# THE OXIDATION OF α-FARNESENE

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## ABSTRACT

Autoxidation products of the sesquiterpene α-farnesene **1** increase rapidly in apples during cold storage and are believed to play an important role in the production of the cold storage disorder, superficial scald. The site selectivity of the oxidation of α-farnesene was investigated with a variety of useful reagents for photochemical allylic oxidation, hydroxylation and epoxidation. Oxidation products **33-47** were isolated and characterised.

The synthesis of conjugated trienes and related oxidation products of α-farnesene **1**, principally from the epoxides of α-farnesene, is described. Base-promoted ring opening of 6,7-epoxide **44** by the mixed base potassium *tert*-butoxide / lithium disopropylamide afforded the conjugated triene **3** whilst the 3,4-epoxide **45** afforded triene **50**. In contrast, 10,11-epoxide **43** failed to undergo epoxide ring opening; rearranging instead to the conjugated triene epoxide **51**. Base-promoted ring opening of *bis*-epoxide **46** afforded trienol epoxide **56** at -30°C, whilst cyclisation to tetrahydrofurans **55a** and **55b** occurred at room temperature. Photosensitised oxidation of 10,11-epoxide **43** followed by *in situ* treatment with acid gave the cyclic peroxide **4** and upon reduction, tetrahydrofurans **55a** and **55b**. Bisallylic alcohol **61** was prepared by alkylation of 3-methylsulpholene **29** with geranial **59** followed by thermolysis. Trienes **3** and **4** have been isolated previously as autoxidation products of α-farnesene **1** and are implicated as the causal agents of the superficial scald of stored apples.

The asymmetric dihydroxylation of α-farnesene **1** using the Sharpless ligands $(DHQ)_2$-PHAL and $(DHQD)_2$-PHAL was investigated. The isolation and characterisation of the 3,4-, 6,7- and 10,11-diols **41, 42** and **114** as well as the tetraol **115** is described. High enantioselectivity and preferential addition to the 6,7-olefin was observed. The isomeric β-farnesene **2** showed a preference for reaction at the 10,11-position.

The enantioselective synthesis of an apple aroma constituent, bicyclic acetal **17**, is described. Asymmetric dihydroxylation of 6-methylhept-5-en-2-one **15** was carried out using the ligands $(DHQ)_2$-PHAL and $(DHQD)_2$-PHAL according to the method of Sharpless. Acid-catalysed cyclisation then afforded the required acetal **17** in high enantiomeric excess. Enantiomeric excesses were measured using chiral solvating agent **113** and/or synthesis of the corresponding Mosher ester derivatives, followed by $^1H$ or $^{19}F$ nmr.

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# ABBREVIATIONS

AD = asymmetric dihydroxylation
AD-mix-α = asymmetric dihydroxylation mixture containing 1,4-*bis*-(9-*O*-dihydroquininyl)phthalazine
AD-mix-β = asymmetric dihydroxylation mixture containing 1,4-*bis*-(9-*O*-dihydroquinidinyl)phthalazine
BHT = butylated hydroxytoluene
*t*-BuOK = potassium *tert*-butoxide
cat. = catalytic
COSY = correlated spectroscopy
DATMP = diethylaluminium 2,2,6,6-tetramethylpiperidide
DEPT = distortionless enhancement by polarisation transfer
DHQ = dihydroquinine
DHQD = dihydroquinidine
DHQD-IND = (9-*O*-indolinylcarbamoyl)dihydroquinindine
(DHQ)$_2$-PHAL = 1,4-*bis*-(9-*O*-dihydroquininyl)phthalazine
(DHQD)$_2$-PHAL = 1,4-*bis*-(9-*O*-dihydroquinidinyl)phthalazine
(DHQ)$_2$-PYR = *bis*-dihydroquinine pyrimidine
(DHQD)$_2$-PYR = *bis*-dihydroquinidine pyrimidine
DMAP = 4-dimethylaminopyridine
DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DPA = diphenylamine
ee = enantiomeric excess
equiv. = equivalent
ethoxyquin = 6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline
GC = gas chromatography
GC/MS = gas chromatography - mass spectroscopy
HETCOR = heteronuclear correlation spectroscopy
HPLC = high pressure liquid chromatography
IR = infra red
LDA = lithium diisopropylamide
*m*-CPBA = *meta*-chloroperbenzoic acid
MEQ = 9-*O*-(4'-methyl-2'-quinidyl)
NBS = *N*-bromosuccinimide
n.O.e. = nuclear Overhauser enhancement
NMO = *N*-methylmorpholine-*N*-oxide
nmr = nuclear magnetic resonance
NOESY = nuclear Overhauser enhancement spectroscopy

*p*-TSA = *para*-toluenesulphonic acid
PCB = *para*-chlorobenzoate
PHN = 9-*O*-(9'-phenanthryl)
RT = room temperature
*R*-(-)-TFAE = *R*-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol
THF = tetrahydrofuran
tlc = thin layer chromatography
TMEDA = tetramethylethylenediamine
TMS = tetramethylsilane
UV = ultraviolet
$VO(acac)_2$ = vanadium oxide acetylacetonate