13,14-Seco-steroids: A New Type of Modified Steroids Containing a Nine-Membered Ring

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In memory of Prof. *D.H.R. Barton,* deceased on March 16, 1998

Oxidations of 14α-hydroxy-5α-cholestan-3β-yl acetate (**5**) with lead tetraacetate under thermal or photolytic conditions or in the presence of iodine proceed mainly by fragmentation of the C(13)–C(14) bond to give as the primary products the 13,18-didehydro-13,14-seco derivative **6** and the (*E*)-Δ^{12}-13,14-seco ketone **11**, respectively. Further transformations of these compounds under conditions of their formation afforded, in addition, the acetoxy derivatives **7**–**9** (from **6**), and the D-homo-C-nor compound **12** and (12*R*,13*R*)-epoxide **13** (from **11**). Unexpectedly, the photolytic lead-tetraacetate oxidation of **5** resulted partly (to *ca.* 20%) in a reversible fragmentation involving scission and recombination of the C(8)–C(14) bond followed by formation of the 14β,22-ether **10**. Possible mechanisms for the observed transformations are discussed.

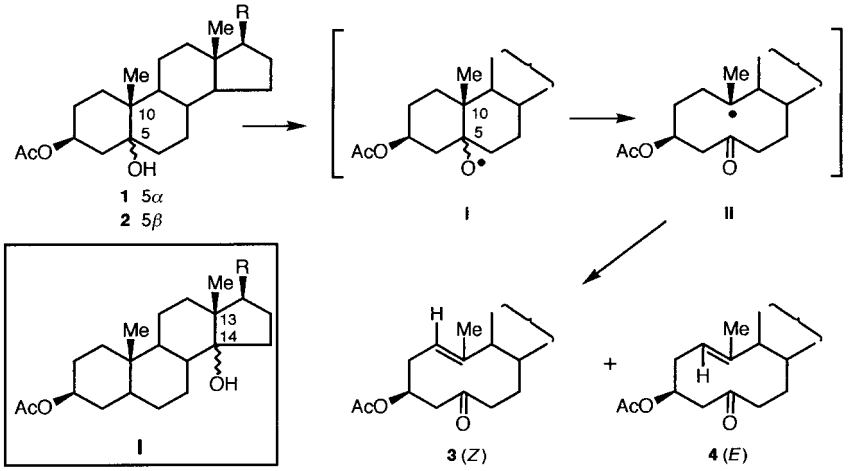
1. Introduction. – Previous studies have shown that alkoxy radicals of type **i** (obtained by oxidation of 5α- or 5β-hydroxy steroids such as **1** and **2** with lead tetraacetate under thermal or photolytic conditions or with hypoiodite-forming reagents) readily undergo β-fragmentation of the C(5)–C(10) bond (*Scheme 1*). *Via* the C-radical intermediates **ii** are formed, thereby, in high yield and, depending on the oxidant used, in different proportions [1], the diastereomeric (*Z*)- and (*E*)-1(10)-unsaturated 5,10-secosteroidal 5-ketones **3** and **4**. The direction of β-fragmentation in **1** and **2** to give exclusively the 5,10-seco ketones 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 the angular Me(18) group would likewise stabilize the corresponding C(13)-radical intermediate, which could be generated by similar oxidative processes starting from 14-hydroxy steroids of type **I** (*Scheme 1*). In that case, one could expect as final products 13,14-secosteroidal derivatives containing, instead of the steroid rings C and D, a nine-membered ring[1]). In the present work, we investigated, therefore, the possibility of inducing an oxidative β-fragmentation of the C(13)–C(14) bond in 14-hydroxy steroids. As substrate, we

† Our esteemed teacher, colleague, and friend, deceased on June 8, 1998.

[1]) A single example of oxidative β-fragmentation of the C(13)–C(14) bond in a 14α-hydroxy-17-oxo steroid with LTA/I_2 to the corresponding 13-iodo-14,17-dioxo derivative has been mentioned by *Kalvoda* and *Heusler* [2].

Scheme 1



used the 14α-hydroxy-5α-cholestan-3β-yl acetate (**5**) [3]. Oxidations of **5** with lead tetraacetate (LTA) and hypoiodite-forming reagents (hypoiodite reaction [2]) were performed under conditions similar to those previously applied to the 5-hydroxy steroids [1].

2. Results. – 2.1. *Thermal Lead-Tetraacetate Oxidation.* The thermal lead-tetraacetate oxidation of **5** was carried out with an excess of oxidant in the presence of $CaCO_3$ in boiling benzene for 47 h (*Scheme 2*). The resulting product mixture was separated by column chromatography (silica gel). Analysis of the products revealed that oxidation of **5** resulted indeed in a β-fragmentation of the C(13)–C(14) bond to give the methylidene derivative **6** (16.7% yield) and the corresponding acetoxy analogues **7**–**9** (8.5, 21.0, and 22.6%, resp.), along with unreacted starting material (11%). The acetoxy derivatives **7**–**9** arose from the LTA acetoxylation of **6** at the α-positions next to the 14-oxo and/or 13-methylidene group.

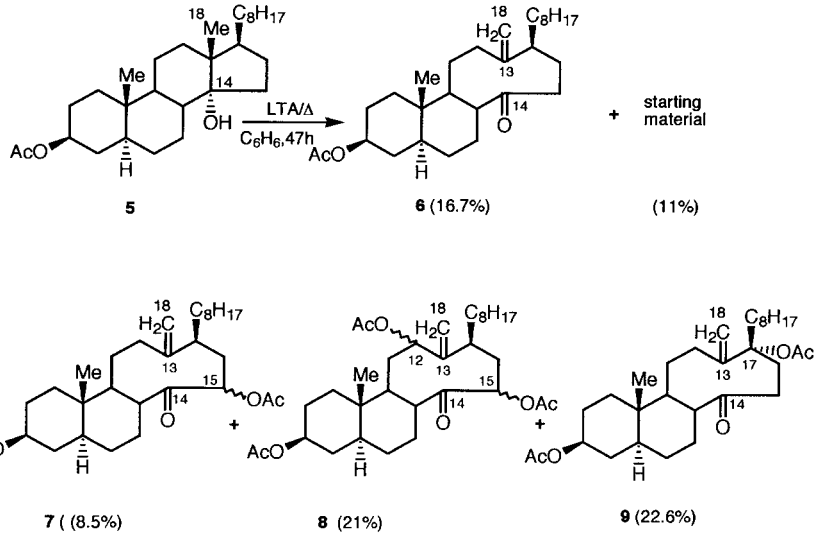
The structures **6**–**9** were deduced from their analytical and spectroscopic data (IR, ^{1}H-NMR, ^{13}C-NMR, MS). In addition, structure **6** was unequivocally confirmed by X-ray analysis[2]).

In the IR spectra of **6**–**9**, the absorption of the original 14α-hydroxyl group was replaced by a new absorption at 1700 cm^{-1} for the 14-oxo group. IR Bands at ca. 3070 and 1640 cm^{-1} indicated that these compounds contain an exocyclic methylidene group which was confirmed by the ^{1}H- and ^{13}C-NMR data. Instead of the signals for the Me(18) group, the ^{1}H-NMR spectra showed a pair of *s* at 4.85–5.25 ppm and the ^{13}C-NMR spectra a *t* at 115–120 ppm.

The positions of acetoxylation in **7**–**9** were deduced mainly from their ^{1}H-NMR data. For **7**, a *s* at 2.07 and a *dd* at 5.41 ppm indicated acetoxylation at C(15) next to the 14-oxo function (calculated value for O=C–C*H*(OAc): 5.40 ppm [4]). For **8**, the new signals, 2 *s* at 2.01 and 2.08 ppm and 2 *m* at 5.26 and 5.38 ppm, showed that C(12) and C(15) next to both the 13-methylidene and the 14-oxo group, respectively,

[2]) There are two independent molecules in the asymmetric part of the unit cell of **6**. These two molecules have very similar conformations. The crystals used for the analysis were of poor quality which explains the rather low 2 Θ_{max} and the high standard deviations in the geometrical parameters.

Scheme 2



were acetoxylated[3]). In contrast to **7** and **8**, the additional AcO group of compound **9** gave rise to only 1 *s* at 1.97 ppm, indicating that a tertiary acetate was formed. Its 17α- rather than 8β-position was suggested by a strong deshielding effect exerted by this acetoxy group on one of the protons of the 13-methylidene group, causing their *s* to almost coincide (5.23 and 5.25 ppm, resp.).

2.2. *Photolytic Lead-Tetraacetate Oxdiation.* The photolytic lead-tetraacetate oxidation of **5** was carried out in benzene solution with 3 mol-equiv. of oxidant in the presence of $CaCO_3$, by irradiation with a high-pressure mercury lamp (*Q81*) at room temperature for 1 h (*Scheme 3*). By that time, practically all starting material was consumed. Separation of the products by column chromatography (silica gel) afforded the six-membered cyclic 14β,22-ether **10** (20.4% yield), the previously described 13(18)-unsaturated 13,14-seco ketone **6** (14.9%), its isomeric 12-unsaturated (*E*)-13,14-seco ketone **11** (35.0%), and the D-homo-C-nor cyclization product **12** (10.0%). The structures of **10**–**12** were established by spectroscopic methods, and the (*E*)-configuration of **11** was confirmed by X-ray analysis.

The absence of the 14α-hydroxy groups in the IR spectrum of **10** and the appearance of a new ether band at 1092 cm^{-1} indicated an intramolecular cyclization involving the initial OH group. In the ^{1}H-NMR spectrum, 2 *s* at 0.97 and 0.83 ppm for Me(18) and Me(19) and a *t* at 3.05 ppm for a proton next to an ether moiety established that the steroidal character of **10** was preserved and, also, that the oxidative cyclization had occurred at a CH_2 group. Several possible structures consistent with these data and with the steric requirements for cyclization had to be considered; however, evidence for the 14β,22-ether structure of **10** was obtained from its mass spectrum ($M^{+\cdot}$ 444 (52.5%)).

A strong peak at *m*/*z* 344 ($[M^+ - 100]^{+\cdot}$ (100%)) clearly demonstrated that a C_6-aldehyde fragment was eliminated (see *Scheme 4*). This is feasible only for a compound possessing an ether O-atom attached at C(22). The Δ^{12}-unsaturated 13,14-seco ketone **11** showed the following characteristic ^{1}H- and ^{13}C-NMR signals: the

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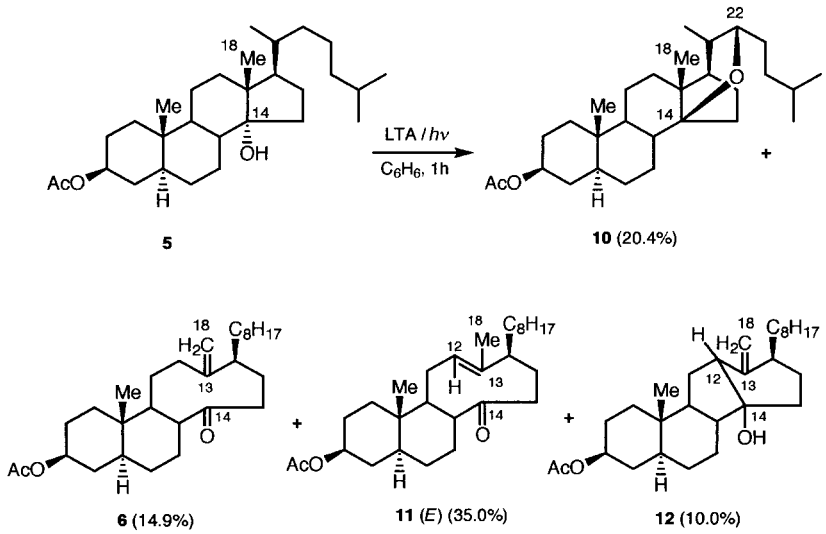
[3]) Although in both compounds **7** and **8**, the position of the acetoxylation is well established, the configuration of the introduced group could not be defined with certainty on the basis of present evidence.

Scheme 3

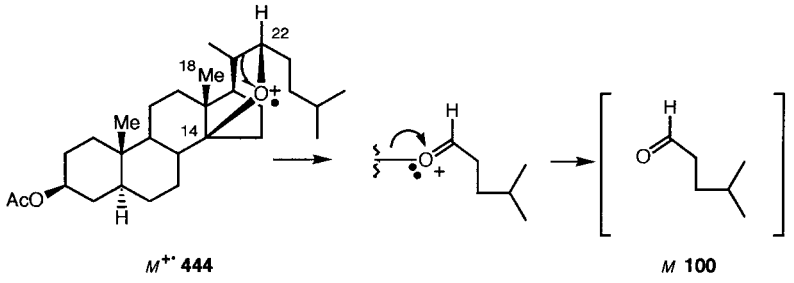


5 **10** (20.4%) **6** (14.9%) **11** (*E*) (35.0%) **12** (10.0%)

original AcO group at 1.76 ppm (*s*), 1 olefinic proton at 4.89 ppm (*d*), 1 Me group at the C=C bond at 1.38 ppm (*s*), and a C=O function at 209.9 ppm (*s*).

For steric reasons, the configuration of the 14α-hydroxy group of the starting molecule **5** had to change prior to cyclization to **10** involving the β-oriented cholestane side chain[4]).

Scheme 4



$M^{+\cdot}$ **444** *M* **100**

Moreover, **12** (data in the *Exper. Part*) was shown to be a secondary product formed from the (*E*)-seco ketone **11** by intramolecular cyclization, either in the course of the reaction or during the workup procedure. The stereochemistry of this cyclization has not been established as yet.

2.3. *Lead-Tetraacetate Version of the Hypoiodite Reaction.* The lead tetraacetate version of the hypoiodite reaction [2] of **5** was carried out with a large excess of oxidant in benzene solution by irradiation with a 800-W lamp at 60 V at room temperature for

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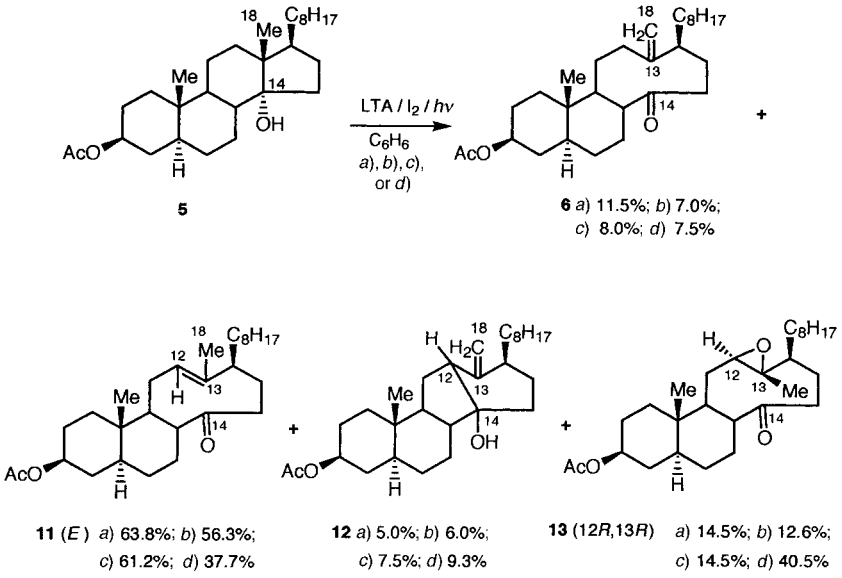
[4]) An analogous cyclization should be possible between the 14α-OH group and C(22) of a side chain with an inverted configuration at C(17).

ca. 1 h, *i.e.*, until **5** was completely consumed (conditions *a* in *Scheme 5*). The resulting mixture was separated by chromatography (silica gel), affording both isomeric 13,14-seco ketones **6** and **11** (11.5 and 63.8% yield, resp.), the cyclization product **12** (5.0 % yield), and, unexpectedly, the (12*R*,13*R*)-epoxide **13** (14.5%) derived from the 12-unsaturated (*E*)-13,14-seco ketone **11**. Similar results were obtained when the reaction was performed under Ar (conditions *b*) or O_2 (conditions *c*), thus indicating that the epoxide O-atom does not originate from air. However, when the reaction temperature was raised to 70° (conditions *d*), epoxide **13** was formed in considerably higher yield (40.5%). Its structure was deduced from spectral data (see *Exper. Part*), and confirmed by X-ray analysis.

Scheme 5

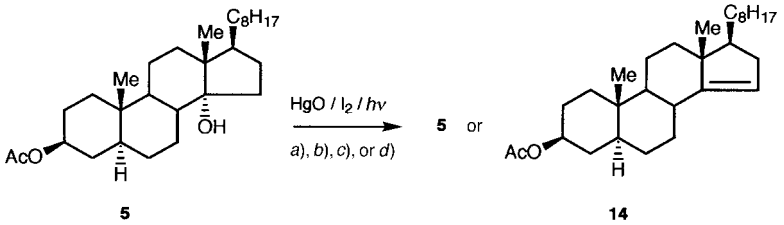


a) 1 h, air, r.t. b) 0.5 h, Ar, r.t. c) 0.5 h, O_2, r.t. d) 6 min, Ar, 70°.

To establish whether epoxide **13** was formed from **5** directly or after its fragmentation to the unsaturated seco ketone **11**, the latter compound was subjected to the LTA/I_2 oxidation in benzene solution at 70° which afforded **13** in almost quantitative yield.

2.4. *Mercury(II) Oxide/Iodine Version of the Hypoiodite Reaction.* The HgO/I_2 version of the hypoiodite reaction of **5** performed with an excess of oxidant in CCl_4 solution by irradiation with a 800-W lamp at 60 V at room temperature for 1 h left the starting material practically unchanged (recovery of **5** > 90%, besides an unresolvable complex mixture). After a prolonged irradiation for 60 h, *ca.* 70% of **5** was recovered. Similarly, attempted HgO/I_2 oxidation of **5** in benzene solution by irradiation with a high pressure mercury lamp (*Q 81*) at room temperature for 17 h was without effect (by TLC monitoring). However, when the above irradiation was performed at 70° for 5 h, the starting molecule was dehydrated to give the known 14-unsaturated compound **14** [5] in *ca.* 95% yield (*Scheme 6*).

Scheme 6



5 **14**

a) CCl_4, 1 h, r.t.; 93% of **5**. b) CCl_4, 60 h, r.t.; 70% of **5**. c) C_6H_6, 17 h, r.t.; unchanged **5**. d) C_6H_6, 5 h, 70°; 95% of **14**.

3. X-Ray Crystal-Structure Analysis of Compounds 11 and 13. – As mentioned above, the structures deduced for compounds **11** (*Fig. 1*) and **13** (*Fig. 2*) were confirmed by X-ray analysis (*cf. Table*).

H-Atom positions were calculated with the assumption of normal geometry. Lists of fractional atomic coordinates, isotropic thermal parameters, and bond lengths and angles have been deposited at the *Cambridge Crystallographic Data Centre* as supplementary publication No. 102113 (for **11**) and 102114 (for **13**).

Table. *Crystal Data of Compounds* **11** *and* **13**

	11	**13**
Formula	$C_{29}H_{48}O_3$	$C_{29}H_{48}O_4$
M_r	444.67	460.67
Temperature	293(2) K	293(2) K
Wavelength	1.54178 Å	1.54178 Å
Crystal system	orthorhombic	orthorhombic
Space group	*P*212121	*P*212121
Unit-cell dimension	$a = 10.2000(10)$ Å $\alpha = 90°$ $b = 11.952(2)$ Å $\beta = 90°$ $c = 22.503(3)$ Å $\gamma = 90°$	$a = 10.148(10)$ Å $\alpha = 90°$ $b = 12.095(2)$ Å $\beta = 90°$ $c = 22.300(3)$ Å $\gamma = 90°$
Volume	2743.3(6) Å^3	2737.1(10) Å^3
Z	4	4
Density (calc.)	1.077 Mg/m^3	1.118 Mg/m^3
Absorption coefficient	0.518 mm^{-1}	0.5563 mm^{-1}
F (000)	984	1016
Crystal size	0.24 × 0.20 × 0.18 mm	0.28 × 0.16 × 0.16 mm
Θ range for data collection	3.93–67.50°	3.96–67.45°
Index ranges	$0 \le h \le 12$, $0 \le k \le 14$, $-26 \le l \le 26$	$0 \le h \le 12$, $0 \le k \le 14$, $-26 \le l \le 26$
Reflections collected	5493	5458
Independent reflection	4956 (R(int) = 0.0467)	4937 (R(int) = 0.0576)
Refinement method	full-matrix least squares on Fsqd	full-matrix least squares on Fsqd
Data/restraints/parameters	4956/0/293	4937/0/303
Goodness-of-fit (all data)	1.045 (1.126)	0.956 (1.135)
Final *R* indices ($I > 2\sigma(I)$)	$R1 = 0.0641$, $wR2 = 0.1796$	$R1 = 0.0626$, $wR2 = 0.1486$
R indices (all data)	$R1 = 0.0789$, $wR2 = 0.1922$	$R1 = 0.0976$, $wR2 = 0.1629$
Absolute structure parameter	−0.1 (4)	1.2 (4)
Extinction coefficient	–	0.0033 (4)
Largest diff. peak and hole	0.189 and −0.203 e · Å^{-3}	0.195 and −0.190 e · Å^{-3}

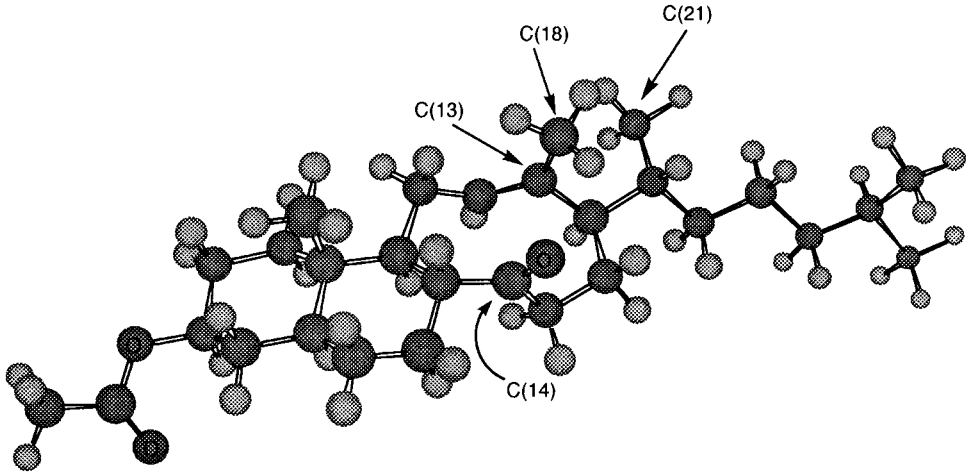


Fig. 1. *X-Ray crystal structure of* **11**

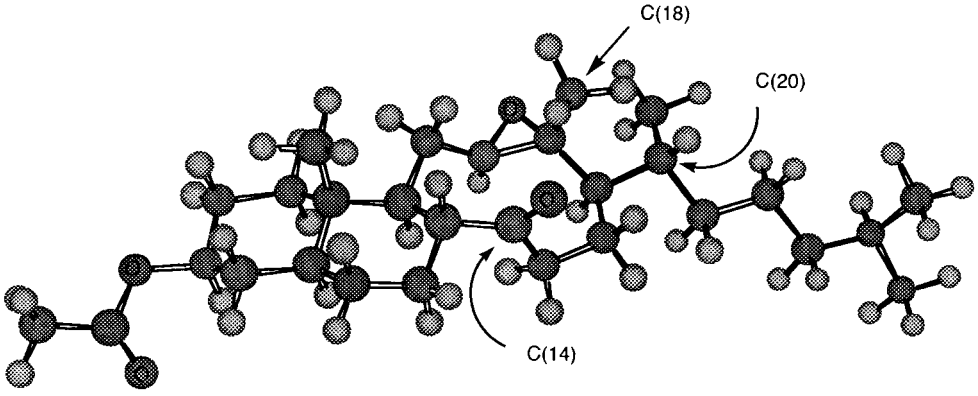


Fig. 2. *X-Ray crystal structure of* **13**

Conformations of the nine-membered rings in **11** and **13** are very similar (*cf. Fig. 3*) and fit one of the low-energy conformations of the corresponding monocyclic compound.

Discussion. – From the above results it follows that the described oxidations of 14α-hydroxycholestane derivative **5** proceed (exclusively with LTA/heating, with LTA/I_2, and preferentially with LTA/*hv*) as expected *via* the C(13)-centered radical **C** (*Scheme 7*), which is formed according to the generally accepted mechanism[5]); *i.e.*, homolysis of the O–X bond (X = $Pb(OAc)_3$ or I) in the primarily formed species **A** is

[5]) For a more detailed mechanistic scheme of oxidative β-fragmentation of alcohols with LTA and hypoiodite-forming reagents, see [6][7].

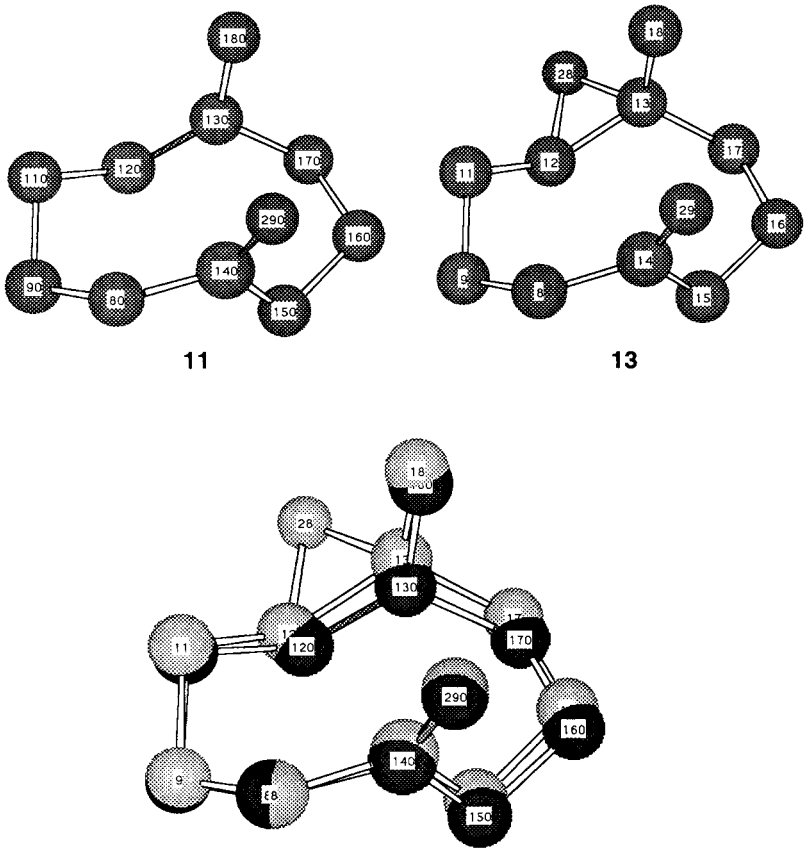


Fig. 3. *Comparison of the conformations of the nine-membered rings in* **11** *and* **13**

followed by fragmentation of the C(13)–C(14) bond in the alkoxy radical **B** thus obtained.

However, the behavior of the C(13)-radical **C** differs considerably from that of the corresponding ten-membered ring analogue **ii** (see *Scheme 1*). Radical **C** is stabilized either by elimination of a H-atom from Me(18) (path *a*) to give the 13-methylidene seco ketone **6**, or by elimination of H_β–C(12) (path *b*) to produce stereoselectively the 12-unsaturated (*E*)-seco ketone **11**[6]).

In addition, the primarily formed 13,14-seco derivatives **6** and **11**, under conditions of their formation, react further either with the oxidant or with some other species present in the reaction solution.

Thus, in the thermal LTA oxidation, seco ketone **6** undergoes the known allylic and α-acetoxylation with LTA [8] to give products **7**–**9**.

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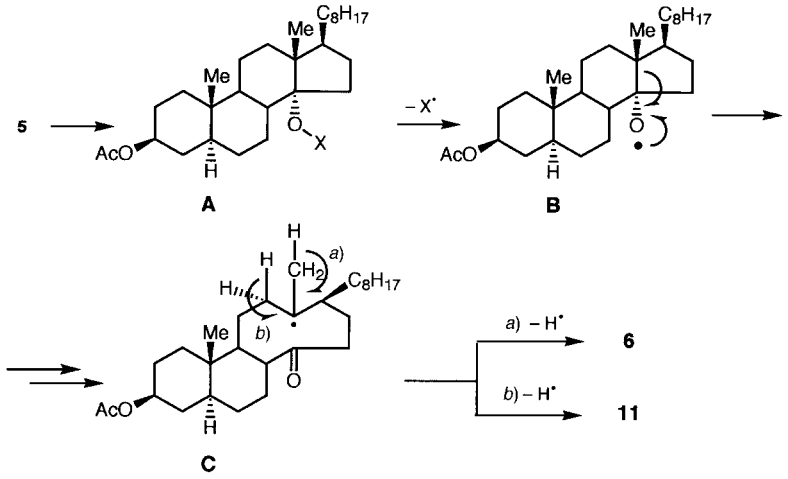
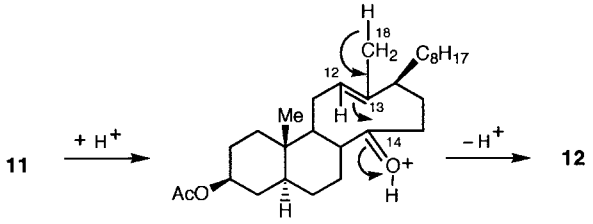
[6]) The corresponding (*Z*)-stereoisomer, if formed at all, is probably only a minor component of the reaction mixture, and could not be isolated in pure form.

Scheme 7



Under conditions of the photolytic LTA oxidation and of the hypoiodite (LTA) reaction, the primarily formed (*E*)-seco ketone **11** is rearranged to the D-homo-C-nor compound **12**[7]). Presumably, the reaction is initiated by protonation of the 14-oxo group to proceed with transannular participation by π-electrons of the C(12)=C(13) bond, as shown in *Scheme 8*.

Scheme 8



Moreover, an unexpected epoxidation of the (*E*)-Δ^{12}-double bond of seco ketone **11** leading to **13** was observed under the LTA/I_2 oxidation conditions. Most probably, the active species in this reaction is I_2O[8]) which could be formed from the intermediates participating in the hypoiodite reaction of alcohols (see *Scheme 9*).

The unusual formation of a tetrahydro-2*H*-pyran derivative, the 14β,22-ether **10**, in the photolytic LTA oxidation of **5** deserves a more detailed discussion. In this remarkable case, the configuration at C(14) has been reversed (*cf. Fig. 4*).

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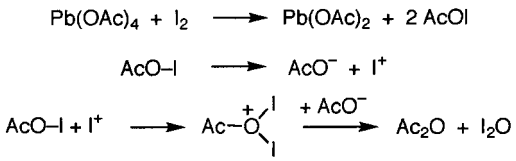
[7]) Similar B-homo-A-nor cyclization products, arising from the ten-membered ring of (*E*)-5,10-seco ketones of type **4** (*Scheme 1*) are formed in the LTA/I_2 and HgO/I_2 oxidations of 5α- and 5β-hydroxy steroids **1** and **2**.

[8]) Epoxidation of some unsaturated steroid derivatives with I_2O was observed during their oxidation with the HgO/I_2 reagent [9].

Scheme 9



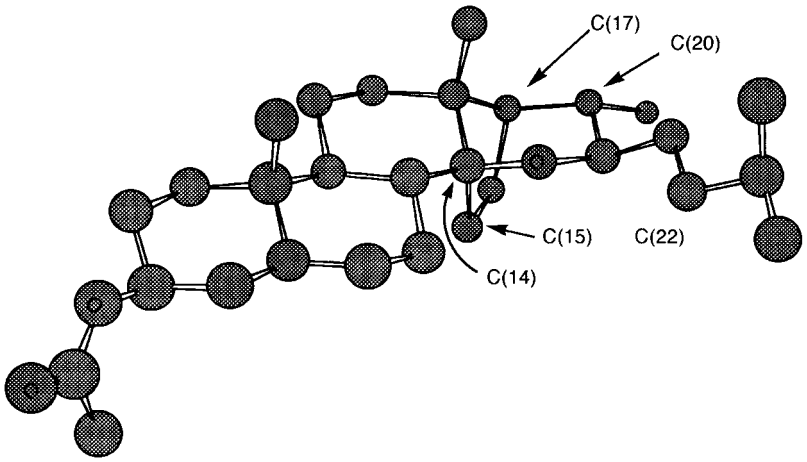
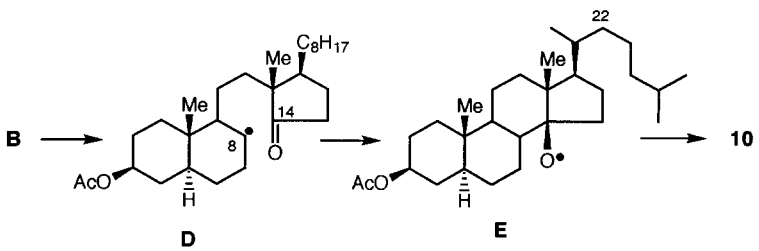


Fig. 4. *C-Skeleton of the energy-minimized structure of* **10**

This observation can be explained by a reversible fragmentation[9]) of radical **B** (*cf. Scheme 7*), proceeding probably *via* radicals **D** and **E** (*Scheme 10*) and involving a splitting and regeneration of the C(8)–C(14) bond[10]). The generally higher thermodynamic stability of the *cis- vs.* the *trans*-hydrindan structure might, at least partially, explain the formation of the isomeric 14β-derivative.

Scheme 10



Two conditions must be fulfilled for an intramolecular H-abstraction from C(22) by the O-radical **E**, the first step in the generation of a cyclic ether [6], namely an optimal O$^{\bullet}\cdots$C(H) distance (*ca.* 2.5–3 Å), and a quasi-linear arrangement of the three

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9) For analogous processes in the course of LTA oxidations of steroidal alcohols, *cf.* [10] or [11].

10) The alternative transannular ring closure of radical **C** (*cf. Scheme 7*), the compulsory intermediate in the formation of compounds **6** and **11**, appears less probable.

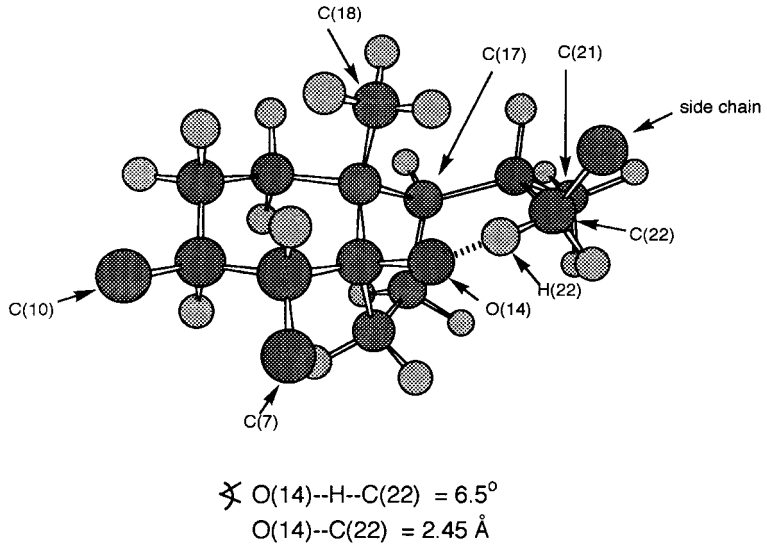

Fig. 5. *Possible transition state for the H-abstraction at C(22)* (**E** → **10**)

involved centers (−O˙···H···C−). These prerequisites are usually met by the 6-membered transition state leading to the formation of tetrahydrofurans. Nevertheless, various examples of generation of a tetrahydro-2*H*-pyrane *via* a 7-membered transition state have been described [2][6][12][13], a transition state proposed for the step **E** → **10**, as the O-radical and the H-atoms of CH_2(22) lie on the same β side of ring D (see *Fig. 5*). The distance between O(14) and C(22) can be calculated as a function of the rotation angle of the cholestane C_8 side chain about the C(17)–C(20) bond (*Fig. 6*); as expected, the optimal distance is reached after a rotation of the side chain by *ca.* 300–330° from the starting position[11]). The starting conformation (rotation by 0 or 360°) represents indeed one of the thermodynamically more stable arrangements of the side chain (cf. relative-energy profile in *Fig. 6*). These two pieces of evidence combined could, therefore, be used to explain the generation of compound **10** in the photochemical[12]) LTA oxidation of **5**.

The authors from the University of Belgrade wish to thank the *Serbian Academy of Sciences and Arts* and the Ministry of Sciences and Technology of Serbia for financial support.

Experimental Part

1. *General.* Column chromatography (CC): silica gel 0.04–0.063 mm. Anal. and prep. TLC: silica gel *G* (*Stahl*), detection with aq. 50% H_2SO_4 soln. M.p.: uncorrected. IR Spectra: *Perkin-Elmer-337* spectropho-

[11]) The starting position is obtained by the formal scission of the O(14)–C(22) bond in **10**, followed by energy minimization (by the MM2 program of *CS Chem3D Pro*).

[12]) The difference in the thermal and photochemical LTA oxidation of alcohol **5** is not easy to explain. Speculating, one might consider a stronger involvement of radical intermediates having a more polar character in the thermal reaction compared to the situation in the photochemical case. In the presence of I_2 (hypoiodite reaction), a reversible fragmentation has not been observed, as the C-radical formed primarily can be trapped by I_2.

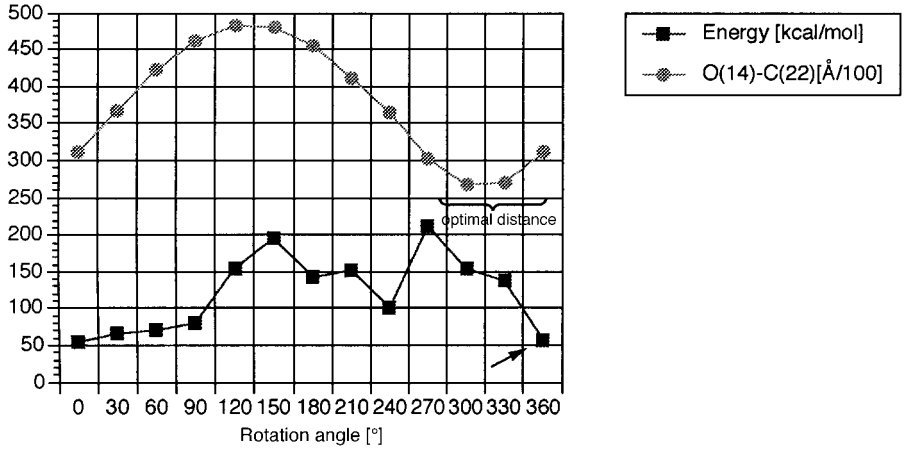

Fig. 6. *Rotation of the side chain in* **E**: *rotation angle* vs. *the distance O(14)···C(22) and* vs. *the energy*

tometer; ν in cm^{-1}. NMR Spectra: *Varian Gemini 200* and *Bruker AM-250* (^1H at 200 or 250 MHz, ^{13}C at 50 or 62.5 MHz); $CDCl_3$ or C_6D_6 soln. at r.t.; $SiMe_4$ as internal standard; δ in ppm, J in Hz. Mass spectra: *Finnigan-MAT 8230*; *m/z* (rel. intensity in %); ionization energy 70 eV.

2. *Oxidations.* 2.1. *Thermal LTA Oxidation of 14α-Hydroxy-5α-cholestan-3β-yl Acetate* (**5**). A suspension of **5** (500 mg, 1.12 mmol), LTA (730 mg, 1.65 mmol), and $CaCO_3$ (165 mg, 1.65 mmol) in dry benzene (45 ml) was heated under reflux with stirring for 20 h, after which time the starch/KI test was negative. Additional amounts of LTA (500 mg, 1.13 mmol) and of $CaCO_3$ (113 mg, 1.13 mmol) were added, and the heating under reflux continued for 27 h. The mixture was cooled to r.t. and diluted with Et_2O, the insoluble precipitate filtered off through *Celite* and washed with Et_2O, the org. soln. washed successively with aq. $Na_2S_2O_3$ soln., aq. $NaHCO_3$ soln., and H_2O, dried (Na_2SO_4), and evaporated, and the resulting mixture (590 mg) separated by CC (SiO_2 (150 g), toluene/AcOEt 96:4): **6** (83 mg, 16.7%), **7** (48 mg, 8.5%), **5** (55 mg, 11%), **8** (132 mg, 21.0%), and **9** (127 mg, 22.6%).

14-Oxo-13,14-seco-5α-cholest-13(18)-en-3β-yl Acetate (**6**): M.p. 91–92° (MeOH). $[\alpha]_D = +1.0$ ($c = 1$, $CeHCl_3$). IR (KBr): 3070, 1733, 1697, 1639, 1240, 1034, 891. ^1H-NMR (250 MHz, $CDCl_3$): 0.74 (*d*, Me(21)); 0.80 (*s*, Me(19)); 0.87 (*d*, Me(26), Me(27)); 2.03 (*s*, AcO); 2.41 (*t*, $J = 11.6$, H–C(17)); 2.65 (*d*, $J = 13.7$, H–C(8)); 4.72 (*m*, H–C(3)); 4.85, 5.00 (2 *s*, CH_2(18)). ^{13}C-NMR (50 MHz, $CDCl_3$): 219.4 (*s*, C(14)); 170.6 (*s*, Me*C*OO); 147.9 (*s*, C(13)); 114.9 (*t*, C(18)); 73.2 (*d*, C(3)); 56.3 (*d*, C(8)); 54.0 (*d*, C(17)); 44.5 (*d*, C(9)); 44.0 (*d*, C(5)); 39.4 (*t*, C(24)); 37.1 (*d*, C(20)); 36.3 (*t*, C(1)); 36.3 (*s*, C(10)); 34.2 (*t*, C(4)); 33.8 (*t*, C(22)); 33.6 (*t*, C(7)); 29.3 (*t*, C(6)); 27.9 (*d*, C(25)); 27.5 (*t*, C(2)); 26.7 (*t*, C(16)); 26.4 (*t*, C(12)); 25.4 (*t*, C(15)); 24.5 (*t*, C(23)); 22.7 (*q*, C(27)); 22.5 (*q*, C(26)); 21.4 (*q*, *M*eCOO); 17.6 (*q*, C(21)); 11.9 (*q*, C(19)). MS: 444 (26, M^+), 384 (6, $[M-60]^+$), 332 (62, $[M-112]^+$), 223 (100). Anal. calc. for $C_{29}H_{48}O_3$ (444.696): C 78.33, H 10.88; found: C 77.98, H 10.58.

14-Oxo-13,14-seco-5α-cholest-13(18)-ene-3β,15ξ-diyl Diacetate (**7**): Oil. $[\alpha]_D = +7.65$ (c = 0.85, $CHCl_3$). IR ($CHCl_3$): 3069, 1735, 1713, 1636, 1241, 1031, 895. ^1H-NMR (250 MHz, $CDCl_3$): 0.76 (*d*, Me(21)); 0.81 (*s*, Me(19)); 0.87 (*d*, Me(26), Me(27)); 2.04 (*s*, AcO–C(3)); 2.07 (*s*, AcO–C(15)); 2.63 (*m*, H–C(8)); 4.72 (*m*, H–C(3)); 4.91, 5.10 (2 *s*, CH_2(18)); 5.41 (*dd*, $J = 2.8$, 4.1, H–C(15)). ^{13}C-NMR (62.5 MHz, $CDCl_3$): 212.4 (*s*, C(14)); 170.6 (*s*, Me*C*OO–C(3)); 169.9 (*s*, Me*C*OO–C(15)); 146.8 (*s*, C(13)); 117.7 (*t*, C(18)); 73.1 (*d*, C(3)); 71.7 (*d*, C(15)); 54.8 (*d*, C(8)); 51.1 (*d*, C(17)); 43.6 (*d*, C(5)); 39.3 (*t*, C(24)); 36.7 (*s*, C(10)); 36.5 (*d*, C(20)); 36.4 (*t*, C(1)); 34.8 (*t*, C(4)); 34.1 (*t*, C(7)); 33.8 (*t*, C(22)); 29.5 (*t*, C(6)); 27.9 (*d*, C(25)); 27.4 (*t*, C(2)); 27.3 (*t*, C(16)); 26.9 (*t*, C(12)); 24.3 (*t*, C(23)); 22.7 (*q*, C(27)); 22.5 (*q*, C(26)); 21.4 (*q*, *M*eCOO–C(3)); 21.0 (*q*, *M*eCOO–C(15)); 17.3 (*q*, C(21)); 11.9 (*q*, C(19)).

14-Oxo-13,14-seco-5α-cholest-13(18)-ene-3β,12ξ,15ξ-triyl Triacetate (**8**). Oil. $[\alpha]_D = +22.6$ ($c = 1$, $CHCl_3$). IR($CHCl_3$): 1736, 1240, 1037. ^1H-NMR (250 MHz, $CDCl_3$): 0.79 (*d*, Me(21)); 0.81 (*s*, Me(19)); 0.86 (*d*, Me(26), Me(27)); 2.01 (*s*, AcO–C(12)); 2.02 (*s*, AcO–C((3)); 2.08 (*s*, AcO–C(15)); 2.28 (*m*, H–C(17)); 2.75 (*m*,

H–C(8)); 4.69 (*m*, H–C(3)); 5.09, 5.20 (2 *s*, CH_2(18)); 5.26 (*t*, *J* = 7, H–C(12)); 5.38 (*d*, *J* = 5.1, H–C(15)). ^{13}C-NMR (50 MHz, $CDCl_3$): 210.6 (*s*, C(14)); 170.5 (*s*, Me*C*OO–C(3)); 169.8 (*s*, Me*C*OO-C(15)); 169.6 (*s*, Me*C*OO–C(12)); 145.1 (*s*, C(13)); 119.3 (*t*, C(18)); 74.7 (*d*, C(12)); 72.9 (*d*, C(3)); 72.0 (*d*, C(15)); 51.8 (*d*, C(8)); 45.3 (*d*, C(17)); 43.5 (*d*, C(5)); 43.3 (*d*, C(9)); 39.3 (*t*, C(24)); 37.5 (*d*, C(20)); 36.7 (*s*, C(10)); 36.2 (*t*, C(1)); 33.8 (*t*, C(4)); 33.7 (*t*, C(7)); 32.6 (*t*, C(22)); 28.9 (*t*, C(6)); 27.9 (*d*, C(25)); 27.4 (*t*, C(2)); 27.1 (*t*, C(6)); 24.6 (*t*, C(23)); 22.7 (*q*, C(27)); 22.5 (*q*, C(26)); 21.4 (*q*, *Me*COO–C(3)); 21.3 (*q*, *Me*COO–C(12)); 21.0 (*q*, *Me*COO–C(15)); 17.2 (*q*, C(21)); 12.1 (*q*, C(19)). MS: 444 (95.5, $[M-2\times60]^+$), 327 (100, $[444-113]^+$). Anal. calc. for $C_{33}H_{52}O_7$ (560.753): C 70.68, H 9.35; found: C 70.76, H 9.58.

14-Oxo-13,14-seco-5α-cholest-13(18)-ene-3β,17α-diyl Diacetate (**9**): Oil. $[\alpha]_D = -6.57$ (c = 1.05, $CHCl_3$). IR ($CHCl_3$): 3077, 1734, 1702, 1643, 1240, 1035, 890. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.75 (*d*, Me(21)); 0.80 (*s*, Me(19)); 0.86 (*d*, Me(26), Me(27)); 1.97 (*s*, AcO–C(17)); 2.03 (*s*, AcO–C(3)); 2.56 (*m*, H–C(8)); 4.71 (*m*, H–C(3)); 5.23, 5.25 (2 *s*, CH_2(18)). ^{13}C-NMR (50 MHz, $CDCl_3$): 217.1 (*s*, C(14)); 170.7 (*s*, Me*C*OO–C(3)); 169.7 (*s*, Me*C*OO–C(17)); 146.6 (*s*, C(13)); 119.8 (*t*, C(18)); 73.0 (*d*, C(3)); 70.0 (*s*, C(17)); 55.9 (*d*, C(8)); 45.2 (*d*, C(9)); 43.9 (*d*, C(5)); 39.4 (*t*, C(24)); 37.4 (*d*, C(25)); 36.5 (*s*, C(10)); 36.3 (*t*, C(1)); 35.3 (*t*, C(4)); 33.8 (*t*, C(7)); 33.1 (*t*, C(22)); 28.8 (*t*, C(6)); 27.9 (*d*, C(25)); 27.4 (*t*, C(2)); 27.2 (*t*, C(16)); 26.5 (*t*, C(12)); 24.3 (*t*, C(23)); 22.8 (*q*, C(27)); 22.5 (*q*, C(26)); 21.4 (*q*, *Me*COO–C(3)); 21.2 (*q*, *Me*COO–C(17)); 17.4 (*q*, C(21)); 12.0 (*q*, C(19)). CI-MS: 503 (93, $[M+1]^+$), 443 (100, $[M-60+1]^+$); 383 (12, $[M-2\times60+1]^+$).

2.2. *Photolytic LTA Oxidation of* **5**. To a soln. of **5** (500 mg, 1.1 mmol) in dry benzene (80 ml) placed in a cylindrical irradiation vessel, LTA (1.46 g, 3.3 mmol) and $CaCO_3$ (330 mg, 3.3 mmol) were added. The stirred suspension was irradiated at r.t. with a high pressure Hg lamp (*Q81*) contained in a water-cooled jacket (*Pyrex*) with stirring for 1 h (monitoring by the starch paper/KI test). The mixture was worked up as above leaving a mixture (620 mg) which was separated by CC (SiO_2 (150 g), toluene/AcOEt 98:2 → 95:5): **10** (102 mg, 20.4%), **6** (74 mg, 14.9%); **11** (174 mg, 35.0%), and **12** (50 mg, 10.0%).

14β,22-Epoxy-5α-cholestan-3β-yl Acetate (**10**): Oil. $[\alpha]_D = -12.7$ (c = 0.89, $CHCl_3$). IR ($CHCl_3$): 1735, 1243, 1127, 1092. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.74 (*d*, Me(21)); 0.83 (*s*, Me(19)); 0.87 (*d*, Me(26), Me(27)); 0.97 (*s*, Me(18)); 2.02 (*s*, AcO); 3.05 (*t*, *J* = 8, H–C(22)); 4.68 (*m*, H–C(3)). ^{13}C-NMR (50 MHz, $CDCl_3$): 170.7 (*s*, Me*C*OO); 84.8 (*s*, C(14)); 75.8 (*d*, C(22)); 73.7 (*d*, C(3)); 51.1 (*d*, C(17)); 49.5 (*d*, C(9)); 44.6 (*d*, C(5)); 44.5 (*s*, C(13)); 37.7 (*d*, C(8)); 36.9 (*t*, C(1)); 35.9 (*s*, C(10)); 35.5 (*t*, C(24)); 34.2 (*d*, C(20)); 34.0 (*t*, C(4)); 31.9 (*t*, C(7)); 31.5 (*t*, C(12)); 28.5 (*t*, C(6)); 27.9 (*t*, C(25)); 27.9 (*d*, C(15)); 27.4 (*t*, C(2)); 27.1 (*t*, C(16)); 22.8 (*q*, C(27)); 22.6 (*q*, C(26)); 21.4 (*q*, *Me*COO); 19.9 (*t*, C(11), C(23)); 16.5 (*q*, C(21)); 15.0 (*q*, C(18)); 12.2 (*q*, C(19)). MS: 444 (52.5, M^+); 429 (7.1, $[M-15]^+$); 373 (11.7, $[M-C_5H_{11}]^+$); 344 (100, $[M-C_6H_{12}O]^+$), 260 (92.4). Anal. calc. for $C_{29}H_{48}O_3$ (444.696): C 78.33, H 10.88; found: C 78.46, H 10.64.

*(*E*)-14-Oxo-13,14-seco-5α-cholest-12-en-3β-yl Acetate* (**11**). M.p. 114–115° (from acetone). $[\alpha]_D = +13.3$ (c = 1.08, $CHCl_3$). IR (KBr): 1734, 1688, 1245, 1032. ^{1}H-NMR (200 MHz, C_6D_6): 0.53 (*s*, Me(19)); 0.94 (*d*, Me(21), Me(26), Me(27)); 1.38 (*s*, Me(18)); 1.76 (*s*, AcO); 1.98 (*d*, *J* = 11, CH_2(11)); 4.85 (*m*, H–C(3)); 4.89 (*d*, *J* = 11, H–C(12)). ^{13}C-NMR (50 MHz, C_6D_6): 209.9 (*s*, C(14)); 169.7 (*s*, Me*C*OO); 138.5 (*s*, C(13)); 128.3 (*d*, C(12)); 73.0 (*d* C(3)); 23.0 (*q*, Me(27)); 22.7 (*q*, Me(26)); 21.0 (*q*, *Me*COO); 19.0 (*q*, Me(21)); 13.3 (*q*, Me(18)); 11.7 (*q*, Me(19)). MS: 444 (1.6, M^+). Anal. calc. for $C_{29}H_{48}O_3$ (444.696): C 78.33, H 10.88; found: C 78.35, H 10.84.

*14-Hydroxy-14(13 → 12)*abeo-*5α-cholest-13(18)-en-3β-yl Acetate* (**12**): M.p. 115° (from acetone). $[\alpha]_D = +16.8$ (*c* = 1, $CHCl_3$). IR ($CHCl_3$): 3528, 3074, 1734, 1646, 1245, 1028, 896. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.73 (*d*, Me(21)); 0.80 (*s*, Me(19)); 0.88 (*d*, Me(26), Me(27)); 2.02 (*s*, MeCOO); 2.24 (*t*, *J* = 8, H–C(12)); 4.72 (*m*, H–C(3)); 4.77, 4.92 (2 *s*, CH_2(18)). ^{13}C-NMR (50 MHz, $CDCl_3$): 170.6 (*s*, Me*C*OO); 149.8 (*s*, C(13)); 109.1 (*t*, C(18)); 79.4 (*s*, C(14)); 73.8 (*d*, C(3)); 52.0 (*d*, C(17)); 50.1 (*d*, C(12)); 50.0 (*d*, C(8)); 49.5 (*d*, C(9)); 45.1 (*d*, C(5)); 39.4 (*t*, C(24)); 36.9 (*t*, C(22)); 35.6 (*s*, C(10)); 35.3 (*t*, C(1)); 33.5 (*t*, C(4)); 30.9 (*d*, C(20)); 30.6 (*t*, C(7)); 28.9 (*t*, C(6)); 28.0 (*d*, C(25)); 27.2 (*t*, C(2)); 25.1 (*t*, C(15)); 24.7 (*t*, C(23)); 24.7 (*t*, C(16)); 22.8 (*q*, C(27)); 22.5 (*q*, C(26)); 21.5 (*q*, *Me*COO); 20.8 (*t*, C(11)); 18.2 (*q*, C(21)); 11.4 (*q*, C(19)). CI-MS: 445 (4, $[M+1]^+$), 427 (76, $[M-18+1]^+$), 367 (100, $[M-60-18+1]^+$). Anal. calc. for $C_{29}H_{48}O_3$ (444.696): C 78.33, H 10.88; found: C 78.19, H 11.04.

2.3. *Hypoiodite LTA Oxidation of* **5**. *a*) A stirred suspension of LTA (828 mg, 1.87 mmol), I_2 (652 mg, 2.56 mmol), and **5** (200 mg, 0.45 mmol) in dry benzene (160 ml) was irradiated with a 800-W *Osram-Halogen-Bellaphot* lamp (at 60 V) at r.t. for 1 h. The solid was filtered off, the filtrate washed with aq. $Na_2S_2O_3$ soln., aq. $NaHCO_3$ soln., and H_2O, dried (Na_2SO_4), and evaporated, and the residue recrystallized from acetone/MeOH to give pure **11** (87 mg, 43.7%). The combined mother liquor was evaporated and the resulting mixture separated by prep. TLC (benzene/AcOEt (18:1)) to yield, in the order of decreasing mobility: **6** (23 mg, 11.55%); **11** (40 mg, 20.10%; total yield of **11**, 63.8%); **13** (30 mg, 14.48%), and **12** (5 mg, 5.0%).

*(12*R*,13*R*)-12,13-Epoxy-14-oxo-13,14-seco-5α-cholestan-3β-yl Acetate* (**13**): M.p. 151° (from MeOH). $[\alpha]_D = -9.4$ ($c = 1$, $CHCl_3$). IR (KBr): 1732, 1689, 1245, 1033. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.82 (*s*, Me(19)); 0.86 (*d*, Me(26), Me(27)); 0.96 (*s*, Me(18)); 0.98 (*d*, Me(21)); 2.03 (*s*, AcO); 2.40–2.76 (*m*, H_α–C(12), H_β–C(8), H_β–C(11)); 4.72 (*m*, H–C(3)). ^{13}C-NMR (50 MHz, $CDCl_3$): 212.5 (*s*, C(14)); 170.6 (*s*, Me*C*OO); 73.0 (*d*, C(3)); 65.6 (*d*, C(12)); 63.0 (*s*, C(13)); 57.0 (*d*, C(8)); 51.0 (*d*, C(17)); 49.6 (*d*, C(9)); 44.0 (*d*, C(5)); 39.4 (*t*, C(24)); 36.6 (*t*, C(1)); 36.3 (*s*, C(10)); 35.0 (*d*, C(20)); 34.0 (*t*, C(4)); 33.9 (*t*, C(22)); 33.7 (*t*, C(7)); 30.6 (*t*, C(6)); 28.1 (*t*, C(16)); 27.9 (*d*, C(25)); 27.4 (*t*, C(2)); 25.8 (*t*, C(15)); 24.8 (*t*, C(23)); 23.6 (*t*, C(11)); 22.7 (*q*, C(27)); 22.5 (*q*, C(26)); 21.3 (*q*, *Me*COO); 17.5 (*q*, C(21)); 13.5 (*q*, C(18)); 11.9 (*q*, C(19)). Anal. calc. for $C_{29}H_{48}O_4$ (460.315): C 75.67, H 10.43; found: C 75.48, H 10.52.

b) A stirred suspension of LTA (414 mg, 0.9 mmol), I_2 (326 mg, 1.28 mmol), and **5** (100 mg, 0.22 mmol) in dry benzene (40 ml) was irradiated at r.t. under Ar for 30 min. The mixture was worked up as above and the residue chromatographed (SiO_2 (10 g), toluene/AcOEt 99:1 → 97:3): **6** (7 mg, 7.03%), **11** (56 mg, 56.28%), **13** (13 mg, 12.61%), and **12** (6 mg, 6.00%).

c) A stirred suspension of LTA (414 mg, 0.9 mmol), I_2 (326 mg, 1.28 mmol), and **5** (100 mg, 0.22 mmol) in dry benzene (40 ml) was irradiated at r.t. under O_2 for 30 min. The mixture was worked up as previously described and chromatographed (SiO_2 (10 g), as above: **6** (8 mg, 8.04%), **11** (61 mg, 61.20%), **13** (15 mg, 14.55%), and **12** (7.5 mg, 7.54%).

d) A stirred suspension of LTA (414 mg, 0.9 mmol), I_2 (326 mg, 1.28 mmol), and **5** (100 mg, 0.22 mmol) in dry benzene (40 ml) was irradiated at 70° under Ar for 6 min. Usual workup gave a mixture which was chromatographed (SiO_2 (10 g), toluene (→ complex, not investigated mixture (16 mg)) toluene/AcOEt 98:2 → 97:3): **6** (7.4 mg, 7.5%), **11** (37 mg, 37.69%), **13** (42 mg, 40.53%), and **12** (9 mg, 9.30%).

Hypoiodite LTA Oxidation of **11**. A stirred suspension of **11** (100 mg, 0.22 mmol), LTA (414 mg, 0.9 mmol), and I_2 (326 mg, 1.28 mmol) in dry benzene (40 ml) was irradiated at 70° under Ar for 6 min. The usual workup of the mixture gave crude crystalline **13** (105 mg) which was purified by recrystallization from acetone (75 mg, 72.6%).

2.4. *Hypoiodite HgO Oxidation of* **5**. *a*) A stirred suspension of **5** (100 mg, 0.22 mmol), yellow HgO (304 mg, 1.4 mmol), and I_2 (406 mg, 1.6 mmol) in CCl_4 (20 ml) was irradiated under Ar with a 800-W *Osram-Halogen-Bellaphot* lamp (at 60 V) at r.t. for 1 h. The mixture was filtered, the filtrate washed successively with aq. $Na_2S_2O_3$ soln., aq. $NaHCO_3$ soln., and H_2O, dried (Na_2SO_4), and evaporated, and the residue chromatographed (SiO_2 column (10 g), toluene/AcOEt 99:1): 93% of recovered **5**.

The same procedure gave, after 60 h irradiation time, 70% of recovered **5**.

b) A stirred suspension of **5** (100 mg, 0.22 mmol), HgO (143 mg, 0.66 mmol), and I_2 (167 mg, 0.66 mmol) in dry benzene (50 ml) in a *Pyrex* vessel was irradiated with a high pressure Hg lamp (*Q81*) at r.t. for 17 h, leaving the starting/unchanged (TLC control).

c) The mixture from *b*) was irradiated at 70° for 5 h and worked up in the usual way. The residue (91 mg, 94.9%) was recrystallized from acetone/EtOH to give **14** which was identified by comparison with an authentic sample [3].

REFERENCES

[1] M. Lj. Mihailović, Lj. Lorenc, M. Gašić, M. Rogić, A. Melera, M. Stefanović, *Tetrahedron* **1966**, *22*, 2345; M. Akhtar, S. March, *J. Chem. Soc. (C)* **1966**, 937; M. Lj. Mihailović, Lj. Lorenc, J. Foršek, V. Pavlović, M. Dabović, J. Kalvoda, *J. Serb. Chem. Soc.* **1989**, *54*, 645.

[2] J. Kalvoda, K. Heusler, *Synthesis* **1971**, 525.

[3] M. Bjelaković, V. Pavlović, Lj. Lorenc, M. Lj. Mihailović, *J. Serb. Chem. Soc.* **1998**, *63*, 903.

[4] R. M. Silverstein, G. C. Bassler, T. C. Morril, 'Spectrometric Identification of Organic Compounds', 4th edn., Wiley, New York, 1981, p. 223.

[5] B. Heath-Brown, J. M. Heilbron, E. R. H. Jones, *J. Chem. Soc.* **1940**, 1482.

[6] K. Heusler, J. Kalvoda, *Angew. Chem. Int. Ed. Engl.* **1964**, *3,* 525.

[7] M. Lj. Mihailović, Ž. Čeković, *Synthesis* **1970**, 209.

[8] M. Lj. Mihailović, Ž, Čeković, Lj. Lorenc, in Organic Syntheses by Oxidation with Metal Compounds, Eds. W. J. Mijs and C. R. H. I. de Jonge, Plenum Press, 1986, pp. 743, 785.

[9] M. Lj. Mihailović, Lj. Lorenc, M. Dabović, M. Bjelaković, *Tetrahedron* **1988**, *44*, 6201; M. Dabović, M. Bjelaković, V. Andrejević, Lj. Lorenc, M. Lj. Mihailović, *ibid.* **1994**, *50*, 1833.

[10] K. Heusler, J. Kalvoda, G. Anner, A. Wettstein, *Helv. Chim. Acta* **1963**, *46*, 352; G. B. Spero, J. L. Thompson, W. F. Schneider, F. Kagan, *J. Org. Chem.* **1963**, *28*, 2225.

[11] K. Heusler, J. Kalvoda, *Tetrahedron Lett.* **1963**, *5*, 1001.
[12] H. Immer, M. Lj. Mihailović, K. Schaffner, D. Arigoni, O. Jeger, *Experientia* **1960**, *16*, 530; *Helv. Chim. Acta* **1962**, *45*, 753.
[13] A. Bowers, E. Denot, *J. Am. Chem. Soc.* **1960**, *82*, 4956.

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