Tetrahedron Letters, Vol. 33, No. 30, pp. 4273-4274, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

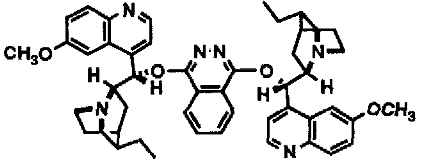
ASYMMETRIC DIHYDROXYLATION OF SQUALENE

Gerard A. Crispino and K. Barry Sharpless*

Department of Chemistry, The Scripps Research Institute,
La Jolla, California 92037, USA

Summary: The asymmetric dihydroxylation of squalene was studied using the new ligand $(DHQD)_2$-PHAL. Moderate positional selectivity for the 2,3-olefin was observed with high % ee.

Recently, we discovered a new ligand, 1,4-bis-(9-*O*-dihydroquinidine) phthalazine **1**, and an improved procedure for the asymmetric dihydroxylation (AD) of olefins.[1] Most notably, this ligand gives very high % ee for trisubstituted olefins such as 2-methyl-2-heptene (98% ee). This result prompted us to investigate the AD of trisubstituted olefins of more practical interest.

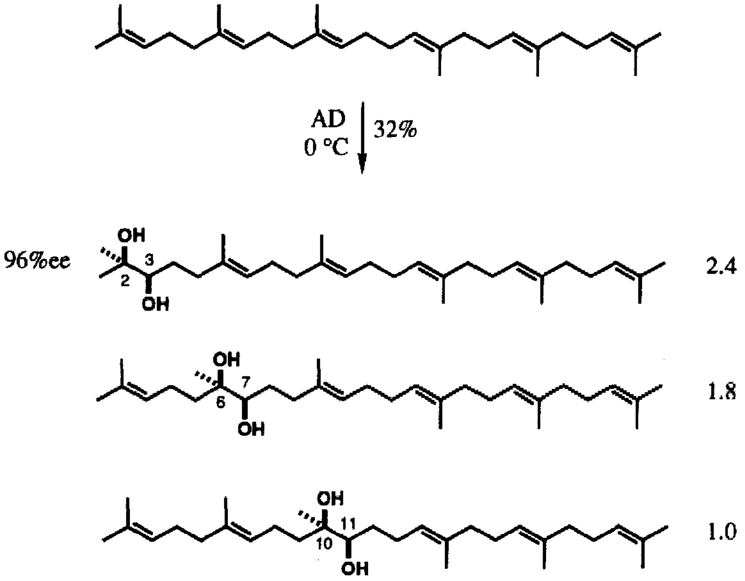


$(DHQD)_2$-PHAL 1

Squalene is a triterpene containing three pairs of trisubtituted double bonds in environments with slightly different degrees of steric encumberance. Dihydroxylation with catalytic OsO_4 using $K_3Fe(CN_6)$ as cooxidant gave a 1:1:1 mixture of the 2,3-, 6,7-, and 10,11-diols, along with polyols and recovered squalene. However, a preference was observed for the less hindered olefins when the reaction was run in the presence of 5 mole % of $(DHQD)_2$-PHAL.[2] At 0 °C after 24 hours,[3] a 32% yield (based on 52 % recovered squalene) of the diols was obtained in a ratio[4] of 2.4:1.8:1.0, with the 2,3-(*R*)-diol formed in 96 % ee[5]. When the reaction was run at room temperature, a 36% yield (based on 26% recovered squalene) of the diols was obtained in approximately the same ratio (2.2:1.8:1.0) but the ee of the 2,3-diol dropped to 92%. Comparison of the optical rotation of the 2,3-diol ($[\alpha]_D^{24} = +4.6$ (c 1.5, $CHCl_3$), 0 °C reaction) with the literature value[6] showed that $(DHQD)_2$-PHAL gave the (*R*) enantiomer.

Squalene has been selectively oxidized by N-bromosuccinimide to give the 2,3-bromohydrin exclusively.[7] Although coiling of the polyolefin in the polar solvent has been suggested[7] to explain this result, it seems more likely that solvent-clustering around the charged active species (e. g. bromonium ion) at the transition state may, by simple steric effects, inhibit reaction at the internal olefinic sites due to their more crowded, albeit subtly so, steric environments.[8] The results described here agree with this latter explanation, since the more sterically demanding osmium-ligand complex gives a slight preference for the less encumbered olefins nearer the terminus. This is the first example of selectivity in the oxidation of squalene with a "neutral" oxidizing species.

In conclusion, the asymmetric dihydroxylation of squalene with $(DHQD)_2$-PHAL gave modest regioselectivity for the more sterically accessible 2,3-olefin with high enantioselectivity.



Acknowledgement: Financial support was provided by the National Science Foundation.

References and Notes:

1. Sharpless, K.B., Amberg, W., Bennani, Y.L., Crispino, G.A., Hartung, J., Jeong, K.-S., Kwong, H.-L., Morikawa, K., Wang, Z.-M., Xu, D., Zhang, X.-L., *J. Org. Chem.*, **1992**, issue # 10.
2. Due to the low rate of reaction, more ligand and osmium were needed and AD-mix-β[1] could not be used
3. To a well stirred solution of (DHQD)$_2$-PHAL, (40 mg, 5.0 mole%), K$_3$Fe(CN$_6$), (0.99 g, 3 mmol), K$_2$CO$_3$, (0.42 g, 3 mmol), CH$_3$SO$_2$NH$_2$, (0.096 g, 1 mmol), and OsO$_4$, (1.0 mole %) in 10 mL of 1:1 *tert*-butyl alcohol-water at 0 °C was added squalene (418 mg, 1 mmole). The mixture was stirred for 24 hours, then 1.5 g of Na$_2$S$_2$O$_5$ was added and the suspension warmed to room temperature. CH$_2$Cl$_2$ (10 mL) was added and the aqueous layer was further extracted with CH$_2$Cl$_2$. The combined organic layers were washed with a 2N NaOH solution, dried over MgSO$_4$, and concentrated. Chromatography on silica with 3:1 EtOAc : hexane gave a coeluting mixture of the 6,7- and 10,11-diols and a more polar fraction containing the 2,3-diol.
4. The ratios were determined by ^{1}H-NMR, GLC (cyclic carbonates, 100% methylsilicon, J&W DB-1, (30 m x 0.32 mm I.D.), 255 °C) and isolated yields.
5. The ee's were determined by direct injection of the diol on a Chiralcel OD HPLC column using 1.0 % iPrOH in hexane, and a 0.5 mL/min. flow rate. The UV detector was set at 230 nm. Neither the % ee nor the absolute configuration was determined for the 6,7- and 10,11- diols, however, they are both likely to have the *R,R*- configurations indicated in the above scheme.
6. Boar, R.B., Damps, K., *J. Chem. Soc. Perkin I*, **1977**, 709.
7. van Tamalen, E.E., Curphey, T.J., *Tetrahedron Lett.*, **1962**, 121.
8. van Tamalen, E.E., Sharpless, K.B., *Tetrahedron Lett.*, **1967**, 2655.

(Received in USA 15 April 1992)