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Original scientific paper

Oxidative fragmentations of 5-hydroxy-1-oxo-5α-cholestan-3β-yl acetate

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Abstract: 5-Hydroxy-1-oxo-5α-cholestan-3β-yl acetate (**11**) was prepared in 5 steps starting from (*E*)-3β-acetoxy-5,10-seco-1(10)-cholesten-5-one (**6**). Treatment of the 1-oxo-5-hydroxy derivative **11** with lead tetraacetate (LTA) (under thermal or hypoiodite conditions) or with mercuric oxide/iodine (HgO/I_2) reagent resulted in the oxidative β-fragmentation of the C(5)–C(10) bond affording 1,5-dioxo-5,10-secocholest-10(19)-en-3β-yl acetate (**12**), in different yields, depending on the reagent. Also the stereochemistry of the 1β,6β-cyclization product **13**, formed by transannular cyclization of the 1,5-diketone **12** on silica gel, is discussed in this work.

Keywords: 5-Hydroxy-1-oxo-5α-cholestan-3β-yl acetate, 1,5-dioxo-5,10-secocholest-10(19)-en-3β-yl acetate, β-fragmentation, transannular cyclization.

INTRODUCTION

It is well known that the alkoxy radical ***i*** (generated by the oxidation of the 5-hydroxy steroids **1** and **2** with lead tetraacetate (LTA) under thermal or photolytic conditions or with hypoiodite-forming reagents) readily undergoes β-fragmentation involving scission of the C(5)–C(10) bond, to afford, *via* the C(10)-radical intermediate ***ii***, the diastereomeric (*Z*)- and (*E*)-1(10)-unsaturated 5,10-secosteroidal 5-ketones **3** and **4** in different proportions and, depending on the oxidant used, in high yield (Scheme 1).[1–3]

The direction of β-fragmentation in **1** and **2** to give exclusively the 5,10-secoketones **3** and **4** was explained by the stability of the tertiary C-radical intermediate ***ii***, due to the presence of the angular Me(19) group at the C(10)-radical center.

In accordance with such an explanation, it was anticipated that other 5-hydroxy steroids with similar structures and with the same reagents should react in the same way. However, when LTA oxidations (thermal and hypoiodite) of the 5-hydroxy-8,9-seco-8,9-diketone **5**, a

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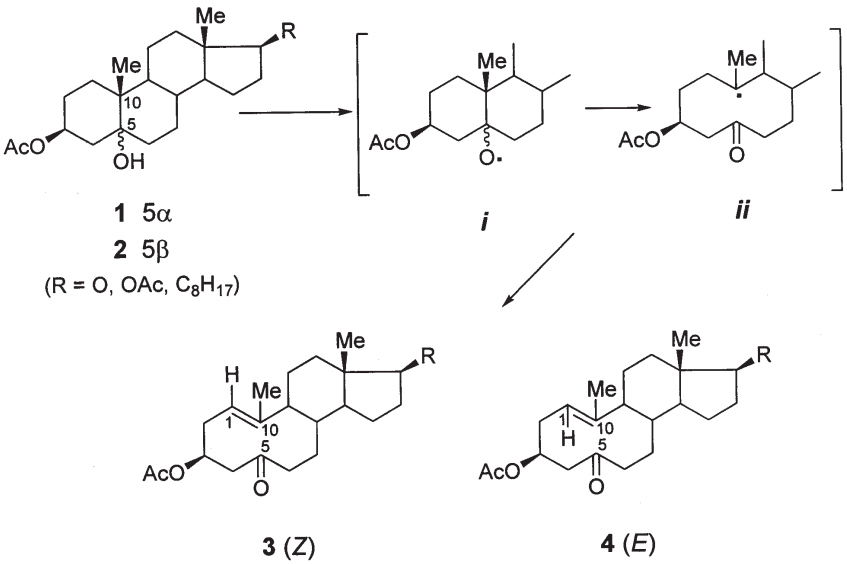
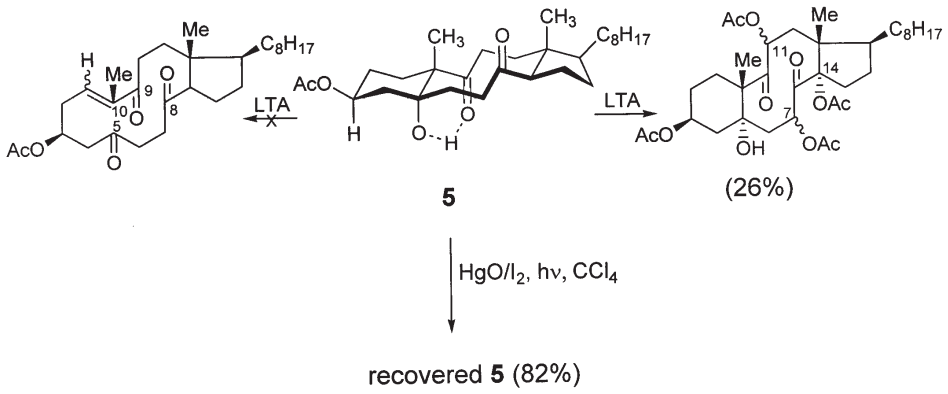


Scheme 1.

substrate with a polar oxo-group located at the α-position to the corresponding C(10)-radical center (type ***ii***), were performed under similar experimental conditions, the only obtained product was an unresolvable mixture of the 7-, 11- and 14-acetoxy derivatives arising from the competing acetoxylation of the α-positions next to the C(8)- and C(9)-oxo groups.



Scheme 2.

On the other hand, when the oxidative fragmentation of the C(5)–C(10) bond in compound **5** was attempted with HgO/I_2 reagent, practically all the starting material remained unchanged (recovery being ≈ 82 %, while the rest was an unresolvable mixture) (Scheme 2).[4]

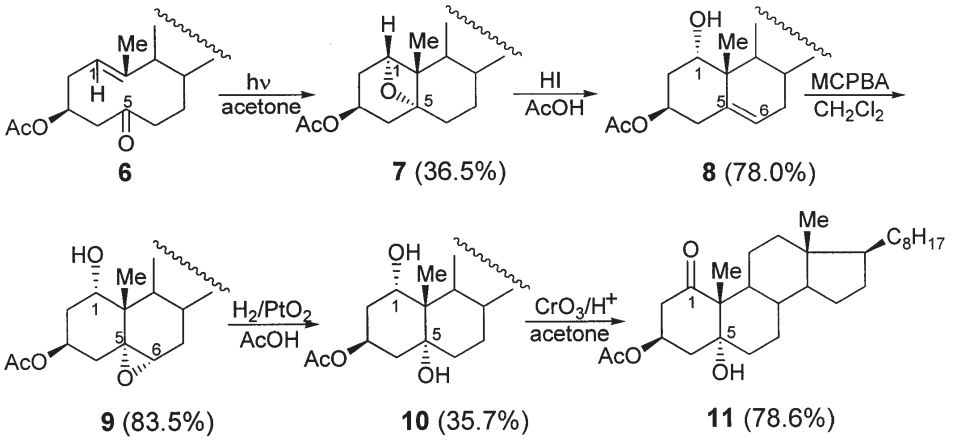
The resistance of compound **5** to undergo oxidative β-fragmentation of its C(5)–C(10) bond was explained by strong hydrogen bonding between the 5-OH group and the 9-oxo

function. As a consequence of this interaction, the formation of the alkoxy radical was suppressed.

RESULTS AND DISCUSSION

In order to obtain more information concerning the influence of an oxo-group in the α-position to the C(10) on the oxidative fragmentation of the C(5)–C(10) bond, in the present work the possibility of inducing oxidative β-fragmentation of 5-hydroxy-1-oxo-5α-cholestan-3β-yl acetate (**11**) was investigated.

For the introduction of an oxygen function at the C(1)-position, the ten-membered ring containing (*E*)-3β-acetoxy-5,10-seco-1(10)-cholesten-5-one (**6**) was required. This compound was prepared from cholestane-3β,5α-diol 3-acetate according to the procedure given in Ref. 3. Substrate **11** was then synthesized in 5 steps, as shown in Scheme 3.



6 **7** (36.5%) **8** (78.0%)

9 (83.5%) **10** (35.7%) **11** (78.6%)

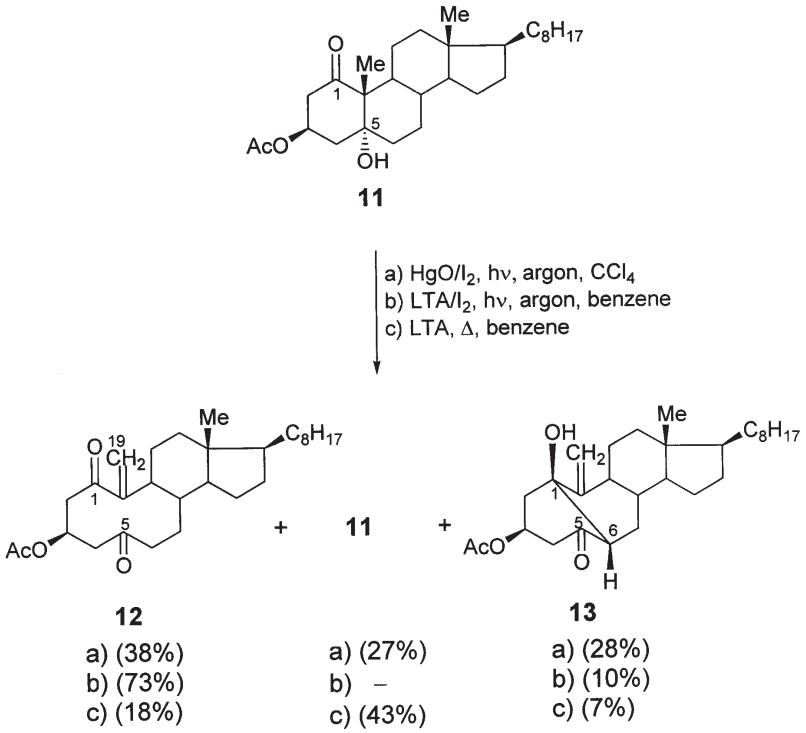
Scheme 3.

UV irradiation of **6** in acetone solution with a high pressure mercury lamp (TQ 150 Z2) afforded a photoproduct (Paterno-Büchi reaction) with an oxetane structure, *i.e.* 1α,5-epoxy-5α-cholestan-3β-yl acetate (**7**)[5] in 36.5 % yield. Treatment of the oxetane derivative **7** with hydroiodic acid in glacial acetic acid at 5 ºC resulted in the opening of the four-membered ether ring and the formation of cholest-5-en-1α,3β-diol 3-acetate (**8**) in high yield (78.0 %).[5] The epoxy derivative **9** was prepared by *m*-chloroperbenzoic acid (MCPBA) oxidation of **8** (in 83.5 % yield).[6] This product under conditions of catalytic hydrogenation (performed over PtO_2 in acetic acid solution) gave 5α-cholestan-1α,3β,5-triol 3-acetate (**10**)[7] (35.7 %). Jones oxidation of the triol-monoacetate **10** in acetone solution at –5 ºC afforded the 5-hydroxy-1-oxo-5α-cholestan-3β-yl acetate (**11**) in 78.6 % yield.

Oxidations of alcohol **11** were performed with hypoiodite-forming reagents and LTA (thermal) under conditions similar to those previously applied to compounds **1**, **2** and **5**.[1–4]

The HgO/I_2 version of the hypoiodite reaction of **11** performed with an excess of oxidant in CCl_4 solution by irradiation with a 15 W-lamp at 220 V at room temperature for

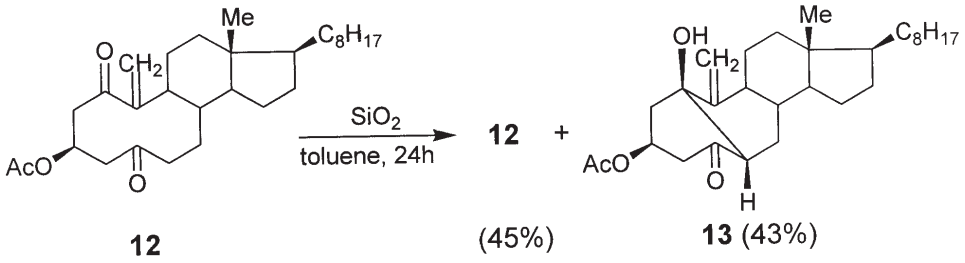
90 min in the presence of air gave, besides starting material **11** (20 %), an unresolvable complex mixture from which not one product with a defined structure could be isolated. The same results were obtained when the reaction was performed under O_2. However, when the above irradiation was performed under Ar, the resulting mixture of reaction products, after separation by column chromatography on silica gel, gave the 1,5-dioxo-5,10-secocholest-10(19)-en-3β-yl acetate (**12**) (38 %), the starting compound **11** (27 %) and the cyclization product **13** (28 %) (Scheme 4).



Scheme 4.

The structure of the product **12** was deduced from its analytical and spectral data (IR, ^{1}H-NMR, ^{13}C-NMR, MS). In the IR spectrum, the absorption of the 1-oxo group migrates from 1716 to 1670 cm^{-1}, indicating an α,β-unsaturated carbonyl, and the absorption for the original 5α-hydroxyl group was missing and instead a new absorption at 1701 cm^{-1} for the 5-oxo group appeared. In the ^{13}C-NMR spectrum, a new singlet appeared at 207.7 ppm for C(5). The presence of the exocyclic methylidene group CH_2=C(10) was evident from the IR spectrum (absorptions at 3100 and 1620 cm^{-1}) and confirmed by ^{1}H- and ^{13}C-NMR data. Instead of the signal for the Me(19) group, the ^{1}H-NMR spectrum showed a pair of singlets at 5.83 and 6.15 ppm, and the ^{13}C-NMR spectrum showed a triplet at 124.6 ppm for C(19) and a singlet at 155.0 ppm for C(10). Also, in the ^{13}C-NMR spectrum, a singlet at 199.4 ppm for C(1) in the 1,5-diketone **12** was situated upfield when compared to the resonance at 209.4 ppm for C(1) in compound **11**, indicating the influence of the exocyclic methylidene group in the α-position.

Compound **13** is a secondary reaction product, formed by intramolecular 1,6-cyclization of the 1,5-diketone **12**. This was confirmed by prolonged stirring (24 hours) of compound **12** with SiO_2 in toluene solution which afforded, besides the starting material, only one product, *i.e.* compound **13** (Scheme 5).



Scheme 5.

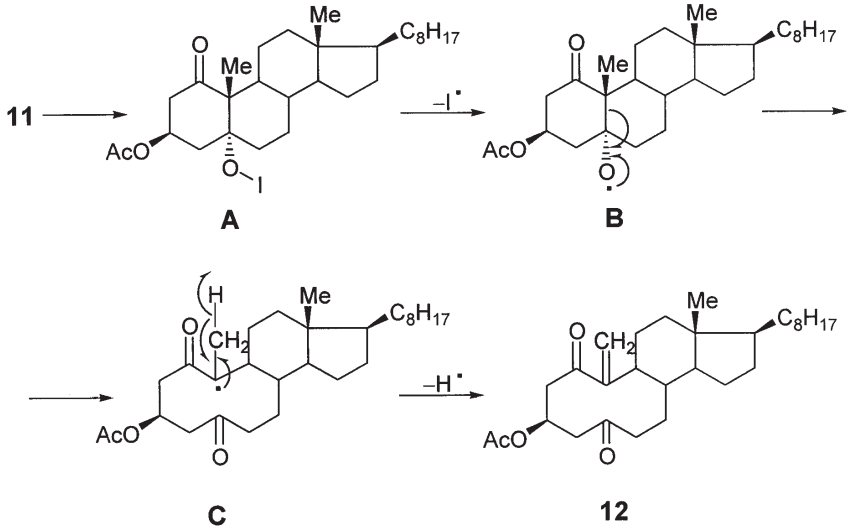
The structure of **13** was deduced from its analytical and spectral data (IR, ^{1}H-NMR, ^{13}C-NMR, MS). In the IR spectrum, the absorption of the 1-oxo group was replaced by a new absorption at 3483 cm^{-1} of the 1-hydroxy group. The IR band at 1643 cm^{-1} indicates that the exocyclic methylidene group still existed, which was confirmed by ^{1}H- and ^{13}C-NMR data. Its ^{1}H-NMR spectrum contained a pair of singlets at 4.86 and 5.00 ppm of the CH_2=C(10) group. Also, the ^{13}C-NMR spectrum contained the following characteristic signals: a triplet at 105.4 ppm of the C(19), a singlet at 74.0 ppm of the C(1) and a doublet at 56.0 ppm of the C(6). The *cis*-1β,6β-stereochemistry for the cyclization product **13** was deduced from its ^{1}H-NMR spectral characteristics. The signal for the H_β–C(6) (due to the deshielding influence by the 5-carbonyl group), was shifted downfield and appeared at 2.88 ppm as a *fine doublet of doublets*, indicating a dihedral angle of about 60º (J = 5.5 Hz) between the H_β–C(6) and H_β–C(7) and 180º (J = 13.5 Hz) between the H_β–C(6) and H_2C(7), and the "W" arrangement of the H_β–C(6)–C(5)–C(4)–H_β (J = 1.8 Hz), which is present only in the 1β,6β-isomer.

The LTA version of the hypoiodite reaction[8] of **11** was carried out with a large excess of oxidant in benzene solution by irradiation with a 15 W-lamp at 220 V at room temperature for 30 min, *i.e.*, until **11** had been completely consumed. The resulting mixture was separated by column chromatography (silica gel), affording the previously described compound **12** in a very good yield of 73 % and the cyclization product **13** in a 10 % yield (Scheme 4).

The thermal LTA oxidation of **11** was carried out with an excess of oxidant in the presence of $CaCO_3$ in boiling benzene for 48 h (practically, the reaction mixture was not changed after 4 h). After separation by chromatography on silica gel, the reaction mixture gave 1,5-dioxo-5,10-secocholest-10(19)-en-3β-yl acetate (**12**) (18 %), the starting compound **11** (43 %) and the cyclization product **13** (7 %) (Scheme 4).

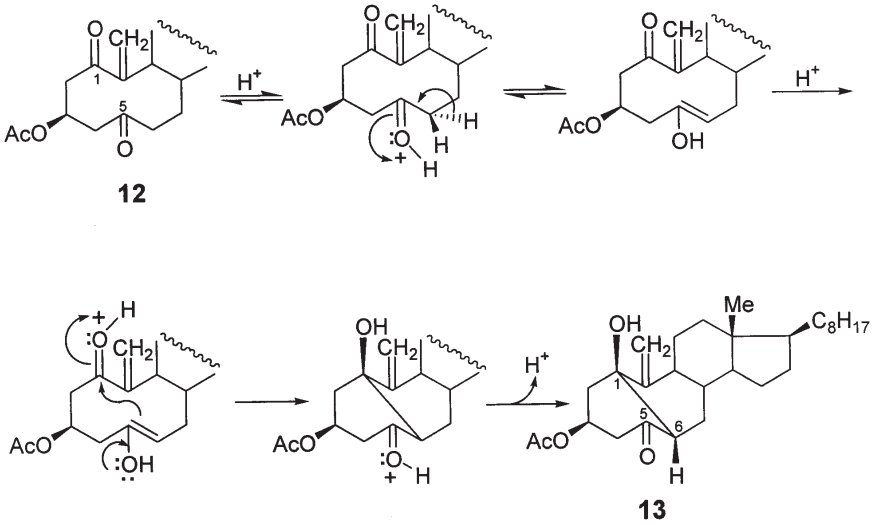
From the above results it follows that the described oxidations of 5-hydroxy-1-oxo-5α-cholestan-3β-yl acetate (**11**) proceed (exclusively with HgO/I_2 and LTA/I_2 under Ar) as

expected *via* the C(10)-centered radical **C** (Scheme 6) which is formed according to the generally accepted mechanism,[8,9] *i.e.*, the homolysis of the O–I bond in the primarily formed species **A** is followed by fragmentation of the C(5)–C(10) bond in the thus obtained alkoxy radical **B**. The radical **C** is then stabilized by elimination of a H-atom from the Me(19) to give the 10-methylidene seco ketone **12**.



Scheme 6.

The formation of the cyclization product **13** may be explained by an acid-catalyzed intramolecular aldol reaction in compound **12** during the chromatography on SiO_2 (Scheme 7).



Scheme 7.

EXPERIMENTAL

General.

Prep. column chromatography: silica gel Merck 0.063–0.200 mm. TLC: control of reaction and separation of products on silica gel 60 F_{254} (Merck) with benzene/EtOAc 9:1, 8:2 and 7:3, detection with 50 % aq. H_2SO_4 soln. Mps.uncorrected. IR spectra: Perkin-Elmer-337 spectrophotometer; ν in cm^{-1}. NMR spectra: Varian Gemini 200 (^1H at 200 MHz, ^{13}C at 50 MHz); $CDCl_3$ soln. at r.t., TMS as internal standard; chemical shifts in ppm as δ values. *J* in Hz. Mass spectra: Finnigan-MAT 8230.

*1α 5-Epoxy-5α-cholestan-3β-yl acetate (**7**)*[5]

A stirred solution of (*E*)-5-oxo-5,10-secocholest-1(10)-en-3β-yl acetate (**6**) (2 g) in acetone (200 ml) was irradiated with a high pressure mercury lamp TQ 150 Z2 (Hanau) at room temperature for 6 h, evaporated to dryness and the oily residue (2.16 g) chromatographed on silica gel (100 g). Elution with toluene-EtOAc (98:2) gave the unchanged (*E*)-secoketone **6** (0.36 g, 18 %). Further elution with the same eluent gave 1α,5-epoxy-5α-cholestan-3β-yl acetate (**7**) (0.73 g, 36.5 %) as a white solid, m.p. 101–102 ºC (from acetone). $[\alpha]_D$ = +20±2 (*c* = 1.0). IR (CH_2Cl_2): 1732, 1238, 1025. ^1H-NMR: 0.68 (*s*, 3H, CH_3(18)), 0.85 (*s*, 3H, CH_3(19)), 0.88 (*d*, 6H, CH_3(26), CH_3(27)), 0.92 (*d*, 3H, CH_3(21)), 2.07 (*s*, 3H, AcO), 2.41 (*dd*, *J* = 9.8, 14.8, 1H, H_α–C(4)), 2.71 (*m*, 1H, H_α–C(2)), 3.99 (*d*, *J* = 5.8, 1H, H–C(1)), 5.24 (*m*, 1H, H–C(3)). ^{13}C-NMR: 170.7 (*s*, O*C*OCH$_3$), 88.6 (*s*, C(5)), 83.2 (*d*, C(1)), 66.7 (*d*, C(3)), 56.1 (2*d*, C(14), C(17)), 47.0 (*d*, C(9)), 45.4 (*s*, C(10)), 42.4 (*s*, C(13)), 39.8 (*t*, C(12)), 39.5 (*t*, C(24)), 38.6 (*t*, C(4)), 36.1 (*t*, C(22)), 35.8 (*d*, C(20)), 34.1 (*d*, C(8)), 31.5 (*t*, C(2)), 31.0 (*t*, C(6)), 28.1 (*t*, C(16)), 28.0 (*d*, C(25)), 27.8 (*t*, C(7)), 24.4 (*t*, C(15)), 23.8 (*t*, C(23)), 23.1 (*t*, C(11)), 22.8 (*q*, C(27)), 22.5 (*q*, C(26)), 21.3 (*q*, OCO*C*H$_3$), 18.7 (*q*, C(21)), 11.8 (*q*, C(18)), 11.7 (*q*, C(19)). MS: *m*/*z* = 444 (M^+). Anal. calcd. for $C_{29}H_{48}O_3$ (444.696): C 78.33, H 10.88; found: C 78.18, H 10.87.

*Cholest-5-en-1α,3β-diol 3-acetate (**8**)*[5]

The oxetane derivative **7** (2.30 g) was dissolved in glacial AcOH (47 ml) and cooled to 5 ºC. To this semi-solid solution, a cooled solution of hydroiodic acid (0.98 ml 57 % HI) in glacial AcOH (30.5 ml) was added portionwise. The resulting mixture was left at 5 ºC for 30 min, diluted with H_2O and extracted with Et_2O. The ethereal extract was washed with H_2O, saturated aq. $NaHCO_3$ and H_2O, dried over Na_2SO_4 and evaporated to dryness, leaving a crystalline solid (2.4 g) which was chromatographed on SiO_2 (100 g). Elution with toluene-EtOAc (95:5) gave cholest-5-en-1α,3β-diol 3-acetate (**8**) (1.80 g, 78 %), m.p. 166–168 ºC (from acetone). $[\alpha]_D$ = – 41 (*c* = 0.7). IR (KBr): 3450, 3020, 1730, 1275, 1040. ^1H-NMR: 0.68 (*s*, 3H, CH_3(18)), 0.86 (*d*, 6H, CH_3(26), CH_3(27)), 0.91, (*d*, 3H, CH_3(21)), 1.04 (*s*, 3H, CH_3(19)), 2.03 (*s*, 3H, AcO), 3.86 (*brs*, 1H, H–C(1)), 5.03 (*heptet*, 1H, H–C(3)), 5.61 (*bd*, *J* = 5.2, 1H, H–C(6)). ^{13}C-NMR: 170.6 (*s*, O*C*OCH$_3$), 136.2 (*s*, C(5)), 126.5 (*d*, C(6)), 72.5 (*d*, C(1)), 69.5 (*d*, C(3)), 56.5 (*d*, C(17)), 56.0 (*d*, C(14)), 42.2 (*s*, C(13)), 41.7 (*s*, C(10)), 41.4 (*d*, C(9)), 39.4 (2*t*, C(12), C(24)), 37.2 (*t*, C(2)), 36.1 (*t*, C(22)), 35.7 (*d*, C(20)), 34.4 (*t*, C(4)), 31.7 (*d*, C(8)), 31.7 (*t*, C(7)), 28.1 (*t*, C(16)), 28.0 (*d*, C(25)), 24.3 (*t*, C(15)), 23.8 (*t*, C(23)), 22.8 (*q*, C(27)), 22.5 (*q*, C(26)), 21.3 (*q*, OCO*C*H$_3$), 20.1 (*t*, C(11)), 19.3 (*q*, C(21)), 18.7 (*q*, C(19)), 11.8 (*q*, C(18)). MS: *m*/*z* = 384 (M^+ – 60, 99 %). Anal. calcd. for $C_{29}H_{48}O_3$ (444.696): C 78.33, H 10.88; found: C 78.31, H 10.69.

*5,6α-Epoxy-5α-cholestan-1α,3β-diol 3-acetate (**9**)*[6]

A solution of **8** (1.00 g) in CH_2Cl_2 (25 ml) was treated with 85 % *m*-chloroperbenzoic acid (500 mg in 25 ml CH_2Cl_2) at room temperature for 1 h. After the usual work–up, the obtained residue (0.980 g, 96.4 %) was recrystallized from acetone to give 5,6α-epoxy-5α-cholestan-1α,3β-diol 3-acetate (**9**) (0.865 g, 83.5 %), m.p. 156 ºC. $[\alpha]_D$ = –11.0 (*c* = 1.09). IR (KBr): 3450, 3030, 1730, 1710, 1275, 1042. ^1H-NMR: 0.62 (*s*, 3H, CH_3(18)), 0.86 (*d*, 6H, CH_3(26), CH_3(27)), 0.89 (*d*, 3H, CH_3(21)), 1.10 (*s*, 3H, CH_3(19)), 2.02 (*s*, 3H, AcO), 2.82 (*d*, *J* = 4.8, 1H, H–C(6)), 3.90 (*brs*, 1H, H–C(1)), 5.30 (*heptet*, 1H, H–C(3)). ^{13}C-NMR: 170.1 (*s*, O*C*OCH$_3$), 72.8 (*d*, C(3)), 67.6 (*d*, C(1)), 64.0 (*s*, C(5)), 56.7 (*d*, C(17)), 56.5 (*d*, C(6)), 55.8 (*d*, C(14)), 42.3 (2*s*, C(10), C(13)), 39.4 (*t*, C(24)), 39.0 (*t*, C(12)), 36.6 (*d*, C(9)), 36.1 (*d*, C(20)), 35.7 (*t*, C(4)), 35.6 (*t*, C(2)),

34.7 (*t*, C(22)), 29.8 (*d*, C(8)), 28.6 (*t*, C(16)), 28.0 (*d*, C(25)), 27.9 (*t*, C(7)), 24.1 (*t*, C(15), 23.8 (*t*, C(23)), 22.8 (*q*, C(27)), 22.5 (*q*, C(26)), 21.2 (*q*, OCO*C*H$_3$), 19.7 (*t*, C(11)), 18.6 (*q*, C(21)), 16.5 (*q*, C(19)), 11.8 (*q*, C(18)). Anal. calcd. for $C_{29}H_{48}O_4$ (460.699): C 75.61, H 10.50; found: C 74.43, H 10.68. CI-MS: *m*/*z* = 461 ($M^+ + 1$).

*5α-Cholestan-1α,3β,5-triol 3-acetate (**10**)*[7]

A solution of **9** (1.8 g) in AcOH–EtOH (10:1, 110 ml) was hydrogenated over PtO_2 (180 mg) in a Parr Hydrogenator at room temperature and 3 atm pressure, for 13 h. After removal of the catalyst and solvent, the residue was chromatographed on SiO_2 (120 g). Elution with toluene–EtOAc (95:5) afforded the unchanged starting compound **9** (0.86 g, 44.0 %). Elution with toluene–EtOAc (90:10) gave 5α-cholestan-1α,3β,5-triol 3-acetate (**10**) (0.70 g, 35.7 %), m.p. 178–179 ºC (from acetone). IR (KBr): 3368, 1737, 1467, 1374, 1247. ^{1}H-NMR: 0.66 (*s*, 3H, CH_3(18)), 0.85 (*d*, 6H, CH_3(26), CH_3(27)), 0.92 (*d*, 3H, CH_3(21)), 0.94 (*s*, 3H, CH_3(19)), 2.03 (*s*, 3H, AcO), 2.99 (*s*, 1H, OH–C(5)), 3.82 (*m*, 2H, H–C(1) and OH–C(1)), 5.41 (*heptet*, 1H, H–C(3)). ^{13}C-NMR: 170.8 (*s*, O*C*OCH$_3$), 77.3 (*s*, C(5)), 74.0 (*d*, C(3)), 67.8 (*d*, C(1)), 56.2 (*d*, C(17)), 56.0 (*d*, C(14)), 42.7 (*s*, C(13)), 41.4 (*s*, C(10)), 40.1 (*d*, C(9)), 39.7 (*t*, C(12)), 39.4 (*t*, C(24)), 36.1 (*t*, C(4)), 35.8 (*d*, C(20)), 35.1 (*t*, C(22)), 34.7 (*t*, C(6)), 34.6 (*d*, C(8)), 29.6 (*t*, C(2)), 28.2 (*t*, C(16)), 28.0 (*d*, C(25)), 25.6 (*t*, C(7)), 24.1 (*t*, C(15)), 23.9 (*t*, C(23)), 22.8 (*q*, C(27)), 22.5 (*q*, C(26)), 21.4 (*q*, OCO*C*H$_3$), 20.7 (*t*, C(11)), 18.6 (*q*, C(21)), 16.6 (*q*, C(19)), 12.1 (*q*, C(18)). CI-MS: *m*/*z* = 445 (463–18), 385 (463–60–18).

*5-Hydroxy-1-oxo-5α-cholestan-3β-yl acetate (**11**)*

To a cooled (–5 ºC) solution of **10** (1.26 g) in acetone (165 ml), a slight excess of Killiani's chromic acid solution was added with constant stirring. After 20 min ice-cold H_2O was added, the precipitate was filtered off, washed thoroughly with H_2O and air-dried to give a residue (1.2 g, 95.7 %), which was chromatographed on SiO_2 (40 g). Elution with toluene–EtOAc (95:5) afforded 5-hydroxy-1-oxo-5α-cholestan-3β-yl acetate (**11**) which was recrystallized from acetone (0.98 g, 78.6 %), m.p. 138.5–140 ºC. IR (KBr): 3494, 3454, 1716, 1377, 1245, 1032. ^{1}H-NMR: 0.66 (*s*, 3H, CH_3(18)), 0.85 (*d*, 6H, CH_3(26), CH_3(27)), 0.88 (*d*, 3H, CH_3(21)), 1.28 (*s*, 3H, CH_3(19)), 2.04 (*s*, 3H, AcO), 2.62 (*dd*, *J* = 6.8, 13.4, 1H, H_α–C(4)), 2.81 (*dd*, *J* = 10.8, 12.8, 1H, H_β–C(2)), 5.30 (*m*, H–C(3)). ^{13}C-NMR: 209.4 (*s*, C(1)), 170.2 (*s*, O*C*OCH$_3$), 76.0 (*s*, C(5)), 69.2 (*d*, C(3)), 56.2 (*d*, C(17)), 55.8 (*d*, C(14)), 53.8 (*s*, C(10)), 43.1 (*t*, C(2)), 42.7 (*s*, C(13)), 41.0 (*d*, C(9)), 39.8 (*t*, C(12)), 39.4 (*t*, C(24)), 39.2 (*t*, C(4)), 36.1 (*d*, C(22)), 35.8 (*t*, C(20)), 34.9 (*d*, C(8)), 33.6 (*t*, C(6)), 28.0 (*t*, C(16)), 27.9 (*d*, C(25)), 24.9 (*t*, C(7)), 24.0 (*t*, C(15)), 23.9 (*t*, C(23)), 22.8 (*t*, C(11)), 22.8 (*q*, C(27)), 22.5 (*q*, C(26)), 21.2 (*q*, OCO*C*H$_3$), 18.5 (*q*, C(21)), 16.4 (*q*, C(19)), 12.3 (*q*, C(18)). MS: *m*/*z* = 460 (M^+), 443 (460–17), 401 (460–59), 383 (460–60–17).

*Oxidation of 5-hydroxy-1-oxo-5α-cholestan-3β-yl acetate (**11**)*

(i) Hypoiodite mercuric oxide/iodine oxidation. A stirred suspension of **11** (100 mg, 0.217 mmol), yellow HgO (325 mg, 1.5 mmol) and I_2 (437 mg, 1.7 mmol) in CCl_4 (30 ml) was irradiated with a 15 W (220 V) fluorescent lamp for 90 min without heating. All the time argon was introduced through the reaction mixture. The solid was removed by filtration, washed with Et_2O, and filtrate washed successively with water, 10 % aq. $Na_2S_2O_3$, saturated $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to dryness. The resulting mixture (111 mg) was chromatographed on silica gel (10 g). Elution with toluene-EtOAc (99:1, 98:2, 97:3) afforded a complex mixture (11 mg) which was not further investigated. Toluene–EtOAc (96:4) eluted 1,5-dioxo-5,10-secocholest-10(19)-en-3β-yl acetate **12** which was recrystallized from acetone/methanol (38 mg, 38 %), m.p. 157–158 ºC. IR (KBr): 1735, 1701, 1672, 1620, 1251, 1032. ^{1}H-NMR: 0.74 (*s*, 3H, CH_3(18)), 0.86 (*d*, 6H, CH_3(26), CH_3(27)), 0.90 (*d*, 3H, CH_3(21)), 2.05 (*s*, 3H, AcO), 2.44 (*m*, 2H, H_2–C(6)), 2.65 (*dd*, *J* = 3.5, 15.7, 1H, H–C(4)), 2.93 (*d*, *J* = 11.4, 1H, H–C(4)), 3.00 (*ABq*, *J* = 3.6, 2H, H_2C(2)), 5.60 (*m*, H–C(3)), 5.83 and 6.15 (2*s*, 2H, H_2C(19)). ^{13}C-NMR: 207.7 (*s*, C(5)), 199.4 (*s*, C(1)), 169.8 (*s*, O*C*OCH$_3$), 155.0 (*s*, C(10)), 124.6 (*t*, C(19)), 68.8 (*d*, C(3)), 56.1 (*d*, C(17)), 54.2 (*d*, C(14)), 46.5 (*t*, C(4)), 44.5 (*d*, C(9)), 43.1 (*t*, C(2)), 42.5 (*s*, C(13)), 41.8 (*t*, C(12)), 39.7 (*t*, C(24)), 39.5 (*t*, C(6)), 38.3 (*d*, C(8)), 36.0 (*t*, C(22)), 35.7 (*t*, C(20)), 33.4 (*t*, C(7)), 28.0 (*d*, C(25)), 27.8 (*t*, C(16)), 26.8 (*t*, C(15)), 24.9 (*t*, C(11)), 23.8 (*t*, C(23)), 22.8 (*q*, C(27)), 22.5 (*q*, C(26)), 21.1 (*q*, OCO*C*H$_3$), 18.6 (*q*, C(21)), 11.8 (*q*, C(18)), CI-MS: *m*/*z* = 459 ($M^+ + 1$).

Further elution with the same eluent afforded the starting compound **11** (27 mg, 27 %).

Further elution with toluene–EtOAc (95:5) gave compound **13** (28 mg, 28 %). Oil. IR (KBr): 3483, 1732, 1708, 1643, 1269, 1028. ^{1}H-NMR: 0.67 (*s*, 3H, CH_3(18)), 0.85 (*d*, 6H, CH_3(26), CH_3(27)), 0.92 (*d*, 3H, CH_3(21)), 2.08 (*s*, 3H, AcO), 2.20–2.64 (*m*, 4H, H_2C(2), H_2C(4)), 2.88 (*fdd*, *J* = 1.8, 5.5, 13.5, 1H, H_β–C(6)), 4.86 and 5.00 (2*fs*, *J* = 1.6, 2H, H_2–C(19)), 5.38 (*heptet*, 1H, H–C(3)). ^{13}C-NMR: 206.2 (*s*, C(5)), 170.2 (*s*, O*C*OCH$_3$), 154.3 (*s*, C(10)), 105.4 (*t*, C(19)), 74.0 (*s*, C(1)), 69.2 (*d*, C(3)), 56.7 (*d*, C(17)), 56.0 (2*d*, C(6), C(14)), 46.5 (*t*, C(4)), 42.8 (*s*, C(13)), 42.3 (*d*, C(9)), 41.1 (*d*, C(8)), 40.4 (*t*, C(2)), 39.4 (*t*, C(12)), 39.3 (*t*, C(24)), 36.1 (*t*, C(22)), 35.8 (*d*, C(20)), 29.7 (*t*, C(7)), 28.2 (*t*, C(16)), 28.0 (*d*, C(25)), 25.3 (*t*, C(15)), 24.8 (*t*, C(11)), 23.8 (*t*, C(23)), 22.8 (*q*, C(27)), 22.5 (*q*, C(26)), 21.2 (*q*, OCO*C*H$_3$), 18.6 (*q*, C(21)), 12.0 (*q*, C(18)).

(ii) Hypoiodite lead tetraacetate/iodine oxidation. A stirred suspension of LTA (450 mg, 0.91 mmol), I_2 (94 mg, 0.37 mmol) and **11** (100 mg, 0.217 mmol), in dry benzene was irradiated with a 15 W (220 V) fluorescent lamp at room temperature for 30 min. All the time argon was introduced through the reaction mixture. The solid was removed by filtration, washed with Et_2O and filtrate washed successively with water, 10 % aq. $Na_2S_2O_3$, saturated $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to dryness. The resulting mixture (141 mg) was chromatographed on silica gel (10 g). Elution with toluene–EtOAc (99:1, 98:2, 97:3) afforded a complex mixture (17 mg) which was not further investigated. Toluene–EtOAc (96:4) eluted 1,5-dioxo-5,10-secocholest-10(19)-en-3β-yl acetate **12** which was recrystallized from acetone/methanol (73 mg, 73 %), m.p. 157–158 ºC.

Further elution with toluene–EtOAc (95:5) gave compound **13** (10 mg, 10 %).

(iii) Thermal lead tetraacetate oxidation. A suspension of **11** (100 mg, 0.217 mmol), LTA (450 mg, 0.900 mmol) and anh. $CaCO_3$ (95 mg, 0.960 mmol) in anh. benzene (15 ml) was heated under reflux with stirring for 48 h, after which time the starch-iodine test became negative. The cooled mixture was diluted with Et_2O, washed with water, sat. aq. $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to dryness. The resulting mixture (116 mg) was chromatographed on silica gel (20 g). Elution with toluene–EtOAc (99:1, 98:2, 97:3) afforded a complex mixture (15 mg, 15 %) which was not further investigated. Toluene–EtOAc (96:4) eluted the 1,5-dioxo compound **12** (18 mg, 18 %).

Further elution with same eluent afforded the starting compound **11** (43 mg, 43 %).

Elution with toluene–EtOAc (95:5) gave the cyclic compound **13** (7 mg, 7 %).

*Cyclization of 1,5-dioxo-5,10-secocholest-10(19)-en-3β-yl acetate **12** on SiO_2*

1,5-Diketone **12** (40 mg) was stirred with SiO_2 (Merck, 0.063–0.20 mm) in toluene (5 ml) for 24 h at room temperature. After removal of the SiO_2 and solvent the residue was chromatographed on SiO_2 (4 g). Elution with toluene–EtOAc (96:4) gave unchanged starting material **12** (18 mg, 45 %).

Further elution with toluene–EtOAc (95:5) afforded compound **13** (17.2 mg, 43 %).

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ИЗВОД

ОКСИДАТИВНЕ ФРАГМЕНТАЦИЈЕ 5-ХИДРОКСИ-1-ОКСО-5α-ХОЛЕСТАН-3β-ИЛ-АЦЕТАТА

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Синтетизован је 5-хидрокси-1-оксо-5α-холестан-3β-ил-ацетат (**11**) у 5 фаза полазећи од (*E*)-3β-ацетокси-5,10-секо-1(10)-холестен-5-она (**6**). Дејством олово-тетраацетата (LTA) (под термичким или хипојодитним условима), или меркури-оксид/јодног реагенса (HgO/I_2) на 1-оксо-5-хидрокси дериват **11**, врши се оксидативна β-фрагментација његове C(5)–C(10) везе, при чему се добија 1,5-диоксо-5,10-секохолест-10(19)-ен-3β-ил-ацетат (**12**), у различитим приносима у зависности од употребљеног реагенса. Такође, дискутована је стереохемија 1β,6β-циклизационог производа **13**, насталог интрамолекулском циклизацијом 1,5-диоксо-5,10-секо једињења **12** на силика гелу.

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