

*Towards the Synthesis of the Monoterpene
Furanoid Oxides via the Ozonolysis of
Bicyclic Bridged 1,2-Dioxines*

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requirements for the degree of*

Doctor of Philosophy

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Abstract

1,2-Dioxines, also known as endoperoxides are a specific type of cyclic peroxide, characterised by an unsaturated six-membered peroxide ring. They are abundant in nature and have been isolated from many natural products and have been shown to exhibit a wide spectrum of biological roles. Ozonolysis is a well established method for the oxidative cleavage of alkenes, although examples involving 1,2-dioxines are extremely rare.

The furanoid and anhydrofuran linalool oxides have been established as common compounds in wine and as natural products from other sources. Previous methods of synthesis have followed a variety of different routes although many experimental details are unclear and of limited value. It was therefore felt that a gap exists in the literature with regard to an effective synthesis for these compounds and the development of a new synthetic pathway to afford both compounds, and analogues thereof, from a common starting material would be of value.

The aim of this project was therefore to combine these areas and utilise 1,2-dioxine chemistry for the synthesis of the furanoid and anhydrofuran linalool oxides, with a key step in the synthesis being the ozonolysis of a bicyclic bridged 1,2-dioxine to yield the necessary keto-aldehyde precursor.

Since little attention has been focussed on exploring the ozonolysis reaction of bicyclic alkenes, particularly the alkene moiety of bicyclic 1,2-dioxines, the first part of this thesis is focussed on investigating the scope of this novel reaction. A range of 1,4-disubstituted bicyclic 1,2-dioxines and a steroidal 1,2-dioxine were used for this study, with their synthesis outlined in Chapter 2. Chapter 3 presents the results for this section of work, where it was found that upon reaction with ozone, the nature of substrates at the bridgehead positions of the 1,2-dioxines had a major influence on the outcome of the reaction; with some of the substrates giving the expected dialdehydes, whilst others behaved in an unexpected manner towards ozone. Additional experiments were then conducted to provide further insight into these unusual results. The potential mechanism

involved in these rearrangements is also discussed, with several plausible options presented.

Chapter 4 presents some *Ab-Initio* computational analyses to support the preliminary mechanistic insights into the ozonolysis reaction, with specific regard to bicyclic 1,2-dioxine systems. This was done by examining the relative energy differences for all possible isomers involved in each stage of the proposed mechanism in order to locate the lowest energy pathway, and therefore that which is most likely followed.

The second part of this thesis, presented in Chapter 5, was to utilise this novel transformation as a key step in the synthesis of both the furanoid and anhydrofuran linalool oxides, from a common starting material. The pathway began with the synthesis of a new bicyclic 1,2-dioxine, followed by successful ozonolysis and ring-contraction into the core 2,2,5-trisubstituted THF. It was found that having a hydroxyl α to either the furan or dioxine ring systems could be problematic and led to unwanted ring-opening and further rearrangements. Investigations revealed that this could be overcome upon protection of the hydroxyl, thereby enabling structural manipulation of the other functional groups to proceed smoothly.

Research along the synthetic pathway did reveal a new potential route to dioxabicyclo[3.2.1]octanes, with two new bicyclic compounds formed as a result of selective 1,6-cyclisation of a *cis*- γ -hydroxydione intermediate, a reaction previously unseen within the literature.

Time was a limiting factor in being able to complete the total synthesis of the desired compounds, but the major ground work was achieved. The C₂ functionalisation of the THF ring was successfully completed, and some new and novel chemistry was uncovered, which has further enhanced the understanding of the chemical nature of these types of compounds, along with their potential use in the synthesis of these important wine aroma compounds and other natural products.

Declaration

This thesis contains no material that has been accepted for the award of any other degree or diploma in any university or other tertiary institution. To the best of my knowledge it contains no material published or written by any other person, except where due reference has been made.

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Nicole Marie Cain

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Abbreviations

Å	angstroms
Ac	acetyl
AIBN	2,2-azobisisobutyronitrile
apt	apparent
ASTM	American Society for Testing and Materials
Bn	benzyl
br	broad
<i>c</i>	concentration
<i>ca</i>	approximately
COSY	correlation spectroscopy
d	doublet
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
Δ	heat
DMAP	4- <i>N,N</i> -dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
dmgH ₂	dimethylglyoxime
<i>ds</i>	diastereoselectivity
E _a	activation energy
<i>ee</i>	enantiomeric excess
E _h	Hartree
equiv	equivalent(s)
ESI	electrospray ionisation
Et	ethyl
FTMS	fourier transform mass spectroscopy
GC	gas chromatography
GO-O	gas chromatography-olfactometry
HF	Hartree-Fock
HMBC	heteronuclear Multiple Bond coherence
HMQC	heteronuclear Multiple Quantum Coherence

HRMS	high resolution mass spectroscopy
hrs	hours
<i>hν</i>	light
Hz	hertz
<i>i</i> -Pr	<i>iso</i> -propyl
IR	infra red
J	coupling constant
KJ	kilojoules
lit	literature
LPM	litres per minute
LSIMS	liquid secondary ion mass spectrometry
m	multiplet
M	moles per litre
<i>m/z</i>	mass to charge ratio
<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
Me	methyl
Me ₂ S	dimethyl sulfide
MHz	mega-hertz
min	minutes
MIRC	Michael Initiated Ring Closure
mol	mole(s)
mp	melting point
nm	nanometers
NMR	nuclear magnetic resonance
nOe	nuclear overhauser effect
Ph	phenyl
ppm	parts per million
PTSA	<i>p</i> -toluenesulfonic acid
q	quartet
quin	quintet
R _f	retention factor
ROESY	rotational overhauser effect spectroscopy

sept	septet
t	triplet
TBHP	<i>t</i> -butyl hydroperoxide
TCNE	tetracyanoethylene
tert	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethyl silane