A soln of **5a** (900 mg, 2.3 mmol) in CH_2Cl_2 (60 ml) containing $N(Et_3)$ (0.39 ml, 3 mmol), was stirred for 30 min at room temp whereupon it was cooled to −78°, solid PhSeCl (550 mg, 2.7 mmol) was then added. After 1 hr, another portion of PhSeCl (550 mg) was added. Stirring was continued for 1 hr at −78°, and then for 12 hr at −18°, till disappearance of **5a** acc. to TLC. The solvent was removed by distillation, and the product was purified chromatographically (silica gel, hexane–EtOAc, 95:5), 530 mg (60%) of **6a**, m.p. 157–159° (MeOH) were obtained. IR ($CHCl_3$) ν_{max}: 1760 (γ-lactone); 1100 (C—O—C) cm^{-1}. PMR: 5.60 (m, 1H, C-16—H); 5.33 (m, 1H, C-6—H); 3.32 (s, 3H, OCH_3); 3.00 (m, 1H, C-3—H); 1.52 (s, 3H, C-21—H); 1.00 (s, 3H) and 0.98 (s, 3H)—protons of angular Me groups, MS (*m/e*): 384 (M^+, 40%); 369 ($M^+ - CH_3$, 23%); 352 ($M^+ - CH_3OH$, 36%); 337 ($M^+ - (CH_3)$—(CH_3OH), 45%); 285 ($M^+ - C_5H_7O_2$, 51%); 99 ($C_5H_7O_2^+$, 100%). (Found: C, 78.04; H, 9.65. Calc for $C_{25}H_{36}O_3$: C, 78.07; H, 9.45%.)

(20S)-*3β-Methoxy-chol-5,16-diene-24,20-lactone* (**6b**). Compound **6b** was obtained similarly as **6a**. The following amounts of reagents were used: acid **5b** (290 mg, 0.75 mmol), $N(Et)_3$ (0.13 ml, 1.1 mmol), PhSeCl (360 mg, 1.8 mmol) and CH_2Cl_2 (20 ml). 60 mg (55%) of **6b**, m.p. 145–148° (acetone), were obtained. IR ($CHCl_3$) ν_{max}: 1765 (γ-lactone); 1100 (C—O—C) cm^{-1}. PMR: 5.63 (m, 1H, C-16—H); 5.33 (m, 1H, C-6—H); 3.32 (s, 3H, OCH_3); 3.00 (m, 1H, C-3—H); 1.53 (s, 3H, C-21—H); 1.00 (s, 3H) and 0.94 (s, 3H)—protons of angular Me groups. MS (*m/e*): 384 (M^+, 32%); 369 ($M^+ - CH_3$, 23%); 352 ($M^+ - CH_3OH$, 34%); 337 (352–CH_3, 40%); 285 ($M^+ - C_5H_7O_2$, 76%); 253 (285–CH_3OH, 40%); 99 ($C_5H_7O_2^+$, 100%). MS HR (*m/e*): (Found: 384.2677. Calc for $C_{25}H_{36}O_3$: 384.2664.)

(20R)-*3β-Methoxy-5-cholen-24,20-lactone* (**7a**). To a soln of **6a** (430 mg, 1.2 mmol) in EtOH (40 ml), addition was made of 80% hydrazine hydrate (3 ml, 50 mmol) and propionic acid (3.6 ml, 50 mmol). The mixture was refluxed for 6 hr, with air stream bubbling. The product was extracted with $CHCl_3$ and purified chromatographically (silica gel, hexane–EtOAc, 95:5); 250 mg (58%) of **7a**, m.p. 150–152° (EtOH) were obtained. IR (KBr) ν_{max}: 1780 (γ-lactone), 1095 (C—O—C) cm^{-1}. PMR: 5.35 (m, 1H, C-6—H); 3.35 (s, 3H, OCH_3); 3.05 (m, 1H, C-3—H); 1.43 (s, 3H, C-21—H); 1.00 (s, 3H, C-19—H); 0.77 (s, 3H, C-18—H). MS (*m/e*): 386 (M^+, 35%); 371 ($M^+ - CH_3$, 14%); 354 ($M^+ - CH_3OH$, 50%); 339 ($M^+ - (CH_3)$—(CH_3OH), 24%); 99 ($C_5H_7O_2^+$, 100%). (Found: C, 77.27; H, 10.11. Calc for $C_{25}H_{38}O_3$: C, 77.67; H, 9.91%.)

(20S)-*3β-Methoxy-5-cholen-24,20-lactone* (**7b**). Compound **7b** was obtained similarly as **7a**, with the use of the following amounts of reagents: compound **6b** (100 mg, 0.28 mmol), 80% hydrazine hydrate (0.75 ml, 12.5 mmol), propionic acid (0.9 ml, 12.5 mmol) and EtOH (20 ml), 50 mg (50%) of **7b**, m.p. 150–180° (dec)—(MeOH), were obtained. IR (KBr) ν_{max}: 1780 (γ-lactone), 1100 (C—O—C) cm^{-1}. PMR: 5.35 (m, 1H, C-6—H); 3.35 (s, 3H, OCH_3); 3.05 (m, 1H, C-3—H); 1.45 (s, 3H, C-21—H); 1.00 (s, 3H, C-19—H); 0.83 (s, 3H, C-18—H). MS (*m/e*): 386 (M^+, 18%); 354 ($M^+ - CH_3OH$, 46%); 339 ($M^+ - (CH_3)$—(CH_3OH), 21%); 99 ($C_5H_7O_2^+$, 100%). MS HR (*m/e*): (Found: 386.2831. Calc for $C_{25}H_{38}O_3$: 386.2821.)

(20R)-*3β-Methoxy-5-cholen-20,24-diol* (**8a**). To a soln of **7a** (30 mg, 0.08 mmol) in dry THF (4 ml), $LiAlH_4$ (30 mg, 0.78 mmol) was added. The mixture was vigorously stirred for 1 hr at room temp. The excess of reagent was decomposed with sat Na_2SO_4 aq; the ppt was removed by filtration and the filtrate was evaporated; 25 mg (83%) of **8a**, m.p. 128–130° (MeOH), were obtained. IR ($CHCl_3$) ν_{max}: 3650 (OH), 3450 (OH), 1095 (C—O—C) cm^{-1}. PMR: 5.38 (m, 1H, C-6—H); 3.70 (m, 2H, C-24—H); 3.38 (s, 3H, OCH_3); 3.01 (m, 1H, C-3—H); 1.16 (s, 3H, C-21—H); 1.00 (s, 3H, C-19—H); 0.87 (s, 3H, C-18—H).

(20S)-*3β-Methoxy-5-cholen-20,24-diol* (**8b**). To a soln of **7b** (30 mg, 0.08 mmol) in dry THF (4 ml), $LiAlH_4$ (30 mg, 0.78 mmol) was added. The procedure was the same as for **8a**; 25 mg (83%) of **8b** (oil) were obtained. IR ($CDCl_3$) ν_{max}: 3650 (—OH), 3500 (—OH), 1095 (C—O—C) cm^{-1}. PMR: 5.38 (m, 1H, C-6—H); 3.72 (m, 2H, C-24—H); 3.38 (s, 3H, OCH_3); 3.01 (m, 1H, C-3—H); 1.28 (s, 3H, C-21—H); 1.00 (s, 3H, C-19—H); 0.86 (s, 3H, C-18—H).

Reactions of acid **5a** *with* PhSeCl

(A) A mixture of **5a** (39 mg, 0.1 mmol), $N(Et)_3$ (0.013 ml, 0.11 mmol) and CH_2Cl_2 (5 ml) was stirred for 30 min at room temp, whereupon it was cooled to −78°, and PhSeCl (22 mg, 0.11

mmol) was added. Stirring at −78° was continued for 1 hr, then the mixture was heated to room temp and left to stand for 24 hr. Acid **5a** remained unchanged.

(B) *Cf.* preparation of (20 R)-3β-methoxy-chol-5,16-diene-24,20-lactone (**6a**).

(C) To a soln of **5a** (420 mg, 1.09 mmol) in CH_2Cl_2 (25 ml) at room temp anhyd K_2CO_3 (200 mg, 1.54 mmol) and—after cooling to −78°—solid PhSeCl (300 mg, 1.6 mmol) were added. The mixture was stirred for 1 hr at −78°, and then for 12 hr at −18°, whereupon it was heated to room temp. K_2CO_3 was removed by filtration, and the filtrate was concentrated to an oily residue which was chromatographed on silica gel (hexane–EtOAc, 95:5); 157 mg (38%) of **6a** and 123 mg (30%) of **5a**, both being identical with the earlier prepared compounds, were obtained.

(D) (20 R)-*3β-Methoxy-17β-methyl-18-nor-chol-5,13-diene-24,20-lactone* (**9a**). To a soln of **5a** (117 mg, 0.3 mmol) in CH_2Cl_2 (15 ml), at −78° solid PhSeCl (115 mg, 0.6 mmol) was added. The mixture was stirred at −78° for 1 hr and then for 12 hr at −18°, till disappearance of **5a** acc. to TLC. From the postreaction mixture the solvent was removed by evaporation; the residue dissolved in $CHCl_3$ and filtered through silica gel. Steroid products—thus separated from diphenyl diselenide—were separated into pure compounds by HPLC (hexane–EtOAc, 85:15); 20 mg (17%) of **6a** identical with that previously prepared, as well as 50 mg (43%) of **9a**, m.p. 173–175° (MeOH), were obtained. IR ($CHCl_3$) ν_{max}: 1760 (γ-lactone), 1100 (C—O—C) cm^{-1}. PMR: 5.30 (m, 1H, C-6—H); 3.35 (s, 3H, OCH_3); 3.01 (m, 1H, C-3—H); 1.30 (s, 3H) and 1.17 (s, 3H); —C-21—H and C-18—H; 0.96 (s, 3H, C-19—H). ^{13}C-NMR signals above 120 ppm: 177.00 (C-24); 141.80 (C-5); 140.60 (C-13); 137.97 (C-14); 121.27 (C-6). MS (*m/e*): 384 (M^+, 6%); 285 ($M^+ - C_5H_7O_2$, 100%); 253 (285–CH_3OH, 43%); 99 ($C_5H_7O_2^+$, 22%). (Found: C, 77.67; H, 9.53. Calc for $C_{25}H_{36}O_3$: C, 78.07; H, 9.45%.)

(20 R)-*3β-Methoxy-17α-(phenylseleno)-5-cholen-24,20-lactone* (**10**). A mixture of **5a** (384 mg, 1.0 mmol), CH_2Cl_2 (20 ml) and anhyd K_2CO_3 (2g, 14 mmol) was cooled to −78°, whereupon solid PhSeCl (220 mg, 1.1 mmol) was added. After vigorous stirring for 1 hr, the postreaction mixture was poured into water and extracted with $CHCl_3$. The product was purified chromatographically using silica gel (hexane–EtOAc, 94:6); 351 mg (65%) of **10**, m.p. 179–182° (hexane–EtOAc), were obtained. IR ($CHCl_3$) ν_{max}: 1750 (γ-lactone); 1100 (C—O—C) cm^{-1}. PMR: 7.68 (m, 2H) and 7.31 (m, 3H) aromatic protons; 5.38 (m, 1H, C-6—H); 3.35 (s, 3H, OCH_3); 3.00 (m, 1H, C-3—H); 1.75 (s, 3H, C-21—H); 1.10 (s, 6H, protons of angular Me groups). MS (*m/e*): 285 (M^+ −(HSePH)—($C_5H_7O_2$), 93%); 253 (285–CH_3OH, 56%); 157 ($^{80}SePh^+$, 47%); 155 ($^{78}SePh^+$, 21%); 99 ($C_5H_7O_2^+$, 100%). (Found: C, 68.66; H, 7.90. Calc for $C_{31}H_{42}O_3Se$: C, 68.74; H, 7.82%.)

Reactions of selenolactone **10** *with* PhSeCl

(a) To a mixture of **10** (50 mg, 0.09 mmol), Et_3N (0.012 ml, 0.1 mmol) and CH_2Cl_2 (5 ml), cooled to −78, PhSeCl (40 mg, 0.21 mmol) was added. The mixture was stirred for 30 min at −78°, and then for 12 hr at −18°, until the disappearance of **10** acc. to TLC. The solvent was removed by evaporation, and the residue was chromatographed using silica gel (hexane–EtOAc, 95:5), 25 mg (72%) of **6a** were obtained.

(b) To a soln of **10** (50 mg, 0.09 mmol) in CH_2Cl_2 (5 ml), at −78° PhSeCl (20 mg, 0.1 mmol) was added. The mixture was stirred at −78° for 6 hr and then at −18° for 12 hr, until the disappearance of **10** acc. to TLC. The solvent was removed by evaporation, and the residue was dissolved in $CHCl_3$ and filtered through silica gel. Thus the steroid products were separated from diphenyl diselenide. This treatment afforded a mixture of **9a** and **6a** (24 mg, 74%) in a 4:1 ratio, whose identity with the previously obtained substances (**9a** and **6a**) was demonstrated by identity of R_f in TLC (the chromatogram was developed 4 times at a 10 cm distance in a mixture of hexane–EtOAc, 9:1), as well as by the PMR spectrum of the mixture, which agreed with the superposed PMR spectra of pure **9a** and **6a**. The above given composition of the mixture was established by integration of signals at 5.60 ppm (C-16—H) and at 5.33 ppm (C-6—H) in its PMR spectrum.

(c) To a soln of **10** (50 mg, 0.09 mmol) in CH_2Cl_2 (5 ml), at −78° PhSeCl (20 mg, 0.1 mmol) was added, whereupon the mixture was heated to room temp and left to stand for 2 hr (until the disappearance of **10** acc. to TLC). The solvent was removed by evaporation, and the residue was chromatographed as in item (b). A mixture of **9a** and **6a** (23 mg, 70%) in a 1:1 ratio was obtained; its composition was determined as in item (b).

Reaction of selenolactone **10** *with hydrogen chloride*

To a soln of **10** (54 mg, 0.1 mmol) in dry CH_2Cl_2, under argon at room temp a 0.12 M HCl in CH_2Cl_2 (0.1 ml, 0.1 mmol HCl) was added. The mixture was left to stand for 48 hr at 5°. The solvent was removed by evaporation, and the residue was chromatographed on silica gel (hexane–EtOAc, 96:4); 1 mg of **6a** (2.5%). 1 mg of **9a** (2.5%), 26 mg of **5a** (68%) and 2 mg of **10** (5%) were obtained. The identity of the resulting **6a**, **9a**, **5a** and **10** with those prepared previously was confirmed by measurement of m.ps, and in case of acid **5a**—also by the spectroscopic data (PMR, IR).

Reaction of acid **5a** with iodine

To a soln of **5a** (230 mg, 0.6 mmol) in dioxane (10 ml), addition was made of an aqueous soln (0.5 M) of $NaHCO_3$ (4.8 ml), and then of an I_2 soln in KI aq (440 mg I_2, 1.7 mmol; 800 mg KI, 4.8 mmol; 2.4 ml H_2O), the mixture was left to stand at room temp for 24 hr, in the dark. The postreaction mixture was diluted with water and extracted with ether. The ethereal extract was washed with $Na_2S_2O_3$ aq and dried, the solvent was removed by evaporation to an oily residue which was chromatographed on silica gel (hexane–EtOAc, 95:5), 180 mg of the main product **9a** (identical with that previously found) and 40 mg of mixed fraction containing **9a** and a side-product. The mixture fraction was rechromatographed on silica gel (hexane–EtOAc, 96:4), 20 mg of **9a** and 18 mg (8%) of side-product which proved to be **6a** were obtained. In total, 200 mg (87%) of **9a** were prepared.

Reaction of the **5b** *with iodine, yielding* (20 S)-*3β-methoxy-17β-methyl-18-nor-chol-5,13-diene-24,20-lactone* (**9b**)

The reaction was carried out as in case of **5a**. The following amounts of reagents were used: **5b** (70 mg, 0.2 mmol); 0.5 M $NaHCO_3$ (1.45 ml); I_2 (130 mg, 0.5 mmol); KI (265 mg, 1.6 mmol); water (0.7 ml) and dioxane (4 ml). The products were separated by HPLC (hexane–EtOAc, 85:15), 16 mg (23%) of **6b** identical with that previously prepared and 45 mg (64%) of **9b**, m.p. 147–149° (MeOH), were obtained. IR ($CHCl_3$) ν_{max}: 1760 cm^{-1} (γ-lactone), 1100 (C—O—C) cm^{-1}. PMR: 5.38 (m, 1H, C-6—H), 3.35 (s, 3H, OCH_3), 3.00 (m, 1H, C-3—H); 1.28 (s, 3H) and 1.08 (s, 3H) C-21—H and C-18—H; 0.96 (s, 3H, C-19—H). MS (*m/e*): 384 (M^+ 0.5%); 285 ($M^+ - C_5H_7O_2$, 100%); 253 (285–CH_3OH, 49%); 99 ($C_5H_7O_2^+$, 17%). MS HR (*m/e*): (Found: 384.2664. Calc for $C_{25}H_{36}O_3$: 384.2664.)

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