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The Directed Dihydroxylation of Allylic Alcohols

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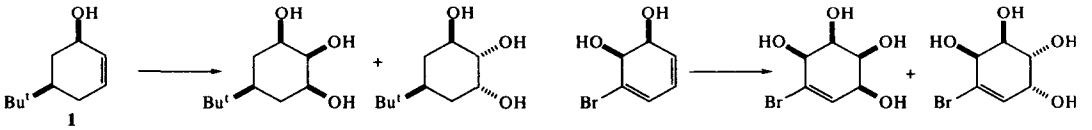
Abstract: The preparation and dihydroxylation of a series of polyenes and cyclic allylic alcohols using the TMEDA/osmium tetroxide mixture is reported. Remarkably, these reagents lead to high levels of regiochemical and stereochemical control as the oxidant hydrogen-bonds to the allylic alcohol group. A mechanistic hypothesis is presented which invokes the formation of a reactive, bidentate complex between osmium tetroxide and TMEDA at low temperatures. © 1997 Elsevier Science Ltd.

The dihydroxylation of alkenes using osmium tetroxide is an exceptionally useful and versatile reaction.[1] Studies on the oxidation of chiral allylic alcohols have raised some interesting points: seminal work by Kishi showed that the dihydroxylation of cyclic allylic alcohols occurred from the face of the alkene that was *opposite* to the hydroxyl group.[2] In addition, oxidation of polyenes with osmium tetroxide revealed that alkene units substituted with an allylic hydroxyl group were somewhat deactivated with respect to similar but unfunctionalised alkenes in the same molecule.[3] The conclusion that can be drawn from these observations is that coordination between osmium tetroxide and a hydroxyl group is not an efficient process.

We are interested in encouraging osmium tetroxide to associate with a hydroxyl group, so producing a directed dihydroxylation of allylic alcohols.[4] There are several reports in the literature of directed dihydroxylations using sulfoximines,[5] sulfoxides[6] and amines[7] to coordinate to osmium tetroxide, although these appear to be rather isolated examples without generality. Recently, Corey has introduced the *p*-methoxybenzoate ester as a derivative of allylic alcohols which encourages regioselective (and stereoselective) dihydroxylation of polyenes when used in conjunction with the Sharpless $(DHQD)_2PYDZ$ catalyst.[8]

We decided to examine hydrogen-bonding as a control element for the dihydroxylation of allylic alcohols. Indeed, recent work by ourselves[9,10] and others[11] has shown that hydrogen-bonding between osmium tetroxide and a hydroxyl group is possible and is encouraged in aprotic media. Unfortunately, the magnitude of this effect was rather small and the process did not appear to be particularly general (**Scheme 1**).



OsO_4 (cat), NMO, acetone/water 13:87 (84%)

OsO_4 (cat), $Me_3NO.2H_2O$, CH_2Cl_2 55:45 (55%)

OsO_4 (cat), NMO, acetone/water 47:53 (84%) Ref 14

OsO_4 (cat), $Me_3NO.2H_2O$, CH_2Cl_2 82:18 (79%)

Scheme 1

We now wish to report that the simple expedient of adding TMEDA to osmium tetroxide produces a reagent which is capable of hydrogen-bonding to an allylic hydroxyl group in a highly efficient manner. The new protocol involves mixing the allylic alcohol (1 eq.) with TMEDA (1.2 eq.) in CH_2Cl_2 and cooling to -78 °C before addition of osmium tetraoxide (1.2 eq.): the ensuing reactions are very rapid and are complete in approximately 15-30 minutes.[12] Our initial studies were confined to issues of regiochemistry in polyene systems (**Table 1**).[13]

Oxidation of the methyl ether of geraniol with the TMEDA/osmium tetroxide reagent gave preferential oxidation of the 6,7-alkene unit over the 2,3-alkene (2.5:1). This result clearly implicates *hydrogen-bonding* as the key feature responsible for the aforementioned regioselectivity.

The results described herein reveal a remarkable *reversal* of regioselectivity when compared to oxidation of the same substrate with osmium tetroxide under any other conditions that we have examined. We now have the ability to functionalise allylic alcohols regioselectively using this reagent combination.

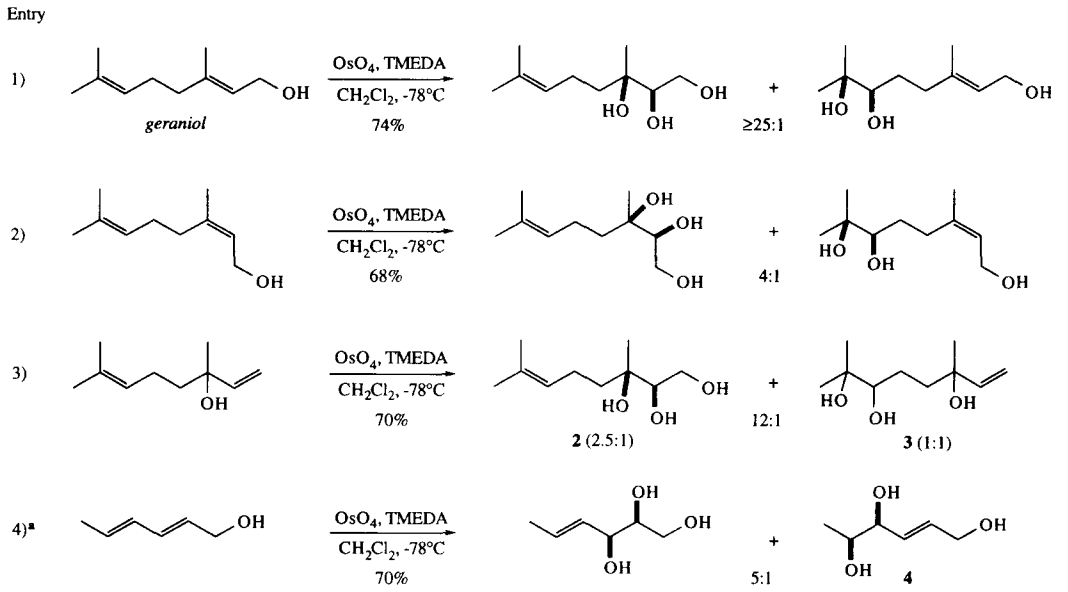


Table 1: All selectivities were confirmed at ≤10% conversion so as to minimise further reaction of the products with excess oxidant. All products are racemic. Ratios were determined by HPLC and ^1H nmr spectroscopy. Compound **2** was formed as a 2.5:1 mixture of diastereoisomers (major shown); compound **3** was formed as a 1:1 mixture of diastereoisomers. [a] Products were peracetylated *in situ*, prior to isolation. The triacetate of compound **4** was isolated as a mixture of isomers.

Intrigued by this result, we turned our attention to the stereoselective dihydroxylation of cyclic allylic alcohols. We hoped that hydrogen-bonding would favour the formation of the *syn,syn* diastereoisomer (this is normally a disfavoured process and the *syn,syn* triols that are formed are difficult to make by other means). Remarkably, the TMEDA/osmium tetroxide combination was capable of directing the oxidation onto the same face of the alkene as the hydroxyl group with good to excellent levels of stereocontrol (**Table 2**). This reaction is particularly amenable to the oxidation of five- and six-membered cyclic alkenes, and each entry represents a reversal of selectivity to that observed under typical dihydroxylation conditions (Upjohn), as first reported by Kishi.[2] Entry 3 represents a single step synthesis of conduritol D which proceeds with a high level of

stereocontrol. Moreover, oxidation of the methyl ether of alcohol **1** under these conditions gave predominantly the *anti* diasteroisomer (20:1 selectivity), further implicating hydrogen-bonding in the TMEDA process.

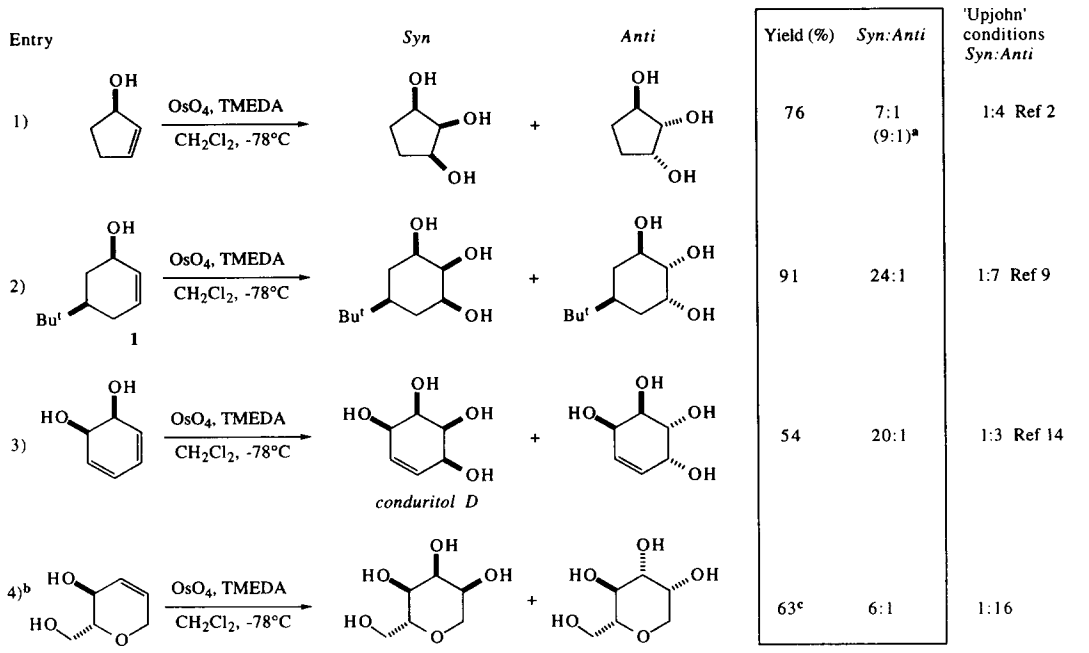


Table 2: All compounds are either racemic or *meso* (except entry 4). Ratios were determined by ^{1}H nmr spectroscopy. [a] Ratio at -90°C. [b] Products were peracetylated *in situ* before isolation. [c] Yield of pure *syn* isomer.

At the present time, it is difficult to be sure of the origins of the selectivity displayed by TMEDA/OsO_4, especially in light of the uncertainty regarding the mode by which osmium tetroxide adds to an alkene. However, we feel that a question of fundamental importance regards the mechanism by which this reagent hydrogen-bonds to an allylic alcohol, *i.e.* does it bond *via* an oxo ligand or *via* the TMEDA ligand? We wish to present the following observations:

1) Oxidation of **1** using standard (TMEDA) conditions at room temperature gave 6:1 (*syn:anti*) selectivity. Replacement of TMEDA with $Me_2N(CH_2)_3NMe_2$ under otherwise identical conditions gave similar (4:1 *syn:anti*) selectivity. However, replacing TMEDA with $Me_2NCH_2NMe_2$ gave a different ratio (60:40 *syn:anti*): this selectivity is within the range observed when TMEDA is replaced by a monodentate amine (*eg.* quinuclidine).[10]

2) In an attempt to investigate whether one amine group on TMEDA could be replaced with another hydrogen-bond acceptor or even a hydrogen bond donor, compound **1** was oxidised (OsO_4, RT) with both $MeOCH_2CH_2NMe_2$ and $HOCH_2CH_2NMe_2$. In each case the result was marginally selective (52:48 *syn: anti*).

From these preliminary studies we presume that in order to be effective in directed dihydroxylation reactions, the amine promoter must have the ability to form a bidentate complex with the transition metal. Evidence in favour of bidentate amine/OsO_4 complexes (formally 20 electron) has been provided recently by Corey in the form of an X-ray crystal structure of such a complex.[15] Reaction *via* such a bidentate complex points to hydrogen bonding *via* an oxo ligand on osmium (**Figure 1**).

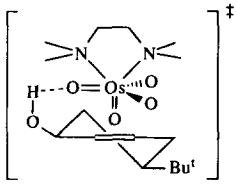


Figure 1

We have observed a clear trend in our studies, which reveal that the ability of the oxidant to act as a hydrogen-bond acceptor follows the sequence, OsO_4 < OsO_4 + amine < OsO_4 + diamine (stoichiometric oxidant in CH_2Cl_2).[9,10] One explanation of this sequence presumes that addition of a single amine ligand to osmium (VIII) places extra electron density on the metal, which weakens the osmium-oxygen double bonds: this would make the oxygen atoms more electron-rich and, therefore, better hydrogen-bond acceptors. Extrapolation of this argument to include the formation of two amine-osmium bonds (as in a bidentate complex) would lead to the conclusion that a diamine/OsO_4 complex should be a superior hydrogen bond acceptor.

Of course, reaction of an alkene with OsO_4 (with or without added ligands) could in principle proceed through either a [2+2] or [3+2] mode. This makes accurate prediction of the detailed geometry of the hydrogen-bond in the transition structure difficult, as it could involve the rate-limiting formation of an osmate ester in a single step [3+2] or ring expansion of an intermediate osmaoxetane [2+2].[16]

In conclusion this study has defined a new system for the directed dihydroxylation of cyclic and acyclic allylic alcohols and is capable of displaying high levels of regiochemical and stereochemical control. Work is continuing to explore the scope, applicability and mechanism of this reaction and will be reported in due course.

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10. Donohoe, T. J.; Moore, P. R.; Beddoes, R. L. *J. Chem. Soc., Perkin Transactions 1*, **1997**, 43: the stereoselectivity observed upon oxidation of **1** with osmium tetroxide and a monodentate amine (in CH_2Cl_2 at RT) normally ranges from 50:50 to 60:40 *syn:anti*, depending on conditions and exact structure of the amine.
11. (a) ref 1(c). See also (b) Kon, K.; Isoe, S. *Tetrahedron Lett.*, **1980**, *21*, 3399. (c) Smith III, A. B.; Boschelli, D. *J. Org. Chem.*, **1983**, *48*.
12. Representative experimental procedure: a solution of geraniol (100 mg, 0.65 mmol) and TMEDA (92 mg, 0.78 mmol) in CH_2Cl_2 (65 ml) was cooled to -78°C under an atmosphere of nitrogen and a solution of osmium tetroxide (198 mg, 0.78 mmol) in DCM (2 ml) was added. After 5 minutes, allyl alcohol (2 ml) was added and the reaction stirred at -78°C for 1 h. The reaction was warmed to room temperature and the solvent removed *in vacuo* and replaced with THF (10 ml) and (aq.) sodium sulfite (10 ml). This mixture was heated at reflux for 3 h and then poured into brine (50 ml) and extracted with ethyl acetate (3 x 100 ml). The combined organic extracts were dried ($MgSO_4$) and filtered through celite. Evaporation under reduced pressure gave a yellow oil which crystallised on standing to give the C-1,2,3-triol as a single compound (90 mg, 74%). ^{1}H nmr (300 MHz, $CDCl_3$) 5.10 (1H, t, *J*= 7.5 Hz), 3.57 (2H, d, *J*= 5.2 Hz), 3.50 (1H, t, *J*= 5.2 Hz), 2.05 (2H, br q, *J*= 7.5 Hz), 1.67 (3H, s), 1.60 (3H, s), 1.60-1.46 (2H, m), 1.15 (3H, s).
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