Novel Estrones by Oxidation of the Benzylic Positions of the Estrane Skeleton with *tert*-Butyl Hydroperoxide and Cobalt Acetate

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Four new estrone derivatives were isolated after treatment of estrone 3-methyl ether (3-methoxyestra-1,3,5(10)-trien-17-one (**3**) with *tert*-butyl hydroperoxide and cobalt acetate. Three of the four steroidal compounds – the 9α-(*tert*-butylperoxy)-6-one **4**, the 9α-hydroxy-6-one **5**, and the 9β-hydroxy-6-one **7** – originated from oxidation at the 6- and 9-positions. In contrast, oxidation of **3** to a 9β-(*tert*-butylperoxy) compound afforded the 8-hydroxy-9-cyclodecanone derivative **6** through a molecular rearrangement involving the cleavage of the 8–9 bond. The structures of the compounds were secured by spectroscopic evidence including COSY, HSQC, and NOESY experiments combined with X-ray crystallographic analysis and molecular modeling studies.

Introduction

Benzylic oxidations have been widely applied to the conversion of estrones into their 6-oxo derivatives (e.g., **1**), which are intermediates of potential value in the synthesis of a variety of estrogens of considerable pharmaceutical interest.[1−10] One of these, (7α,17α)-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one (tibolone, **2**),[8−10] is the active principle of Livial, a drug of great interest in hormone replacement therapy in menopausal women at risk of osteoporosis.

Benzylic and allylic oxidations have traditionally been performed with chromic acid or by use of chromium(VI) complexes,[11,12] methods that require large excess of reagents and production of environmentally hazardous chromium residues. More recently, hydroperoxides in combination with different types of catalysts have been used;[13−21] in particular, the use of *tert*-butyl hydroperoxide with cobalt acetate in homogeneous and heterogeneous forms has been reported to be effective in allylic oxidations of unsaturated steroidal substrates.[22,23]

Here we report our findings in the area of estrane benzylic oxidations by the use of *tert*-butyl hydroperoxide and cobalt acetate when applied to 3-methoxyestra-1,3,5(10)-trien-17-one (**3**), a key intermediate[9,19] in the synthesis of tibolone (**2**). Unfortunately, the original goal − a selective oxidation at the benzylic 6-position − was not attained, as the 9-position was also always oxidized, but the reaction did result in the isolation of new estrane derivatives, interesting from a synthetic point of view. Here we describe their structural and stereochemical elucidation by spectroscopic, crystallographic, and theoretical studies.

Results and Discussion

The reported procedure for allylic oxidations of steroidal alkenes[22,23] was applied to the oxidation of 3-methoxyestra-1,3,5(10)-trien-17-one (**3**). Performed under the conditions described (ca. 7 equiv. of *tert*-butyl hydroperoxide, cobalt acetate, CH_3CN, at 50 °C for 20 h), the reaction afforded a mixture of four different products (Scheme 1), never reported before in the literature, among which the expected 6-oxo derivative **1** was not detected. The mixture was separated by flash chromatography on silica gel to yield, in their order of elution, the following four oxidation products: (9α)-9-(*tert*-butylperoxy)-3-methoxyestra-1,3,5-(10)-triene-6,17-dione (**4**), (9α)-9-hydroxy-3-methoxyestra-1,3,5(10)-triene-6,17-dione (**5**), (8*R*)-8-hydroxy-3-methoxy-8,9-secoestra-1,3,5(10)-triene-9,17-dione (**6**), and (9β)-9-hydroxy-3-methoxyestra-1,3,5(10)-triene-6,17-dione (**7**). Although all the starting compound had disappeared, the overall yield of isolated products was no better than 65% because of the formation of highly polar materials, retained on the column during the chromatographic separation. This

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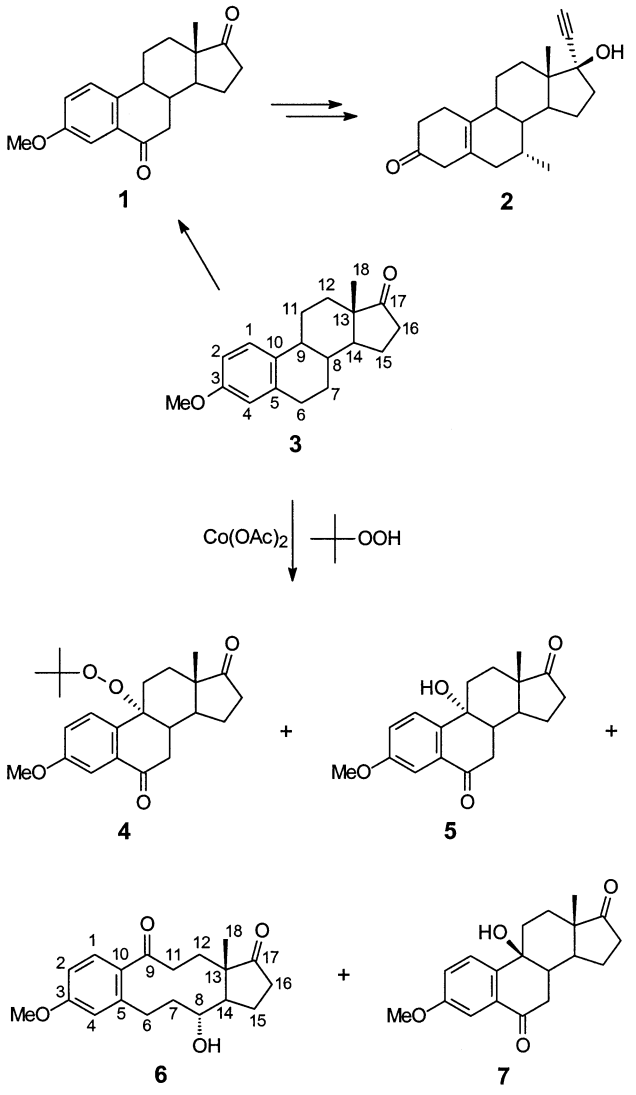


Scheme 1

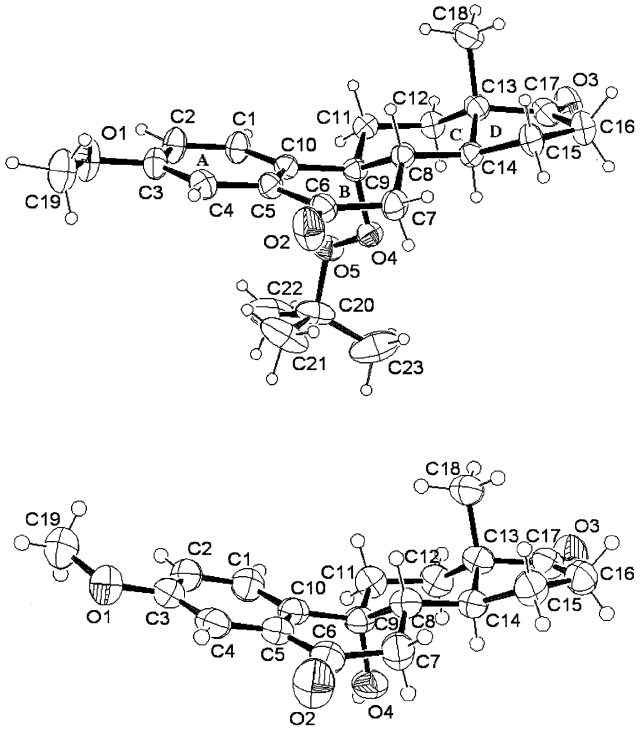


Figure 1. ORTEP views of compound **4** (top) and compound **5** (bottom) with atom labeling (the H atom are drawn as spheres of arbitrary radii); for sake of clarity, the ring letter is reported only for **4**, being the same in **5**

also lowers the yields in the case of chromic oxidations.[24−29]

The structural and stereochemical assignments were performed through careful spectroscopic investigations and, when possible, by X-ray analysis. In the case of the seco-steroid **6**, an accurate conformational study through theoretical methods was also necessary.

Of the four reaction products, two, compounds **4** and **5**, afforded crystals suitable for an X-ray analysis. Their molecular structures are reported in Figure 1 as ORTEP[30] views with the relative atom numbering schemes. Compound **5** was a product of oxidation at the 9- and 6-positions, while compound **4** was the corresponding 9-(*tert*-butylperoxy) derivative. They have quite similar overall geometries, though with some small differences in the puckering of the rings.

Although only the relative stereochemistry of the stereogenic centers of the compounds was determined, their absolute configurations were assigned from the known (*S*) configuration of C13, bearing the C18 methyl group and C14, which are unaffected in the reaction pathway.

In **4**, ring B has a twisted 8β-envelope conformation with a distance between C8 and the best plane of the remaining five atoms of 0.678(4) Å. In **5**, in which the twisting is more pronounced, its conformation is again an envelope, with a deviation of C8 of 0.750(4) Å, from the calculated best mean plane of the remaining ring atoms. Ring C has an 8β,12α-chair conformation in both cases, while the five-membered ring D adopts a 14α-envelope conformation distorted towards a 13β,14α-half chair [the distances between C14 and the planes of the four other atoms are 0.651(4) Å in **4** and 0.635(4) Å in **5**, respectively]. These conformations are similar to those observed in 17β-hydroxy-3-methoxyestra-1,3,5(10)-triene-6,7-dione 7-oxime[31] even though ring D in this latter is described as a 13β,14α-half chair conformer distorted towards a 13β-envelope. The 3-methoxy group is differently oriented in the two derivatives, being on the same side of the skeleton with regard to the 6-oxo group in **4**, with a torsion angle C−OMe−O1−C3−C4 of 7.2(7)° and in the opposite orientation in **5** with a torsion angle C−OMe−O1−C3−C4 of 172.2(4)°. The presence of a hydroxy group at C9 in **5** produces a strong intermolecular hydrogen bond with the oxygen atom of the oxo group of ring D, with an O4···O3′ distance of 2.876(5) Å, O4−H···O3′ of 2.21(7) Å, and a corresponding angle of 161(7)° (′ at 1/2 − *x*, 1 − *y*, 1/2 + *z*). This H bond can explain the slightly different conformation of ring B in relation to its counterpart in **4**, due to the involvement of the

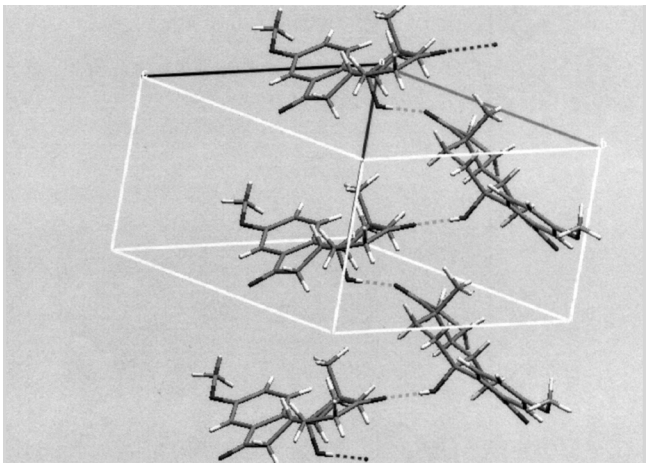


Figure 2. Crystal cell content of **5**, showing the development of the molecular chains along *a*

hydroxy group at C9 in these interactions. The crystal packing of **5** (Figure 2) shows a polymeric structure with molecular chains in the direction of the crystallographic *a* axis produced by the previously described intermolecular H-bond interaction. In **4**, the *tert*-butylperoxo group is characterized by a torsion angle C9−O4−O5−C20 of −149.9(4)°, with an O4−O5 peroxo bond length of 1.466(3) Å and C9−O4 of 1.452(5) Å, and C20−O5 bond lengths of 1.431(5) Å, in agreement with the literature data.[32] Its steric hindrance does not cause significant variations in the overall molecular conformation with respect to **5**, except for a slightly different puckering of the cyclic systems. The crystal packing of **4** is determined only by van der Waals interactions.

The ^{1}H NMR spectrum of compound **4** showed a signal at δ = 0.80 ppm [s, 9 H, $C(CH_3)_3$], whereas the ^{13}C NMR spectrum displayed two quaternary C−O functions at δ = 78.2 and 79.9 ppm corresponding to the presence of the *tert*-butoxy group, while the ^{13}C NMR resonance at δ = 198.2 ppm is characteristic of the benzylic carbonyl group. The presence of the peroxide bridge was not detectable either from the NMR or from the PCI-MS spectrum, which showed (*m*/*z* = 371 $[M - 16 + H]^+$), due to the molecular ion after the loss of an oxygen atom, as the main peak.

In contrast, the PCI mass spectrum of **5** (*m*/*z* = 315 $[M + H]^+$), in agreement with the crystallographic determination, showed the presence of additional carbonyl and hydroxy moieties with respect to compound **3**. The analogous mass spectrum of compound **7** (*m*/*z* = 315 $[M + H]^+$) suggested strict structural analogy between **7** and **5** and, in the absence of crystals suitable for X-ray analysis, the structure of the former as the 9β isomer of **5** was assigned by comparative analysis of the spectroscopic data of the two compounds (see Table 1), which were submitted to a combination of 1D and 2D NMR experiments (COSY, HSQC, and NOESY) recorded in dimethyl sulfoxide solutions. In particular, the α stereochemistry of the benzylic 9-hydroxy group of **5**, determined by X-ray crystallography, was also

Table 1. δ_C, δ_H assignments and significant NOESY correlations of compounds **5**, **6**, and **7**

	5[a]			**7**[a]			**6**[b]		
	δ_C	δ_H	NOESY[c]	δ_C	δ_H	NOESY[c]	δ_C	δ_H	NOESY[c]
1	126.6	7.55	OH, 11β	128.3	7.54	11α	128.0	7.36	11β, 12β
2	120.2	7.19	OCH_3	120.8	7.21	OCH_3	111.6	6.85	OCH_3
3	158.5			158.5			161.8		
4	109.6	7.35	OCH_3	109.3	7.33	OCH_3	116.28	6.97	6β, 7β, OCH_3
5	141.0[d]			136.2[d]			142.2[d]		
6α	197.2			196.7			27.6	3.40	14
6β								2.73	
7α	36.4	2.70	14	36.0	2.42	15α	38.4	2.09	15α
7β		2.38−2.45			3.26			1.98	
8	40.5	2.25	11β, 15β, 18	42.8	2.41	11β, 18	65.3	3.58	12β
9	67.8			71.1			208.8		
10	132.4[d]			132.7[d]			134.7[d]		
11α	31.0	2.38−2.45		32.3	2.57		40.8	2.62	14
11β		1.78	18		1.91	18		3.16	
12α	27.3	1.65	14	28.2	0.88		32.6	2.23−2.32	
12β		1.57	18		1.52			1.84−1.92	
13	47.0			47.5			52.5		
14	42.9	2.06		45.5	1.33	12α, 16α	43.7	2.35	7α
15α	20.5	1.83		20.8	1.65		17.4	1.84−1.92	
15β		1.52	18		1.58	18		2.23−2.32	
16α	35.3	2.08		35.2	1.91		37.4	2.15	
16β		2.38−2.45			2.35	18		2.46	
17	219.2			218.2			221.5		
18	12.5	0.81		13.2	0.94		19.5	1.08	8, 11β, 12β, 15β, 16β
OCH_3	55.3	3.78		55.2	3.78		55.4	3.72	
OH		4.99	7α, 12α, 14		5.33	7β, 8, 11α, 11β		5.20	

[a] $[D_6]$DMSO, 298 K. [b] $[D_5]$Pyridine, 338 K. [c] NOESY correlations from H to H. [d] Assignments may be interchanged within the column.

supported by a cross-peak in the NOESY spectrum of **5** between the proton on the 9-hydroxy group (δ = 4.99 ppm) and 14-H (δ =2.06 ppm), while the NOE between the proton of the 9-hydroxy group of **7** (δ = 5.33 ppm) and 8-H (δ = 2.41 ppm) accounted for the β configuration of this alcoholic function.

The structure deduced from NMR spectroscopic data for compound **7** was also confirmed by the determination of its preferred conformation through theoretical calculations performed within the DFT framework at the B3LYP/6-31G* level[33,34] as implemented in GAUSSIAN98. Compound **7** has a certain degree of conformational freedom at the B/C junction, which, as in *cis*-decalin, makes the existence of two minimum-energy conformations possible. One of these (**7A**, Figure 3) was preferred by > 5 kcal/mol over the other one (**7B**) when the geometries were optimized in the gas phase. To take account of the solvent influence, the energies were recalculated in DMSO by use of a continuum solvation model (C-PCM),[35] and **7A** still remained the only populated conformation. The corresponding ^{1}H NMR coupling constants, calculated by means of the Haasnoot et al. equation[36] for each pair of vicinal hydrogen atoms, were very close to the experimentally ascertained values (Table 2). Finally, all the distances between hydrogen atoms presenting NOE contacts in the NOESY experiment, measured in the preferred conformation, proved to be < 3 Å.

Lastly, the PCI mass spectrum of compound **6** (*m*/*z* = 317 [M + H]$^+$), together with the presence in the ^{13}C NMR spectrum of two carbonyl carbon signals at δ = 221.5 ppm and 208.8 ppm and of a resonance at δ = 65.3 ppm due to a tertiary alcoholic carbon atom, could be accounted for by a breaking of the 8−9 bond with the formation of a hydroxydecanone derivative. To confirm this structure, compound **6** was subjected to a combination of 1D and 2D experiments (COSY, HSQC, and NOESY) recorded in pyridine at 338 K, as this solvent gave the best spread of the proton resonances. The stated temperature was also necessary, in order to resolve some signals present as broad multiplets at lower temperatures, due to coalescence phenomena. Two cross-peaks in the NOESY spectrum of **6** (Table 2) between the aromatic 1-H (δ = 7.36 ppm) and 4-H (δ = 6.97 ppm) protons and, respectively, 11β-H (δ = 3.16 ppm) and 6β-H (δ = 2.73 ppm), were the starting point for the complete ^{1}H and ^{13}C NMR signal assignments. These NOE contacts and three COSY cross-peaks of 14-H (δ = 2.35 ppm) and the two 7-H methylenic protons (δ = 1.98 and 2.09 ppm) with the proton at δ = 3.58 ppm, linked to the tertiary alcoholic carbon signal at δ = 65.3 ppm (from the HSQC spectrum), indicated the location of the benzylic carbonyl group (δ =208.8 ppm) on C-9, and not at the C-6 position, with the hydroxy group (δ =5.20 ppm) linked to the C-8 carbon atom (δ = 65.3 ppm) of the 8,9-secosteroid.

The stereochemistry of the hydroxy group at C-8 of this compound was assigned as (8*R*) through a modeling study by the same approach as described for **7**.

The ten-membered ring should endow compound **6** with a high degree of conformational flexibility, limited, how-

Table 2. Experimentally determined ^{1}H NMR coupling constants [Hz] for compounds **5**, **6**, and **7**, in comparison with the calculated values

J	**5** exp.[a]	**5** calcd.	**7** exp.[a]	**7** calcd.	**6** exp.[b]	**6** exp.[c]	**6** calcd.
1,2	8.7		8.7		8.4	8.7	
2,4	3.4		3.4		2.8	2.7	
6α,6β					13.3	13.9	
6α,7α					4.9	4.8	3.6
6α,7β					13.3	12.9	12.0
6β,7α					3.5	3.2	4.5
6β,7β					5.6	5.3	3.6
7α,7β	17.4		16.8		13.3	n.d.	
7α,8	12.7	12.3	2.7	2.4	11.2	11.2	11.4
7β,8	4.0	3.7	4.7	3.8	3.5	3.5	2.9
8,14	12.1	12.6	12.7	12.4	< 1.0	< 1.0	0.5
11α,11β	13.4		14.1		16.1	16.1	
11α,12α	4.0	4.2	3.4	3.2	1.4	1.5	1.4
11α,12β	2.7	2.5	3.4	3.4	11.9	12.1	11.7
11β,12α	13.4	13.3	14.1	13.7	8.4	8.0	7.6
11β,12β	4.7	4.6	3.4	3.5	1.4	2.0	1.4
12α,12β	12.7		14.1		n.d.	14.7	
14,15α	5.4	5.2	6.0	4.7	6.3	n.d.	5.3
14,15β	12.1	12.0	12.1	12.1	11.9	n.d.	11.8
15α,15β	12.1		12.1		n.d.	n.d.	
15α,16α	9.0	9.7	8.7	9.9	9.1	8.7	8.6
15α,16β	< 1.0	0.5	< 1.0	0.5	1.0		0.3
15β,16α	9.0	9.9	8.7	9.5	11.2	10.7	10.9
15β,16β	9.0	9.9	8.7	10.0	7.7		8.8
16α,16β	18.0		19.5		18.2	19.00	

[a] [D$_6$]DMSO, 298 K. [b] [D$_5$]Pyridine, 338 K. [c] [D$_6$]DMSO, 338 K.

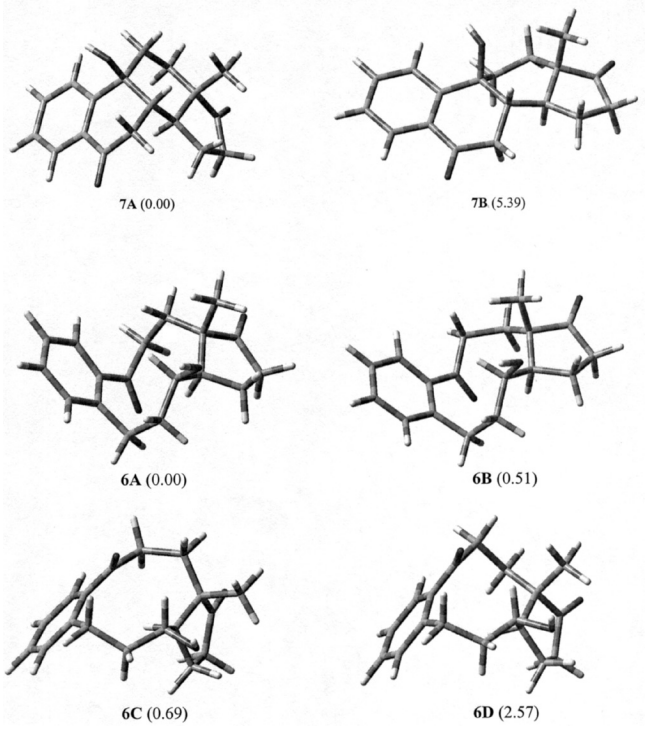


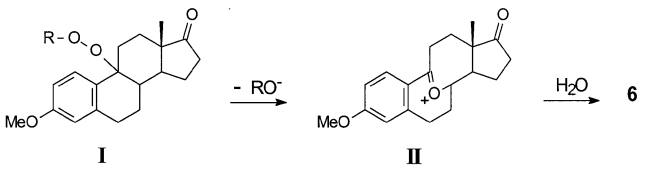
Figure 3. Three-dimensional plots of the most significant conformations of compounds **6** and **7** (the 3-methoxy group is replaced by a hydrogen atom); the relative energies [kcal/mol] in DMSO are in parentheses

ever, by the presence of the A and D rings, while the carbonyl group at C-9 also reduces the flexibility due to its tendency towards a planar arrangement with respect to the aromatic A ring. The modeling study allowed about 20 different conformations to be located for each of the two epimers at C-8. Four conformations emerged as the most stable both for the (8*R*) compound and for its (8*S*) epimer, all with the C-9 carbonyl group pointing inside the ten-membered ring. Figure 3 shows the three-dimensional plots of the four conformations of (8*R*)-**6**; the four conformations of the epimer correspond exactly with the obvious differences in the orientation of the hydroxy group at C-8. Conformations **6A** and **6B** are similar except for the arrangement around the C-11−C-12 bond, and the conversion **6A** to **6B**, or vice versa, appears to be quite easy. The same holds true in the couple **6C** and **6D**. The conversion of **6A** (or **6B**) to **6C** (or **6D**) appears more energy-demanding, as it requires a complete rearrangement of the molecule, accounting for the coalescence phenomena mentioned above. The theoretical ^{1}H NMR vicinal coupling constants were calculated for each conformation and averaged on the basis of the equilibrium percentages calculated through the Boltzmann equation from their relative stability in DMSO. A comparison of the calculated values in DMSO with the experimental determined ones shows a good agreement (Table 2). Moreover, the NOE contacts determined in the NOESY are consistent with this conformational description. In contrast, the four conformations of the (8*S*) epimer appear to be in disagreement with the experimentally determined coupling constants as well as with the NOE contacts presented by 8-H.

In conclusion, compound **6** has the (8*R*) configuration and its conformational behavior is mainly described by conformation **6A** but with significant contributions from **6B** and **6C**.

Lastly, inspection of the geometries of **6A**−**D** accounts for the absence of a further oxidation step at the 6-position. In fact, neither of the two hydrogen atoms at C-6 appears to be correctly oriented in an orthogonal arrangement with respect to the aromatic ring.[37]

A question still remains: What is the origin of compound **6**? A rearrangement of a 9-(*tert*-butylperoxy) derivative **I** (Scheme 2) formed in the initial step by oxidation of the tertiary benzylic position might give the secosteroid **6**. Actually, both the 9α and 9β derivatives **I** might undergo the same rearrangement with migration of the C-8−C-9 bond. In order to determine whether one of the epimers **I** can be transformed more easily than the other one, the energies of the possible conformations of **II** were calculated, and are reported in Figure 4. Conformers **II-A** and **II-B**, deriving from the 9β-(*tert*-butylperoxy) derivative **I**, are much more stable than **II-C**, which originates from 9α-**I**. The preferred path to **6** thus starts from 9β-**I**, which rearranges through **II-A** (or through a transition state of geometry close to it) to afford the 8-hydroxy-9-cyclodecanone derivative **6**. Unlike 9β-**I**, its epimer 9α-**I** is not able to give the same easy rearrangement and is oxidized at the 6-position to give the 6-one **4**.



Scheme 2

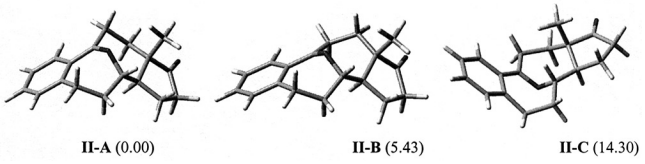


Figure 4. Three-dimensional plot of the possible conformations of intermediate **II**; the relative energies [kcal/mol] are in parentheses

Conclusion

In summary, a combination of theoretical and experimental techniques has allowed us to elucidate the structures of four new estrone derivatives **4**−**7**, obtained by oxidation of estrone 3-methyl ether **3** with *tert*-butyl hydroperoxide and cobalt acetate, and to suggest a possible mechanism for the formation of the new 8,9-secosteroid **6**. Although oxidation solely at position 6 could not be achieved under the reaction conditions employed, the compounds oxidized at position 9 obtained here are interesting from a synthetic point of view.

Experimental Section

General: Uncorrected melting points were determined with a Büchi apparatus. Optical rotations were determined with a Perkin−Elmer 241 polarimeter in a 1-dm cell at 20 °C in chloroform solutions, UV spectra were taken with a Jasco UVIDEC-430A in dichloromethane solution. IR spectra were recorded with a Perkin−Elmer 1420 spectrophotometer; NaCl crystal windows (Nujol, unless otherwise stated). Solvents were purified in the usual way, acetonitrile was dried with 4-Å molecular sieves. All reagents were purchased from Aldrich. 3-Methoxyestra-1,3,5(10)-trien-17-one was purchased from Sigma. All reactions were monitored by TLC on 60 F-254 silica gel plates (Merck) with detection by spraying with 50% H_2SO_4 solution and heating to 110 °C. Flash column chromatography[38] was performed on silica gel 60 (230−400 mesh, Merck). Mass spectrometry was performed with a Hewlett−Packard HP 5988A particle beam quadrupolar mass spectrometer equipped with a PB 5998A interface and an HP 1050 low-pressure HPLC. The mass spectrometric analyses were performed by positive ion chemical ionization (PCI-MS) with methane as the chemical reactant gas at an electron energy of 240 eV and with a source temperature of 250 °C. Samples were dissolved in methanol and introduced into the mass spectrometer via the particle beam LC-MS interface directly connected with the HPLC system. Elution was performed with methanol (0.4 mL/min). The NMR spectra were recorded with a Bruker AM 500 spectrometer operating at 500.13 and 125.76 MHz for ^{1}H and ^{13}C, respectively,

by use of a 5-mm broadband reverse probe. Chemical shifts are reported as δ [ppm] relative to TMS as internal reference and *J* values are given in Hz. Analytical samples (ca 15 mg) were dissolved in $CDCl_3$ (compound **4**), [D_6]DMSO (compounds **5**, **6**, and **7**), or [D_5]pyridine (compound **6**) (0.5 mL) under N_2, and their spectra were recorded at 298 K (compounds **4**, **5**, and **7**) or 338 K (compound **6**). All the assignments were made by a combination of 1D and 2D COSY, HSQC, and NOESY experiments, through the use of standard Bruker pulse programs.

Oxidation of 3-Methoxyestra-1,3,5(10)-trien-17-one (3): A catalytic amount (ca. 10 mg) of cobalt(II) acetate tetrahydrate and *tert*-butyl hydroperoxide (5.0−6.0 M solution in decane, 4.8 mL), were added under argon to a solution of 3-methoxyestra-1,3,5(10)-trien-17-one (**3**, 1.00 g, 3.52 mmol) in acetonitrile (36 mL). After 24 h under magnetic stirring at 50 °C, the solution was poured into sodium sulfite solution (10% aq.) and extracted with diethyl ether (3 × 50 mL). The extracts were washed with saturated aqueous $NaHCO_3$ and water, and dried with sodium sulfate, and the solvents were evaporated to dryness. The resulting crude reaction mixture was purified by flash chromatography (hexane/ethyl acetate, 8:2 to 1:1). In their order of elution the fractions contained the following compounds:

(9α)-9-(*tert*-Butylperoxy)-3-methoxyestra-1,3,5(10)-triene-6,17-dione (4): Yield 0.15 g (11%), m.p. 159−160 °C (from methanol). $[\alpha]_D^{20}$ = +73 (*c* = 1). λ_{max} (nm) = 228 (ε = 14050 $dm^3\ mol^{-1}\ cm^{-1}$), 255 (7100) and 312 (2050). IR (neat): $\tilde{\nu}$ = 1280 cm^{-1}, 1600, 1680, 1740, 2950, 3450. Selected ^1H NMR signals: δ = 0.80 (s, 9 H, CMe_3), 0.90 (s, 3 H, Me), 3.80 (s, 3 H, OMe), 7.07 (dd, *J* = 8.4, 2.8 Hz, 1-H, 2-H), 7.48 (d, *J* = 8.4 Hz, 1 H, 1-H), 7.54 (d, *J* = 2.8 Hz, 1 H, 4-H) ppm. ^{13}C NMR: δ = 22.0, 26.8, 27.0, 28.1, 28.6, 36.4, 37.6, 42.2, 44.4, 45.9, 48.3, 56.2, 78.2, 79.9, 110.3, 120.7, 129.4, 134.3, 138.1, 160.2, 198.2, 220.3. PCI MS: *m*/*z* = 371 [M − 16 + H]$^+$. $C_{23}H_{30}O_5$ (386.48): calcd. C 71.48, H 7.82; found C 71.30, H 7.83.

(9α)-9-Hydroxy-3-methoxyestra-1,3,5(10)-triene-6,17-dione (5): Yield 0.28 g (25%), m.p. 195 °C (decomp.) (from methanol), $[\alpha]_D^{20}$ = +75 (*c* = 1). λ_{max} (nm) = 228 (ε = 18850 $dm^3\ mol^{-1}\ cm^{-1}$), 255 (9900) and 315 (3250). IR: $\tilde{\nu}$ = 1280 cm^{-1}, 1610, 1680, 1740, 3440. For the NMR signals see Table 1. PCI MS: *m*/*z* = 315 [M + H]$^+$. $C_{19}H_{22}O_4$ (314.38): calcd. C 72.59, H 7.05; found C 72.47, H 7.04.

(8*R*)-8-Hydroxy-3-methoxy-8,9-secoestra-1,3,5(10)-triene-9,17-dione (6): 0.13 g (12%), m.p. 142 °C (from chloroform), $[\alpha]_D$ = +100 (*c* = 1). λ_{max} (nm) = 210 (ε = 5400 $dm^3\ mol^{-1}\ cm^{-1}$), 228 (5 850) and 264 (6 200). IR: $\tilde{\nu}$ = 1300 cm^{-1}, 1670, 1710, 3420. For the NMR signals see Table 2. PCI MS: *m*/*z* = 317 [M + H]$^+$. $C_{19}H_{24}O_4$ (316.39): calcd. C 72.13, H 7.65; found C 72.21, H 7.64.

(9β)-9-Hydroxy-3-methoxyestra-1,3,5(10)-triene-6,17-dione (7): Yield 0.17 g (15%), m.p. 62 °C (from methanol), $[\alpha]_D$ = +118 (*c* = 1). λ_{max} (nm) = 230, (ε =15200 $dm^3\ mol^{-1}\ cm^{-1}$), 254 (7250) and 317 (2850). IR: $\tilde{\nu}$ = 1280 cm^{-1}, 1380, 1600, 1680, 1730, 3400. For the NMR signals see Table 1. PCI MS: *m*/*z* = 315 [M + H]$^+$. $C_{19}H_{22}O_4$ (314.38): calcd. C 72.59, H 7.05; found C 72.51, H 7.06.

X-Ray Crystallography: The crystals of $C_{23}H_{30}O_5$ (**4**) and of $C_{19}H_{22}O_4$ (**5**) were obtained by recrystallization from methanol as colorless prisms. A summary of the crystal data, data collection, and structure refinement is presented in Table 3. The intensity data were collected with a CAD4 diffractometer with use of graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). The cell parameters were determined and refined by a least-squares fit of 20 high-angle reflections. The structures were solved by direct methods by use of Sir-92[39] and conventional Fourier synthesis (SHELX-97[40]). The refinement of the structures was carried out by full-matrix, least-squares on F^2. All non-H atoms were refined

Table 3. Crystal data and structure refinement for compounds **4** and **5**

	4	**5**
Empirical formula	$C_{23}H_{30}O_5$	$C_{19}H_{22}O_4$
Formula mass	386.48	314.38
Temperature	293(2) K	293(2) K
Wavelength	0.71073Å	0.71073 Å
Crystal system	monoclinic	orthorhombic
Space group	$P2_1$ (no. 4)	$P2_12_12_1$ (no. 19)
Unit cell dimensions	*a* = 8.482(3) Å *b* = 12.159(7) Å *c* = 10.927(7) Å β = 105.55(5)°	*a* = 7.844(3) Å *b* = 13.695(7) Å *c* = 14.926(8) Å
Volume	1085.7(10) $Å^3$	1603.4(13) $Å^3$
Z	2	4
Calculated density	1.182 Mg/m^3	1.302 Mg/m^3
Absorption coefficient	0.082 mm^{-1}	0.090 mm^{-1}
F(000)	416	672
Crystal size	0.9 × 0.9 × 0.5 mm	0.8 × 0.8 × 0.6 mm
θ range	2.49−25.05°	2.02−24.99°
Limiting indexes	−10 = *h* = 9, −14 = *k* = 1, −1 = *l* = 13	−9 = *h* = 9, −1 = *k* = 16, −1 = *l* = 17
Refl. collected/unique	2592/2225 (R_{int} = 0.0352)	7136/2809 (R_{int} = 0.0628)
Completeness to θ	25.05° (99.9%)	24.99° (99.8%)
Refinement method	Full-matrix, least-squares on F^2	Full-matrix, least-squares on F^2
Data/restraints/parameters	2225/1/321	2809/0/282
Goodness-of-fit on F^2	1.063	1.060
Final *R* ind.[$I > 2\sigma(I)$]	*R*1 = 0.0500, *wR*2 = 0.0844	*R*1 = 0.0515, *wR*2 = 0.1322
R indices (all data)	*R*1 = 0.1074, *wR*2 = 0.1008	*R*1 = 0.0774, *wR*2 = 0.1533
Largest diff. peak and hole	0.164 and −0.184 e·$Å^{-3}$	0.217 and −0.251 e·$Å^{-3}$

Table 4. Selected bond lengths [Å] and angles [°] for **4** and **5**

	4	**5**
O(1)−C(3)	1.377(6)	1.382(5)
O(1)−C(19)	1.401(6)	1.438(7)
O(2)−C(6)	1.213(5)	1.211(5)
O(3)−C(17)	1.217(5)	1.204(6)
O(4)−C(9)	1.452(5)	1.433(5)
O(4)−O(5)	1.466(3)	
O(5)−C(20)	1.431(5)	
C(5)−C(6)	1.485(6)	1.495(6)
C(6)−C(7)	1.503(7)	1.516(6)
C(7)−C(8)	1.522(6)	1.518(6)
C(8)−C(14)	1.513(6)	1.521(6)
C(8)−C(9)	1.535(5)	1.553(6)
C(9)−C(11)	1.522(6)	1.530(6)
C(9)−C(10)	1.536(6)	1.529(5)
C(11)−C(12)	1.536(7)	1.543(6)
C(12)−C(13)	1.505(6)	1.522(6)
C(13)−C(17)	1.510(7)	1.528(6)
C(13)−C(14)	1.523(6)	1.533(6)
C(13)−C(18)	1.563(6)	1.560(6)
C(14)−C(15)	1.532(6)	1.536(6)
C(15)−C(16)	1.523(7)	1.531(7)
C(16)−C(17)	1.515(6)	1.505(6)
C(3)−O(1)−C(19)	118.3(4)	117.0(5)
C(9)−O(4)−O(5)	106.2(3)	
C(20)−O(5)−O(4)	109.3(3)	
C(4)−C(3)−O(1)	124.7(4)	115.0(4)
C(2)−C(3)−O(1)	115.7(4)	125.0(4)
O(4)−C(9)−C(11)	110.2(3)	110.1(3)
O(4)−C(9)−C(8)	103.4(3)	105.8(3)
O(4)−C(9)−C(10)	109.0(3)	109.3(3)
O(3)−C(17)−C(16)	125.4(5)	125.2(5)
O(3)−C(17)−C(13)	126.5(4)	127.1(4)
O(5)−C(20)−C(22)	101.3(4)	
O(5)−C(20)−C(21)	110.8(5)	
O(5)−C(20)−C(23)	108.9(5)	

anisotropically. In compounds **4** and **5** the H-atom positions were detected by a difference Fourier synthesis and refined with isotropic thermal factors except for the methyl hydrogen atoms, introduced at calculated positions in their described geometries and were allowed during refinement to ride on the attached carbon atoms with fixed isotropic thermal parameters ($1.2U_{eq}$ of the parent carbon atom). Selected bond lengths and angles for both compounds are reported in Table 4. CCDC-203898 (**4**) and -203899 (**5**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Theoretical Calculations: The conformational spaces of compounds **6** and **7** were explored by a two-step approach. First of all, several molecular dynamics calculations based on the MM^+ force field, implemented in the HyperChem program,[41] were performed at 2000 K for 1000 ps starting from different initial geometries. The torsional angles inside rings B and C of compound **7** and the ten torsional angles defining the ten-membered ring of compound **6** were plotted against time and analyzed to determine the different conformations passed through. The frames corresponding to each new conformation were collected and fully optimized. The procedure was repeated several times until no new conformation was located. Each MM^+-optimized geometry was fully re-optimized by a DFT approach at the B3LYP/6-31G(d) level. The conformations of the intermediate **II** were directly optimized at the B3LYP/6-31G(d) level. All calculations were performed on model compounds in which the 3-methoxy group was replaced by a hydrogen atom.

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