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Study of the Regio- and Enantioselectivity of the Reactions of Osmium Tetroxide with Allylic Alcohols and Allylic Sulfonamides§

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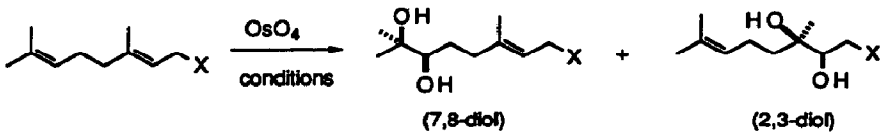
Abstract: *The regioselectivities of the osmylation of geraniol, its derivatives and geranyl sulfonamides suggest the presence of a moderate attractive interaction between OsO_4 and the allylic groups bearing acidic protons. This allylic directing effect may be due to the development of a hydrogen bonding interaction between OsO_4 and the substrates during the osmylation process. The potential for a hydrogen bond can also have a substantial effect on the enantioselectivities of the osmium tetroxide catalyzed asymmetric dihydroxylation of allylic alcohols.*

While the osmium catalyzed asymmetric dihydroxylation (AD) is compatible with a large variety of functional groups in the olefinic reactants,[1] we now report that the presence of an acidic proton at the allylic position of a substrate may have a substantial effect on both the regio- and stereoselectivity of the dihydroxylation process.[2]

Under both stoichiometric and catalytic conditions, dihydroxylation of geraniol **1** gives a mixture of the 1,6,7-triol **2** and the 1,2,3-triol **3** in an *ca* 80:20 ratio (entry 1, Table I).[3] In contrast, dihydroxylation of the methyl ether (**4**) and acetate (**5**) derivatives gave the products of remote double bond oxidation almost exclusively (entries 2 and 3, Table I). The preference for remote bond oxidation was anticipated because of the electron withdrawing inductive effect of the allylic oxygen substituents. However, the dramatic drop in regioselectivity for geraniol suggests an attractive interaction between the hydroxyl group and OsO_4 which partly counters the repulsive electronic effect. The moderate directing effect[4] from the allylic hydroxyl group is reminiscent of the results in peracid oxidations.[5] It is speculated that a hydrogen bonding interaction between the allylic hydroxyl and an oxo group on osmium maybe occur during the osmylation process. A similar trend in the regioselectivity was observed for dihydroxylations of sulfonylated derivatives of geranyl amine (Table I). An even higher selectivity for oxidation of the double bond proximate to the acidic N-H is observed than for geraniol, despite the more unfavorable steric and electronic influences of the sulfonamido substituents.[6] This phenomenon is probably due to the increased acidity, relative to geraniol, of the protons on the nitrogen in substrates **6**, **7** and **8**, which enhances the strength of the putative hydrogen bond and leads to greater allylic selectivity.

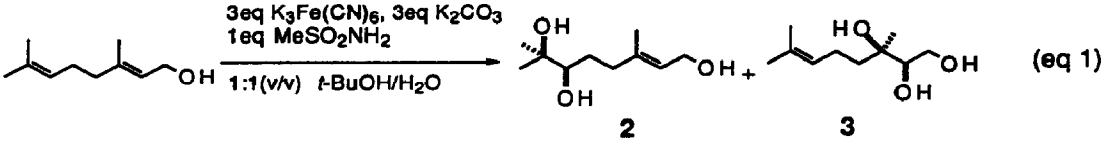
Table I



entry	X[a]	condition[b]	7,8-diol/ 2,3-diol	
1	OH, 1	A , B	(2)80	(3)20
2	OMe, 4	A, B	>98	2
3	OAc, 5	A	>99	1
4	NHMs, 6	B	67	33
5	NHTs, 7	B	60	40
6	NHNs, 8	B	60	40

a: Ms = methanesulfonyl, Ts = *p*-toluenesulfonyl, Ns = *p*-nitrobenzenesulfonyl. b: conditions A: 5% OsO_4, 3 eq $K_3Fe(CN)_6$,1 eq $MeSO_2NH_2$, 3 eq K_2CO_3, 1:1 (v/v) t-BuOH:H_2O, RT; B: 1 eq OsO_4, PhMe, RT.

The magnitude of the allylic hydroxyl effect appears to be sensitive to several factors including ligand influences and substrate structural changes. As shown in eq 1, the regioselectivity of the dihydroxylation of geraniol is significantly altered in the presence of ligands.[2b] Application of quinuclidine as the ligand suppressed oxidation of the 2,3-double bond in the catalytic dihydroxylation of geraniol **1** giving a mixture of the 1,7,8-triol **2** and the 1,2,3-triol **3** in a ratio of 9:1 as compared with 4:1 ratio when no ligand was used. Reversible association of the olefinic substrate with OsO_4 (e.g. complexation, metalloxatane formation etc.) prior to the osmium glycolate formation would provide a simple explanation for this phenomenon.[7] Continuing this trend, AD of **1** using the $(DHQD)_2$-PHAL ligand[1] gave the 1,7,8-triol *R*- **2** as the only isolated product in 89% yield and 94%ee (eq 3).[8-10]



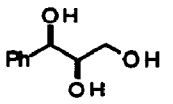
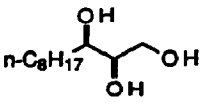
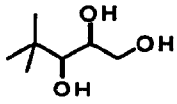
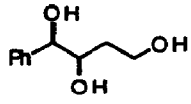
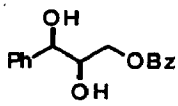
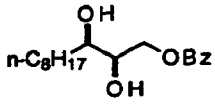
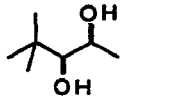
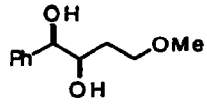
(eq 1)

5% OsO_4, NO ligand, RT	4	: 1	
1% OsO_4, 5% quinuclidine, RT	9	: 1	
1% OsO_4, 5% $(DHQD)_2$-PHAL, 0 °C	≥49	: 1	(2: 89% yield, 94% ee)

The presence of an allylic hydroxyl has in varying degrees a deleterious effect on the enantioselectivity of AD of *trans*-disubstituted olefins. A comparison of the ee values for the dihydroxylation products of olefinic alcohols and their structurally similar analogs is shown in Table II.[11] All the AD reactions were carried out under the standard conditions at 0 °C using the $(DHQD)_2$-PHAL

ligand.[1a, 11] Only a slight drop is seen for the AD of cinnamyl alcohol and 2-decen-1-ol as compared to their benzoate derivatives. It is interesting to note that, with the DHQD-CLB as the ligand, AD of cinnamyl alcohol gave the triol **9** in only 71% ee as compared with 91% ee for the dihydroxylation product of cinnamyl acetate using the same ligand.[12] A large ee reduction is observed for the AD of 4,4-dimethyl-2-penten-1-ol (*cf.* **13** and **14**). Finally, a homoallylic hydroxyl does not appear to have as much effect on the enantioselectivity as an allylic hydroxyl (*cf.* **15** and **16**). Although these trends in enantioselectivities for the AD of olefinic alcohols are not very clear at the present, it appears that for a substrate which gives poorer selectivity in the AD, the presence of an unprotected allylic hydroxyl may cause a serious drop in the enantioselectivity for *trans*-allylic alcohols.[13]

Table II

			
9, 97%ee	**11**, 93%ee	**13**, 74%ee	**15**, 98%ee
			
10, 99%ee	**12**, 99%ee	**14**, 95%ee	**16**, 99%ee

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§: These results were presented at the 204th ACS meeting, Washington, D.C., August 23-28.

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(3) Triols **2** and **3** can be separated by flash chromatography and characterized independently. However, the product distribution between these two compounds as well as of others were more conveniently determined by either integration of the ^{1}H NMR spectra or GC analysis.

(4) Other functional groups have been reported to have directing effects in osmylation processes. See:(a) Hauser, F. M.; Ellenberger, S. R.; Clardy, J. C.; Bass, L.S. *J. Am. Chem. Soc.* **1984**, *106*, 2458. (b) Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 2459. (c) Solladié, G.; Fréchou, C. Demailly, G. *Tetrahedron Lett.* **1986**, *27*, 2867.(d) Trost, B. M.; Kuo, G.-H.; Benneche,.T. *J. Am..Chem. Soc.* **1988**, *110*, 621. (e) Poli, G. *Tetrahedron Lett.* **1989**, *30*, 7385.

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(8) Procedure for the AD of geraniol **1**: A 100 mL round bottomed flask equipped with a magnetic stirrer was charged with 10 mL of tert-butyl alcohol, 10 mL of water, $K_3Fe(CN)_6$ (1.98g, 6.0mmol), K_2CO_3 (0.83g, 6.0mmol), $MeSO_2NH_2$ (0.19g, 2.0mmol), $(DHQD)_2$-PHAL [1,4-bis-9-O-dihydroquinidine-phthalazine] (39mg, 0.05 mmol), and OsO_4 (57μL, 0.175M in H_2O). Geraniol **1** (0.347mL, 2.0mmol) was added and the heterogeneous slurry was stirred vigorously at 0°C for 12 hours. The reaction was quenched by addition of solid sodium sulfite (*ca* 2g) followed by aqueous workup.[1b] Flash chromatography on silica gel (7:3(v/v) EtOAc/acetone) afforded the 1,7,8-triol **2** as a clear, colorless oil (0.336g, 89%). The spectral data are consonant with those in the literature.[9a] $[\alpha]_D^{24}$ = -30.2° (c = 1.1, EtOH). The ee value was determined by HPLC analysis of the correponding 1-benzoate on a Chiralcel OB column.

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(10) The AD of geraniol and related compounds has appeared recently on this journal during the revision of this manuscript: (a) Corey, E. J.; Neo, M. C.; Shieh, W.-C. *Tetrahedron Lett.* **1993**, *34*, 5995. (b) Vidari, G.; Dapiaggi, A.; Zanoni, G.; Garlaschelli, L. *Tetrahedron Lett.* **1993**, *34*, 6485. (c) Vidari, G.; Giori, A.; Dapiaggi, A.; Lanfranchi, G. *Tetrahedron Lett.* **1993**, *34*, 6925.

(11) All the AD reactions were run as for geraniol (ref 7). The ee values of compounds **9-16** were determined by the following methods: **9**, derivatized as its tris-parachlorobenzoate , was analyzed on a Chiralcel OG column (HPLC); **10** was analyzed directly on a Chiralcel OG column (HPLC); **11**, derivatized as its mono-benzoate, was analyzed as for **12**; **12** was analyzed directly on a Chiralcel OD-H column (HPLC); **13**, derivatized as its tris-benzoate, was analyzed on a Chiralcel OD-H column (HPLC); **14**, derivatized as its bis-Mosher ester, was analyzed on a J&W DB-1 column (GLC); **15**, derivatized as its tris-acetate, was analyzed on a Chiralcel OD column (HPLC); **16** was analyzed directly on a Chiralcel OF column (HPLC).

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(13) We recently found that the presence of a free hydroxyl group enhances the enantioselectivity in the AD of the *cis*-allylic alcohol. VanNieuwenhze, M. S.; Sharpless, K. B. *Tetrahedron Lett.* in press.

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