The solid-phase oxidation of steroidal alkenes with potassium permanganate and metal salts

Jorge A.R. Salvador[a] and James R. Hanson[b]*

[a]*Laboratorio Quimica Farmaceutica, Faculdade de Farmacia, Universidade de Coimbra, 3000 Coimbra, Portugal*

[b]*Department of Chemistry, University of Sussex, Brighton, Sussex, BN1 9QJ UK*

The oxidation of steroidal alkenes by potassium permanganate and metal salts in the solid phase gives epoxides with a stereochemistry that can differ from that obtained by the use of per-acids.

Keywords: potassium permanganate, metal salts, steroidal alkenes, epoxidation introduction

Potassium permanganate is an oxidant that has been used in organic chemistry for many years particularly in the conversion of alkenes into *cis* diols and their further oxidation products.[1] Potassium permanganate has been used in acidic, neutral, slightly alkaline and strongly alkaline media. The extent of the oxidation of organic substrates is very dependent on the pH.[2] Manganese(VII) is reduced to manganese(IV) in alkaline or weakly acidic solution but in more strongly acidic solution it can be reduced further to manganese(III) or even manganese(II). In general, oxidations with potassium permanganate are performed in aqueous media with organic co-solvents that are water miscible. Although potassium permanganate shows appreciable solubility in *t*-butanol, acetone, acetonitrile, pyridine and acetic acid, it is insoluble in hydrocarbon and non-polar solvents.

Alkenes are readily oxidised by the permanganate ion. Classic examples are the conversion of oleic acid into *erythro*-9,10-dihydroxystearic acid.[3,4] Cholesterol **1** is oxidised to the triol, 3β,5α,6α-trihydroxycholestane **2**[5] in an alkaline medium and, in an acetic acid medium, to 5α-hydroxycholestane-3,6-dione. Oxidation of ergosterol with potassium permanganate in methylcyclohexane gave 3β,5α,6α-trihydroxyergosta-7,14,22-triene,[6] an oxidation which reveals the potential selectivity of the reagent. Cholestanol **5** was oxidised to cholestanone **6** in acetic acid solution.[5] When potasssium permanganate is used catalytically in conjunction with sodium periodate, cleavage of steroidal alkenes takes place. This reaction can be used to cleave 3-keto-Δ^4-steroids such as testosterone acetate to the 4-nor-5-keto-3-carboxylic acid.[7] The oxidation of the Δ^5-double bond of pregnenolone acetate using this reagent in aqueous pyridine has also been studied.[8]

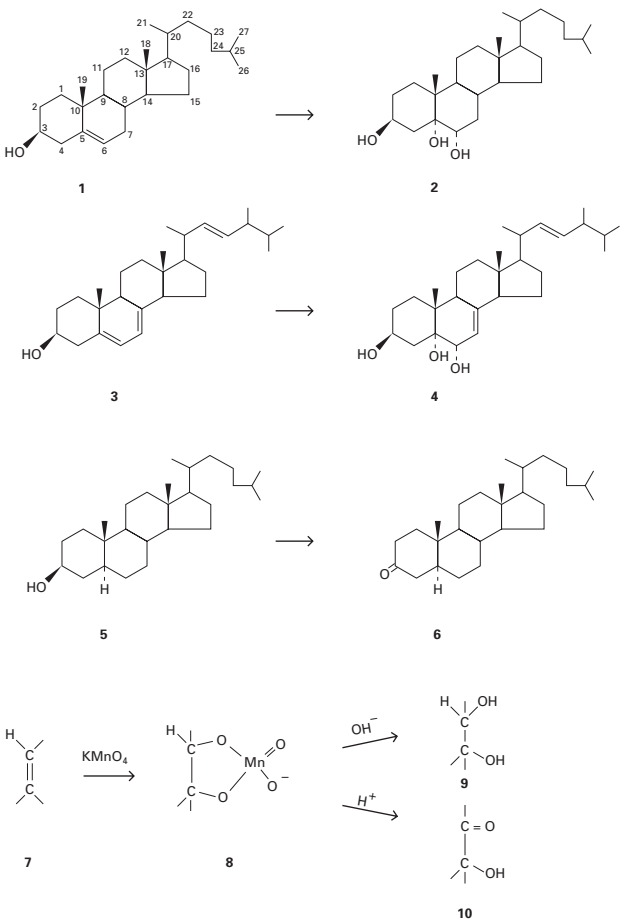
However, the use of potassium permanganate as an oxidant is limited by the low solubility of potassium permanganate in most non-polar solvents and by the difficulties that can be experienced in recovering the product from insoluble manganese salts unless sulfur dioxide is used to solubilise the manganese. The solubility problems can be overcome by the use of phase-transfer catalysts such as benzyltriethylammonium chloride[9] or by the use of modified reagents such as cetyltrimethylammonium permanganate.[10] Another widely used method is to solubilise the potassium permanganate in solvents such as benzene with 18-crown-6.[11]

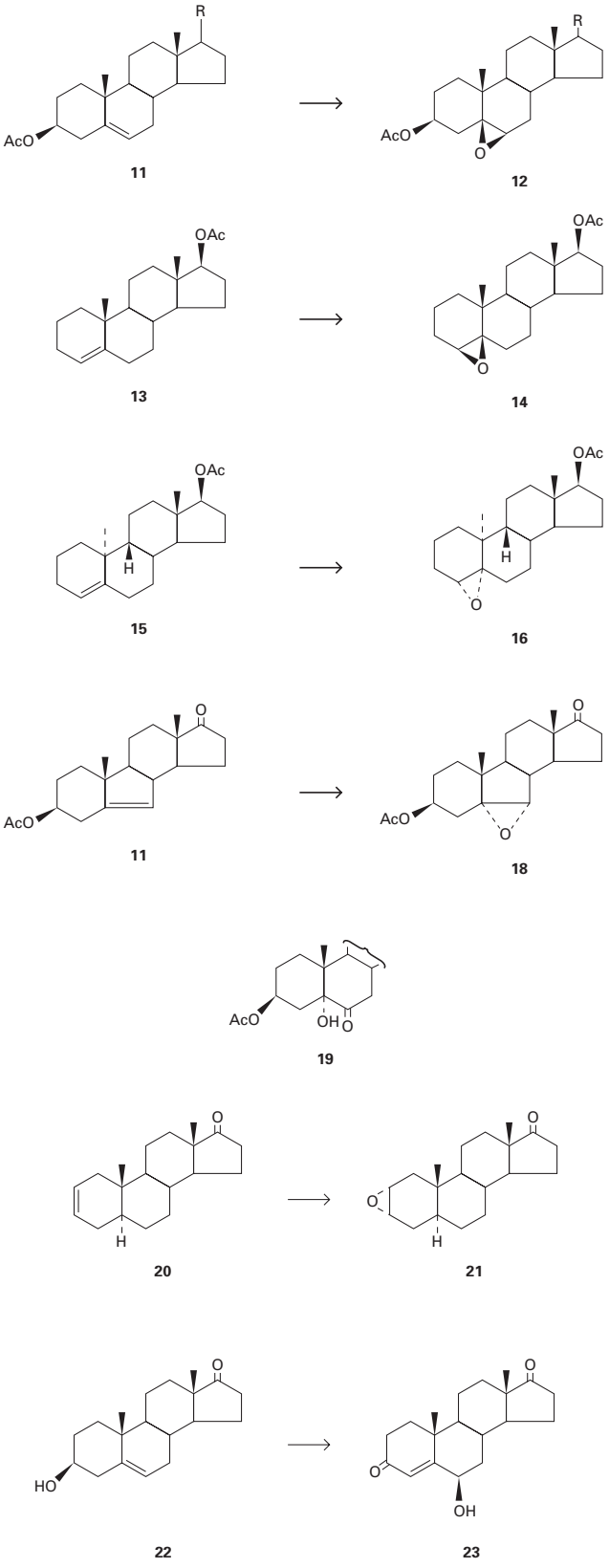
The formation of a cyclic ester **8** involving the permanganate ion and the alkene **7** and its decomposition to give the *cis*-diol **9** or ketol **10**, is a well-established mechanism for permanganate oxidations.[12] Recently the interesting observation has been made[13] that in acetone or acetonitrile solution Lewis acids such as ferric chloride or zinc chloride, which form complexes with potassium permanganate, enhance the oxidising power of the reagent.

* Correspondence. E-mail: j.r.hanson@susx.ac.uk

Heterogeneous oxidations with potassium permanganate

When potassium permanganate is impregnated into inorganic supports such as Linde molecular sieve,[14] silica gel or certain clays, it can be used as an oxidant for alcohols in benzene solution. Thus cholestan-3β-ol **5** in benzene gave cholestan-3-one **6** in 91% yield when it was stirred for 1.5h at 70°C with Linde molecular sieves coated with potassium permanganate. Control experiments using powdered potassium permanganate alone did not give any oxidation. It was proposed that the molecular sieve supplied trace quantities of water to facilitate the oxidation. This led to the finding that a solid phase mixture of potassium permanganate:copper sulfate ($KMnO_4$:$CuSO_4.5H_2O$) provided a good reagent for the conversion of secondary alcohols into ketones, (*e.g.* cholestanol **5** to cholestanone **6**).[15] The fact that the presence of traces of water was a factor in these oxidations was established by drying the reagent mixture over phosphorus pentoxide. This reduced the yield of the oxidation.





Potassium permanganate:copper sulfate in dichloromethane in the presence of a catalytic amount of water proved to be an effective reagent for the conversion of alcohols into carbonyl compounds,[16] γ-hydroxy terminal alkenes to γ-lactones[17] and sulfides to sulfones.[18] The significance of traces of water and the *t*-butanol was ascribed to the formation of an omega (Ω) phase over the oxidant and in which the oxidation took place.[19-21]

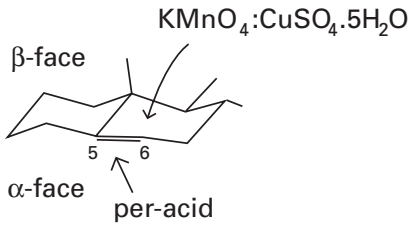


Fig. 1

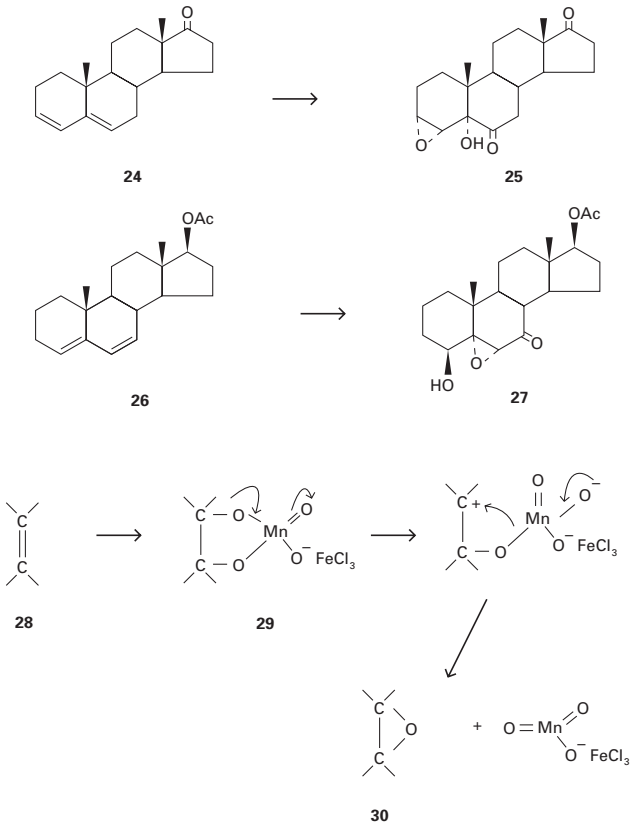
Epoxide formation

The oxidation of a number of Δ^5-steroids **11** was examined with the potassium permanganate:copper sulfate reagent and shown to give 5β,6β-epoxides **12**.[22] This observation was noteworthy for two reasons. Firstly oxidation with potassium permanganate in aqueous solution rarely forms epoxides[23] and secondly the epoxides that were formed were the 5β, 6β-epoxides rather than the 5α,6α-epoxides that are typical of epoxidation with per-acid.[24] Epoxidation with per-acids takes place from the less-hindered face of the molecule whereas the potassium permanganate:copper sulfate reaction had taken place on the more hindered face of the alkene (see Fig. 1). It was subsequently shown that potassium permanganate can be used catalytically with sodium perborate in glacial acetic acid to give the β-epoxides.[25] The formation of these β-epoxides is of interest in the context of the partial synthesis of steroidal analogues of the tumour-inhibitory withanolides that possess a 5β,6β-epoxide.[26]

The stereochemistry of many reactions of the Δ^4- and Δ^5-double bonds of the steroids is dominated by the presence of the 10β-methyl group (C-19) which directs attack of various reagents to the opposite, less-hindered, α-face (see Fig. 1). The factors which affect the stereochemistry of the β-face epoxidation by potassium permanganate were therefore studied in several laboratories. The epoxidation of 17β-acetoxyandrost-4-ene **13** and 3β-acetoxyandrost-5-en-17-one **11,** R=0, by the biphasic system potassium permanganate: copper sulfate in dichloromethane afforded[27] the β-epoxides (**13 – 14; 11,** R = 0 – **12**, R = 0) whilst the retro-steroid, 17β-acetoxy-9β,10α-androst-4-ene and 3β,17β-diacetoxy-B-norandrost-5-ene gave the α-epoxides (**15 – 16; 17 – 18**). The stereochemistry of this epoxidation was rationalised in terms of the formation of a π-complex between the alkene and the electron-deficient manganese of the permanganate ion. This is most likely to take place in a Markownikoff sense and with the initial attack on the alkene taking place in an axial direction. In these cases the axial positions are C-4β and C-6β in the normal series, C-4α in the retro-steroid and C-6α in the B-nor-steroid.

Comparable results were obtained[28] in a parallel study with other androstenes and in the pregnene and lanostene series.

The epoxidation took place in the presence of a range of metal sulfates including those of zinc, silver, iron, cobalt, manganese, cerium and aluminium. However, there was no reaction in the presence of sodium sulfate.[29] In another study[30,31] a range of metal sulfates, nitrates, perchlorates tungstates as well as vanadyloxysulfate and zirconium oxychloride were used. It was concluded that the best results were obtained with ferric sulfate. When ferric perchlorate was used[32] in conjunction with potassium permanganate, the initially formed 5β,6β-epoxide was rapidly hydrolysed and the product was oxidised to the 5α-hydroxy-6-ketone **19**. In the light of the sensitivity of potassium permanganate oxidations to pH, an important observation was made that sodium dihydrogenphosphate could replace or enhance the effect of the metal salts.[32]



Whilst the epoxidation was successful with the trisubstituted 4- and 5-enes, epoxidation of the disubstituted 5α-androst-2-en-17-one **20** in the presence of silver sulfate gave the 2α, 3α-epoxide **21** in low yield.[29] The reaction of disubstituted alkenes with potassium permanganate leads to α-ketols and further oxidation products. The β-face stereospecificity was reduced by the presence of a neighbouring allylic β-acetoxy group.[27] The electronegative group, apart from providing steric hindrance will also diminish the tendency for the permanganate anion to attack the alkene on the same face.

Oxidation of the homoallylic 3β-hydroxy- Δ^5-steroids **22** with potassium permanganate:copper sulfate in dichloromethane in the presence of *t*-butanol and a trace of water gave 6β-hydroxy- Δ^4-3-ketones **23** directly.[33] In this study it was also shown that other inorganic transition metal salts with non-co-ordinating anions (*e.g.* copper nitrate but not copper acetate) might replace the copper sulfate. An alternative explanation for the facial selectivity was advanced[34] in which it was proposed that the metal ion co-ordinated to the less hindered α-face of the double bond. This π-complex both weakened the double bond and directed the permanganate to attack from the β-face.

Oxidation of androsta-3,5- **24** and 4,6-dienes **26** by the potassium permanganate:copper sulfate system afforded[35] the 3α.4α-epoxy-5α-hydroxy-6-ketone **25** and 5α,6α-epoxy-4β-hydroxy-7-ketone **27** respectively, as the major products. The results of the oxidation of the dienes would suggest that the initial attack of the manganese took place on the pseudo-axial terminal position of the diene to allow any carbocationic character to be stabilised by the adjacent double bond. The stereochemistry of the products would then be determined by the orientation of this position. In the case of the 3,5-diene these are C-3α and C-6β and in the case of the 4,6-diene these are C-4β and C-7α. The initial diepoxidation may then be followed by partial hydrolysis to the diols and oxidation to the α-ketols. In the case of the 4,6-diene there is a Payne rearrangement of a 6-hydroxy-4,5-epoxide to a 4β-hydroxy-5,6-epoxide. Oxidation of an androsta-3,5-dien-7-one and an androsta-4,6-dien-3-one gave the 3α,4α- and 6α,7α-epoxides as the major products. Here oxidation has taken place at the γδ-position and from the pseudo-axial direction.

An interpretation[32] of all these results is as follows. The initial kinetically-controlled attack of the permanganate ion in the omega phase on the alkene **28** takes place in a Markownikoff manner and in an axial sense. The metal salts that are active in promoting the epoxidation may co-ordinate with the permanganate and promote the stepwise decomposition of the complex **29** to form the epoxide **30**. These metal salts also possess insoluble hydroxides and, along with sodium dihydrogenphosphate, may prevent the oxidation medium from becoming too alkaline. The presence of the hydrated metal salts may also provide some of the water for the omega phase. This variation of the classic potassium permanganate reagent may have some applications in the synthesis of epoxides that are not readily available by conventional per-acid epoxidation.

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