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New Functionalised Hydroxymethyl Ketones from the Mild and Chemoselective $KMnO_4$ Oxidation of Chiral Terminal Olefins

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Various terminal olefinic compounds are directly converted into the corresponding α-hydroxy ketones in good yields by potassium permanganate oxidation. The reaction is also highly chemoselective in the presence of differently protected hydroxy groups and can be utilised for the preparation of polyfunctional compounds such as polyols.

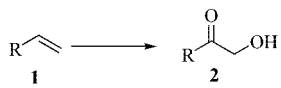
Introduction

The synthesis of α-hydroxy carbonyl compounds is a topic of interest because of their use in organic synthesis and their widespread occurrence in numerous important natural products such as cortisone acetate and adriamycin acetate. This importance has prompted the investigation of a wide variety of methodologies for their diastereoselective and enantioselective synthesis.[1]

Although the oxidation of olefins to oxygen-containing compounds is considered one of the most important synthetic transformation (most successful are the asymmetric dihydroxylation[2] and epoxidation[3] reactions), the preparation of α-hydroxy ketones through the direct oxidation of an olefins has only rarely been investigated.[4]

The α-hydroxylation of oxygen-containing substrates, such as ketones, silyl enol ethers, or different enolates, is one of the simplest and most frequently used approaches to the preparation of α-hydroxy ketones, and several asymmetric versions of these methodologies have also been developed recently.[5,6]

Since the introduction of terminal olefins in many functionalised compounds can easily be achieved, a direct method for the synthesis of α-ketols such as **2** (Scheme 1) appears quite desirable.

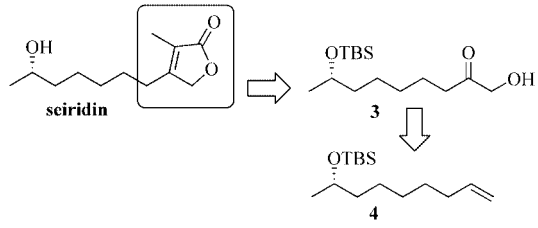


Scheme 1.

The oldest methodologies, utilising stoichiometric amounts of $KMnO_4$ in aqueous acetone and catalytic acetic acid,[7] $KMnO_4/CuSO_4·5H_2O$,[8] or isobutylaldehyde/O_2 in the presence of OsO_4 and $Ni(mac)_2$ catalyst,[9] were found to be less than optimal with terminal olefins, either affording the desired α-ketols in only 49–67% yields or giving rise to the corresponding carboxylic acid. More recently a direct and regioselective ruthenium-catalysed two-step ketohydroxylation of simple internal and terminal alkenes has been reported,[10] with overall yields of 64–66% for the terminal alkenes.

Results and Discussion

Some years ago, in our approach to the synthesis of seiridin, the major phytotoxic metabolite of the cultures of *Seiridium sp.*, we needed such a transformation for the preparation of an α,β-unsaturated lactone system (Scheme 2) in which the stereocenter was five carbons away from the oxidation site.[11] We utilised the old procedure with $KMnO_4$ in aqueous acetone with acetic acid[7] upon the olefin **4**, obtaining the desired product **3** but in low yield.



Scheme 2.

More recently, in work on the synthesis of the C12–C24 fragment of macrolactin A,[12] the enantiopure key *anti* 1,3-diol fragment **5** (Scheme 3) was built up through the oxi-

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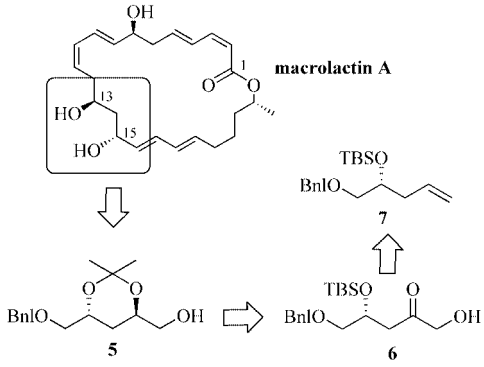
dation of the homoallylic alcohol **7** to the α-hydroxy methyl ketone **6** followed by diastereoselective reduction.



Scheme 3.

However in the oxidation step, in which we needed to maintain the protection on the chiral hydroxy group, the addition of $NaNO_2$ and aqueous H_2SO_4 during the workup as in the reported procedure resulted in the partial removal of the silyl group, which caused a lower overall yield. We therefore modified the workup of the reaction by adding ethanol to the mixture and, after the effervescence had stopped, by filtering the obtained crude mixture through a pad of celite (see Experimental Section). This modification gave the desired compound **6** with high chemoselectivity and in good overall yield (80%).

Although recent catalytic oxidative methodologies have been used to address differently substituted internal olefins, interest in the use of permanganate in acidic medium is still topical from synthetic,[13] industrial[14] and environmental[15] points of view.

We therefore found it interesting to extend this new procedure to other functionalised substrates and in this communication we report the preparation of a series of acyclic hydroxymethyl ketones from the corresponding functionalised chiral monosubstituted olefins.

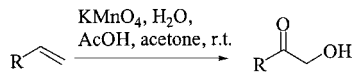
As shown in Table 1, differently prepared terminal alkenes, mostly bearing an allylic, homoallylic or more distant secondary hydroxy group, were subjected to our oxidation conditions. It is noteworthy that all the other oxidative methodologies have never started from such chiral terminal acyclic olefins. The starting compounds **7**–**13** were synthesised by use of organometallic nucleophiles with suitable epoxides (compounds **7**, **10**, **11**, **13**) or appropriate aldehydes (compounds **8**, **9**, **12**).[16–20] Many of them were prepared (Entries 2–7) in racemic form in order to test (after prior protection as silyl ethers[21]) the oxidation of the compounds.

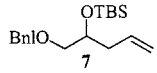
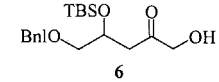
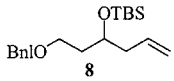
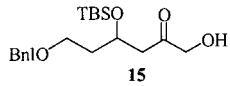
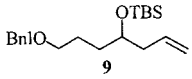
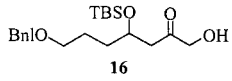
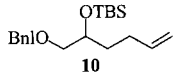
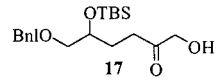
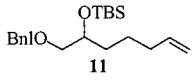
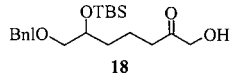
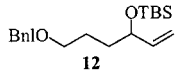
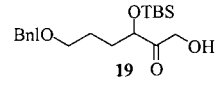
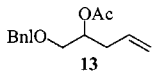
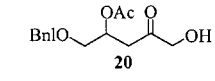
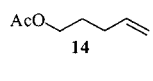
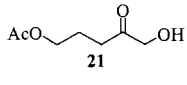
Under these conditions the reaction always afforded the desired hydroxymethyl ketone without any traces of deprotected products, diols or carboxylic acids.[22] The reaction yields have continually been good and above all this mild procedure has been usable for the preparation of polyoxygenated fragments for use in multistep syntheses of more complex molecules.

When the oxidation was performed on the homoallylic silyl ethers **7**, **8**[23] and **9** the α′,β-dihydroxy ketones **6**, **15** and **16** (Entries 1, 2 and 3) were produced in similar yields (80, 72, and 70%) and the length of the lateral chain was not influential in the reaction. Similar behaviour was found when the distance between the chiral centre and the oxidation site was elongated; in fact, essentially identical results were obtained with compounds **10** and **11** (78% and 75% yields, Entries 4 and 5), in which the hydroxy groups were two and three carbon atoms, respectively, away from the double bond. The oxidation of the allylic alcohol **12** to the corresponding α,α′-dihydroxy ketone **19** (Entry 6) gave a lower yield (68%), probably due to major steric hindrance. Notably good yields were also obtained when an acetyl group was present in the framework during the oxidation of compounds **13** and **14** (Entries 7 and 8) to hydroxy ketones **20** (70%) and **21** (72%).

The preservation of the silyl and acetyl groups on the hydroxy functions was important for prevention of the formation of overoxidised products, the anchoring of permanganate anion or intramolecular cyclisation.

Table 1. Oxidation of chiral terminal olefins with $KMnO_4/H_2O$/AcOH.[a]



Entry	Olefin	Hydroxymethyl ketone	Yield [%][b]
1[12]	 **7**	 **6**	80
2	 **8**	 **15**	72
3	 **9**	 **16**	70
4	 **10**	 **17**	78
5	 **11**	 **18**	75
6	 **12**	 **19**	68
7	 **13**	 **20**	70
8	 **14**	 **21**	72

[a] Each reaction was carried out on a 2 mmol scale of olefin in a solution of acetone/water/acetic acid (17 mL/3.8 mL/0.8 mL) in the presence of $KMnO_4$ (3.4 mmol) in acetone/water (6.4 mL/2.1 mL) solution. [b] Yields of isolated products purified by column chromatography on silica gel.

All the final compounds obtained can be seen as examples of useful chiral building blocks incorporating highly functionalised motifs including primary and secondary hydroxy groups and carbonyl groups.

Above all, compounds **6**, **15**, **16** and **20** are direct precursors for the preparation of 1,3-diol frameworks with *syn* or *anti* relative configurations, as important building blocks in the synthesis of natural products such as macrolide or ionophore antibiotics.[24] The direct hydride reduction of β-hydroxy ketones is one of the most widely employed methodologies for access to this kind of compound.[25]

As an example, the reduction of the derived compound **6** with tetramethylammonium triacetoxyborohydride[26] afforded the desired 1,3-*anti* diol in excellent yield and with good diastereoselectivity (*de* > 98%).[12]

However some preliminary studies on the reduction of the prepared ketols (**6**, **15**, **16** and **20**) to the corresponding 1,3-diols still require further developments in the use of appropriate reduction reagents.

Of particular importance are the chiral synthons **17** and **19**. The first compound, ketol **17**, is a useful intermediate for the preparation of 1,4-diol units, present in several natural products such as acetogenin, a promising anticancer, antibiotic and pesticidal natural compound product,[27] while the second one, **19**, is a direct precursor of amino diols.

Conclusions

In conclusion, simple chiral terminal alkenes could be utilised in a multistep synthetic strategy involving initial oxidation of the double bond to an α-hydroxymethyl ketone in order to access different functionalities. The overall method is practical and quite efficient, and is compatible with the presence of protective groups for the hydroxy functions. Moreover, the environmentally friendly (with respect to other oxidants) $KMnO_4$ oxidation and the use of aqueous media as solvent make this procedure quite appealing.

Experimental Section

General Procedure for Ketohydroxylation of Olefins: The olefin (2.1 mmol) was added to a solution of acetone (17 mL), water (3.8 mL) and acetic acid (0.8 mL). A solution of $KMnO_4$ (0.5 g, 3.4 mmol) in acetone (6.4 mL) and water (2.1 mL) was added dropwise, and the resulting mixture was stirred at room temperature until complete disappearance on TLC. After complete conversion (about 2 h), EtOH was added until effervescence stopped. The crude mixture was filtered through a pad of Celite and washed several times with hexane. The filtrate was concentrated, diluted with Et_2O and washed with saturated aqueous $NaHCO_3$ solution until pH = 8. The organic layer was then washed with brine and dried with Na_2SO_4. The crude product was purified by column chromatography on silica gel.

Supporting Information (see footnote on the first page of this article): Characterisation of all new compounds.

Acknowledgments

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[21] All secondary alcohol protection was performed with use of TBSCl (1.5 equiv.), imid. (3 equiv.), DMF for 16 h, at room temp.

[22] It is generally accepted that the mechanism of permanganate oxidation of alkenes proceeds via a (3+2) transition state with the formation of a cyclic ester intermediate. Oxidative decomposition of the cyclic ester to the Mn^{IV} ester of the ketol is then followed by the hydrolysis of the product: a) Th. Strassner, M. Busold, *J. Org. Chem.* **2001**, *66*, 672–676; b) S. Wolfe, C. F. Ingold, *J. Am. Chem. Soc.* **1981**, *103*, 938–939.

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[25] The Sharpless AD was tested on compound **6** as reported in Ref.,[11] but the *de* was unsatisfactory for such a functional transformation (*syn*/*anti* 42:58).

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