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Oxidations with Potassium Permanganate - Metal Sulphates and Nitrates. β-Selective Epoxidation of Δ^5-Unsaturated Steroids

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Abstract: The β-epoxidation of 3β-acetoxy-Δ^5-unsaturated steroids has been achieved with numerous potassium permanganate-metal sulphates and nitrates with a high degree of stereoselectivity. 5β,6β-Epoxides are formed in a one step reaction in good yields and using very low cost reagents. The best results were achieved with $KMnO_4/Fe_2(SO_4)_3.nH_2O$.

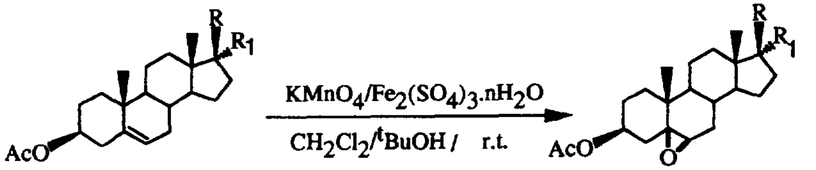
The synthesis of 5β,6β-epoxides from Δ^5-unsaturated steroids is a very important reaction since the former functionality is present in a number of biologically active steroids[1]. Moreover, epoxides are extremely useful, for further elaboration since their facile ring opening allows the introduction of various substituents in a stereospecific manner.

Peracid reagents, e.q. MCPBA[2], were largely used in the past, and more recently the milder dioxiranes[3] serve as efficient reagents for the epoxidation of steroids. Nevertheless both of these reagents usually approach the unsaturated compounds from the less hindered side of the double bond. To overcome this undesired result, steric hindrance on the α-face can be installed. The insertion of 3α-halo substituents in Δ^5-unsaturated steroids affords an epimeric mixture of epoxides where the β-epimer predominates[4]. 5β,6β-Epoxidation has also been achieved from Δ^5 -steroidal compounds, using chromyl diacetate, but in moderate yields, along with by-products[5]. The use of hydrogen peroxide in the presence of iron (II), iron (III),and titanium (III) ions[6] or alkyl hydroperoxides catalysed by molybdenum compounds[7] yielded mixtures of α- and β-5,6-epoxides accompanied by some by-products.

Of greater preparative interest are the metalloporphyrins which are used as efficient catalysts with molecular oxygen or air for this type of β-epoxidation, but the major drawback of this method is the synthesis of the catalyst, which is not always easy[8]. Similar results have been reported for the use of a Mn (II) complex as catalyst[9]under the same type of oxidative conditions. Recently S. Chandrasekaran *et al.*[10] subjected a number of Δ^5-unsaturated steroids to heterogeneous permanganate oxidation ($KMnO_4$ /$CuSO_4.5H_2O$) in dichloromethane in the presence of a catalytic amount of water and *t*-butyl alcohol. 5β,6β-Epoxides were formed in good yield. More recently Hanson *et al.*[11] examined a group of steroids with $C_{4,5}$ or $C_{5,6}$ double bonds in order to study the role of the C-10 methyl group, the effect of the ring size and the influence of allylic substituents in epoxidation reactions using the same reagent.

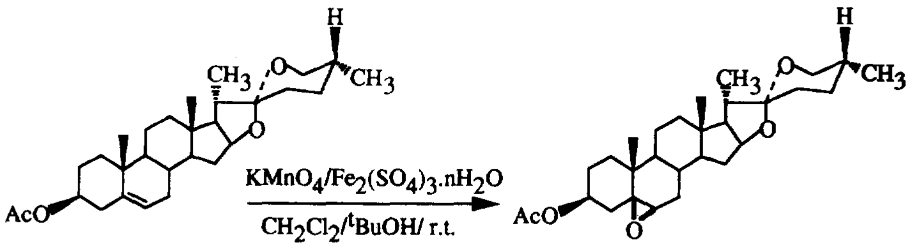
In this communication we report the use of numerous potassium permanganate -metal sulfate and nitrate systems for the oxidation of carbon-carbon double bonds. The commonly available 3β-acetoxy-Δ^5-steroids **1**, **3**, **5** and **7** were used in this study, and the respective 5β,6β-epoxides **2**, **4**, **6** and **8**[12] were produced in good to high overall yields and with a high degree of stereoselectivity for most of the oxidative systems investigated (Schemes 1 and 2).

In a typical procedure a mixture of $KMnO_4$ (2g/12.7mmoles) and $Fe_2(SO_4)_3.nH_2O$ (1g) was ground to a fine powder, water (100μl) was added, and the mixture transferred to the reaction flask. To a stirred suspension of this mixture in CH_2Cl_2 (5ml), 17-oxoandrost-5-en-3β-yl acetate **1** (330.45mg /1mmole) was added followed by *t*-butyl alcohol (0.5ml). After 20 min. at room temperature the reaction was complete (t.l.c. control), and the product was separated from the inorganic residue by adding ether (10ml), stirring for 5 min. and filtering through a pad of celite. The filtrate was washed with water and dried over anhydrous sodium sulphate. After evaporation of the solvent, the crude product was recrystallized from methanol to give the 5β,6β-epoxy-17-oxo-5α-androstan-3β-yl acetate **2** in 93% yield.



1.................................. R;R_1=O..................................2
3............................R=C_8H_{17};R_1=H..........................4
5............................R=$COCH_3$;R_1=H..........................6

Scheme 1



7 8

Scheme 2

Although the stereoselective epoxidation has been efficiently achieved with both systems used, the permanganate-metal sulphates in general gave better results than the metal nitrates and among these, $KMnO_4/Fe_2(SO_4)_3.nH_2O$ is the most advantageous, leading to faster reactions in combination with high yields and very high stereoselectivity. (Tables 1 and 2). Furthermore, the environmentally friendly reagent $Fe_2(SO_4)_3.nH_2O$ is even cheaper than $CuSO_4.5H_2O$.

In general, using metal sulphates, as the time of the reaction increases the observed stereoselectivity decreases, leading to a larger amount of α-epoxide in the epimeric mixture (Table1). However with

$(NH_4)_2Fe(SO_4)_2.6H_2O$ in spite of the long reaction time (12h), the stereoselectivity is still very high (97:3), probably due to the formation of the permanganate-metal sulphate complex.

Attempts in order to perform the reactions, either with Zn $(AcO)_2$. $2H_2O$ or with a clay (bentonite) in place of a metal sulphate yielded no products.

In the absence of water or *t*-BuOH the reactions are very slow. However the use of ultrasound improves the rate of the reaction , without altering the stereoselectivity observed.

Table1. Permanganate-Metal Sulphate Epoxidations

Substrate (1 mmole)	$KMnO_4$ (g)	Metal Sulphate[a]	H_2O (µl)	Time (h)	Yield (%)	Ratio of isomers [b] (ß:α)	Product
1	2	$Fe_2(SO_4)_3nH_2O$	100	0.3	93	98:2	2
	0.35		"	2	"	97:3	
	2	$ZnSO_4 .6H_2O$	"	1	90	94:6	
	"	$NiSO_4 .6H_2O$	"	1.5	92	"	
	"	$FeSO_4 .7H_2O$	"	"	"	"	
	"	$CuSO_4 .5H_2O$	"	1	90	"	
	"	$CuSO_4 .5H_2O$ /)))	"	0.3	"	"	
	0.5	$Ce(SO_4)_2 .4H_2O$	"	18	92	88:12	
	1.5	$(NH_4)_2Fe(SO_4)_2 .6H_2O$	"	12	90	97:3	
3	0.35	$Fe_2(SO_4)_3nH_2O$	75	4	92	88:12	4
5	"	$Fe_2(SO_4)_3nH_2O$	"	"	91	91:9	6
7	0.5	$Fe_2(SO4)_3nH2O$	"	16	89	90:10	8

[a] The amount of metal sulfate (g) is half of the amount of $KMnO_4$(g).
[b] Calculated by integration of the 6-H signals in crude samples.

The use of potassium permanganate as a catalyst for the oxidation of this type of substrates is under investigation. Studies on the mechanism of the reaction and experiments with different unsaturated compounds will be performed, to further evaluate the extension of the use of the title reagents.

In summary, the usually recalcitrant β-epoxidation of 3β-acetoxy-Δ^5-unsaturated steroids has been very efficiently achieved with a large variety of inexpensive oxidative reagents. This development has significantly expanded the scope of these types of mild oxidative systems through a common and facile methodology.

Table 2. Permanganate-Metal Nitrate Epoxidations

Substrate (1 mmol)	$KMnO_4$ (g)	Metal Nitrate[a] (g)	H_2O (µl)	Time (h)	Yield (%)	Ratio of isomers[b] (ß:α)	Product
1	0.5	$Fe(NO_3)_3.9H_2O$	100	4	92	94:6	2
	2	$Cu(NO_3)_2.3H_2O$	"	0.3	91	88:12	
	1	$Zn(NO_3)_2.6H_2O$	"	8	90	90:10	
	0.5	$Bi(NO_3)_3.5H_2O$	75	6	89	86:14	
	"	$Co(NO_3)_2.6H_2O$	"	0.5	90	98:2	
3	"	$Fe(NO_3)_3.9H_2O$	100	"	"	90:10	4
5	1	$Fe(NO_3)_3.9H_2O$	"	"	88	84:16	6

[a]The amount of metal sulfate (g) is half of the amount of $KMnO_4$(g).
[b]Calculated by integration of the 6-H signals in crude samples.

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11. Hanson, J. R.; Hitchcock, P. B.; Liman, M. D.; Nagaratnam, S.; Manickavasagar, R. *J. Chem. Res. (S)* **1995**, 220-221.
12. **2**: ^1H NMR ($CDCl_3$, 500MHz) δ 0.84 (s,18-H3), 1.03 (s,19-H3), 3.14 (m,6-H), 4.77 (m,3-H); ^{13}C NMR ($CDCl_3$,75MHz) (C_5) 62.56, (C_6) 63.15, (C_3)71.12, (CH_3CO) 170.49, (C_{17}) 220.57, **4**: δ 0.63 (s,18-H3), 1.00 (s,19-H3), 3.07 (m,6-H), 4.76 (m,3-H) ; (C_5) 62.51, (C_6) 63.56, (CH_3CO) 170.51; **6**: δ 0.59 (s,18-H3), 1.01 (s,19-H3), 3.09 (m, 6-H), 4.77 (m,3-H); (C_5) 62.34, (C_6) 63.55, (C_3) 71.13 ,(CH_3CO) 170.41, (C_{20}) 209.13; **8**: δ 0.74 (s,18-H3), 1.02 (s,19-H3), 3.08 (m,6-H), 4.76 (m,3-H); (C_5) 62.45, (C_6) 63.37, (C_{26}) 66.83, (C_3) 71.24, (C_{16}) 80.63, (C_{22}) 109.22, (CH_3CO) 170.45.

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