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One-pot, high yield synthesis of α-ketols from Δ^5-steroids

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ABSTRACT

α-Hydroxy ketones (α-ketols) are present in many compounds with biological activity. Several methods are available for the preparation of α-ketols but only a few of them describe the synthesis of steroid α-ketols from olefins. In this work, a new system consisting of $KMnO_4/Fe(ClO_4)_3{\cdot}nH_2O$ was used in order to achieve the direct conversion of Δ^5-steroids to their corresponding α-ketols, in high yields. Consideration of the probable reaction mechanism is provided. 2D homo- and heteronuclear correlation NMR spectroscopic techniques were used to assign ^1H and ^{13}C resonances of some synthesized compounds. This method has potential for the preparation of α-hydroxy ketones of biological interest.

1. Introduction

α-Hydroxy ketones (α-ketols) occur in many biologically active compounds [1]. The dihydroxyketone side chain is not only common to a wide variety of corticosteroid antiinflammatory drugs, but is also a structural component of adriamycin, a potent antitumor agent [2,3]. Moreover, such functionalization of steroid substrates is important because polyoxygenated steroids have been isolated from marine organisms and are considered a growing group of metabolites with potential biological and pharmacological activities [4,5], and are intermediates in the synthesis of secosterols [6,7]. Two polyoxygenated steroids isolated from the sponge *Dysidea incrustans* showed cytotoxicity against human non-small-cell lung, renal and melanoma carcinoma cell lines [8]. A racemic mixture of α-ketols isolated from *Plexaurella grisea* collected at Punta Cana, exhibited strong and selective cytotoxicity against the HT-29 cell line with an $ED_{50} = 0.1\,\mu g/ml$ [9]. Furthermore, 5α-hydroxy-6-ketosteroids have been used to synthesize various structural analogs of natural ecdysteroids, which are the basis for the development of a new class of ecologically safe insecticides [10]. In particular, certain simple synthetic sterol derivatives are active insecticides against the Colorado beetle. These compounds are prepared via chemical transformation of cholesterol or β-sitosterol by replacing the sterol 3β-hydroxy by chlorine with subsequent introduction of oxygen-containing functional groups in rings A and B of the corresponding 3β-chloro derivatives. 3β-Chloro-5α-hydroxycholestan-6-one is one of the most toxic compounds against the Colorado beetle larvae [11].

Available methods for the preparation of α-ketols include the oxidation of diols [12–15], oxidation of ketones via enol ethers [16,17] or enolate anions [18], benzoin condensation

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[19], the oxidation of epoxides [20–26], reaction of acyl lithium compounds with ketones and aldehydes [27], reductive coupling reactions of acid halides with ketones and aldehydes [28,29], partial reduction of 1,2-diketones [30] and those from olefins [31–34].

There are only a few methods reported for the synthesis of α-ketols from steroid olefins. These include RuO_4 oxidation of monoene [35], conjugated diene [6,36], and Δ^2, $\Delta^{2,4}$, $\Delta^{4,6}$ steroids [6], $RuCl_3$ catalyzed oxidation of olefins with peroxyacetic acid [37] and OsO_4 catalyzed oxidation of the $\Delta^{17,20}$ steroid position with Mila's reagent (H_2O_2 in anhydrous *t*-BuOH) [38].

Oxidations with $KMnO_4/CuSO_4{\cdot}5H_2O$ were not effective in the conversion of steroidal olefins to the corresponding α-ketols [31] instead the 5β,6β-epoxides were obtained [39]. The authors then hypothesized that traces of water and *t*-butyl alcohol in the reaction medium could be responsible for the formation of an omega phase over the oxidant where the reaction actually took place and therefore, the greater lipophilicity of the steroid substrates would account for these unexpected results [39].

Further work on the synthesis of steroid 5β,6β-epoxides from olefins using $KMnO_4$/metal sulphate and nitrate systems has been published [40] and two mechanistic approaches have been proposed for this reaction. Parish and Li suggested that there was coordination of the copper ion on the less hindered α-face of the double bond, forming a π-complex that weakened it and provided for the subsequent permanganate attack on the β-face [41,42]. Another study, however, suggested that the mechanism involved the kinetically controlled attack of the MnO_4^- ion in the omega phase on the alkene, in a Markovnikoff manner and in an axial sense. The role of the metal salts would be to co-ordinate with the MnO_4^- ion to allow the decomposition of the complex to the corresponding epoxide [43,44].

With this work, we report a novel, one-step procedure for the conversion of Δ^5-steroids to their corresponding α-ketols in high yields, using $Fe(ClO_4)_3{\cdot}nH_2O$ as the metal salt in the $KMnO_4$/metal salt system and further shed some light onto the mechanism by which the reaction occurs. Homo- [45] and heteronuclear [46] 2D NMR techniques were used in the assignment of ^1H and ^{13}C resonances not directly attributable from the 1D ^1H NMR and ^{13}C NMR spectra.

2. Experimental

2.1. General methods

Steroid starting materials of high purity were available from Sigma–Aldrich Co. Solvents were distilled before use according to standard procedures. Kieselgel $60HF_{254}$/Kieselgel 60G was used for TLC plates. Melting points were determined on a BUCHI Melting Point B-540 and are uncorrected. IR spectra were performed in a Jasco FT/IR 420 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded either on a Bruker AMX 300 or on a Varian UNITY-500 spectrometer in $CDCl_3$ solution with Me_4Si as internal standard. 2D homonuclear correlation (COSY) and 2D heteronuclear multiple quantum correlation (HMQC) spectra were recorded on the Varian UNITY-500 spectrometer. Mass spectral analyses were made on a KRATOS model MS 25RF or a Fisons VG Autospec instrument.

2.2. General procedure for the preparation of steroidal α-ketols

Steroid substrates (Table 1, entries 1–9) were dissolved in dichloromethane at room temperature, in a reaction flask. A mixture of $KMnO_4$ and $Fe(ClO_4)_3{\cdot}nH_2O$ was ground to a fine powder (*Caution*: appropriate precautions should be undertaken in the manipulation of iron(III) perchlorate hydrate). Water was added and the final mixture was transferred to the reaction flask, followed by the addition of *t*-butyl alcohol. All reactions were monitored by TLC control. The final products were separated from the inorganic residues by addition of diethyl ether to the reaction flask which was allowed to stay under magnetic stirring for a few minutes. The mixture was then filtrated through a celite pad and the solid residue thoroughly washed with hot ether (total volume of 150 ml). The filtrates were washed with water (30 ml) and dried over anhydrous sodium sulphate. The organic phases were filtered and the solvent was evaporated under vacuum to give the final products.

2.2.1. 5α-Hydroxy-6,17-dioxoandrostane-3β-yl acetate (10)

Mp (diethyl ether) 196–198 °C; lit. 197–198 °C [47]. IR (cm^{-1}) 3470.28, 1737.73, 1705.85, 1264.11; ^1H NMR ($CDCl_3$, 300 MHz)

Table 1 – General procedure for the preparation of steroidal α-ketols

Entry	Substrate	(mmol)	CH_2Cl_2 (ml)	$KMnO_4$ (g)	$Fe(ClO_4)_3{\cdot}nH_2O$ (g)	H_2O (μl)	*t*-BuOH (ml)	Time (h)	Isolated yield (%)	Product
1	**1**	0.5	4.5	1.5	0.75	75	0.25	20	70	**10**
2	**2**	0.5	4.5	1.5	0.75	75	0.25	18	75	**11**
3	**3**	1	9	3	1.5	150	0.5	24	78	**12**
4	**4**	0.5	4.5	1.5	0.75	75	0.25	24	71	**13**
5	**5**	0.5	4.5	1.5	0.75	75	0.25	24	76	**14**
6	**6**	0.5	4.5	1.5	0.75	75	0.25	15	80	**15**
7	**7**	1	9	3	1.5	150	0.5	20	76	**16**
8	**8**	0.5	4.5	1.5	0.75	75	0.25	8	81	**10**
9	**9**	0.5	4.5	1.5	0.75	75	0.25	20	78	**17**

δ = 0.80 (s, 3H, 18-H_3), 0.82 (s, 3H, 19-H_3), 1.98 (s, 3H, CH_3CO), 2.85 (dd, J = 12.8 Hz and 11.8 Hz, 7α-H), 4.99 (m, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 70.58 (C_3), 80.06 (C_5), 171.17 (CH_3COO), 211.71 (C_6), 220.19 (C_{17}); MS [*m*/*z* (%)] 362 (30) M^+, 302 (81), 220 (68), 205 (61), 110 (78), 95 (71), 81 (64), 43 (100).

*2.2.2. 5α-Hydroxy-6-oxoandrostane-3β-yl acetate (**11**)*
Mp (diethyl ether–petroleum ether) 220–221 °C; lit. 220–221 °C [48] IR (cm^{-1}) 3411.46, 1728.87, 1700.91, 1365.35, 1272.79, 1240.00; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.65 (s, 3H, 18-H_3), 0.79 (s, 3H, 19-H_3), 1.99 (s, 3H, CH_3CO), 2.76 (dd, J = 12.5 Hz and 12.8 Hz, 7α-H), 5.01 (m, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 70.62 (C_3), 80.19 (C_5), 171.00 (CH_3COO), 212.32 (C_6); MS [*m*/*z* (%)] 348 (24) M^+, 288 (92), 206 (74), 135 (89), 109 (95), 95 (100), 81 (77), 43 (94).

*2.2.3. 5α-Hydroxy-6,20-dioxopregnane-3β-yl acetate (**12**)*
Mp (diethyl ether) 220–223 °C; lit. 222.5–224 °C [47]. IR (cm^{-1}) 3394.10, 1728.87, 1708.62, 1362.46, 1240.97; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.57 (s, 3H, 18-H_3), 0.79 (s, 3H, 19-H_3), 2.00 (s, 3H, CH_3CO), 2.10 (s, 3H, 21-H_3), 2.75 (dd, J = 12.5 Hz and 12.8 Hz, 7α-H), 5.01 (m, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 70.51 (C_3), 80.16 (C_5), 171.03 (CH_3COO), 209.28 (C_{20}), 211.76 (C_6); MS [*m*/*z* (%)] 390 (6) M^+, 330 (47), 248 (24), 110 (27), 95 (23), 81 (22), 55 (18), 43 (100).

*2.2.4. 3β-Chloro-5α-hydroxycholestan-6-one (**13**)*
Mp (acetone–petroleum ether) 181–183 °C; lit. 180–186 °C [11]. IR (cm^{-1}) 3455.81, 1706.69, 1465.63, 1377.89; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.64 (s, 3H, 18-H_3), 0.84 (s, 3H, 19-H_3), 0.86 (d, J = 6.5 Hz, 6H, 26-H_3 and 27-H_3), 0.91 (d, J = 6.5 Hz, 3H, 21-H_3), 2.69 (dd, J = 12.0 Hz and J = 13.0 Hz, 1H, 7α-H), 4.21 (m, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 41.83 (C_7), 69.80 (C_3), 80.74 (C_5), 211.48 (C_6).

*2.2.5. 5α-Hydroxy-6-oxocholestane-3β-yl benzoate (**14**)*
Mp (dibutyl ether) 228–230 °C; lit. 230–231 °C [49]. IR (cm^{-1}) 3414.35, 1711.51, 1275.68; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.65 (s, 3H, 18-H_3), 0.87 (d, J = 6.1 Hz, 6H, 26-H_3 and 27-H_3), 0.88 (s, 3H, 19-H_3), 0.92 (d, J = 6.3 Hz, 3H, 21-H_3), 2.77 (dd, J = 12.6 Hz and 12.7 Hz, 1H, 7α-H), 5.31 (m, 1H, 3α-H), 7.42 (t, J = 7.3 Hz, 2H, 3′-H and 5′-H), 7.55 (t, J = 7.2 Hz, 1H, 4′-H), 8.01 (d, J = 7.1 Hz, 2H, 2′-H and 6′-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 41.76 (C_7), 71.23 (C_3), 80.53 (C_5), 128.30 ($C_{3'}$ and $C_{5'}$), 129.57 ($C_{2'}$ and $C_{6'}$), 130.47 ($C_{1'}$), 132.91 ($C_{4'}$), 166.31 (C_6H_5CO), 212.20 (C_6); MS [*m*/*z* (%)] 522 (2) M^+, 400 (72), 318 (16), 122 (28), 105 (100), 77 (41), 57 (32), 43 (37).

*2.2.6. 5α-Hydroxy-6-oxocholestane-3β-yl acetate (**15**)*
Mp (methanol) 222–225 °C; lit. 226.5–228 °C [47]. IR (cm^{-1}) 3394.10, 1733.69, 1713.44, 1365.35, 1280.50, 1243.86; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.62 (s, 3H, 18-H_3), 0.79 (s, 3H, 19-H_3), 0.84 (d, J = 6.2 Hz, 6H, 26-H_3 and 27-H_3), 0.88 (d, J = 6.5 Hz, 3H, 21-H_3), 1.99 (s, 3H, CH_3CO), 2.71 (dd, J = 12.5 Hz and 12.6 Hz, 1H, 7α-H), 4.99 (m, 1H, 3α-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 70.66 (C_3), 80.25 (C_5), 171.02 (CH_3CO), 212.40 (C_6); MS [*m*/*z* (%)] 460 (6) M^+, 400 (100), 318 (21), 110 (42), 93 (25), 81 (26), 55 (22), 43 (54).

*2.2.7. 5α-Hydroxyandrostane-3,6,17-trione (**16**)*
Mp (ethyl acetate–hexane) 253–255 °C; lit. 254–256 °C [50]. IR (cm^{-1}) 3435.99, 1737.55, 1715.37, 1703.80, 1243.86; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.85 (s, 3H, 18-H_3), 1.00 (s, 3H, 19-H_3), 2.84 (dd, J = 12.3 Hz and 12.6 Hz, 1H, 7α-H), 2.88 (d, J = 15.9, 1H, 4α-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 82.62 (C_5), 210.15 and 210.55 (C_3 and C_6), 219.82 (C_{17}); MS [*m*/*z* (%)] 318 (39) M^+, 275 (82), 220 (97), 101 (56), 85 (87), 67 (65), 55 (77), 41 (100).

*2.2.8. 5α-Hydroxyandrostane-6,17-dione (**17**)*
Mp (diethyl ether) 236–238 °C; lit. 236–238 °C [51]. IR (cm^{-1}) 3431.71, 1737.55, 1697.05, 1247.72; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.78 (s, 3H, 18-H_3), 0.82 (s, 3H, 19-H_3), 2.84 (dd, J = 12.2 Hz and 12.4 Hz, 1H, 7α-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 79.03 (C5), 212.29 (C6), 220.27 (C17); MS [*m*/*z* (%)] 304 (22) M^+, 273 (41), 233 (100), 220 (42), 205 (71), 67 (42), 57 (62), 41 (78).

3. Conversion of Δ^5-steroids to the corresponding 5β,6β-epoxides using the $KMnO_4/Fe(ClO_4)_3{\cdot}nH_2O$ system, in the presence of $NaH_2PO_4{\cdot}3H_2O$

20-Oxo-pregn-5-ene-3β-yl acetate **3** (358.51 mg; 1 mmol) was dissolved in dichloromethane (9 ml) at room temperature, in a reaction flask. A mixture of $KMnO_4$ (2 g; 12.6 mmol), $Fe(ClO_4)_3{\cdot}nH_2O$ (0.5 g; 1.96 mmol) and $NaH_2PO_4{\cdot}3H_2O$ (0.5 g, 3.20 mmol) was ground to a fine powder. Water (150 μl) was added and the final mixture was transferred to the reaction flask, followed by the addition of *t*-butyl alcohol (0.39 g; 0.5 ml). After 1 h at room temperature, TLC control showed that the reaction was complete and the final product was separated from the inorganic residue by addition of diethyl ether to the reaction flask which was allowed to stay under magnetic stirring for a few minutes. The mixture was then filtrated through a celite pad and the solid residue thoroughly washed with hot ether (total volume of 150 ml). The filtrate was washed with water (30 ml) and dried over anhydrous sodium sulphate. Evaporation of the solvent under vacuum afforded **18** (320 mg, ratio β/α 78:22 as calculated by integration of the 6-H signals in crude samples).

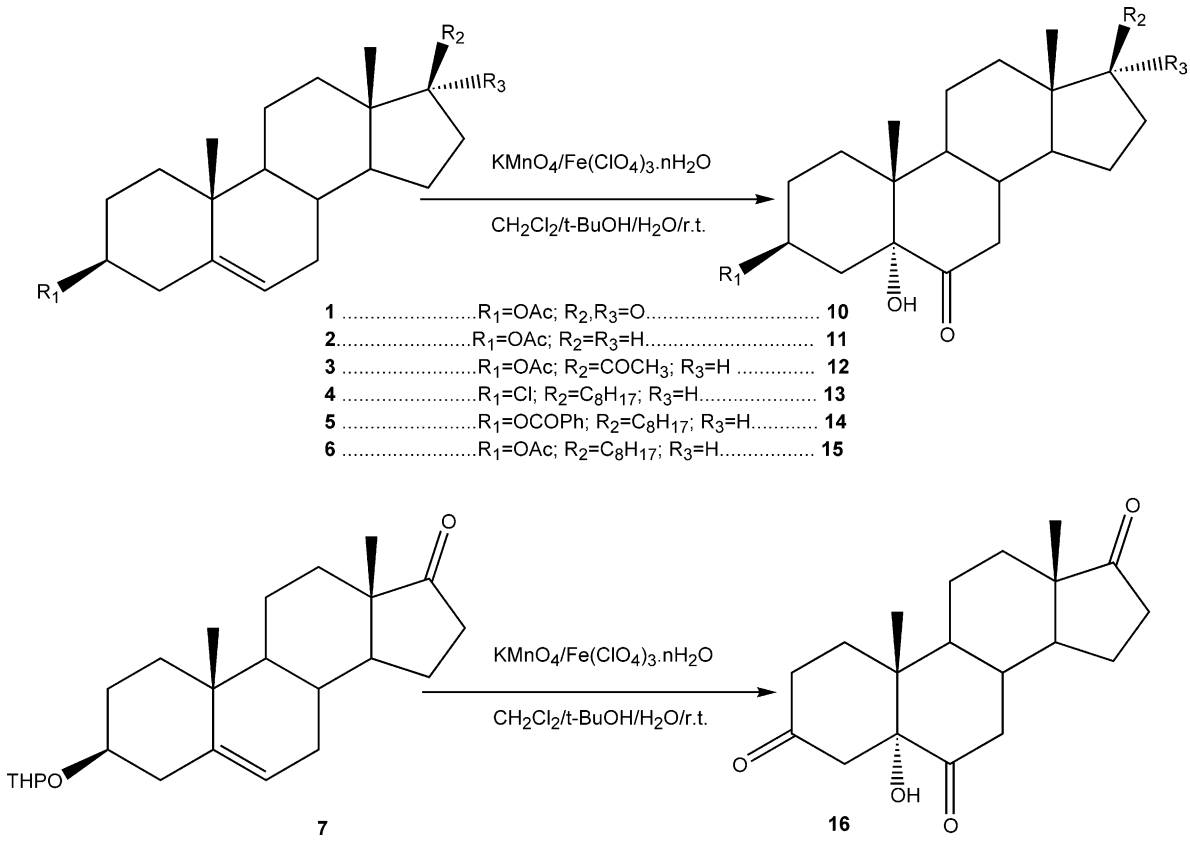
3.1. 5β,6β-Epoxy-20-oxopregnane-3β-yl acetate (18)

Mp (methanol) 129–132 °C; lit. 129–131 °C [52]. Spectroscopic data according to literature [40].

4. Results and discussion

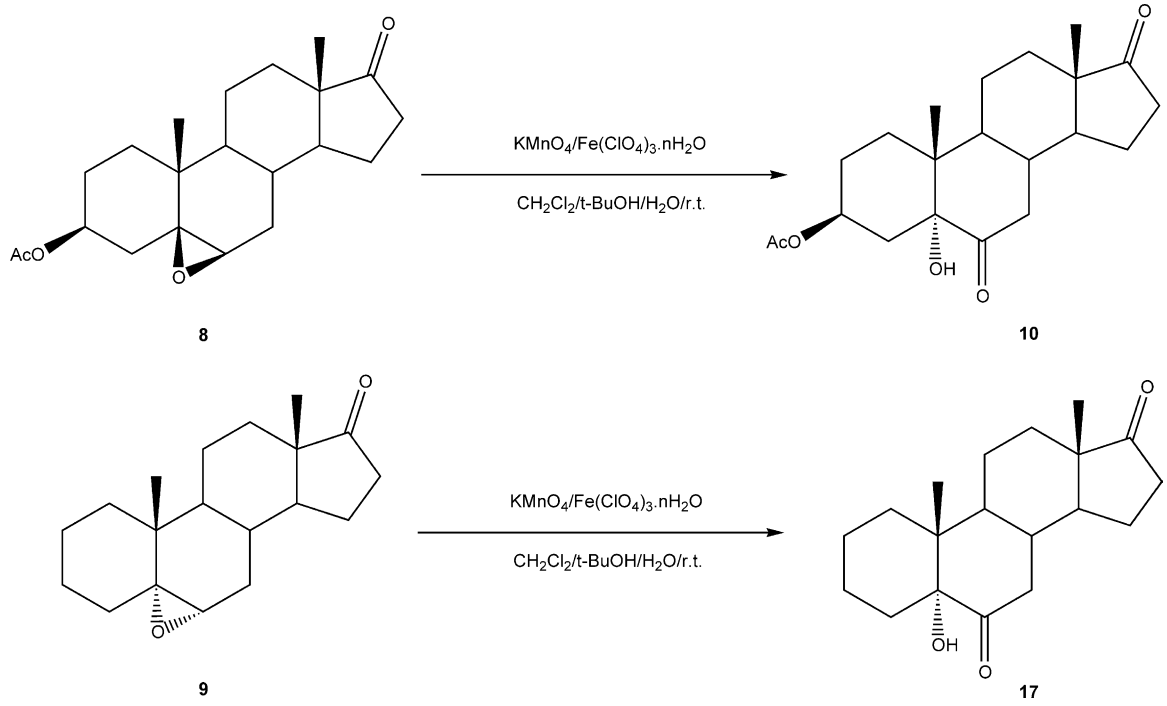
By using the $KMnO_4/Fe(ClO_4)_3{\cdot}nH_2O$ system on our Δ^5-steroids (Scheme 1), we were able to achieve direct synthesis of the corresponding α-ketols in high yields (Table 1, entries 1–7). The protecting groups for the 3β-hydroxy group (acetate, benzoate) were resistant to these reaction conditions. However, the tetrahydropyranyl group was unstable and the 3-keto derivative was obtained (Table 1, entry 7; Scheme 1). The 3β-chloro group also resisted to these reaction conditions.

On the reaction with substrate **6**, a mixture of the 5,6-epoxide (ratio β/α 80:20), the corresponding *trans*-diol and the α-ketol was identified by ^{1}H NMR, after 2 h. When the $KMnO_4/Fe(ClO_4)_3{\cdot}nH_2O$ system was applied to the steroidal 5β,6β-epoxide **8** (Table 1, entry 8; Scheme 2), the corresponding

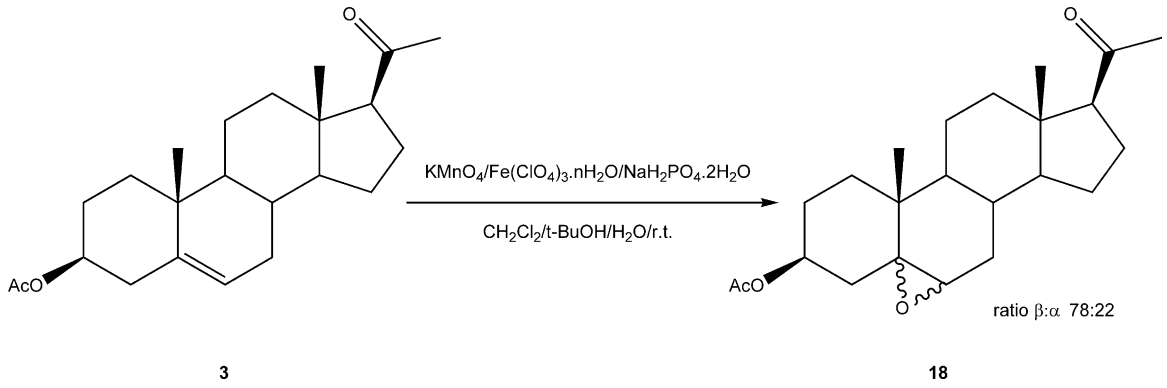


Scheme 1

α-ketol was again obtained. Furthermore, the α-ketol **17** was also obtained from the 5α,6α-epoxide **9** (Table 1, entry 9). However, when the reaction was carried out in the presence of $NaH_2PO_4{\cdot}3H_2O$, the 5,6-epoxide (ratio β/α 78:22) was obtained from the Δ^5-steroid instead of the α-ketol (Scheme 3). Therefore, we assume that the reaction proceeds via an epoxide intermediate that later decomposes to give the *trans*-diol which is then oxidized to the final α-ketol (Scheme 4, route 1),



Scheme 2



Scheme 3

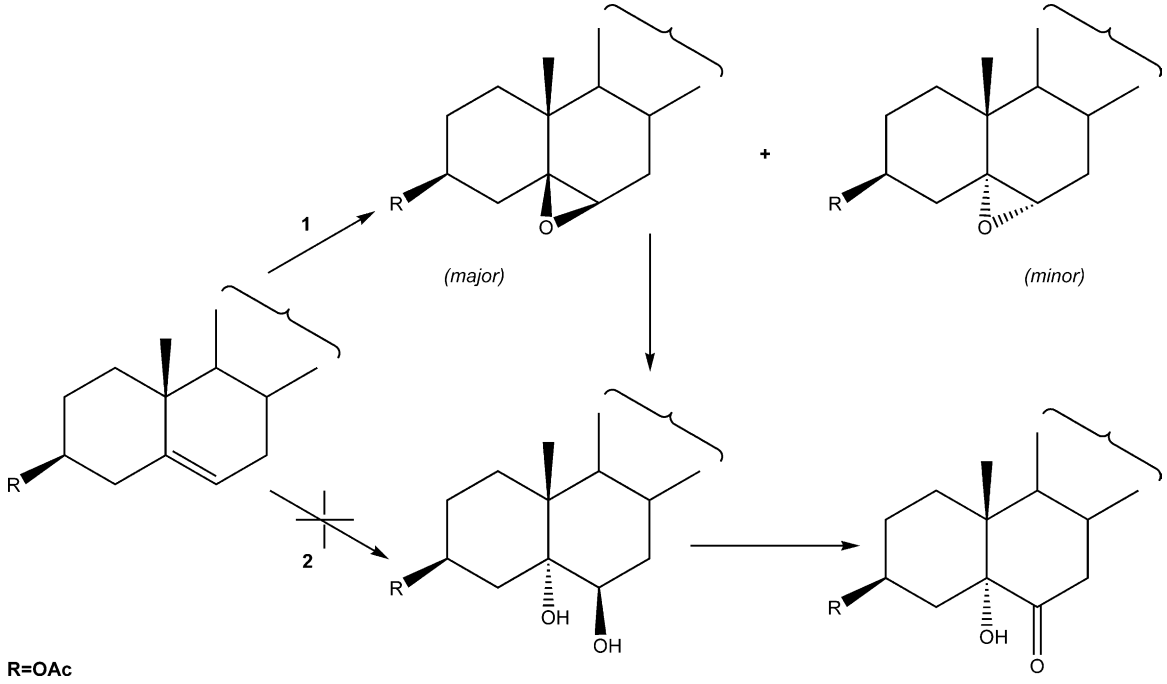
and not directly via the *trans*-diol (Scheme 4, route 2). It is our belief that because iron(III) perchlorate is a strong Lewis acid, it is capable of not only opening the epoxide but also further promote its decomposition to the α-ketol, aided by the metal hydroxide content generated in the reaction medium. The use of $NaH_2PO_4{\cdot}3H_2O$ may account for a stabilization of the pH of the reaction medium closer to neutrality mainly due to the $H_2PO_4^-/HPO_4^{2-}$ buffer system that is generated in situ. This stabilization can be responsible for the fact that no α-ketols are obtained in this way. Alternatively, highly insoluble $FePO_4$ generated in situ could also be responsible for the fact that no α-ketols are obtained in the presence of $NaH_2PO_4{\cdot}3H_2O$.

The assignment of some of the ^1H and ^{13}C resonances for compounds 3β-chloro-5α-hydroxycholestan-6-one **13** and 5α-hydroxy-6-oxocholestane-3β-yl benzoate **14** was made using 2D COSY and HMQC spectra, in order to provide detailed structural information.

The COSY spectrum of compound **14** helped to assign the aromatic region that consisted of three sets of ^1H peaks: 7.42 (t, $J = 7.3$ Hz, 2H, 3′-H and 5′-H), 7.55 (t, $J = 7.2$ Hz, 1H, 4′-H), 8.01 (d, $J = 7.1$ Hz, 2H, 2′-H and 6′-H). Using these ^1H assignments and the HMQC spectrum we assigned the aromatic carbons: 128.30 ($C_{3'}$ and $C_{5'}$), 129.57 ($C_{2'}$ and $C_{6'}$), 132.91 ($C_{4'}$). By exclusion, the fourth resonance in the aromatic region at 130.47 must refer to $C_{1'}$. The combination of COSY and HMQC spectra of compound **14** also allowed us to identify the proton 7α at 2.77 ppm which has a geminal coupling of 12.6 Hz with proton 7β at 2.14 ppm. Carbon 7 (C_7) appears at 41.76 ppm.

For compound **13** the combination of COSY and HMQC spectra allowed us to identify the proton 3α at 4.21 ppm and the proton 7α at 2.69 which has a geminal coupling of 13.0 Hz with proton 7β at 2.16 ppm. Carbon 7 (C_7) appears at 41.83 ppm.

In conclusion, we have achieved a novel, one-step procedure for the conversion of Δ^5-steroids to their corresponding α-ketols in high yields, by using a $KMnO_4/Fe(ClO_4)_3{\cdot}nH_2O$ system. We also have provided detailed structural elucidation of some of the compounds prepared. This method has proven



Scheme 4

to be potentially important for the preparation of α-hydroxy ketones with biological interest.

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