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Asymmetric Dihydroxylation of α- and β-Farnesene

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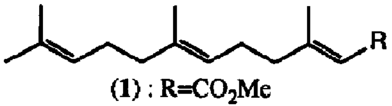
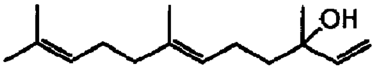
Abstract: *The asymmetric dihydroxylation of α-farnesene was studied using the ligands (DHQ)$_2$-PHAL and (DHQD)$_2$-PHAL. High enantioselectivity and preferential addition to the 6,7-olefin were observed. The isomeric β-farnesene showed a preference for reaction at the 10,11-olefin.*

The osmium catalyzed asymmetric dihydroxylation (AD) of alkenes based mainly on the phthalazine class of ligands developed by Sharpless[1] has adopted a central role in the field of asymmetric synthesis. One important application of the AD reaction is the assembly of polyoxygenated carbon skeletons by selectively adding oxygen functionality onto polyunsaturated hydrocarbons. Towards this end, the regioselectivity of this reaction is of particular importance and a reactivity hierarchy[2] for the different categories of olefin has been established. Sharpless has effected regioselective monohydroxylation[3] of simple dienes affording ene-diols of high optical purity, however the crucial test for regioselectivity of this reaction lies in the hydroxylation of polyenes.

Asymmetric dihydroxylation of squalene established that attack occurred preferentially at the terminal least congested site.[4] Studies on related polyenes such as methyl farnesoate (1),[5] nerolidol (2),[6] and *trans, trans*-farnesyl acetate (3)[7] indicate preference for the terminal trisubstituted double bond over the internal trisubstituted double bond, however, the degree of regioselectivity varies markedly depending on the nature of the functionality at C-1 to C-3. Nerolidol[6] exhibits only a slight preference (1.2:1) for hydroxylation under Sharpless conditions at the 10,11-double bond over the 6,7-double bond. This selectivity, however, increases to 2.2:1 for farnesyl acetate (3)[7] whilst a dramatic increase (20:1) is observed for methyl farnesoate (1).[5]



(1) : R=CO_2Me
(3) : R=CH_2OAc



(2)

Given the synthetic potential of chiral hydroxylated farnesene derivatives as precursors to juvenile hormone analogues[5,8] and the implication that oxidation products of α-farnesene play an important role in the production of the pome fruit storage disorder superficial scald,[9] we now wish to report our studies on the Sharpless asymmetric dihydroxylation of α- and β-farnesene (4) and (8).

Asymmetric dihydroxylation of α-farnesene (4) with 10 mol% of 1,4-bis (dihydroquininephthalazine) [(DHQ)2-PHAL] and 2 mol% OsO_4 using potassium ferricyanide (3 equiv.) as cooxidant in the presence of K_2CO_3 (3 equiv.) and methanesulfonamide (1 equiv.) at 0°C for 6h. afforded a 20:1 ratio of the (*S,S*) -6,7-diol[#] (5) to the 3,4-diol in 28% combined yield, as well as (*S*)-10,11-diol (6) (12%), (*S, S, S*)-6,7:10,11-tetraol (7) (7%) and recovered starting material (25%). Under the same conditions but using 1,4-bis-

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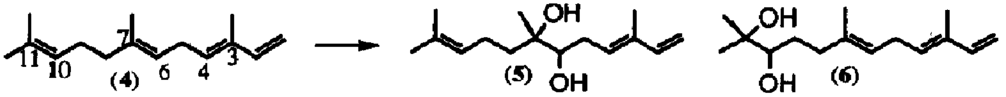
[#] For clarity the numbering system for methyl farnesoate (1) is used throughout.

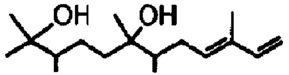
(dihydroquinidinephthalazine) [(DHQD)$_2$-PHAL] as ligand, selectivity for the 6,7-olefin dropped in that a 20:1 ratio of the (*R*) -6,7-diol (**5**) to 3,4-diol was formed in 18% yield, with more of the (*R*)-10,11-diol (**6**) (15%) and (*R,R,R*)-6,7:10,11-tetrol (**7**) 14% together with recovered starting material (29%). Enantiomeric excesses were determined by ^{1}H NMR (270 MHz) upon conversion to the Mosher ester derivatives using (-)-MTPA-Cl. The absolute configuration at the stereogenic carbon atoms C-6 and C-7 of the enantiomeric diols was assigned using the mnemonic device described by Sharpless *et al.*[1]

Asymmetric dihydroxylation of β-farnesene (**8**) using the ligand (DHQ)$_2$-PHAL under the same conditions as described above, resulted in a 2:1 preference for the 10,11-olefin over the 6,7-olefin affording diol (**9**) and diol (**10**) in 18% and 9% yield respectively along with recovered starting material. These results indicate that regioselectivity in the AD reaction of polyenes is extremely sensitive to the presence of additional functionality; with the presence of an appropriate diene being sufficient to overcome the normal preferential reactivity of the terminal 10,11 double bond. Differential steric interactions with the osmium-ligand complex are suggested to account for the observed differences in reaction rates, however a full explanation requires more detailed understanding of the topology of the osmium-ligand complex.



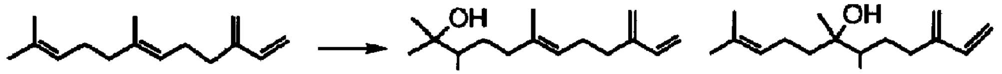
(4) (5) (6)

	(5)	(6)
(DHQ)$_2$-PHAL :	$[\alpha]_D^{20}$-24.5 (c, 1.91, CHCl$_3$) >95% ee (Mosher ester), 28%	$[\alpha]_D^{20}$-20.8 (c, 0.72, CHCl$_3$) 95% ee (Mosher ester), 11%
(DHQD)$_2$-PHAL :	$[\alpha]_D^{20}$+22.8 (c, 1.43, CHCl$_3$) >95% ee (Mosher ester), 18%	$[\alpha]_D^{20}$+21.2 (c, 1.19, CHCl$_3$) >95% (Mosher ester), 15%



(7)

(DHQ)$_2$-PHAL : $[\alpha]_D^{20}$-39.8 (c, 0.8, CHCl$_3$)
>95% ee (6,10-bis-Mosher ester), 7%
(DHQD)$_2$-PHAL : $[\alpha]_D^{20}$+42.0 (c, 1.09, CHCl$_3$)
>95% ee (6,10-bis-Mosher ester), 14%



(8) (9) 18% (10) 9%

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