A One-Step Synthesis of 6β-Hydroxy-Δ⁴-3-ketones. Novel Oxidation of Homoallylic Sterols with Permanganate Ion

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Steroids with 6β-hydroxy-Δ⁴-3-ketone structural features are of interest in metabolic studies and are known metabolites of microbial and microsomal P-450 oxidation.[1] In addition, 6β-hydroxy steroids are key intermediates for the functionalization of the C-19 methyl group.[2] Functionalization and subsequent modification at C-19 has previously yielded a large number and variety of potent inhibitors of the enzyme aromatase (estrogen synthetase).[3,4] Aromatase inhibitors have potential pharmaceutical value in the control of human breast cancer and in the reduction of prostatic hyperplasia in man.[5,6]

There has been considerable interest in recent years in the synthesis of β-epoxides on the steroid nucleus.[7−10] Epoxidation with peroxyacids is known to produce predominantly the β-epoxide because of the steric hindrance from the angular methyl groups at C-10 and C-13. Prevailing methods for the synthesis of β-epoxides include the use of halohydrins as intermediates,[2] the use of 3α-halo substituents that block the entry of reagents from the α-face,[7,8] iodobenzene in the presence of chromyl diacetate,[10] ruthenium tetramesitylporphyrin,[11,12] vanadium and molybdenum catalysts with alkyl hydroperoxides,[13] dioxygen species,[14] potassium peroxomonosulfate in acetone,[15] ferric acetylacetonate and hydrogen peroxide,[16] and quaternary phosphonium or ammonium pertungstate and hydrogen peroxide.[17] Among these methods, a mixture of $KMnO_4-CuSO_4$ in methylene chloride has been found to be convenient and effectively provided steroidal β-epoxides in high yields.[18,19]

This latter reagent system serves as a phase transfer catalyst and is believed to function in the omega phase, which is formed by water and *tert*-butyl alcohol over the surface of the inorganic salt, in the epoxidation with $KMnO_4-CuSO_4$ in methylene chloride and in the presence of water and *tert*-butyl alcohol.[18] In contract to these results, more hydrophilic substrates produced α-hydroxy ketones or α-diketones as a predominant product.[20] To further explore this oxidizing reagent system we studied its reaction with different homoallylic sterol substrates (Figure 1). These results have further confirmed the importance of substrate structure as a factor in product formation.

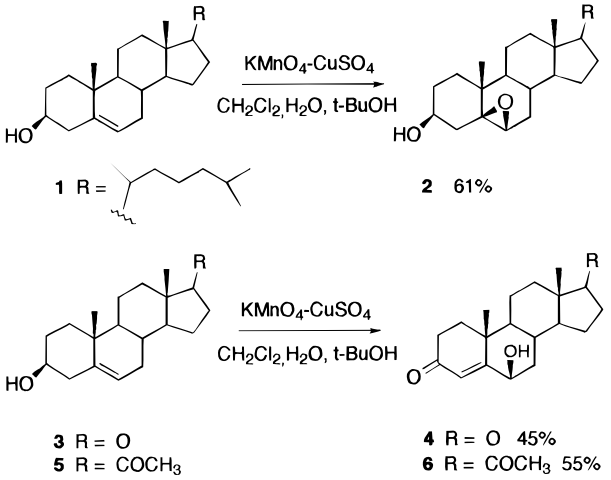

Figure 1. The oxidation of homoallylic sterols with permangnate ion.

Earlier β-epoxidations using this reagent system were conducted on steroid esters.[18,19] In the present study we found that reaction with cholest-5-en-3β-ol (**1**) results in the formation of 5β,6β-epoxycholestan-3β-ol (**2**) in 61% yield (isolated), 20% unreacted starting material and 5% 5α,6α-epoxycholestan-3β-ol. However, using identical reaction conditions, sterols with polar side chains gave 6β-hydroxy-Δ⁴-3-ketones as reaction products. 17-Oxoandrost-5-en-3β-ol (**3**) gave 3,17-dioxoandrost-4-en-6β-ol (**4**) in 45% isolated yield and 25% recovered starting material. 20-Oxopregnen-5-en-3β-ol (**5**) gave 3,20-dioxopregnen-4-en-6β-ol (**6**) in 55% isolated yield and 23% recovered starting material. We have also investigated the influence of other inorganic salts, in equimolar amounts, which might replace copper sulfate and affect the yield of the described products (Table 1). These results show that other selected transition metal salts with noncoordinating anions also give similar yields of products. In the case of main group metal salts and transition metal salts with coordinated anions, no product formation was observed. These results may suggest that the face selectivity of this oxidizing reagent system results from the initial copper ion (or other metal ions) coordination on the less hindered α-face of the double bond forming a π-complex between the double bond and copper ion or other metal ions. The following permanganate attack on the β-face results in the β-epoxide. The formation of a π-complex also weakens the double bond and makes the permanganate attack possible. Apparently, the main group metal ions and metal ions with coordinate anions cannot form a π-complex with the double bond, so the reaction will not proceed. Mechanistically, further rear-

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Table 1. Influence of Various Inorganic Salts on β-Epoxidation and 6β-Hydroxy Δ^4-3-Ketone Formation with Permanganate Ion and Steroidal Alkenes

salt	% yield[a] of 3β-hydroxy 5β,6β-epoxide (alkene, **1**[b])	% yield[a] of 6β-hydroxy Δ^4-3-ketone (alkene, **3**[b])	% yield[a] of 6β-hydroxy Δ^4-3-ketone (alkene, **5**[b])
$CuSO_4 \cdot 5H_2O$	61	45	55
$Cu(NO_3)_2 \cdot 3H_2O$	60	41	50
$CoSO_4 \cdot 7H_2O$	60	42	50
$Ni(NO_3)_2 \cdot 6H_2O$	65	49	57
$Cu(OAc)_2 \cdot H_2O$	0	0	0
$Ni(OAc)_2 \cdot 4H_2O$	0	0	0
$MgSO_4 \cdot 7H_2O$	0	0	0
$CaSO_4 \cdot 2H_2O$	0	0	0
$Al_2(SO_4)_3 \cdot 18H_2O$	0	0	0

[a] Yield of isolated and purified product. [b] Steroidal alkenes: **1**,cholest-5-en-3β-ol; **3**, 17-oxoandrost-5-en-3β-ol; **5** , 20-oxopregnen-5-en-3β-ol.

rangement may occur via the concomitant β-epoxidation of the Δ^5 double bond and oxidation of the 3β-hydroxy group, followed by epoxide ring opening and proton elimination at C-4 to yield the Δ^4 unsaturated ketone. Several synthetic methods have been reported for the synthesis of steroidal 6β-hydroxy-Δ^4-3-ketones, but yields were moderate to low.[21,22] The oxidation with permanganate ion provides an alternative and streamlined synthesis of this type of structure in one step from commercially available starting materials.

Experimental Section

Methods and Materials. Potassium permanganate, copper sulfate, and *tert*-butyl alcohol were obtained from the Aldrich Chemical Co. (Milwaukee, WI). Cholest-5-en-3β-ol (cholesterol, **1**), 17-oxoandrost-5-ene-3β-ol (**3**), and 20-oxopregn-5-en-3β-ol (**5**) were obtained from the Sigma Chemical Co. (St. Louis, MO). Procedures for recording melting points (mp) and of infrared (IR), ^{1}H-NMR, and mass (MS) spectra together with details concerning column chromatography have been described.[23] The described reations were also carried out using equimolar amounts of the salts shown in Table 1 to replace copper sulfate.

5β,6β-Epoxycholestan-3β-ol (2). Oxidation of **1** (1.00 g 2.58 mmol) in CH_2Cl_2 (30 mL) with $KMnO_4$ (6.0 g), $CuSO_4 \cdot 5H_2O$ (3.0, 12.0 mmol), H_2O (0.4 mL), and t-BuOH (1.5 mL) for 5 min reflux and 8 h at 25 °C gave, after silica gel column chromatography (solvent 15% ethyl ether in toluene), 5β,6β-epoxycholestan-3β-ol (2) in 60% yield: mp 131−132 °C (lit.[24] 132 °C). IR (KBr) 3433.7, 2947.6, 1468.0, 1215 cm^{-1}. MS (CI, NH_3) 402.3 (36% M − H_2O + NH_4^+), 385.1 (100% M − H_3O^+). ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.65 (3H, 18-CH_3), 1.05 (3H, 19-CH_3), 3.11 (1H, d, J = 1.92 Hz, 6α-H), 5.03 (1H, m, 3α -H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 71.90 (C-3), 63.54 (C-5), 62.54 (C-6), 56.21, 50.95, 42.29, 39.80, 39.49, 38.09, 37.24, 36.66, 36.14, 35.71, 35.11, 32.50, 29.76, 28.13, 27.98, 27.32, 24.9, 23.81, 22.78, 22.54, 21.93, 18.67, 17.07, 11.75.

3,17-Dioxoandrost-4-en-6β -ol (4). Oxidation of **3** (0.75 g, 2.6 mmol) in CH_2Cl_2 with the same procedure as the oxidation of **1** gave, after silica gel column chromatography (solvent 25% ethyl ether in toluene), 3,17-dioxoandrost-4-en-6β-ol (**4**) in 45% yield: mp 194−195 °C (lit.[21] mp 194−195 °C). MS (EI) 302.0 (1.06% M^+). IR, ^{1}H, ^{13}C NMR data were identical to literature values.[25]

3,20-Dioxopregn-4-en-6β-ol (6). Oxidation of **5** (0.82 g, 2.60 mmol) in CH_2Cl_2 (3.0 mL) with the same procedure as the oxidation of **1** gave, after silica gel column chromatography (solvent 20% ethyl ether in toluene), 3,20-dioxopregn-4-en-6β-ol (**6**) in 55% yield: mp 175−177 °C (lit.[21] mp 174−177 °C). MS (CI, NH_3) 348.2 (14.9%, M + NH_4^+), 331.2 (26% M + H^+). IR, ^{1}H, ^{13}C NMR data were identical to literature values.[25]

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