Reactivity of Steroidal Dienes towards the Methyltrioxorhenium/H_2O_2−Urea Oxidation System: Isolation and Characterization of New Oxygenated Steroids

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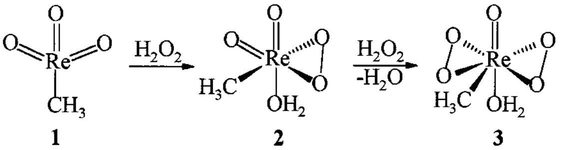
To examine the reactivity of conjugated diene steroids towards methyltrioxorhenium (MTO)-catalysed oxidation with the urea–hydrogen peroxide adduct (UHP) and its possible use in functionalization of the rings of the steroid nucleus, the reactions of the MTO/UHP system with cholesta-3,5-diene (**4**) and 5α-cholesta-7,9(11)-dien-3β-yl acetate (**13**) in aprotic solvents were investigated. These oxidations were performed both at 0 °C and at 25 °C, in either $CHCl_3$ or diethyl ether as solvents, and in the presence of pyridine as ligand. Three new 4,5-epoxy-3,6-dihydroxyl compounds **10**, **11**, and **12** were isolated from the treatment of diene **4** in $CHCl_3$ at 0 °C, while oxidations of the $\Delta^{7,9(11)}$-diene steroid **13** allowed us to isolate the new monoepoxy and diepoxy steroids **14** and **15** and the new triol **19**. The structures of all new steroids were verified on the basis of chemical evidence and interpretation of spectroscopic data including H-H COSY, HMBC, and HMQC experiments.

Introduction

The very stable, easily accessible compound methyltrioxorhenium (CH_3ReO_3, MTO, **1**, Scheme 1) is a highly efficient and selective catalyst for the oxidation of a large number of organic compounds. MTO in the presence of H_2O_2, for instance, is able to catalyse the epoxidation and hydroxylation of olefins cleanly,[1a−1e] as well as the oxidation of [60]fullerene,[2] primary and secondary amines,[3] anilines,[4] symmetric disulfides,[5] arenes (to *para*-quinones),[6] alkynes (to α,β-unsaturated ketones or 1,2-diketones),[1a,7] and sulfides (to sulfoxides).[8] Furthermore, the MTO/H_2O_2 system assists in the synthesis of vitamin K_3.[6,9] MTO acts as a catalyst for olefin metathesis,[10] for aldehyde olefination,[11] for dehydration, amination, and disproportionation of alcohols,[12] and for pyridine *N*-oxide preparation.[13] Methyltrioxorhenium has also proven itself as an efficient and versatile oxidation catalyst with interesting selectivity. High chemoselectivity is observed in the MTO-catalysed sulfoxidation reaction,[8] while good regioselectivity is displayed in the oxidation of geraniol[14] and in the oxidation of 2-methylnaphthalene to vitamin K_3.[6] Diastereoselectivity is also observed in the epoxidation of acyclic[14] and cyclic[15] allylic alcohols.



Scheme 1

The first type of MTO-catalysed reaction to be described was the epoxidation of olefins with hydrogen peroxide.[1a] Although in many cases the oxidation of olefins efficiently and selectively produces the corresponding epoxides, a typical side reaction is the conversion of the hydrolytically sensitive epoxides into 1,2-diols.[1a] This problem can to some extent be overcome by employing the urea−hydrogen peroxide adduct as a stoichiometric oxidant,[16] or by using pyridine as ligand in combination with aqueous hydrogen peroxide in aprotic solvents.[17] The active species involved in oxygen transfer to olefinic double bonds are probably the two Re^{VII} peroxo complexes **2** and **3**, obtained by the addition of one or two molecules of H_2O_2 to MTO, respectively (Scheme 1).[18]

As a part of our studies on the reactivity of unsaturated organic substrates with metal transition oxides and the functionalization of particular positions on the steroid nucleus,[19−22] we have investigated the reaction behaviour of the conjugated diene steroids **4** and **13** with the oxidant urea−hydrogen peroxide in the presence of catalytic amounts of MTO under different of temperature and solvent conditions, while also testing the effect of the pyridine ligand on the oxidative process. From these reactions we have isolated and characterized the new epoxy steroids **10**, **11**, **12**, **14**, and **15**, and the new triol **19**.

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Results and Discussion

The reaction between cholesta-3,5-diene (**4**) and the oxidant urea−hydrogen peroxide (4 equiv.) in the presence of catalytic amounts of MTO (0.1 equiv.) at 25 °C in $CHCl_3$ for 1 h afforded the isomeric compounds cholest-5-ene-3α,4α-diol (**5**, 11% yield), cholest-5-ene-3α,4β-diol (**6**, 14%), cholest-4-ene-3α,6β-diol (**7**, 17%), cholest-4-ene-3α,6α-diol (**8**, 9%), and cholest-4-ene-3β,6β-diol (**9**, 11%) (Figure 1), in a total yield of 62%.

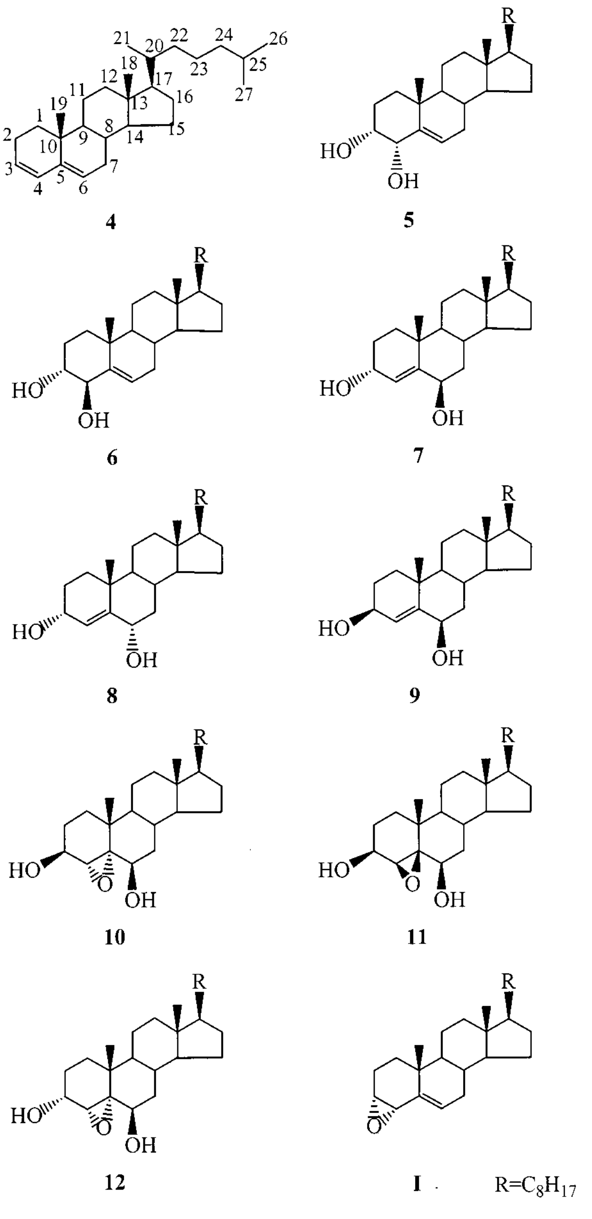

Figure 1. MTO/UHP oxidation products from the diene steroid **4**

Compounds **5**, **6**, **7**, **8**, and **9** are isomers, as indicated by their high resolution EIMS spectra and their very similar ^{1}H and ^{13}C NMR spectroscopic data (see Supporting Information). The difference between these sterols is in the position of the hydroxyl functions and the double bond and in the stereochemistry of the CH(OH) groups. The position of the double bond was established for these compounds on the basis of proton signal multiplicity, using examination of Dreiding models, and was further confirmed by selective H-H decoupling experiments. The stereochemistry of the chiral centres between C-3 and C-6 in compounds **5**, **6**, **7**, **8**, and **9** was established on the basis of proton coupling constants and proton shifts in the ^{1}H NMR spectra, recorded in [D_5]pyridine solution (see Supporting Information), relative to $CDCl_3$.[23] The structures of compounds **7**, **8**, and **9** were also supported by chemical evidence: their oxidation in CrO_3/pyridine solution gave the expected cholest-4-ene-3,6-dione.[24] Compound **7** has recently been isolated from the red alga *Acantophora spicifera*,[25a] while compounds **5**, **6**, **8**, and **9** have been reported in the literature as synthetic products.[25b−25f]

Interestingly, when the reaction between the oxidizing system MTO/UHP and cholesta-3,5-diene (**4**) in $CHCl_3$ was performed at 0 °C, three related new epoxy sterols were formed after 1 h in addition to **7** (8% yield); these were 4α,5-epoxy-5α-cholestane-3β,6β-diol (**10**, 12% yield), 4β,5-epoxy-5β-cholestane-3β,6β-diol (**11**, 15%) and 4α,5-epoxy-5α-cholestane-3α,6β-diol (**12**, 7%) (Figure 1). The degree of conversion of the substrate in this case was 42%.

The molecular formulae of **10**, **11**, and **12** were determined as $C_{27}H_{46}O_3$ on the basis of high resolution EIMS and ^{13}C NMR spectroscopic data, implying two OH functionalities and an epoxide ring. A combination of ^{1}H-^{1}H COSY, HMQC, and HMBC experiments allowed us to assign all the ^{1}H and ^{13}C NMR resonances for **10**, **11**, and **12**, as illustrated in Table 1.

The mass spectrum of compound **10** showed fragments due to the loss of one and two water molecules (m/z = 400 and 382, respectively), confirming the presence of two hydroxyl groups in the molecule. The ^{1}H NMR spectrum of **10** had a singlet at $\delta = 2.95$ (s, 4-H_β) for an epoxide proton and two oxymethine signals at $\delta = 3.38$ (br. t, $J = 2.9$ Hz, 6-H) and 3.97 (br. m, 3-H_α). The epoxide system was assumed to be positioned between C-4 and C-5 on the basis of the shape of the epoxide signal at $\delta = 2.95$ and an analysis of the ^{1}H-^{1}H COSY spectrum, which displays interactions between the 6-H proton signal at $\delta = 3.38$ and the methylene protons at $\delta = 1.22$ and 1.95 (7-H_2) and correlations between the 3-H proton resonance at $\delta = 3.97$ and the methylene protons at $\delta = 1.30$ and 1.70 (2-H_2); no cross-peaks for the epoxide proton at $\delta = 2.95$ were observed. Coupling constant values for the 3-H, 4-H, and 6-H proton signals allowed us to assign the stereochemistry as 3β,4α,5α,6β relative to the steroid nucleus, according to Dreiding molecular model analysis. Furthermore, the ^{1}H NMR spectrum of **10** in [D_5]pyridine exhibited shifts relative to that recorded in $CDCl_3$ for CH_3-19 ($\Delta\delta = -0.36$ ppm), for 4-H ($\Delta\delta = -0.47$ ppm), for 6-H ($\Delta\delta = -0.40$ ppm), and for 3-H ($\Delta\delta = -0.38$ ppm), in agreement with the assigned stereochemistry.[23]

The spectroscopic data of **11** were in agreement with the proposed structure. From a two-dimensional ^{1}H-^{1}H COSY spectrum analysis in combination with an HMQC experiment it was deduced that the proton resonance at $\delta = 3.99$

Table 1. ^1H (500 MHz) and ^{13}C NMR assignments of compounds **10−12** ($CDCl_3$); * denotes that the assignments may be interchangeable within a column

	10			**11**		**12**		
C	δ_H [a]	δ_C [b][c]	HMBC[d]	δ_H [a]	δ_C [b]	δ_H [a]	δ_C [b][c]	HMBC[d]
1	1.40, 1.09	27.5		1.40, 1.20	31.8	1.44, 1.18	29.3	
2	1.70, 1.30	25.7		1.54, 1.46	25.8	1.75, 1.53	27.1	
3	3.97 br. m	66.4		3.99 br. m	66.1	4.08 br. m	63.3	
4	2.95 s	65.8	2, 3, 6	3.25 br. d (3.2)	65.1	3.28 br. d (3.3)	62.8	2, 3, 6
5	−	67.2		−	69.4	−	67.9	
6	3.38 br. t (2.9)	74.6		3.35 br. t (2.6)	74.4	3.30 br. t (2.5)	74.4	
7_{eq}	1.95 dt (14.0, 2.9)	36.8		1.95 dt (14.5, 2.8)	36.8	1.77 dt (14.4, 2.7)	36.8	
7_{ax}	1.22			1.13		1.46		
8	1.88 m	29.5		1.84 m	29.4	1.86 m	30.4	
9	1.24	46.9		0.97	50.3	1.11	50.3	
10	−	35.8		−	35.3	−	34.7	
11	1.45, 1.42	21.1		1.46, 1.42	21.4	1.45, 1.34	20.6	
12_{eq}	2.02 dt (12.6, 2.7)	39.7		2.04 dt (12.5, 2.8)	39.8	2.01 dt (12.7, 2.7)	39.6	
12_{ax}	1.16			1.14		1.17		
13	−	42.6		−	42.6	−	42.7	
14	1.13	56.2		1.00	56.2	1.10	55.5	
15	1.61, 1.18	24.2		1.60, 1.17	24.2	1.61, 1.11	24.2	
16	1.85, 1.29	28.2		1.83, 1.28	28.1	1.85, 1.28	28.1	
17	1.06	56.0		1.09	56.0	1.12	56.2	
18	0.73 s	12.0	12, 13, 14, 17	0.70 s	12.0	0.71 s	12.1	12, 13, 14, 17
19	1.18 s	20.5	1, 5, 9, 10	1.19 s	19.7	1.20 s	17.5	1, 5, 9, 10
20	1.39	35.7		1.39	35.7	1.37	35.7	
21	0.93 d (6.4)	18.6	17, 20, 22	0.91 d (6.6)	18.6	0.91 d (6.6)	18.6	17, 20, 22
22	1.35, 1.10	36.1		1.35, 0.99	36.1	1.33, 1.00	36.1	
23	1.35, 1.13	23.9		1.33, 1.14	23.8	1.34, 1.13	23.8	
24	1.16, 1.12	39.5		1.11, 1.06	39.5	1.13, 1.19	39.5	
25	1.52	27.9		1.52	28.0	1.52	28.0	
26	0.89 d (6.5)	22.5*	24, 25, 27	0.88 d (6.6)	22.5*	0.87 d (6.5)	22.5*	24, 25, 27
27	0.88 d (6.5)	22.8*	24, 25, 26	0.87 d (6.6)	22.8*	0.87 d (6.5)	22.8*	24, 25, 26
OH	2.07 br. s			2.11 br. s		3_α 2.17 br. d (9.8)		

[a] δ values relative to the residual $CHCl_3$ signal (7.26); coupling constants (in Hz) are given in parentheses; δ assignments aided by ^1H-^1H COSY and HMQC experiments. − [b] δ values relative to the $CDCl_3$ signal (77.0); ^{13}C assignments assisted by ^1H-^1H COSY and HMQC experiments. − [c] ^{13}C assignments also aided by HMBC experiments. − [d] HMBC correlations from H to C.

(br. m), which correlated with two methylene protons at δ = 1.54 and 1.46 and with an oxymethine signal at δ = 3.25 (br. d, J = 3.2 Hz), was due to 3-H, while the signal at δ = 3.25, which displayed a cross-peak only with the proton signal at δ = 3.99, was assigned to 4-H. Furthermore, an oxymethine proton resonating at δ = 3.35 (br. t, J = 2.6 Hz), and so vicinal only to a methylene group (cross-peaks with methylene protons at δ = 1.95 and 1.13), was assigned to 6-H. The positions of the OH groups and of the oxirane system, and the stereochemistry of the atoms belonging to the C-3/C-6 segment of **11**, were deduced from the chemical shifts and coupling constants of the 3-H, 4-H, and 6-H proton signals and by a comparison of the spectroscopic data of **11** with those reported in the literature for the analogous 4β,5-epoxy-3β-methoxy-5β-cholestan-6β-ol:[26a] proton signal multiplicities, coupling constants, and chemical shift values of the two compounds were roughly superimposable.

In compound **12**, as in **10** and **11**, the epoxide system was also in the central position, between C-4 and C-5, with respect to the CH(OH) groups. The stereochemistry from C-3 to C-6 was deduced on the basis of the multiplicities, coupling constants and chemical shift values for 3-H, 4-H, and 6-H and was confirmed by comparison of the ^1H and ^{13}C NMR spectroscopic data of compound **12** with those of analogous compounds reported in the literature.[26]

The oxidation of cholesta-3,5-diene (**4**) with the MTO/UHP system was also performed in diethyl ether and THF. The behaviour of the reaction in these two solvents was practically the same as in $CHCl_3$, although solubility problems arising during the course of the reaction slow it down considerably.

Finally, performing the oxidation of **4** with the MTO/UHP system at 25 °C in the presence of pyridine as ligand (10 equiv.) in $CHCl_3$ gave the unsaturated diols **6** (22% yield), **7** (28%), **8** (8%), and **9** (7%) after 30 min. (Figure 1), in an overall yield of 65%. These compounds were also formed in $CHCl_3$ at 25 °C in the absence of pyridine but, as is evident from the product yields, the pyridine endows the oxidative process with higher stereoselectivity. In fact, oxidation in $CHCl_3$ alone produced the five unsaturated diols **5**, **6**, **7**, **8** and **9** in comparable yields, while oxidation in the presence of pyridine preferentially gave compounds **6** and **7**, together with small amounts of **8** and **9** and with a total absence of the 1,2-*cis*-diol **5**. It is likely that diols **6** and **7** is derived from a ring opening of the initially formed unsaturated 3α,4α-epoxide **I** (Figure 1). Water might preferentially approach C-4 of this epoxide from the β face of the molecule to produce the 1,2-*trans*-diaxial product **6**, while compound **7** might derive from water attack at C-6 of **I**. The pyridine probably coordinates to the metal centre, which in turn coordinates to the epoxide oxygen of **I**, and thus provides greater steric hindrance at the α face of the molecule, promoting the attack from the β side.

Treatment of 5α-cholesta-7,9(11)-dien-3β-yl acetate (**13**) with the urea−hydrogen peroxide adduct (4 equiv.) in the presence of catalytic amounts of MTO (0.1 equiv.) in $CHCl_3$ at 25 °C over 1 h afforded the new epoxy steroids 9α,11α-epoxy-5α-cholest-7-en-3β-yl acetate (**14**, 25% yield) and 7α,8α,9α,11α-diepoxy-5α-cholestan-3β-yl acetate (**15**, 7%), the keto steroid 7-oxo-5α-cholest-9(11)-en-3β-yl acetate (**16**, 18%), the epoxy ketone 9α,11α-epoxy-7-oxo-5α-cholestan-3β-yl acetate (**17**, 18%), and the diol 9α,11α-dihydroxy-5α-cholest-7-en-3β-yl acetate (**18**, 15%) (Figure 2), with a level of substrate conversion of 83%. Compounds **16**, **17**, and **18** were identified by comparison with authentic materials. Specifically, compound **18** has spectral properties identical to those of a compound previously obtained by ruthenium tetraoxide oxidation of diene **13**,[20] and compounds **16** and **17** have recently been synthesized in our laboratory.[27] However, the complete ^1H and ^{13}C NMR assignment of keto steroid **16** was now performed with the aid of ^1H-^1H COSY, DEPT, and HMBC experiments (see Supporting Information). The ^1H and ^{13}C NMR spectroscopic data of compounds **14** and **15** are reported in Table 2.

Compound **14** was found by HREIMS and ^{13}C NMR spectroscopy to have the molecular formula $C_{29}H_{46}O_3$. The ^1H NMR spectrum of **14** included a resonance at $\delta = 5.61$ (m) for an olefinic proton belonging to a trisubstituted double bond, the presence of which was confirmed by the two ^{13}C olefinic resonances at $\delta = 125.6$ (CH) and 135.2 (quaternary carbon). The epoxide system in **14** was indicated by the signals at $\delta = 64.6$ (quaternary carbon) and $\delta = 55.4$ (CH) in the ^{13}C NMR spectrum and by the signal at $\delta = 3.21$ (d, $J = 5.7$ Hz) in the ^1H NMR spectrum. HMBC and selective H-H decoupling experiments allowed us to locate the epoxide ring between C-9 and C-11 and the double bond between C-7 and C-8 (see Table 2). The signal for the epoxide proton exhibited the same doublet appearance as reported in the literature for the 11β-proton of 9α,11α-epoxy steroids,[28,29] the 11α-proton of a 9β,11β-epoxide appearing, in contrast, as a triplet ($J \approx 1.5$ Hz).[29] Furthermore, the ^1H and ^{13}C NMR resonances for the A, B, and C rings of steroid **14** were in good agreement with those reported in the literature for the 9α,11α-epoxy-5α-ergosta-7,22-dien-3β-yl acetate analogue.[30]

Compound **15** gave a molecular ion peak in the HREIMS spectrum at *m/z* = 458.3348, corresponding to the molecular formula $C_{29}H_{46}O_4$ and indicating the presence of two more oxygen atoms than in the starting $\Delta^{7,9(11)}$-diene steroid **13**. The ^{13}C NMR spectrum of compound **15** confirmed the presence of four oxygen-bound carbon atoms, at $\delta = 57.2$ (CH), 57.8 (CH), 61.4 (quaternary C), and 64.0 (quaternary C), values that allowed us to infer, in accordance with the HREIMS spectrum, the presence of two epoxide systems in the molecule. These oxirane systems were located between the 7/8 and 9/11 positions on the basis of the ^1H-^1H COSY correlation between the epoxide proton signal at $\delta = 3.09$ (d, $J = 6.0$ Hz, 11-H) and the double doublet at $\delta = 2.19$ ($J = 14.7$, 6.0 Hz, 12-H_{eq}), part of a methylene group next to a blocked position, and also that between the oxirane signal at $\delta = 3.47$ (br. d, $J = 2.6$ Hz, 7-H) and two further coupled methylene protons ($\delta = 1.92$ and 1.67, 6-H_2) (see Table 2). Further analysis of the NMR spectroscopic data of **15** allowed us to establish the stereochemistry of the epoxide systems. The β orientation of 11-H was assigned by the same arguments as previously discussed for the stereochemical assignment at the same hydrogen atom in compound **14**. Analogously, the β orientation of 7-H was suggested by the multiplicity of its signal in the ^1H NMR spectrum, taking the conformational data obtained from Dreiding molecular model analysis into account.

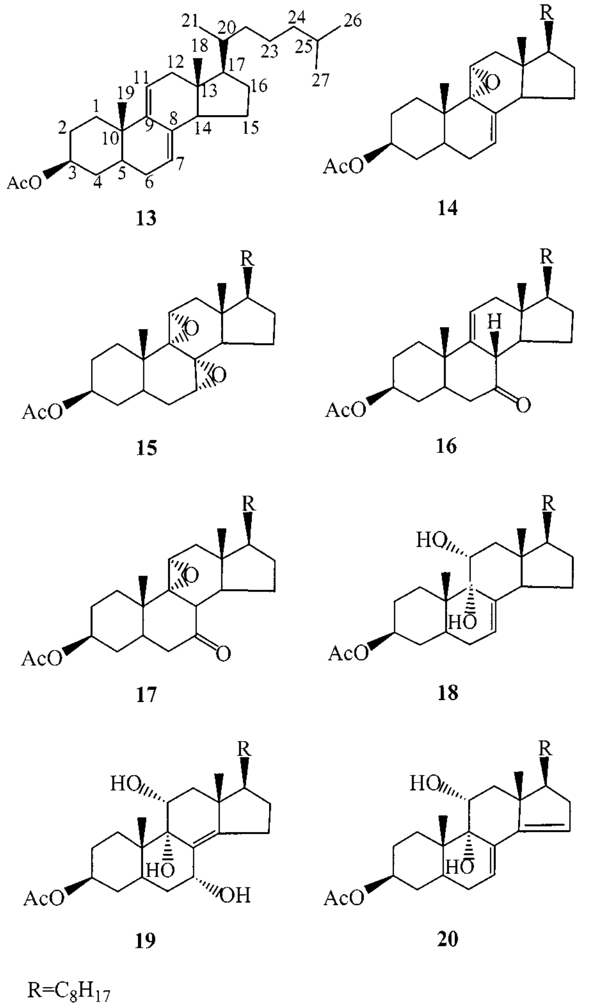

Figure 2. MTO/UHP oxidation products from the diene steroid **13**

Temperature does not affect the behaviour of the $\Delta^{7,9(11)}$-steroid oxidation, apart from a small increase in the reaction time when performed at 0 °C: treatment of **13** with

Table 2. ^1H (500 MHz, $CDCl_3$) and ^{13}C NMR assignments of epoxides **14** and **15**; * denotes the assignments may be interchanged within a column

		14		**15**	
C	δ_H [a]	δ_C [b] [c]	HMBC: H/C	δ_H [a]	δ_C [b]
1_{ax}	1.16	28.7	3, 5	1.10	29.3
2	1.86	26.9	3, 10	1.82, 1.44	26.5
3	4.66 m	72.8	$CH_3\mathit{C}OO$, 2	4.64 m	72.7
4_{eq}		33.6		1.72	32.8
4_{ax}	1.34		2, 3, 5, 6	1.32	
5	2.00 m	36.7	3, 7, 10	2.09 m	31.7
6_{eq}	1.89 ddd (10.5, 4.4, 3.4)	29.6	5, 7, 8, 10	1.92 dt (14.5, 2.6)	29.0
6_{ax}				1.67 dd (14.5, 10.7)	
7	5.61 m	125.6	5, 6, 9, 14	3.47 br. d (2.6)	57.8
8	–	135.2	–	–	61.4
9	–	64.6	–	–	64.0
10	–	34.7	–	–	34.9
11	3.21 d (5.7)	55.4	8, 9, 10, 12, 13	3.09 d (6.0)	57.2
12_{eq}	$_\beta$ 2.12 dd (14.9, 5.7)	40.7	11, 13, 14, 18	$_\alpha$ 2.19 dd (14.7, 6.0)	39.8
12_{ax}	$_\alpha$ 1.80 br. d (14.9)		9,11,13,14,17,18	$_\beta$ 1.71 d (14.7)	
13	–	43.2	–	–	43.8
14	2.25 m	46.9	8, 13		46.8
15	1.45	22.5	8, 14, 16		20.7
16	1.92	28.1	13, 17, 20		27.7
17	1.23	56.5	13, 16, 18, 20	1.22	56.3
18	0.56 s	13.6	12, 13, 14, 17	0.81 s	13.8
19	1.00 s	15.5	2, 5, 9, 10	1.02 s	17.3
20		35.8		1.31	35.6
21	0.89 d (6.2)	18.5	17, 20, 22	0.90 d (5.9)	18.5
22		36.0		1.12, 0.98	35.8
23		23.9		1.34, 0.99	23.8
24		39.5		1.22, 1.17	39.5
25	1.52	28.1	23, 24	1.52	28.0
26	0.861 d (6.5)	22.5*	24, 25, 27	0.860 d (6.6)	22.5*
27	0.857 d (6.6)	22.8*	24, 25, 26	0.856 d (6.6)	22.8*
$\mathit{CH_3}CO$	2.02 s	21.4	$CH_3\mathit{C}OO$, 3	2.00 s	21.4
$CH_3\mathit{CO}$	–	170.5	–	–	170.4

[a] δ values relative to the residual $CHCl_3$ signal (7.26); coupling constants (in Hz) are given in parentheses; ^1H assignments for **15** aided by ^1H-^1H COSY experiments. – [b] δ values relative to the $CDCl_3$ signal (77.0); ^{13}C assignments was assisted by DEPT spectra. – [c] ^{13}C assignments aided also by HMBC experiment.

MTO/UHP in $CHCl_3$ at 0 °C afforded the same products and with the same yields as obtained at 25 °C.

When the reaction between 5α-cholesta-7,9(11)-dien-3β-yl acetate **13** and the MTO/UHP oxidizing system was performed at 25 °C in diethyl ether over 2 h we obtained the monoepoxide **14** (41% yield), the keto steroid **16** (16%), the 9α,11α-diol **18** (18%), and the new triol **19** (21%) (Figure 2), with an increase in the overall yield (96%). Solubility problems were encountered when the same reaction was performed at 0 °C. ^{13}C and DEPT NMR spectra of the new compound **19** indicated the presence in the molecule of a tetrasubstituted double bond, with resonances at δ = 150.1 and 128.6, and of three oxygen-bearing carbon moieties, showing signals at δ = 76.0 (quaternary C), 67.5 (CH), and 66.4 (CH). The ^1H-^1H COSY spectrum revealed the presence of two important spin systems in the molecule. The first spin system started with the acetoxymethine proton 3-H_α at δ = 4.95 (m), which exhibited vicinal couplings with the 4-H_2 methylene protons at δ = 1.80 and 1.41, which in turn showed cross-peaks with the proton signal at δ = 2.75 (m) originating from 5-H. This last was also coupled with methylene protons at δ = 1.79 and 1.47 (6-H_2), which displayed mutual intercoupling together with vicinal couplings with the oxymethine proton signal at δ = 4.80 (br. t, *J* = 2.5 Hz). These considerations, together with the value of the coupling constant of the proton signal at δ = 4.80, allowed us to assign this resonance to 7-H with β equatorial stereochemistry. Furthermore, the 7-H proton signal showed no further correlations other than those with 6-H_2 methylene protons, in agreement with the quaternary character of C-8. The second spin system included a resonance at δ = 4.22 (br. dd, *J* = 12.6, 3.6 Hz) that showed cross-peaks only with the two mutually coupled methylene protons at δ = 2.28 and 1.66 which, having no further correlations, had to be part of a CH_2 group next to a blocked position. It was thus inferred that the signal at δ = 4.22 belonged to 11-H, which was adjacent to the methylene group 12-CH_2 and the quaternary carbon C-9 and which, according to coupling constant values, was of β stereochemistry. The position and stereochemistry of the three hydroxyl groups in the molecule were confirmed on the basis of proton signal shifts (especially for 5-H and 12-*H*$_2$) in the ^{1}H NMR spectrum of compound **19** in [D$_5$]pyridine relative to the spectrum in CDCl$_3$[23] (see Exp. Sect.). Further evidence for structure **19** came from the dehydration that this compound underwent on standing for several hours in CDCl$_3$, giving a compound that was identified as **20** on the basis of ^{1}H NMR spectroscopic data (Figure 2). The ^{1}H NMR spectrum of **20** in fact showed the presence of two olefinic proton signals at $\delta = 5.82$ (dd, $J = 5.2, 2.4$ Hz) and 5.47 (dd, $J = 3.2, 2.8$ Hz) and an oxymethine one at $\delta = 3.95$ (br. td, $J = 9.6, 4.4$ Hz), which were attributed to 15-H, 7-H, and 11-H, respectively, with the aid of selective H-H decoupling experiments and coupling constant values.

The oxidation of **13** with MTO/UHP in diethyl ether at 25 °C was also performed in the presence of pyridine. After 1 h this reaction had afforded steroids **14** (40% yield), **16** (24%), and **18** (25%) (Figure 2), with 89% substrate conversion.

Conclusion

We have reported an investigation into the reactivity of the conjugated diene steroids **4** and **13** towards the methyltrioxorhenium/H$_2$O$_2$−urea oxidative system, which has not yet been applied extensively to 1,3-dienes. The oxidations were performed in CHCl$_3$ and diethyl ether as solvents, at 0 °C and 25 °C, and in presence of pyridine. The major factor determining the stereoselectivity of these reactions is the nature of the starting material. In the case of the $\Delta^{3,5}$-diene **4**, the observed reaction stereoselectivity was generally low, due to the less hindered position of the Δ^3 double bond. In accordance with the reported reactivity of MTO, it seems reasonable that, at 25 °C in CHCl$_3$, the diene **4** gives unsaturated 3,4-epoxides as the primary products and that these then undergo MTO-catalysed ring opening, either through α or β water attack at C-6, affording the bisallylic diols **7**, **8**, and **9**, or through water attack at C-4 from the α or β face of the 3α,4α-epoxide **I**, producing the 3,4-diols **5** and **6**. The same reaction performed in the presence of pyridine exhibited a higher stereoselectivity in the oxidative process. In fact, while oxidation in CHCl$_3$ alone produced the five unsaturated diols **5**, **6**, **7**, **8**, and **9** in similar yields, oxidation in the presence of pyridine preferentially afforded compounds **6** and **7**, with the 1,2-*cis*-diol **5** being totally absent. Pyridine probably coordinates to the metal centre, which in turn coordinates to the epoxide oxygen of **I**, creating greater steric hindrance on the α face of the molecule and thus favouring the attack from the β side. Pyridine furthermore has an accelerating effect on the reaction rate, as demonstrated by the reaction time, according to data previously reported in the literature.[17] Oxidation of **4** in diethyl ether and THF afforded the same products as had been obtained in CHCl$_3$, but with less material recovered because of solubility problems. When the oxidation of **4** with MTO/UHP in CHCl$_3$ was performed at 0 °C, the new 4,5-epoxy-3,6-dihydroxy sterols **10**, **11**, and **12** were formed as well as compound **7**.

Oxidation of the diene steroid **13** with MTO/UHP in CHCl$_3$ and diethyl ether was not affected by temperature. The same products and the same yields were obtained for each solvent at both 0 °C and 25 °C, although solubility problems were encountered with the reaction in diethyl ether at 0 °C. As far as solvents are concerned, in CHCl$_3$ the $\Delta^{7,9(11)}$-diene steroid **13** was attacked from the α face of the molecule at both double bonds, giving the new epoxy steroids **14** and **15** in 25% and 7% yields, respectively, in addition to products probably deriving from epoxide ring-opening and transposition, such as the keto steroid **16** (18% yield), the epoxy ketone **17** (17%), and the diol **18** (15%). When this oxidation of **13** was performed in diethyl ether, a higher yield of the monoepoxide **14** (41%) was obtained, while the diepoxide **15** was not isolated but the new triol **19** (21%) was obtained instead. This last probably derived from **15** through epoxide ring-opening to give the 7α,8α,9α,11α-tetrol, which underwent dehydration between C-8 and C-14. Compound **19** was subject to further dehydration; it in fact lost a water molecule on standing for several hours in CDCl$_3$, giving a compound identified as **20** by ^{1}H NMR spectroscopy. The pyridine ligand did not significantly affect the behaviour of the oxidation of **13**.

To elucidate the behaviour of the oxidative system MTO/UHP fully, we are currently exploring oxidations of other, variously substituted 1,3-dienes under various reaction conditions. The biological activity of all new steroids (**10**, **11**, **12**, **14**, **15**, **16** and **19**) is also under investigation.

Experimental Section

General Remarks: ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AMX-500 and Varian 200 spectrometers in CDCl$_3$ and [D$_5$]pyridine solutions. Proton chemical shifts were referenced to residual C*H*Cl$_3$ ($\delta = 7.26$) or C$_5$*H*D$_4$N ($\delta = 8.71, 7.55, 7.19$) signals. ^{13}C NMR chemical shifts were referenced to the solvent (*C*DCl$_3$: $\delta = 77.0$; *C*$_5$D$_5$N: $\delta = 149.9, 135.5, 123.5$). 2D NMR spectra were recorded at 500 MHz on a Bruker AMX-500 spectrometer. − Positive-ion FAB mass spectra were obtained on a VG Autospec mass spectrometer. Electron impact mass spectra (EIMS) were recorded on a Trio 2000 mass spectrometer. High resolution electron impact mass spectra (HREIMS) were obtained by electron impact at 70 eV on a Kratos AEI-MS 902 mass spectrometer. Melting points were determined with a Reichert microscopic hot stage apparatus and are uncorrected. − High performance liquid chromatography (HPLC) was performed on a Varian 2510 apparatus equipped with a Waters R403 dual cell refractometer, using semipreparative Hibar Lichrosorb Si-60 (250 × 10 mm) and μBondapak C18 (7.8 × 300 mm) columns. Thin layer chromatography (TLC) was performed on precoated F$_{254}$ silica gel plates (0.25 mm, Merck). The reactions were monitored by TLC until all starting material had been consumed.

Oxidation of 4 with the MTO/UHP System in CHCl$_3$ at 25 °C: Methyltrioxorhenium (MTO, 6.8 mg, 0.027 mmol, 0.1 equiv.) was added to a suspension of urea−hydrogen peroxide adduct (UHP, 102 mg, 1.09 mmol, 4 equiv.) in CHCl$_3$ (3 mL) and the mixture was stirred at 25 °C for 10 min. A solution of cholesta-3,5-diene (100 mg, 0.272 mmol, 1 equiv.) in $CHCl_3$ (2.5 mL) was added to this mixture and the suspension was stirred for 1 h, after which 10 mL of H_2O was added. The mixture was extracted with $CHCl_3$ (3 × 15 mL) and the combined organic phases were dried with $MgSO_4$ and then evaporated under reduced pressure to give 110 mg of crude products. Separation of the reaction mixture by HPLC on a Hibar Lichrosorb column, eluting with hexane/AcOEt (75:25 v/v, φ = 3.5 mL/min.), afforded pure samples of the isomeric compounds **5** (12.0 mg, 11% yield, t_R = 10.7 min.), **6** (15.3 mg, 14%, t_R = 18.5 min.), **7** (18.6 mg, 17%, t_R = 21.8 min.), **8** (9.8 mg, 9%, t_R = 22.5 min.) and **9** (12.0 mg, 11%, t_R = 27.5) (Figure 1).

Cholest-5-ene-3α,4α-diol (5): See Supporting Information for ^{1}H NMR ($CDCl_3$ and C_5D_5N, 200 MHz), FABMS (glycerol matrix), EIMS, HREIMS.

Cholest-5-ene-3α,4β-diol (6): See Supporting Information for ^{1}H NMR ($CDCl_3$ and C_5D_5N, 200 MHz), ^{13}C NMR ($CDCl_3$, 50 MHz), EIMS, HREIMS.

Cholest-4-ene-3α,6β-diol (7): See Supporting Information for ^{1}H NMR ($CDCl_3$, 500 MHz), ^{1}H NMR (C_5D_5N, 200 MHz), ^{13}C NMR ($CDCl_3$, 125 MHz), EIMS, HREIMS.

Cholest-4-ene-3α,6α-diol (8): See Supporting Information for ^{1}H NMR ($CDCl_3$ and C_5D_5N, 200 MHz), ^{13}C NMR ($CDCl_3$, 50 MHz), EIMS, HREIMS.

Cholest-4-ene-3β,6β-diol (9): See Supporting Information for ^{1}H NMR ($CDCl_3$ and C_5D_5N, 200 MHz), ^{13}C NMR ($CDCl_3$, 50 MHz), EIMS, HREIMS.

Oxidation of 4 in $CHCl_3$ at 0 °C: MTO (4 mg, 0.0165 mmol), UHP (62 mg, 0.66 mmol) and the diene **4** (61 mg, 0.165 mmol) were maintained at 0 °C whilst stirring, as described above, in $CHCl_3$ (5 mL) for 1 h. After the usual extraction and workup, 70 mg of crude products were separated by HPLC on an Si-60 column, eluting with hexane/AcOEt (7:3 v/v, φ = 3.5 mL/min.). Separation of the reaction mixture afforded pure compounds **7** (5.3 mg, 8% yield, t_R = 20.0 min.) and **12** (4.8 mg, 7%, t_R = 24.0 min.) and two crude sterol fractions: **A** (10 mg, t_R = 12.1 min.) and **B** (30 mg, t_R = 15.8 min.). Fraction **A**, after subjection to HPLC separation on μBondapak C18 (7.8 × 300 mm), eluting with $MeOH/H_2O$ (95:5 v/v, φ = 1 mL/min.), gave compound **10** (8.3 mg, 12%, t_R = 7.4 min.), while **B**, under the same conditions, afforded a pure sample of **11** (10.3 mg, 15%, t_R = 11.1 min.) (Figure 1).

4α,5-Epoxy-5α-cholestane-3β,6β-diol (10): Crystallization from methanol gave fine, white crystals; m.p. 137−140 °C. − ^{1}H NMR ($CDCl_3$, 500 MHz): see Table 1. − ^{1}H NMR (C_5D_5N, 500 MHz): δ = 0.69 (s, 3 H, 18-CH_3), 0.90 (d, J = 6.5 Hz, 6 H, 26-CH_3 and 27-CH_3), 0.97 (d, J = 6.4 Hz, 3 H, 21-CH_3), 1.54 (s, 3 H, 19-CH_3), 2.03 (dt, J = 12.6, 2.7 Hz, 1 H, 12-H_{eq}), 2.08 (dt, J = 14.0, 2.9 Hz, 1 H, 7-H_{eq}), 2.15 (m, 1 H, 8-H), 3.42 (s, 1 H, 4-H_β), 3.78 (br. t, J = 2.9 Hz, 6-H_α), 4.35 (m, 1 H, 3-H_α), 6.68 (br. s, 1 H, OH), 6.92 (br. s, 1 H, OH). − ^{13}C NMR ($CDCl_3$, 125 MHz): see Table 1. − EIMS: m/z (%) = 418 (54) [M^+], 400 [$M^+ - H_2O$] (100), 385 [$M^+ - H_2O - CH_3$] (20), 382 [$M^+ - 2H_2O$] (19), 367 [$M^+ - 2\,H_2O - CH_3$] (12), 348 [$M^+ - C_4H_6O$(A ring)] (69), 331 [$M^+ - C_4H_7O_2$] (59), 313 [$M^+ - C_4H_7O_2 - H_2O$] (29), 287 [$M^+ - C_8H_{17}$(side chain) $- H_2O$] (8), 269 [$M^+ - C_8H_{17} - 2H_2O$] (5), 245 [$M^+ - C_8H_{17} - C_3H_6$(D ring) $- H_2O$] (26), 227 [$M^+ - C_8H_{17} - C_3H_6 - 2H_2O$] (22). − HREIMS: m/z = 418.3442 [M^+, calcd. for $C_{27}H_{46}O_3$, 418.3447).

4β,5-Epoxy-5β-cholestane-3β,6β-diol (11): Crystallization from methanol gave colourless needles; m.p. 150−152 °C. − ^{1}H NMR ($CDCl_3$, 500 MHz): see Table 1. − ^{13}C NMR ($CDCl_3$, 125 MHz): see Table 1. − EIMS: m/z (%) = 418 (74) [M^+], 400 [$M^+ - H_2O$] (66), 385 [$M^+ - H_2O - CH_3$] (17), 382 [$M^+ - 2H_2O$] (13), 367 [$M^+ - 2\,H_2O - CH_3$] (14), 348 [$M^+ - C_4H_6O$(A ring)] (100), 331 [$M^+ - C_4H_7O_2$] (48), 313 [$M^+ - C_4H_7O_2 - H_2O$] (15), 287 [$M^+ - C_8H_{17}$(side chain) $- H_2O$] (8), 269 [$M^+ - C_8H_{17} - 2H_2O$] (5), 245 [$M^+ - C_8H_{17} - C_3H_6$(D ring) $- H_2O$] (23), 227 [$M^+ - C_8H_{17} - C_3H_6 - 2H_2O$] (13). − HREIMS: m/z = 418.3412 (M^+, calcd. for $C_{27}H_{46}O_3$, 418.3447).

4α,5-Epoxy-5α-cholestane-3α,6β-diol (12): Crystallization from methanol gave fine, white crystals; m.p. 158−161 °C. − ^{1}H NMR ($CDCl_3$, 500 MHz): see Table 1. − ^{13}C NMR ($CDCl_3$, 125 MHz): see Table 1. − EIMS: m/z (%) = 418 (46) [M^+], 400 [$M^+ - H_2O$] (37), 385 [$M^+ - H_2O - CH_3$] (13), 382 [$M^+ - 2\,H_2O$] (8), 367 [$M^+ - 2H_2O - CH_3$] (8), 348 [$M^+ - C_4H_6O$(A ring)] (100), 331 [$M^+ - C_4H_7O_2$] (65), 313 [$M^+ - C_4H_7O_2 - H_2O$] (20), 287 [$M^+ - C_8H_{17}$(side chain) $- H_2O$] (6), 269 [$M^+ - C_8H_{17} - 2H_2O$] (5), 263 [$M^+ - C_8H_{17} - C_3H_6$(D ring)] (13), 245 [$M^+ - C_8H_{17} - C_3H_6 - H_2O$] (21), 227 [$M^+ - C_8H_{17} - C_3H_6 - 2H_2O$] (31). − HREIMS: m/z = 418.3420 (M^+, calcd. for $C_{27}H_{46}O_3$, 418.3447).

Oxidation of 4 in the Presence of Pyridine: UHP (102 mg, 1.09 mmol, 4 equiv.) was added with stirring at 25 °C to a solution of MTO (6.8 mg, 0.027 mmol, 0.1 equiv.) and pyridine (220 μL, 2.720 mmol, 10 equiv.) in $CHCl_3$. A solution of the diene **4** (100 mg, 0.272 mmol, 1 equiv.) in $CHCl_3$ was then added to the resulting suspension. After 30 min. the reaction was terminated by addition of H_2O and the usual extractive workup was performed. HPLC separation on an Si-60 column, eluting with hexane/AcOEt (75:25 v/v, φ = 3.5 mL/min.), resulted in the isolation of the isomeric compounds **6** (24.1 mg, 22%, t_R = 18.5 min.), **7** (30.6 mg, 28%, t_R = 21.8 min.), **8** (8.7 mg, 8%, t_R = 22.5 min.) and **9** (7.6 mg, 7%, t_R = 27.5) (Figure 1).

Oxidation of 13 in $CHCl_3$: The diene steroid **13** (46 mg, 0.108 mmol, 1 equiv.), dissolved in $CHCl_3$ (1.5 mL), was added dropwise to a solution, prepared as described for **4**, of MTO (3 mg, 0.011 mmol, 0.1 equiv.) and UHP (41 mg, 0.436 mmol, 4 equiv.) in $CHCl_3$ (2.5 mL) and the suspension was stirred for 1 h at 25 °C. After 1 h the reaction mixture was diluted with $CHCl_3$ and extracted with H_2O. The organic layer was dried with anhydrous $MgSO_4$ and evaporated to dryness under reduced pressure. Separation of the reaction mixture by HPLC on a Hibar Lichrosorb Si-60 column, eluting with hexane/AcOEt (8:2 v/v, φ = 2.5 mL/min.), gave pure samples of **14** (11.9 mg, 25% yield, t_R = 4.8 min.), **15** (3.6 mg, 7%, t_R = 5.7 min.), **16** (8.7 mg, 18%, t_R = 6.3 min.), **17** (9 mg, 18%, t_R = 7.0 min.) and **18** (7.3 mg, 15%, t_R = 8.5 min.) (Figure 2).

9α,11α-Epoxy-5α-cholest-7-en-3β-yl Acetate (14): Crystallization from methanol gave white prisms; m.p. 128−130 °C. − ^{1}H NMR ($CDCl_3$, 500 MHz): see Table 2. − ^{13}C NMR ($CDCl_3$, 125 MHz): see Table 2. − FABMS: m/z = 443 [MH^+]. − EIMS: m/z (%) = 442 (57) [M^+], 427 [$M^+ - CH_3$] (9), 424 [$M^+ - H_2O$] (6), 382 [$M^+ -$ AcOH] (7), 367 [$M^+ -$ AcOH $- CH_3$] (8), 349 [$M^+ -$ AcOH $- CH_3 - H_2O$] (5), 329 [$M^+ - C_8H_{17}$(side chain)] (100). − HREIMS: m/z = 442.3468 (M^+, calcd. for $C_{29}H_{46}O_3$, 442.3447).

7α,8α,9α,11α-Diepoxy-5α-cholestan-3β-yl Acetate (15): Crystallization from methanol gave white needles; m.p. 168−170 °C. − ^{1}H NMR ($CDCl_3$, 500 MHz): see Table 2. − ^{13}C NMR ($CDCl_3$, 125 MHz): see Table 2. − FABMS: m/z = 459 [MH^+]. − EIMS: m/z (%) = 458 [M^+] (100), 442 [$M^+ -$ O] (17), 415 [$M^+ - CH_3CO$]

(10), 398 [M^+ − AcOH] (6), 383 [M^+ − AcOH − CH_3] (13), 345 [M^+ − C_8H_{17}(side chain)] (13), 329 [M^+ − O − C_8H_{17}] (19), 303 [M^+ − C_8H_{17} − C_3H_6(D ring)] (13), 257 [M^+ − C_8H_{17} − C_3H_6 − O − $2CH_3$] (9). − HREIMS: *m/z* = 458.3348 (M^+, calcd. for $C_{29}H_{46}O_4$, 458.3396).

7-Oxo-5α-cholest-9(11)-en-3β-yl Acetate (16): See Supporting Information for complete assignment of ^1H and ^{13}C NMR resonances.

Oxidation of 13 in Diethyl Ether: A suspension of MTO (2.9 mg, 0.012 mmol, 0.1equiv.), UHP (44 mg, 0.469 mmol, 4 equiv.) and diene steroid **13** (50 mg, 0.117 mmol, 1 equiv.) in diethyl ether (4 mL), prepared as described for **4**, was stirred at 25 °C. After 2 h the reaction was terminated by addition of H_2O and extraction with diethyl ether. The recovered material was subjected to HPLC separation, using hexane/AcOEt (8:2 v/v, φ = 2.5 mL/min.) as eluent, to give 21 mg of **14** (41% yield, t_R = 4.8 min.), 8.3 mg of keto steroid **16** (16%, t_R = 6.3 min.), 9.7 mg of diol **18** (18%, t_R = 8.5 min.) and 11.7 mg of triol **19** (21%, t_R = 18.8 min.) (Figure 2).

7α,9α,11α-Trihydroxy-5α-cholest-8(14)-en-3β-yl Acetate (19): Amorphous powder. − ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.82 (s, 3 H, 18-CH_3), 0.86 (d, *J* = 6.6 Hz, 6 H, 26-CH_3 and 27-CH_3), 0.88 (s, 3 H, 19-CH_3), 0.97 (d, *J* = 6.2 Hz, 3 H, 21-CH_3), 1.49 (t, *J* = 12.6 Hz, 1 H, 12-H_{ax}), 2.02 (s, 3 H, CH_3COO), 2.14 (dd, *J* = 12.6, 3.6 Hz, 1 H, 12-H_{eq}), 4.03 (br. dd, *J* = 12.6, 3.6 Hz, 1 H, 11-$H_β$), 4.60 (br. t, *J* = 2.5 Hz, 1 H, 7-$H_β$), 4.72 (m, 1 H, 3-H). − ^1H NMR (C_5D_5N, 500 MHz): δ = 0.83 (s, 3 H, 18-CH_3), 0.86 (d, *J* = 6.6 Hz, 6 H, 26-CH_3 and 27-CH_3), 0.90 (d, *J* = 6.2 Hz, 3 H, 21-CH_3), 0.90 (s, 3 H, 19-CH_3), 1.41 (1 H, 4-H_{ax}), 1.42 (1 H, 20-H), 1.47 (1 H, 6-H_{eq}), 1.52 (1 H, 25-H), 1.58 (1 H, 2-H_{ax}), 1.66 (1 H, 12-H_{ax}), 1.79 (1 H, 6-H_{ax}), 1.80 (1 H, 4-H_{eq}), 1.97 (1 H, 2-H_{eq}), 2.05 (s, 3 H, CH_3COO), 2.28 (1 H, 12-H_{eq}), 2.75 (m, 1 H, 5-H), 4.22 (br. dd, *J* = 12.6, 3.6 Hz, 1 H, 11-$H_β$), 4.80 (br. t, *J* = 2.5 Hz, 1 H, 7-$H_β$), 4.95 (m, 1 H, 3-H). − ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 15.6 (C-19), 17.4 (C-18), 19.1 (C-21), 21.3 (CH_3COO), 22.9 (C-26 or −27), 23.0 (C-26 or −27), 23.9 (C-23), 25.4, 27.0, 28.1, 28.2, 30.0, 31.1, 32.0, 34.5, 36.1, 37.1, 39.7 (C-24), 42.0, 44.7, 45.0, 56.3 (C-17), 66.4 (C-11), 67.5 (C-7), 73.6 (C-3), 76.0 (C-9), 128.6 (C-8), 150.1 (C-14), 170.3 (CH_3COO).

Dehydration of Compound 19: After standing for several hours in $CDCl_3$, compound **19** had undergone elimination of H_2O to give 9α,11α-dihydroxy-5α-cholesta-7,14-dien-3β-yl acetate (**20**, Figure 2).

Compound 20: ^1H NMR (CCl_4, 200 MHz): δ = 0.82 (s, 3 H, 18-CH_3), 0.86 (d, *J* = 6.0 Hz, 6 H, 26-CH_3 and 27-CH_3), 0.94 (d, *J* = 6.0 Hz, 3 H, 21-CH_3), 0.95 (s, 3 H, 19-CH_3), 1.47 (dd, *J* = 12.2, 9.6 Hz, 1 H, 12-H_{ax}), 1.76 (1 H, 6-H_{eq}), 1.86 (1 H, 16-$H_α$), 1.90 (s, 3 H, CH_3COO), 1.96 (dd, *J* = 12.2, 4.4 Hz, 1 H, 12-H_{eq}), 2.17 (dt, *J* = 14.0, 3.6 Hz, 1 H, 1-H_{eq}), 2.30 (ddd, *J* = 15.5, 6.5, 3.2 Hz, 1 H, 16-$H_β$), 3.95 (br. td, *J* = 9.6, 4.4 Hz, 1 H, 11-H_{ax}), 4.53 (m, 1 H, 3-$H_α$), 5.47 (dd, *J* = 3.2, 2.8 Hz, 1 H, 15-H), 5.82 (dd, *J* = 5.2, 2.4 Hz, 1 H, 7-H).

Oxidation of 13 in the Presence of Pyridine: Treatment of the diene **13** (100 mg, 0.235 mmol, 1 equiv.), MTO (5.8 mg, 0.023 mmol, 0.1 equiv.), UHP (88.3 mg, 0.939 mmol, 4 equiv.), and pyridine (190 μL, 2.350 mmol, 10 equiv.) in $CHCl_3$ resulted after 1 h in the isolation by HPLC, eluting with hexane/AcOEt (8:2 v/v, φ = 2.5 mL/min.), of 41.5 mg of **14** (40% yield, t_R = 4.8 min.), 24.9 mg of keto steroid **16** (24%, t_R = 6.3 min.) and 27.0 mg of diol **18** (25%, t_R = 8.5 min.) (Figure 2).

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