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syn Stereocontrol in the directed dihydroxylation of acyclic allylic alcohols

Timothy J. Donohoe,[a,*] Nicholas J. Newcombe [b] and Michael J. Waring [a]

[a] *Department of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, UK*

[b] *Zeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK*

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Abstract

The preparation and directed dihydroxylation of a series of acyclic allylic alcohols is reported. The oxidation reaction is capable of demonstrating high levels of diastereoselection for the *syn* isomer. An explanation of the observed selectivities based on the degree of allylic strain is presented and a transition state model proposed.

We have recently reported that the combination of osmium tetroxide with TMEDA produces a reagent which is capable of dihydroxylating allylic alcohols via a hydrogen-bonded transition state.[1] This reaction manifests itself in the formation of stereochemically defined triols; in particular the oxidation of cyclic allylic alcohols produces the *syn,syn*-triol selectively. Such a result is interesting because it is complementary to that obtained by oxidation of the same substrate under more orthodox dihydroxylation conditions.[2] For example, the oxidation of **1** gives *anti*-**2** when oxidised under 'Upjohn'[3] conditions (Scheme 1) and *syn*-**2** under directed dihydroxylation conditions.[1,4] Selectivity for formation of the *anti* isomer was originally noted by Kishi over a range of cyclic and acyclic allylic alcohols.[2]

During the oxidation of linalool, we observed hydrogen-bonding control of regiochemistry (formation of **3** versus **4**).[1] Moreover, moderate control of acyclic stereochemistry was also possible as **3** was formed as an unequal mixture of stereoisomers, favouring the *syn* compound (Scheme 1). As the stereochemical outcome of this reaction is again opposite to that expected under Upjohn conditions we decided to study it further.

In order to examine the scope of this reaction, we oxidised a series of chiral acyclic allylic alcohols; this would allow access to stereochemically defined acyclic 1,2,3-triols. We investigated the reaction of TMEDA/OsO_4 (1 equiv. of each, CH_2Cl_2, −78°C) with a range of mono- and (*E*)-disubstituted olefins and found that, in some cases, good levels of (*syn*) diastereocontrol were achieved (Scheme 2).[5] The level of *syn*-diastereoselection obtained was essentially unresponsive to the size of the substituents on

* Corresponding author. E-mail: t.j.donohoe@man.ac.uk

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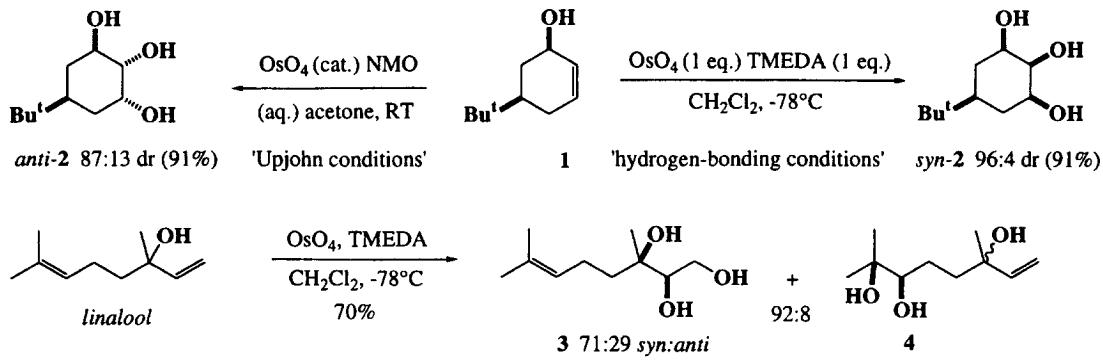
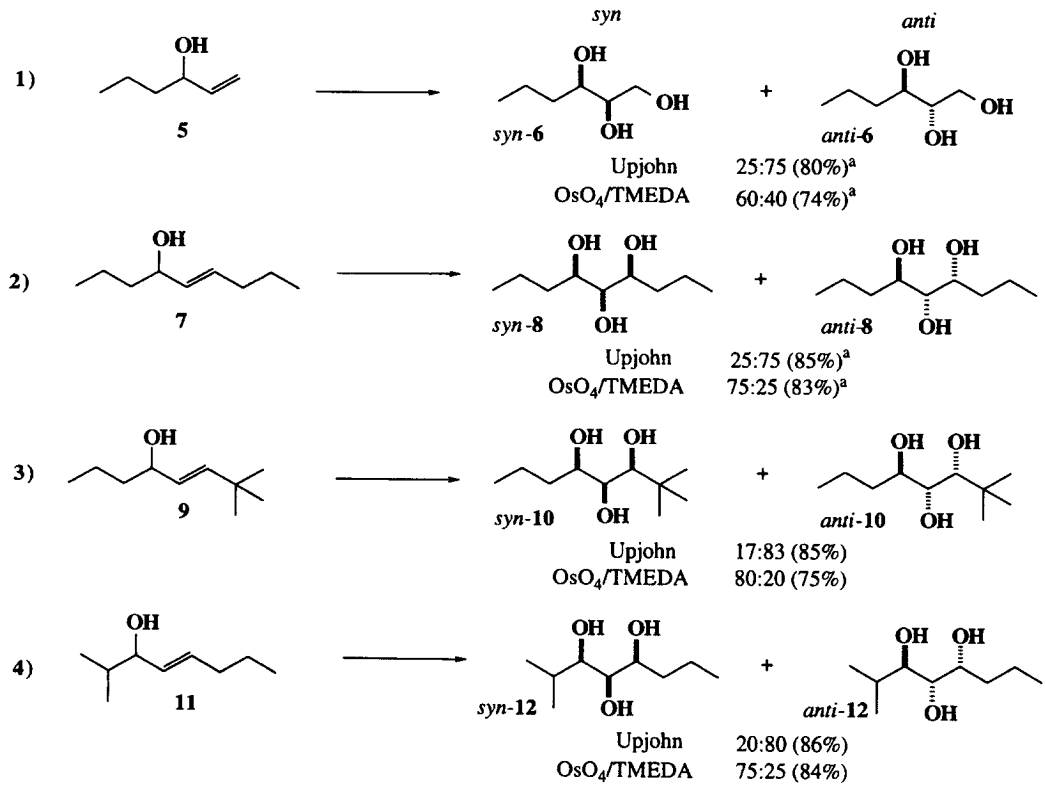


Scheme 1.

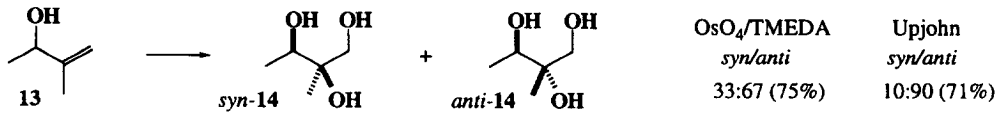
the alkene. The result of oxidation under Upjohn conditions is included for comparison and is clearly in favour of the *anti* diastereoisomer.



Scheme 2. [a]Products per acetylated in-situ prior to isolation. Identity of *syn*-**8** proven by NMR (*meso*). Identity of *syn*-**6** proven by correlation to a known compound.[6] Identity of *syn*-**10** and *syn*-**12** proven by formation of 1,3-benzylidine acetals and examination of coupling constants

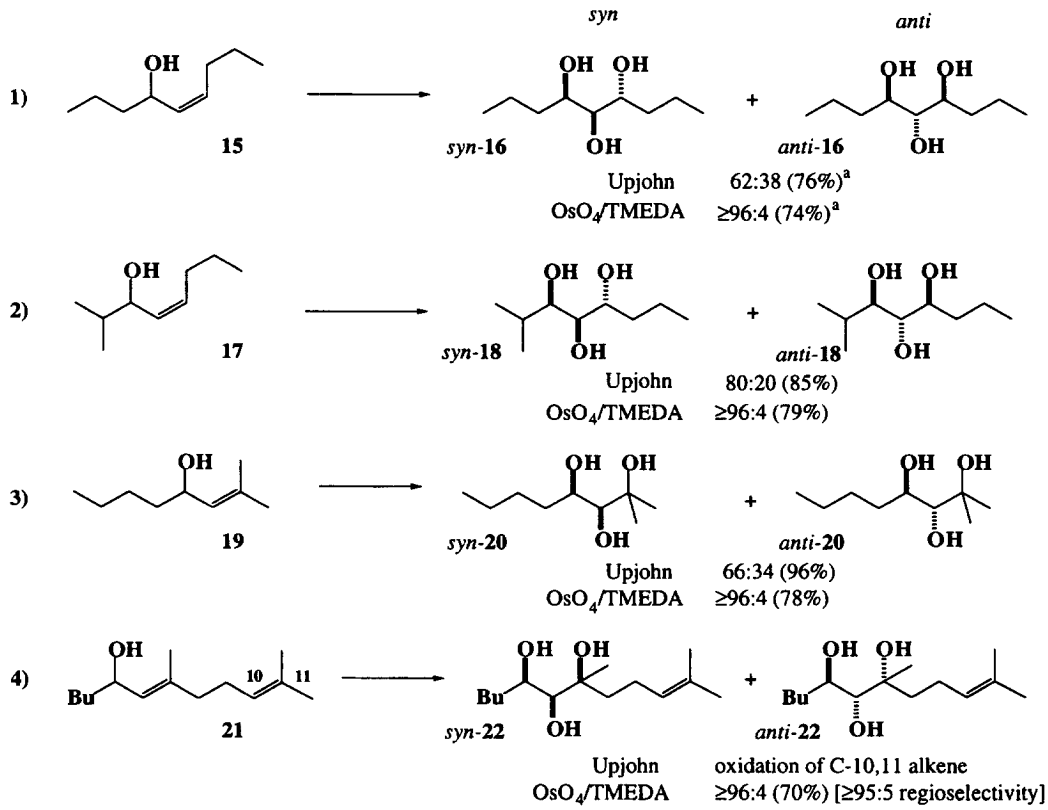
Unfortunately, this methodology does not work well for the oxidation of 1,1-disubstitued alkenes as such substrates show a strong bias for formation of the *anti* isomer under Upjohn conditions and the OsO_4/TMEDA reagent is not able to overturn it (Scheme 3).[7]

We then turned our attention to allylic alcohols bearing a *cis*-substituent and found that, as expected, very high levels of *syn*-selection were obtained (Scheme 4). The lack of *anti*-selectivity observed in



Scheme 3. Products were per-acetylated in-situ, prior to isolation. Relative stereochemistry was proven by correlation to a known compound[7]

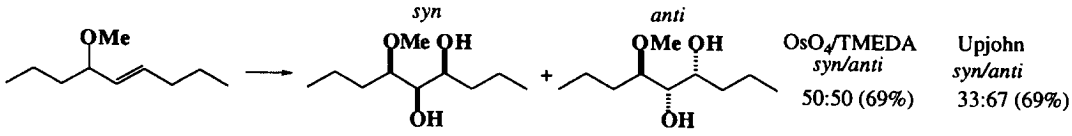
the Upjohn reactions described here is surprising given the literature precedent:[2,6,8] suffice to say at this point that care must be taken when oxidising *cis*-allylic alcohols under Upjohn conditions as any stereoselectivity that is observed cannot be assumed to be in favour of the *anti* isomer without proof. Entry 4, Scheme 4, illustrates a level of stereoselectivity and regioselectivity that cannot be achieved under 'normal' dihydroxylation conditions.



Scheme 4. [a]Products per acetylated in-situ prior to isolation. Relative stereochemistry of *anti*-**16** proven by NMR (*meso*); structure of *syn*-**18** was proven by X-ray crystallography; structure of *syn*-**20** proven by correlation to a known compound and relative stereochemistry of *syn*-**22** assigned by analogy

Further evidence for the role of hydrogen bonding as a control element in these reactions was found in the oxidation of the corresponding methyl ether of **7** (Scheme 5). Here we found the directed dihydroxylation reaction proceeded (at a decreased rate relative to **7**) with no stereoselection at all.

In terms of a transition state model to explain these selectivities we would draw analogy to the directed epoxidation of acyclic allylic alcohols with peracids (most notably *m*-CPBA).[9] Examination of the literature shows that for each class of alkene, we observe similar levels of *syn/anti* stereoselectivity as the epoxidation reaction; perhaps this is not too surprising considering that hydrogen-bonding is the



Scheme 5.

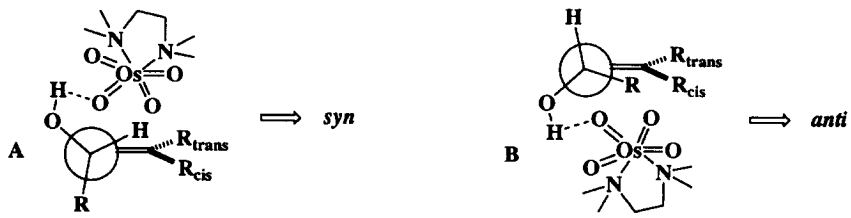


Figure 1.

control element in each case. We suggest that, in the transition state, the dihedral angle between the C–O and the C=C is most favourable at approximately 120°. Approach of the oxidant from the upper face as shown in Fig. 1 (**A**) has the advantage of maintaining a hydrogen-bond between the oxidant and substrate: this does not occur if the oxidant approaches the lower face and so selectivity for the *syn* isomer is observed. Of course, other conformations may also exhibit hydrogen bonding and lead to the *anti* product (see **B**, Fig. 1): however, reaction through these transition structures is (moderately) disfavoured by $A^{[1,3]}$ strain between the R group and the R_{cis} substituent. This explains why a large group in the R_{cis} position leads to higher levels of stereocontrol than the same group in the R_{trans} position. The failure of 1,1-disubstituted alkenes to undergo selective dihydroxylation may be related to the introduction of significant $A^{[1,2]}$ strain in the transition state. Although other mechanistic rationales are possible, we have shown for clarity approach of the (chelated) complex between OsO_4 and TMEDA[1,10] hydrogen-bonding via an oxo-ligand.

Representative experimental procedure: A solution of **9** (100 mg, 0.64 mmol) and TMEDA (116 μL, 0.77 mmol), in CH_2Cl_2 (64 mL) were cooled to –78°C under an atmosphere of N_2. A solution of osmium tetroxide (196 mg, 0.77 mmol) in CH_2Cl_2 (1 mL) was added and the solution was stirred at –78°C for 2 h. After warming to room temperature ethane-1,2-diamine (214 μL, 3.2 mmol) was added and the reaction was then stirred for 48 h. The mixture was poured into brine, extracted with ethyl acetate (3×50 mL), dried (Na_2SO_4), and concentrated in-vacuo. Chromatography on silica (eluting with ethyl acetate:hexane, 30:70) gave **10** as a colourless solid (91 mg, 75%).

Acknowledgements

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