Synthesis and Chemistry of 2,3-dioxabicyclo[2.2.2]octane-5,6-diols

A thesis submitted towards the Degree of
Doctor of Philosophy

by

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Abstract

Compounds containing the 2,3-dioxabicyclo[2.n.n] moiety, otherwise known as bicyclic endoperoxides, are a class of cyclic peroxides that are readily found in nature and can be utilized as important synthetic building blocks. The chemistry of endoperoxides has chiefly been concerned with the relative weakness of the peroxide bond, with comparatively little attention directed towards transformations of the alkene unit within these compounds. Therefore the focus of this thesis is on dihydroxylation of bicyclic endoperoxides and examination of their further utility.

A broad range of 1,4-disubstituted-2,3-dioxabicyclo[2.2.2]oct-5-enes were synthesized featuring a variety of alkyl and aryl substituents. These compounds were subsequently dihydroxylated with osmium tetroxide to yield diols *anti* to the peroxide linkage, as single diastereomers, in excellent yields.

Reduction of the peroxide bond afforded cyclohexane-1,2,3,4-tetraols of toxocarol relative stereochemistry in excellent yield; this configuration of hydroxyl groups is quite prevalent in nature. In order to demonstrate the synthetic scope of dihydroxylation of bicyclic endoperoxides followed by reduction of the peroxide linkage, tetraol formation from alkyl and aryl substituted diols was examined**.** It was confirmed that both alkyl and aryl substituents can be tolerated in the 1,4-positions.

Dihydroxylation of endoperoxides containing H atoms at the 1,4-positions was also documented. The methodology of dihydroxylation followed by reduction of the peroxide linkage was employed to synthesize the reported natural product

(1*S*,2*R*,3*S*,4*R*,5*R*)-2-methyl-5-(propan-2-yl)cyclohexane-1,2,3,4-tetrol in a short sequence from (*R*)-α-phellandrene.

The 2,3-dioxabicyclo[2.2.2]octane-5,6-diols discussed above were also found to undergo an extremely clean rearrangement to yield 1,4-dicarbonyls and glycoaldehyde, a rearrangement not reported in the literature. The possible mechanism of this rearrangement was probed and is discussed in detail. The repercussions of diol orientation to product outcome were also investigated.

Finally, the possibility of expanding the scope of synthetic application for this rearrangement, particularly the potential for synthesis of optically pure 1,4-dicarbonyls is discussed. Some preliminary results are reported.

Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any other university or other tertiary institution and, to the best of my knowledge and belief, this thesis contains no material previously published or written by any other person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University library, being available for loan or photocopying.

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Peter Valente

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Date

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I would firstly like to sincerely thank “The Boss” Dennis for not only giving me the opportunity and freedom to pursue my research but for making it fun at the same time. His keen intellect coupled with a relaxed attitude has been an inspiration for me.

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Last and definitely not least, thanks to my wonderful family. To Mum and Dad, this entire process would have been impossible without your selfless love and support of me and the boys. I will be forever grateful. To my great lads Vin and Cam, thanks for putting up with your grumpy Dad and for accepting a small amount of financial hardship during this time. I am proud of you both and love you very much.

To the 15%: You know who you are!!

Abbreviations

Anal. Calc.	analysis calculated
Ar	aromatic
Bn	benzyl
Bu	butyl
t-Bu	*tert*-butyl
d	day(s)
Δ	heat
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
de	diastereomeric excess
DMSO	dimethylsulphoxide
ee	enantiomeric excess
equiv.	equivalent(s)
Et	ethyl
EW	electron withdrawing group
GC	gas chromatography
gCOSY	gradient correlated spectroscopy
gHMBC	gradient heteronuclear multiple bond connectivity
gHMQC	gradient heteronuclear multiple quantum coherence
gHSQC	gradient heteronuclear single quantum coherence
h	hour(s)
HPLC	high-performance liquid chromatography
hv	irradiation
IR	infra red
L	ligand
LAH	lithium aluminium hydride
LG	leaving group
M	moles per litre
m-CPBA	*meta*-chloroperbenzoic acid
m/z	mass to charge ratio
Me	methyl
MHz	megahertz

mol	mole(s)
mp	melting point
MW	microwave
NMR	nuclear magnetic resonance
p-TSA	*para*-toluene sulphonic acid
Ph	phenyl
ppm	parts per million
i-Pr	isopropyl
rds	rate determining step
R_f	retention factor
ROESY	rotating frame overhauser enhancement spectroscopy
rt	room temperature
S_N2	bimolecular nucleophilic substitution
TBDMS	*tert*-butyldimethylsilyl
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl, tetramethylsilane
TPP	triphenyl phosphine
TPPO	triphenyl phosphine oxide
UV	ultra violet

For Lou

28/08/1972 – 5/061999

Chapter 1: Introduction

1.1 Natural Products

Natural products containing the 2,3-dioxabicyclo[2.n.n]- or bicyclic endoperoxide moiety **1** constitute important biological mediators in various biochemical processes.[1] The discovery of ascaridole in 1908 as the principle constituent of *Chenopodium* oil and its characterisation in 1924 as the endoperoxide structure **2** marks the beginning of the interesting area of biologically relevant peroxides.[2]

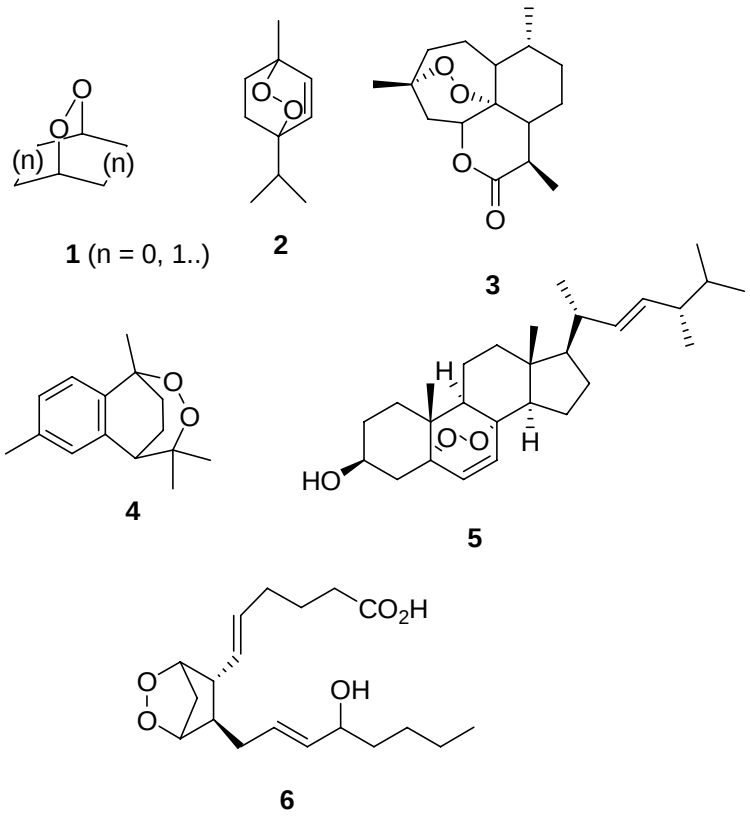


Figure 1. The bicyclic endoperoxide moity **1** and some naturally occurring bicyclic endoperoxides (**2-6**).

Artemisinin (**3**), a sesquiterpene lactone isolated from *Artemisia annua L.*, is of major importance as a frontline treatment for malaria, particularly as it is active against chloroquine-resistant strains of *Plasmodium falciparum.*[3-8] Structure/function relationship studies have shown that the peroxide linkage is essential for its activity. [9]

Another anti-malarial bicyclic endoperoxide, 10,12-peroxycalamenene (**4**), has been isolated from the dried tubers of *Cyperus rotundus*, a common weed native to Africa and southern Asia. [10]

Ergosterol endoperoxide (**5**) was first isolated in 1947 from the fungus *Aspergillus fumigatus.*[11] It is a natural steroid that has since been found in a variety of fungi, yeast, lichens and sponges.[12-14] A number of biological activities have been attributed to this compound. For example, it was found to display anti-tumor activity against carcinosarcoma and breast cancer cell lines,[14] antiviral action against the influenza virus,[15] as well as immunosuppressive activity. [16]

Prostaglandin Endoperoxides (PGEs) are chemically sensitive intermediates in the transformation of essential fatty acids into a large array of biomolecules.[17] The labile endoperoxide **6** serves as a precursor to the pharmacologically potent hormonal agents PGE (**7**), PGF (**8**), thromboxane (**9**), and prostacyclin (**10**), Figure 2. [18]

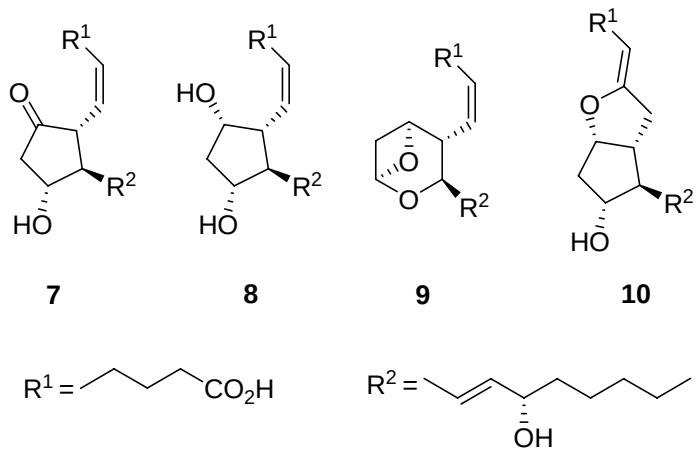
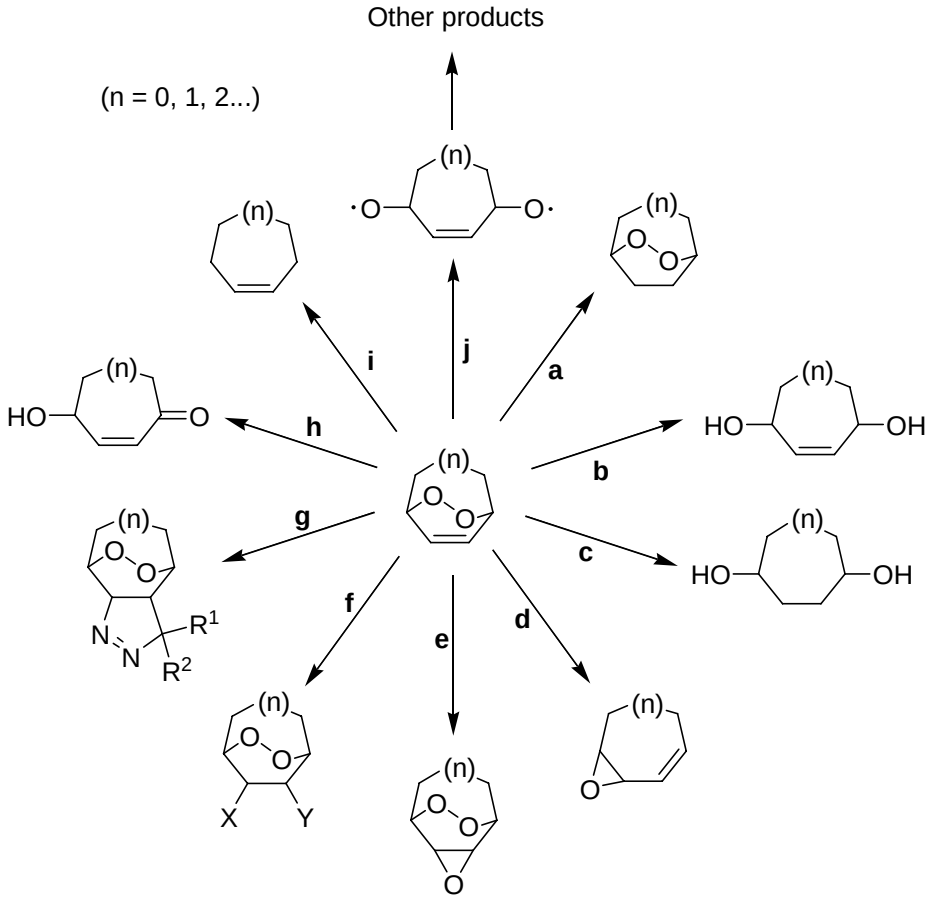


Figure 2. Hormones derived from prostaglandin endoperoxide.

1.2 Reactions of bicyclic endoperoxides

Unsaturated bicyclic endoperoxides are readily available by reaction of singlet oxygen with conjugated cyclic dienes.[19] This photolytic cycloaddition reaction will be discussed in Chapter 2. Such endoperoxides have proven extremely useful in synthesis, due to their ready conversion to a wide range of stereospecifically oxygenated compounds.[20] The chemistry of unsaturated bicyclic endoperoxides pertains to the manipulation of the alkene portion, the peroxide bond or both. A summary of the types of transformations that have been achieved is shown in Scheme 1.

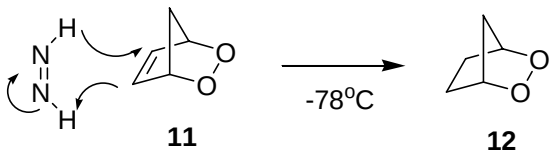
Scheme 1.



1.1.1 Reduction of bicyclic endoperoxides

The pathways **a-d** shown in Scheme 1 represent reductions of bicyclic endoperoxides that can be performed under various conditions. Pathway **a** utilizes diimide to bring about the selective reduction of a carbon-carbon π bond whilst leaving the sensitive and readily reduced peroxide linkage intact. Salomon[17] used this procedure to be the first to synthesise fully characterised derivatives of 2,3-dioxabicyclo[2.2.1]heptane (**12**) Scheme 2, which corresponds to the strained bicyclic core of prostaglandin endoperoxides **3**.

Scheme 2.

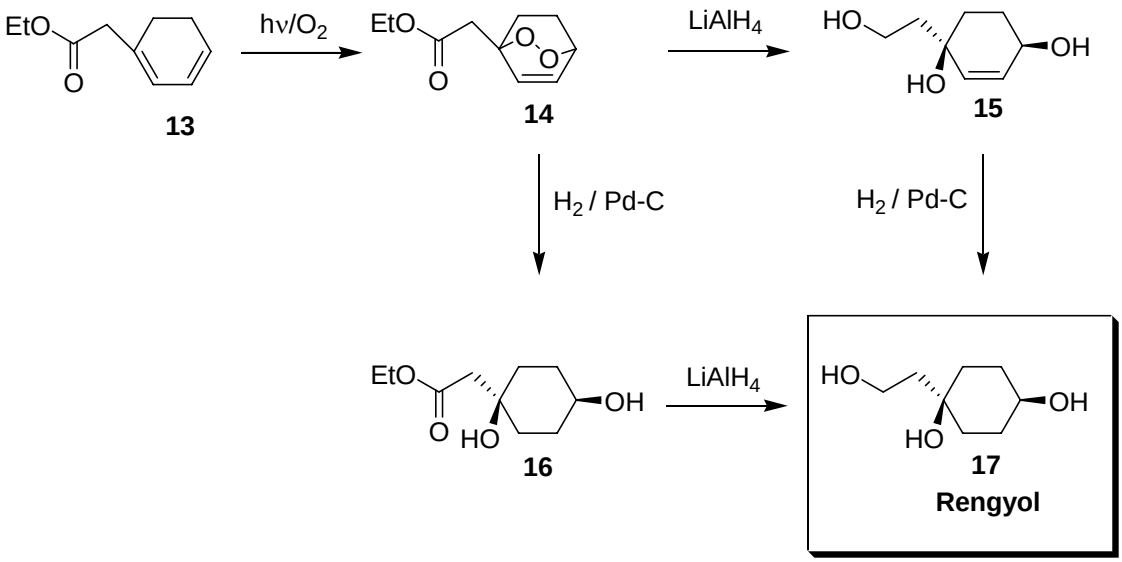


11 **12**

The peroxide linkage can be selectively reduced (pathway **b**) by a number of reagents. There are several methods in the literature, including $LiAlH_4$,[21] Zn/AcOH,[22] Mg/MeOH[23] and thiourea,[24] of which the last has become a popular choice for the mild reduction of bicyclic endoperoxides. This reaction provides convenient and efficient access to diols of the *syn* configuration, which are not readily attainable by other methods.

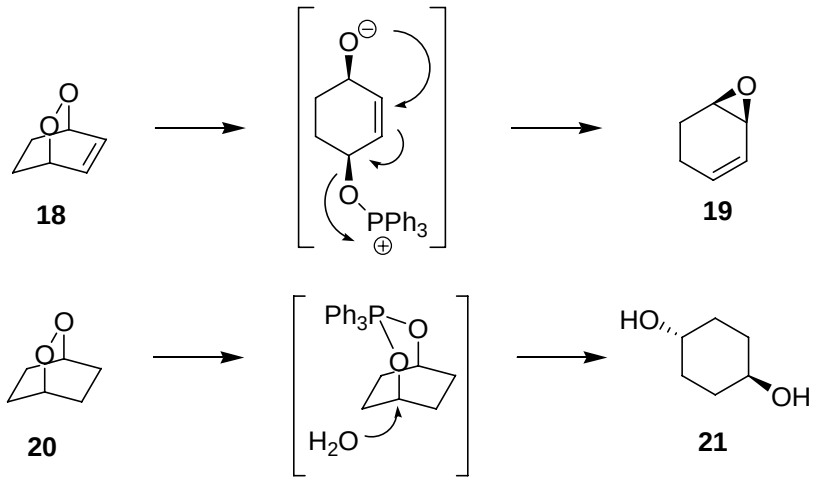
Catalytic hydrogenation with metal catalysts (pathway **c**) usually leads to reduction of both the double bond and the peroxide linkage. An example where both routes have been utilised in the synthesis of a natural product is in the preparation of Rengyol (**17**), from the bicyclic endoperoxide **14**, (Scheme 3).[25]

Scheme 3.



The reaction of trivalent phosphorus compounds with bicyclic endoperoxides also leads to reduction of the peroxide bond, (pathway **d**). Bicyclic endoperoxides containing a double bond such as **18**, (Scheme 4) are reduced by trivalent phosphorus compounds to yield allylic epoxides **19**.[26] Fully saturated bicyclic endoperoxides **20** give *anti* 1,4-diols **21** by hydrolysis of the phosphorus containing intermediates.[27] Both of these processes occur because of the inability of the intermediate ionic species to undergo intramolecular nucleophilic displacement directly at the C-O-$P^{+}Ph_3$ because the constrained cyclic system prevents rotation.[28]

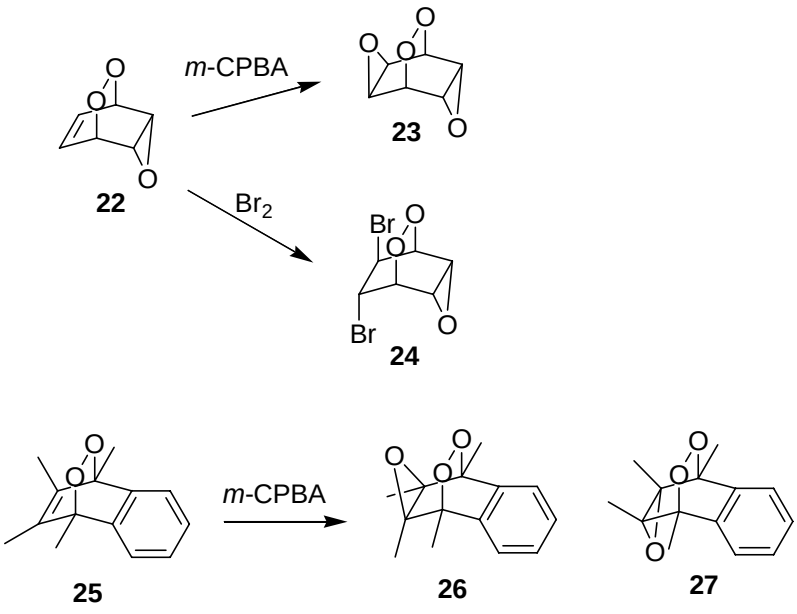
Scheme 4.



1.2.2 Additions to the double bond of bicyclic endoperoxides

Pathways **e** and **f** are reactions of electrophillic addition to the double bond. Previous work in the Taylor group[29] on monocyclic endoperoxides has shown that epoxidation, halogenation, dihydroxylation and halohydrin formation are simple reactions that can be effected at the double bond. Given the relative ease of cleavage of the peroxide linkage it is not surprising that there are very few examples in the literature of addition to the double bond in bicyclic endoperoxides. Berchtold,[30] however, showed that the double bond in oxepin endoperoxide (**22**), (Scheme 5) could be converted to the epoxide **23** by reaction with *m*-chloroperbenzoic acid, and the dibromide **24** by reaction with bromine in chloroform. Using similar methodology Hart et al.[31] reported the epoxidation of endoperoxide **25** to give two isomeric epoxy endoperoxides in a 9:1 ratio, with the *syn* isomer as the major component.

Scheme 5.



The fact that the predominant product was the *syn* isomer (corresponding to *exo* addition) was rationalised in two ways. It is known that the direction of epoxidation can be controlled by coordination of the oxidising agent with an oxygen atom present in the substrate,[32] in this case the peroxide linkage. Alternatively a steric factor may be involved. It has been well documented that most reagents attack bicyclic [2.2.1] systems from the *exo* face thus avoiding the crowded *endo* face, Figure 3.[33] In fact the outcome is most likely a combination of these two effects.

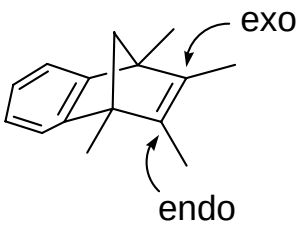


Figure 3.

A final interesting transformation that can be achieved on the double bond of bicyclic endoperoxides is when it acts as a dipolarophile in 1,3-dipolar cycloadditions (pathway **g**, Scheme 1). It is well known that bicyclo[2.2.1] oct-2-ene (**28**) (Figure 4) is reluctant to undergo cycloaddition with 1,3-dipoles, in particular diazoalkanes .[34]

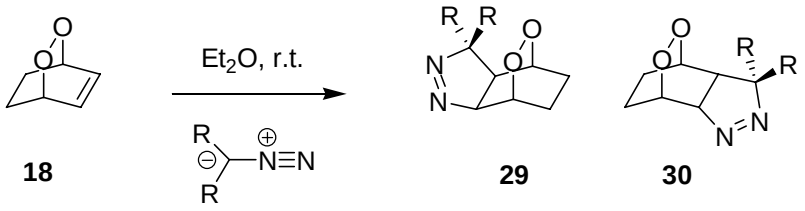
28

Figure 4. Bicyclo[2.2.1]oct-2-ene

However, the presence of the two oxygen atoms comprising the peroxide bond highly enhances the reactivity of **18** towards diazoalkanes, presumably due to an electron-withdrawing effect. High yields of *syn/anti* mixtures were isolated in the reaction of **18**

with excess diazomethane and 2-diazopropane (Scheme 6).[35] The *syn* adduct is the major component of both reactions with the increase in selectivity due to the increased steric effect of the methyl groups.

Scheme 6.

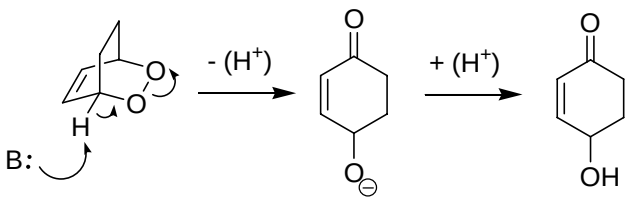


		syn %	*anti* %
a: R = H	4d, 82%	91	9
b: R = Me	6h, 72%	97.5	2.5

1.2.3 Base catalysed rearrangements of bicyclic endoperoxides

Bicyclic endoperoxides which contain hydrogen atoms α to the peroxide linkage can undergo base catalysed rearrangement to form 4-hydroxyenones **31**, Scheme 7. Kornblum and DeLaMare showed the first decomposition of dialkyl peroxides by base catalysed rearrangement in 1951.[36] The mechanism is shown for bicyclic endoperoxides in Scheme 7. The transformation occurs through initial deprotonation of an α hydrogen atom followed by cleavage of the peroxide bond in an elimination type mechanism to ultimately generate the ketone and hydroxyl moieties.

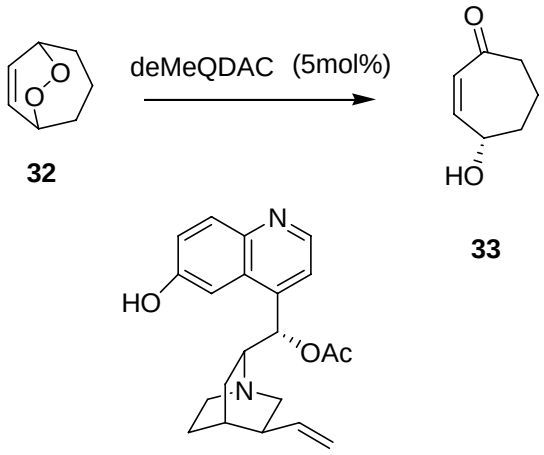
Scheme 7.



18 **31**

The first enantioselective Kornblum-DeLaMare rearrangement based on the desymmetrization of meso-endoperoxides by chiral base catalysis has been developed by Staben et al.[37] This process can be exemplified by the reaction of **32,** (Scheme 8), with 5 mol % of the chiral base deMeQDAc (**34**) to give *γ*-hydroxyenone **33** in 90% yield with an ee of 92%.

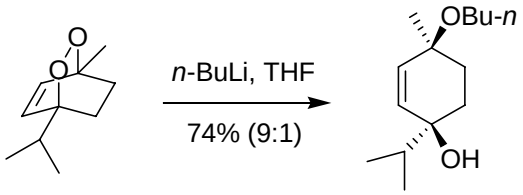
Scheme 8.



32 **33** **34**

Bicyclic endoperoxides can also react with strong bases, such as alkyllithiums and Grignard reagents, via direct attack of the peroxide bond to give hydroxy ethers.[38] For example, treatment of ascaradole (**2**) with *n*-butyllithium afforded a 74% yield of a 9:1 mixture of regiomeric hydroxyl ethers, with **35** corresponding to the major product (Scheme 9).

Scheme 9.

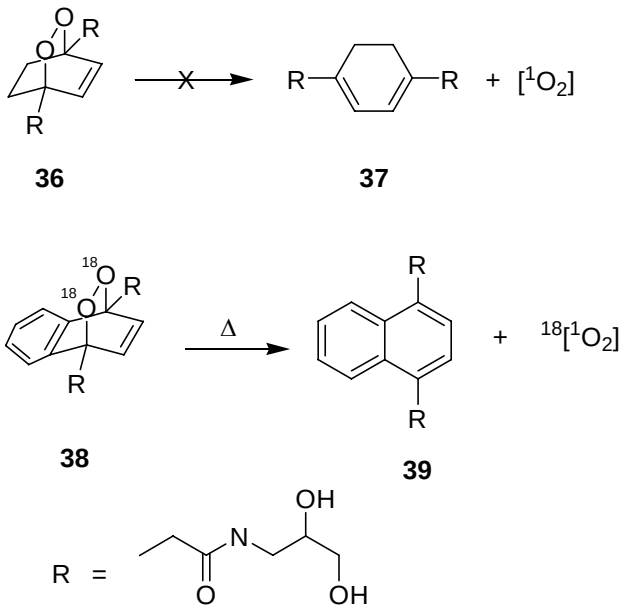


2 **35**

1.2.4. Retro Diels-Alder (RDA) reaction of bicyclic endoperoxides

Pathway **i** (Scheme 1) represents the loss of molecular oxygen in a retro Diels-Alder (RDA) process. Whilst there are many RDA reaction classes including the all carbon based RDA's, only one common RDA reaction involving bicyclic endoperoxides exists.[39] The loss of singlet oxygen ($^1O_2$) from aromatic compounds has been commonly observed and is driven primarily by the favourable energetics of re-aromatisation coupled with the gain in entropy.[40] The RDA reactions of non-highly unsaturated bicyclic endoperoxides **36** to afford 1,3-butadienes **37** are presently not observed, and is primarily a result of the fact that re-aromatisation is not involved (Scheme 10).

Scheme 10.



Martinez has utilised this process to generate a chemical source of isotopically labelled singlet oxygen $^{18}[^1O_2]$ from the bicyclic napthalene endoperoxide **38** (Scheme 10).[41] Aqueous sources of singlet oxygen are required in order to study the reactivity of $^1O_2$ towards biomolecules. For example, reactions of $^1O_2$ with fatty acids, proteins and DNA can induce various types of cell damage that are related to ageing, cancer and other cytotoxic effects.[42]

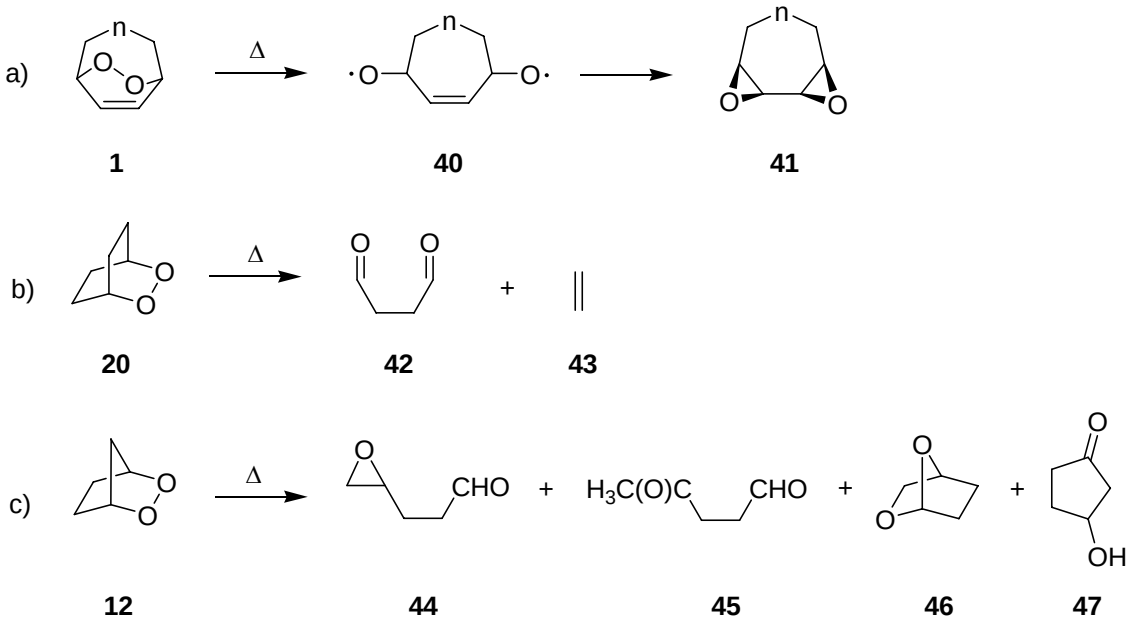
1.2.5 Thermal, photochemical and metal-catalysed rearrangement of bicyclic Endoperoxides

The thermal,[43, 44] photochemical[45, 46] and metal-catalysed[47-50] rearrangement of bicyclic endoperoxides has been extensively studied. All of these processes can be thought of as occurring through initial homolysis of the peroxide bond to afford the dialkoxy radical, as depicted in pathway **j**, Scheme 1. The diradical species thus formed can rearrange to a number of different products depending on the nature of any substituents or whether the endoperoxide is saturated or unsaturated. Each class of reaction will be discussed below.

Thermolysis

Unsaturated bicyclic endoperoxides **1** have been used to synthesise *bis*-epoxides **41** with the *syn* configuration, by thermal rearrangement (Scheme 11).[51] The reaction proceeds by the homolytic cleavage of the weak peroxide bond to give the diradical species **40** followed by addition of the alkoxy radicals to the adjacent double bond.

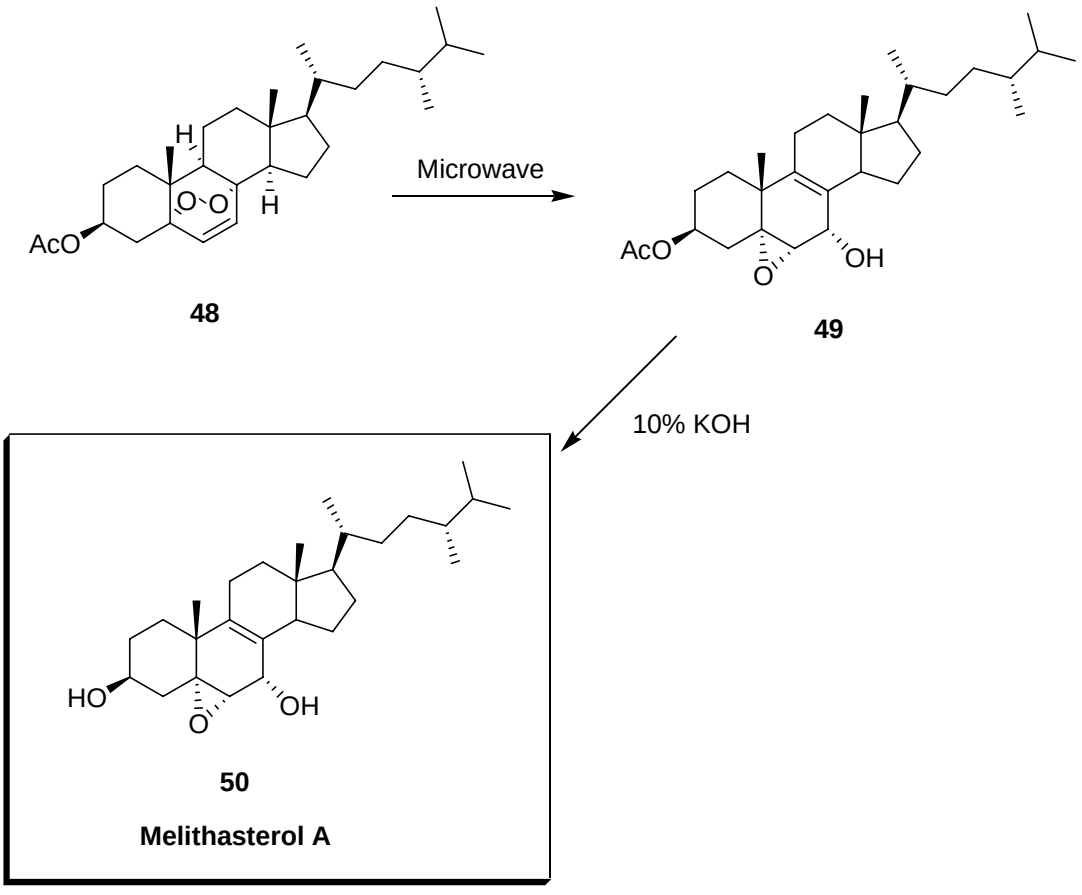
Scheme 11.



When we look at the thermolysis of a saturated [2.2.2] system **20** Scheme 10,[44] we note that the *bis*-epoxide is not formed. The absence of a double bond precludes the oxygen-centred radicals from cyclising. Instead, homolysis of the oxygen-oxygen bond is followed by a double β-scission of the adjacent C-C bonds to furnish the dialdehyde **42** and ethylene (**43**). On the other hand, for strained systems like the bicyclo [2.2.1] system **12** the thermolysis is always accompanied by side reactions.[52] All of the products formed can be rationalised through various radical processes.

Ramesh et al.[53] have utilised the thermal rearrangement of a bicyclic endoperoxide to synthesise the natural product Melithasterol A (**50**), (Scheme12).

Scheme 12.



48

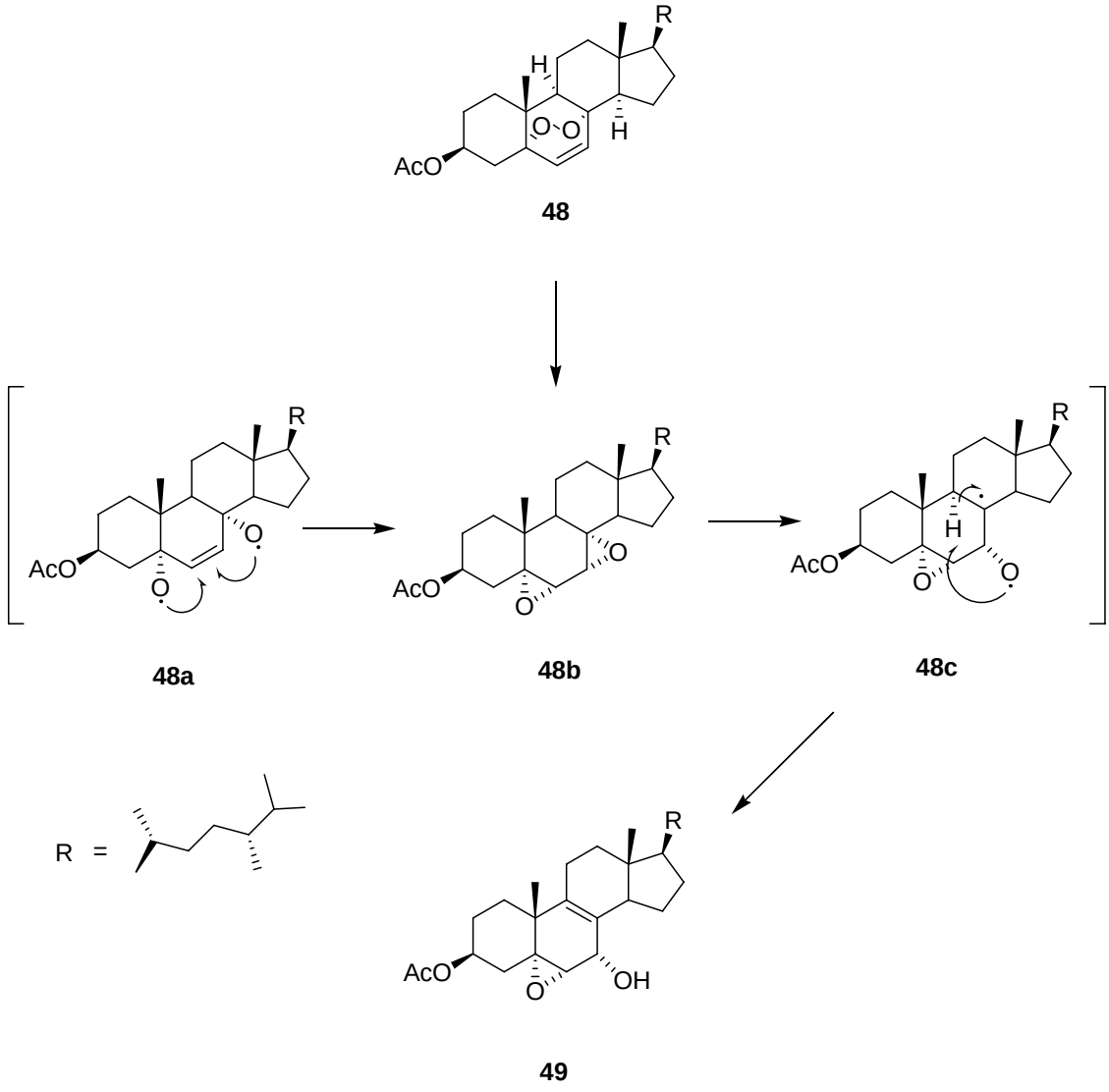
49

50

Melithasterol A

Steroid endoperoxide **48** was irradiated under microwave radiation to furnish compound **49** in 80% yield. Subsequent hydrolysis of the acetyl group with 10% KOH gave the desired product **50**. A tentative mechanism was proposed to explain the formation of **49,** (Scheme 13), the key step in the process.

Scheme 13.



Homolytic rupture of the peroxide bridge **48a** is followed by formation of two oxirane rings between C-5 and C6, C-7 and C-8 **48b**. Further, the oxirane ring between C-7 and C-8 opens to afford the oxygen radical at C-7 **48c**, which would abstract H_{α}-9 involving a five-centred cyclic transition state in which C-7, C-8, C-9, the oxygen radical at C-7, and the hydrogen atom at C-9 participate in a concerted process to give the product **49.**

Photolysis

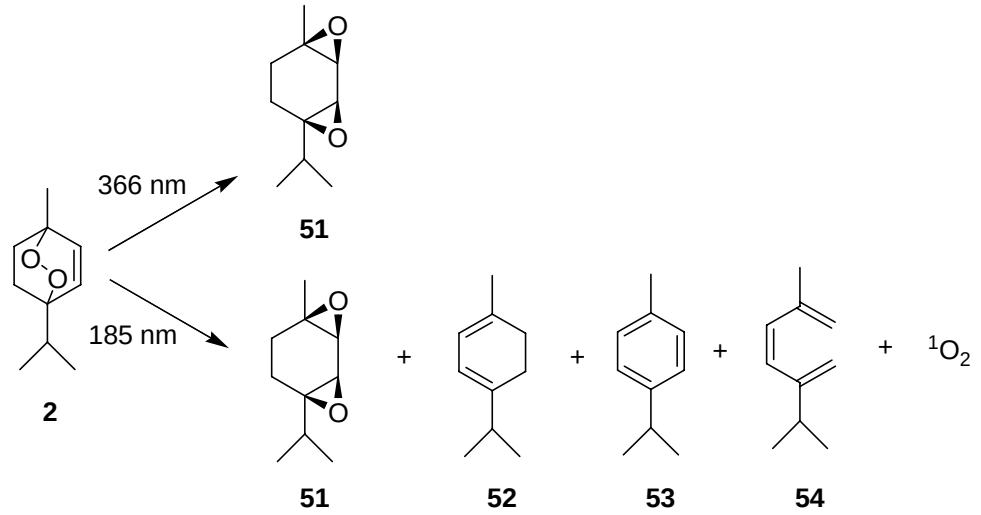
There is relatively little information in the literature regarding the photolysis of bicyclic endoperoxides. Some comparisons can be made with the properties of simple dialkyl and diaryl peroxides. In the first absorption region of the alkyl and aryl peroxides (> 250 nm) the primary photo-dissociation process proceeds with rupture of the weak peroxide bond. At wavelengths below 250 nm a second dissociative mode appears which involves cleavage of the C-O bond (Scheme 14).[54]

Scheme 14.

Therefore, when irradiated with wavelengths greater than 250 nm we would expect bicyclic endoperoxides to give products resulting from the homolysis of the O-O bond to give oxygen-centred radicals. Irradiation with wavelengths less than 250 nm should cause extrusion of molecular oxygen, and the production of carbon-centred radicals.

Indeed, in a study of the photolysis of ascaridole (**2**) at 366 nm (Scheme 15)[45] it was found that the only product was the *bis*-epoxide **51**, which was the expected product formed from cleavage of the O-O bond. This result was consistent with the chemistry of simple alkyl peroxides at wavelengths > 250 nm.

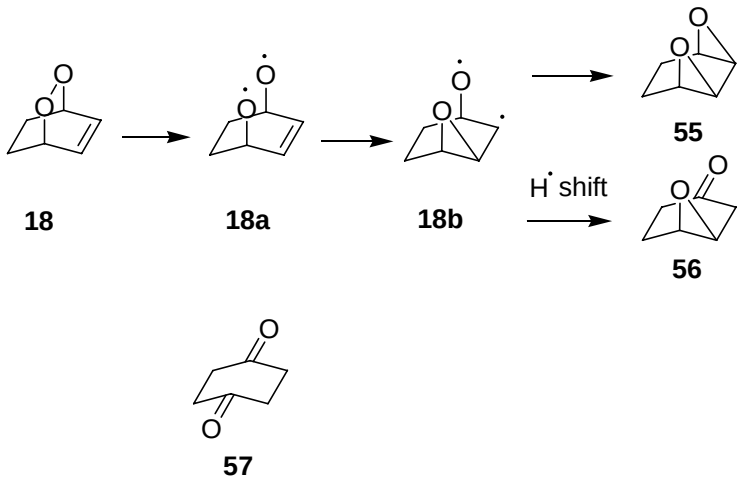
Scheme 15.



Photolysis of ascaridole at 185 nm gave a more complex mixture of products, which included those due to the loss of O_2 and oxidation products (Scheme 15). These facts suggest that at shorter wavelengths the photolysis of ascaridole leads not only to the *bis*-epoxide but also to loss of molecular oxygen. This process appears to be a retro-Diels-Alder reaction (see Chap.1.2.4) but is in fact homolytic in nature.

In another report[55] it was found that photolysis of **18** produces the *bis*-epoxide **55** as well as epoxyketone **56**. A possible mechanism for the reaction is shown in Scheme 16.

Scheme 16.

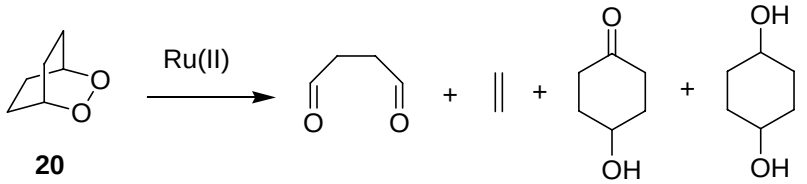


Ring closure of the initially formed biradical **18a** gives the *bis*-epoxide **55**. (The *bis*-epoxide is the same as that formed in the thermal rearrangement, suggesting a similar mechanism). This ring closure is in direct competition with the [1-2]-hydrogen shift required to yield epoxyketone **56**. Since no cyclohexane-1,4-dione (**57**) is formed from **18**, it appears that the first ring closure is rapid, to furnish 1,3-biradical **18b**, and the epoxide ring closures occur sequentially rather than simultaneously.

Metal catalysed rearrangement

The reaction of transition metal complexes with bicyclic endoperoxides has received considerable interest due to their utility as model systems for biosynthetic pathways. In particular, the Fe(II)-induced decomposition has been investigated extensively[50, 56-58] as a model reaction for the bioconversion of the prostaglandin endoperoxides **3** (Figure 1), and to clarify potent antimalarial intermediates in the metabolism of Artemisinin (**4**), (Figure 1). Other metals that have been studied include Co(II),[47] Ru(II)[59], Pd(0),[49] and Os(II).[48] As an example, the reaction of the bicyclic endoperoxide **20** under Ru(II) catalysis is given in Scheme 17.[48, 59]

Scheme 17.

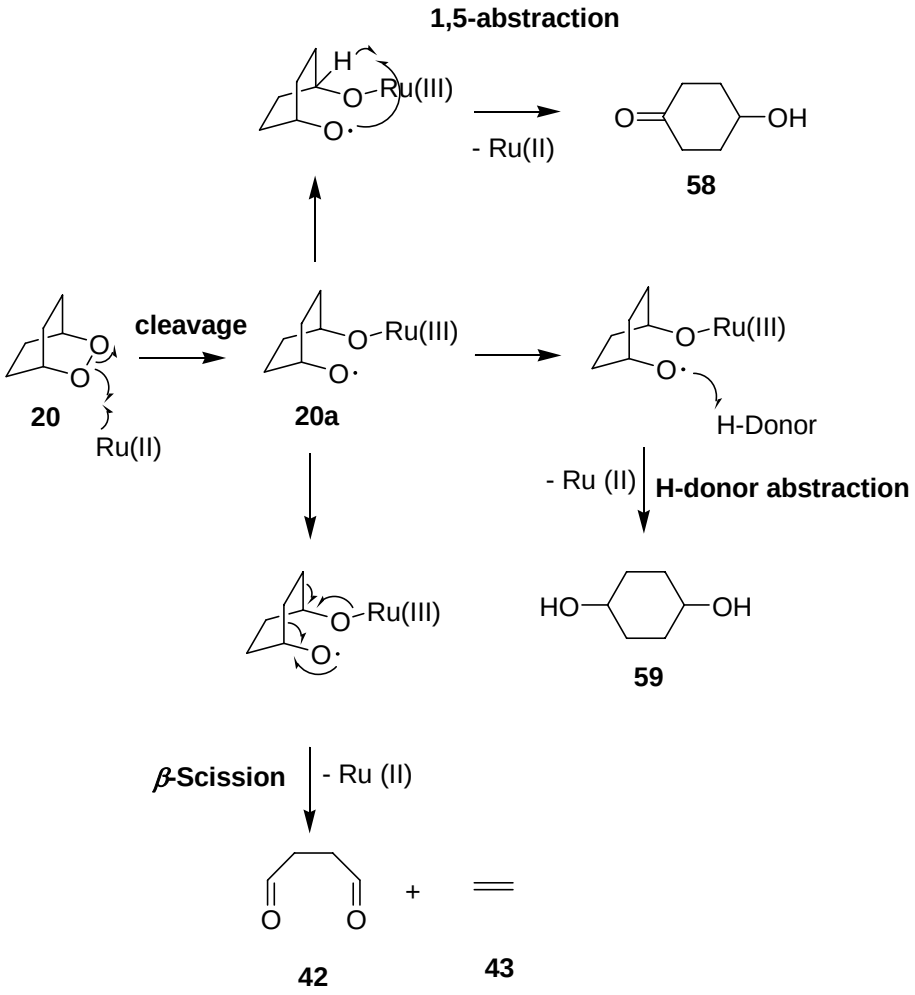


20 **42** **43** **58** **59**

19% 43% 17% 11%

The reaction of transition metal ions with endoperoxides proceed via a one electron redox process. All of the products outlined in Scheme 17 can be rationalised through the mechanism depicted in Scheme 18.

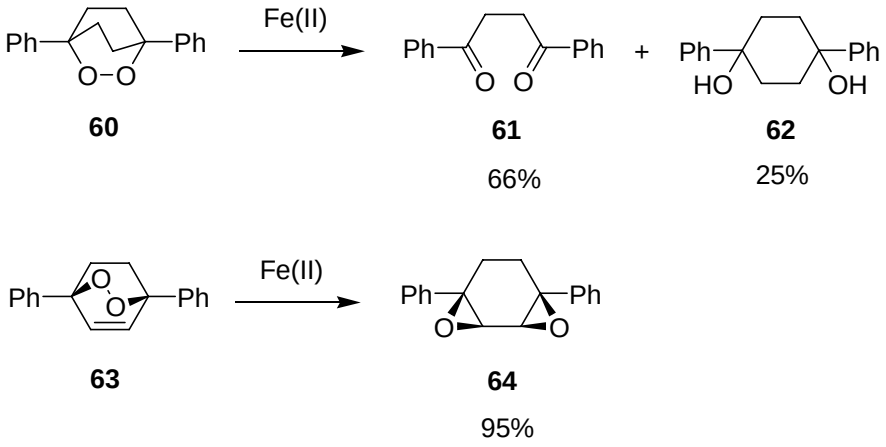
Scheme 18



The inner sphere radical **20a** resulting from the electron transfer reaction between Ru(II) and the endoperoxide **20** serves as the key intermediate in the catalysed decomposition. The radical then can undergo various one electron exchange transformations to give the products outlined in Scheme 18.

The pathway taken and product ratio obtained is very dependant on the substitution pattern of the endoperoxide. Saturated bicyclic endoperoxides with substitution at the bridgehead position, such as **60** (Scheme 19) have no abstractable H atoms and therefore only the diketone **61** and diol **62** are produced.[60] If the compound contains a double bond, as for **63**, 1,2-addition to form the *bis*-epoxide **64** is the favoured route.[50]

Scheme 19.

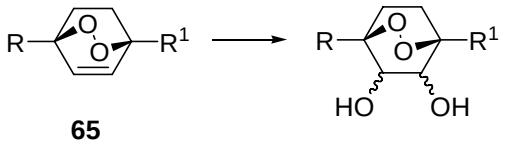


1.3 Aims

This chapter has summarised some of the transformations that have been achieved utilizing bicyclic endoperoxides. It is clear that whilst reactions at the double bond have been explored in some part for unsaturated monocyclic endoperoxides there are very few examples of chemistry at the double bond in unsaturated bicyclic endoperoxides. The specific aims of this project are therefore to:

1. Prepare a number of 1,4-disubstituted 2,3-dioxabicyclo[2.2.2]octanediols **66** containing H, alkyl and aryl substituents (R, R^1), by the dihydroxylation of a series of 1,4-disubstituted 2,3-dioxabicyclo[2.2.2]octanes **65**, Scheme 20. The stereochemical outcome of the dihydroxylation was also to be determined.

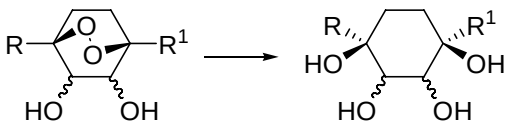
Scheme 20.



65 **66**

2. Examine the reduction of the peroxide bond to afford cyclohexane-1,2,3,4-tetraols **67** in an anticipated highly stereoselective manner (Scheme 21), and to explore their use in natural product synthesis.

Scheme 21.

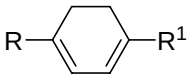


66 **67**

3. Investigate the thermal and photochemical stability of the prepared diols **66** under various conditions, including changes in temperature and solvent.

Chapter 2: Synthesis of dioxabicyclo[2.2.2]octenes

In order to achieve the aims of the project, a range of 1,4-disubstituted 2,3-dioxabicyclo[2.2.2]octenes **65**, (Scheme 20, Chapter 1), incorporating a range of H, alkyl and aryl functional groups, needed to be synthesised. The standard method for the synthesis of these compounds involves the reaction of singlet oxygen with an appropriate 1,3-cyclohexadiendiene **68**. The first step in the project was therefore to obtain a wide range of H, alkyl and aryl substituted 1,3–cyclohexadienes, Figure 5 .



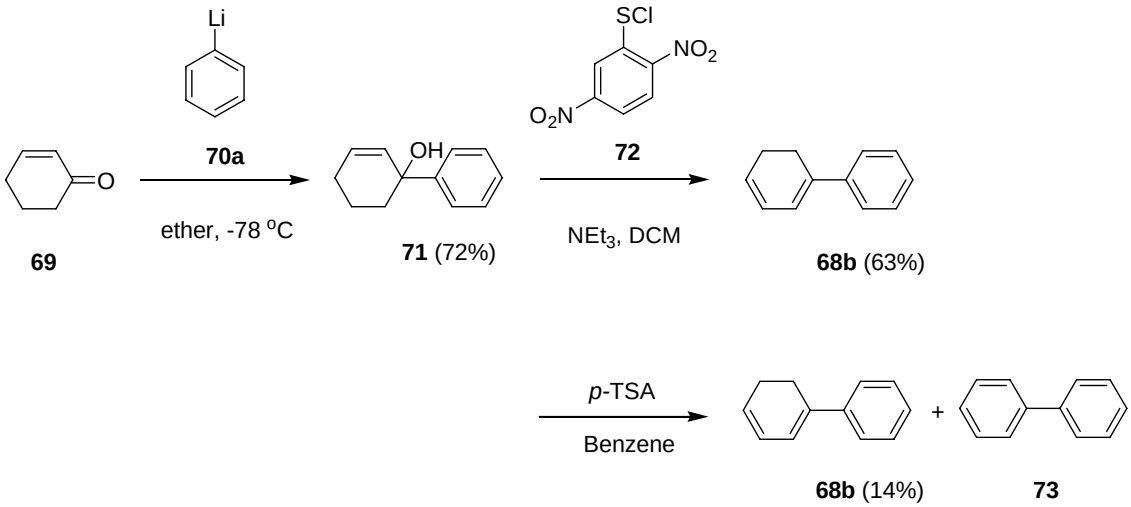
68a: R = R^1 = H
68b: R = Ph, R^1 = H
68c: R = R^1 = Me
68d: R = Me, R^1 = *i*-Pr
68e: R = Me, R^1 = $CH_2CH_2CO_2Me$
68f: R = R^1 = CH_2CO_2Me
68g: R = R^1 = Ph
68h: R = R^1 = *p*-F-Ph

Figure 5. 1,3-Cyclohexadiene with substituents at the 1,4-positions.

2.1 Synthesis of 1,3-cyclohexadienes

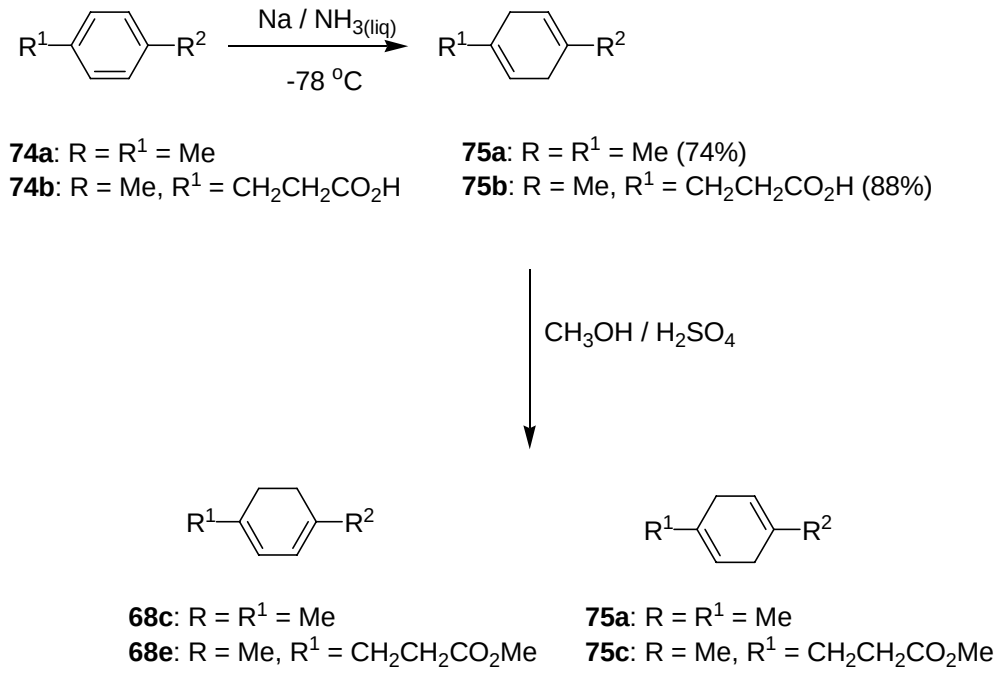
The compounds 1,3-cyclohexadiene (**68a**) and α-terpinene (**68d**) were commercially available and so did not require synthesis. 1-Phenyl-1,3-cyclohexadiene (**68b**)[61] was prepared by a sequential sulfenate-sulfoxide [2,3] sigmatropic rearrangement and *syn* elimination, in good yield (Scheme 22). The technique involved treatment of the allyl alcohol **71,**[62] prepared by the reaction of phenyllithium (**70a**) and 2-cyclohexenone (**69**), with 2,4-dinitrobenzenesulfenyl chloride (**72**) and triethylamine. The alternative route to this compound, the dehydration of the allyl alcohol with *p*-TSA in benzene, only produced 14% yield of the 1,3-diene **68b**. The low yield was attributed to the formation of a large amount of biphenyl (**73**).

Scheme 22.



Dienes **68c**[63] and **68e** were synthesised by dissolved metal (Birch) reduction of the requisite aromatic compound as outlined in Scheme 23.

Scheme 23.



Isomerisation of the initially formed 1,4-dienes **75a**,**b** with sulphuric acid in methanol gave a 70 : 30 mixture of the 1,3- : 1,4-cyclohexadienes, with simultaneous esterification of the diacid **75b** to the methyl esters **68e** and **75c**. Further efforts to increase the percentage of 1,3- to 1,4-isomers above 70% were unsuccessful, suggesting that the equilibrium distribution between them must be 70 : 30. The product ratio was determined from the ^{1}H NMR spectra for both compounds. The signals integrated to quantify each isomer are shown in Figure 6.

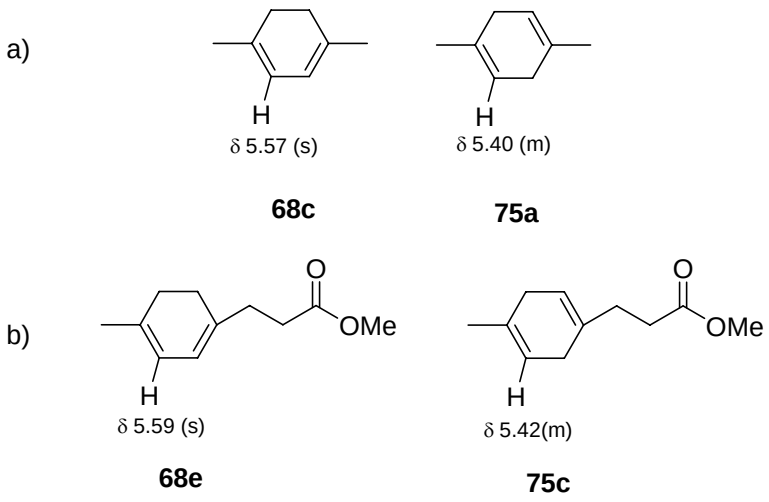
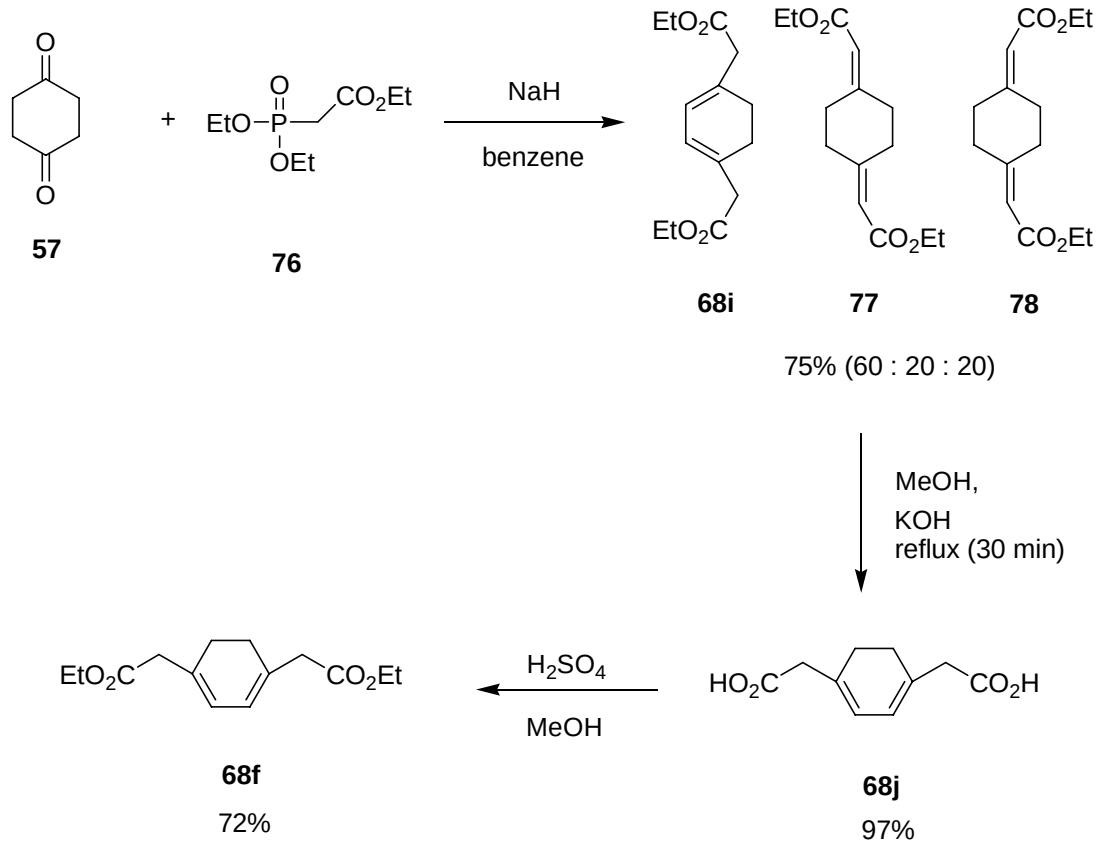


Figure 6. ^{1}H NMR signals used to determine product ratio for a) **68c**:**75a** and b) **68e**:**75c**

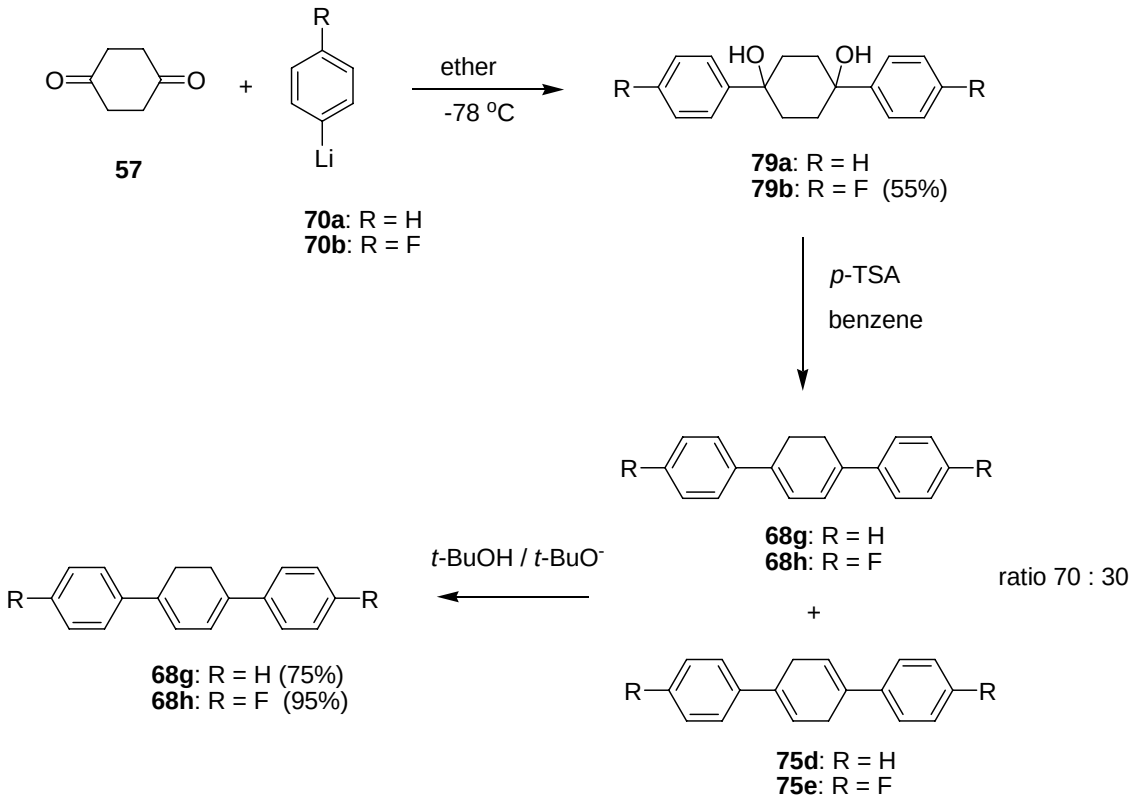
A 60 : 20 : 20 mixture of 1,3-diene **68i**, (*E*)- **77** and (*Z*)- **78** isomers was prepared by following the procedure of Engel *et al*[64] (Scheme 24). The method involves the Horner-Wadsworth-Emmons (HWE) reaction of triethylphosphonoacetate (**76**) with 1,4-cyclohexanedione (**57**) in benzene. The mixture was treated with KOH in boiling methanol to bring about, simultaneously, rearrangement to the 1,3-diene and hydrolysis of the ester groups. The diacid **68** was esterified under acid catalysis to furnish the unknown methyl ester **68f** in good yield (72%).

Scheme 24.



The preparation of 1,3-cyclohexadienes with aromatic substituents at the 1,4-positions (**68g**[65] and **68h**[66]) was achieved as outlined in Scheme 25. The treatment of 1,4-cyclohexanedione (**57**) with the appropriate phenyllithium **70a** or **78b** at -78 ^{o}C furnished the tertiary alcohols **79a** and **79b**. Tertiary alcohol **79b** was isolated in 55% yield. Dehydration with *p*-TSA in benzene, with removal of H_2O by azeotropic distillation, gave a 70 : 30 mixture of the 1,3-diene **68h** and 1,4-diene **75e** respectively. Alcohol **79a** was dehydrated *in situ* with 50% H_2SO_4 to also give a 70 : 30 mixture of the 1,3-diene **68g** and 1,4-diene **75d** respectively.

Scheme 25.



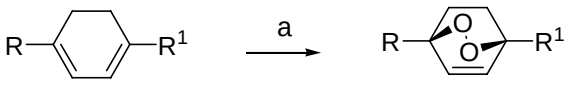
The product ratio for both systems was determined by ^{1}H NMR by integrating the signals for the 1,3-dienes **68g** (singlet at δ 6.53 ppm) and **68h** (singlet at δ 6.44 ppm) versus the signals for the 1,4-dienes **75d** (multiplet at δ 6.28 ppm) and **75e** (multiplet at δ 6.20 ppm). Dale *et al.*[65] proposed that the initial (kinetic) product of the dehydration reaction was the 1,4- (non-conjugated) diene, and that subsequent isomerism takes place to give the 1,3- (conjugated) diene. Complete conversion of the mixture to the 1,3-isomer **68g**,**h** was effected by refluxing in *t*-butanol containing *t*-butoxide, so it is clear that the thermodynamic equilibrium lies on the side of the 1,3-isomer.

2.2 Synthesis of Endoperoxides

The synthesis of all the required bicyclic endoperoxides was carried out by a thermally allowed [4π + 2π] cycloaddition of singlet oxygen to the requisite 1,3-cyclohexadiene. This was effected by dissolving the diene in dichloromethane in the presence of the photosensitiser, rose bengal *bis*(triethylammonium) salt.[67] The photosensitiser is initially excited by light from lamps irradiating the reaction vessel, generating the dye in its excited state. The excited state of the dye is of the appropriate relative energy to excite ground state triplet oxygen, via collision, to form singlet oxygen, with the dye returning to ground state allowing for the process to repeat.

A range of H, alkyl and aryl substituted 2,3-dioxabicyclo[2.2.2]oct-5-enes **65a-h** were synthesized from the requisite 1,3-dienes utilizing the above method, as shown in Scheme 26. The photolysis of all dienes **68a-h** was conducted in CH_2Cl_2 and followed to completion by TLC. Purification by flash chromatography allowed separation from the rose bengal *bis*(triethylammonium) salt and the more polar side products (ene reaction, oxidation) and gave the endoperoxides **65a-h** in good to excellent yield, Table 1.

Scheme 26.



65a-h

68a: R = R^1 = H
68b: R = Ph, R^1 = H
68c: R = R^1 = Me
68d: R = Me, R^1 = *i*-Pr
68e: R = Me, R^1 = $CH_2CH_2CO_2Me$
68f: R = R^1 = CH_2CO_2Me
68g: R = R^1 = Ph
68h: R = R^1 = *p*-F-Ph

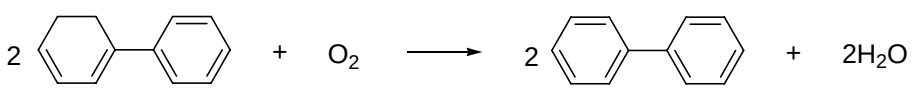
(a) O_2, rose bengal *bis*(triethylamnonium)salt, *hv*, DCM.

Table 1. Photosensitised oxidation of 1,3-cyclohexadienes

entry	Cyclohexadiene	**65** (% yield)
1	**68a**	54
2	**68b**	27
3	**68c**	70
4	**68d**	95
5	**68e**	65
6	**68f**	89
7	**68g**	73
8	**68h**	51

The relatively low yield of the mono phenyl-substituted endoperoxide **65b** can be attributed to the concurrent formation of biphenyl (**71**). Molecular oxygen brings about the oxidation of the 1,3-diene **68b** by a two electron redox process to give the side product **73**, shown in Scheme 27. This reaction is driven by the favourable energetics of re-aromatisation.

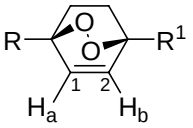
Scheme 27.



68b **73**

A summary of some of the characteristic spectroscopic data for the new compounds **65b**, **65c**, **65e** and **65f** is given in Table 2.

Table 2. Characteristic ^{1}H NMR and ^{13}C NMR for new 2,3-dioxabicyclo[2.2.2]oct-5-enes



65b: R = Ph, R^1 = H
65c: R = R^1 = Me
65e: R = Me, R^1 = $CH_2CH_2CO_2Me$
65f: R = R^1 = CH_2CO_2Me

Compound	δ H_a/H_b (J_{ab}) ppm	δ C_1/C_2 ppm
65b	6.74 and 6.82 (8.5 Hz)	128.5 and 128.7
65c	6.38	136.0
65e	6.42	133.8 and 136.6
65f	6.70	134.0

The known endoperoxides **65a**,[68] **65d**,[69] **65g**[48] and **65h**[70] gave physical data consistent with the literature.

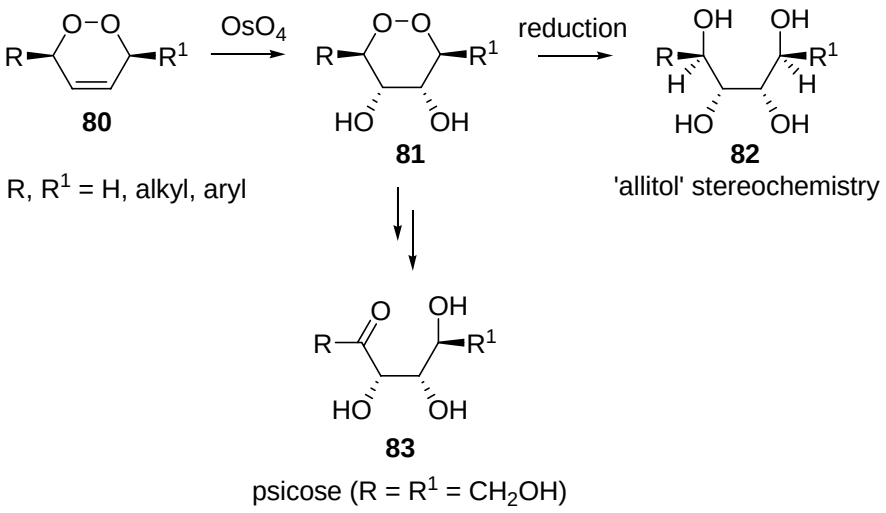
This chapter has described the synthesis and characterisation of a broad range of 1,4-disubstituted 2,3-dioxabicyclo[2.2.2]oct-5-enes. With these compounds now in hand we were in a position to explore the *cis* dihydroxylation of the alkene portion of these molecules, with the aim of producing compounds with "Toxocarol" relative stereochemistry. These reactions will be the focus of the next chapter.

Chapter 3: Dihydroxylation of 1,4-disubstituted endoperoxides

3.1 Introduction

The Taylor group has recently published a method for the dihydroxylation of monocyclic endoperoxides **80** (Scheme 28), using osmium tetroxide.[29] The dihydroxylated products of the reaction were utilized in the synthesis of tetraols of 'allitol' stereochemistry **82** and sugars such as (±)-psicose (**83**), in excellent overall yields.

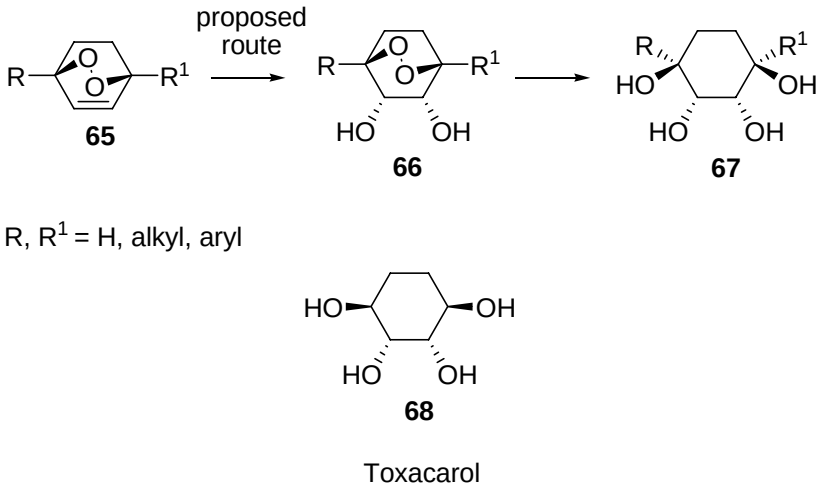
Scheme 28.



With the above results in mind it was proposed to extend this methodology for the ready construction of cyclohexane-1,2,3,4-tetraols **67**, Scheme 29. It was envisaged that dihydroxylation of bicyclic systems **65** (to give **66**) followed by reduction of the peroxide bond would afford cyclohexane-1,2,3,4-tetraols **67** in a highly stereoselective manner, (Scheme 29). It was anticipated that dihydroxylation would occur *anti* to the peroxide bond due to the steric bulk and repulsive effect of the electronegative oxygen atoms on the approach of osmium tetroxide. Moreover, it was considered that variation of the substituents R and R^1 should have little effect on the facial selectivity of

dihydroxylation as the groups have an identical steric presence on either face of the alkene. The configuration of the formed tetrols was therefore expected to be that of toxacarol (**68**), shown in Scheme 29.

Scheme 29.



There are several simple cyclohexane-1,2,3,4-tetraols of the toxocarol configuration such as (-)-quebrachitol (**84**), conduritol A (**85**) and (+)-pinitol (**86**), which are shown in Figure 7.

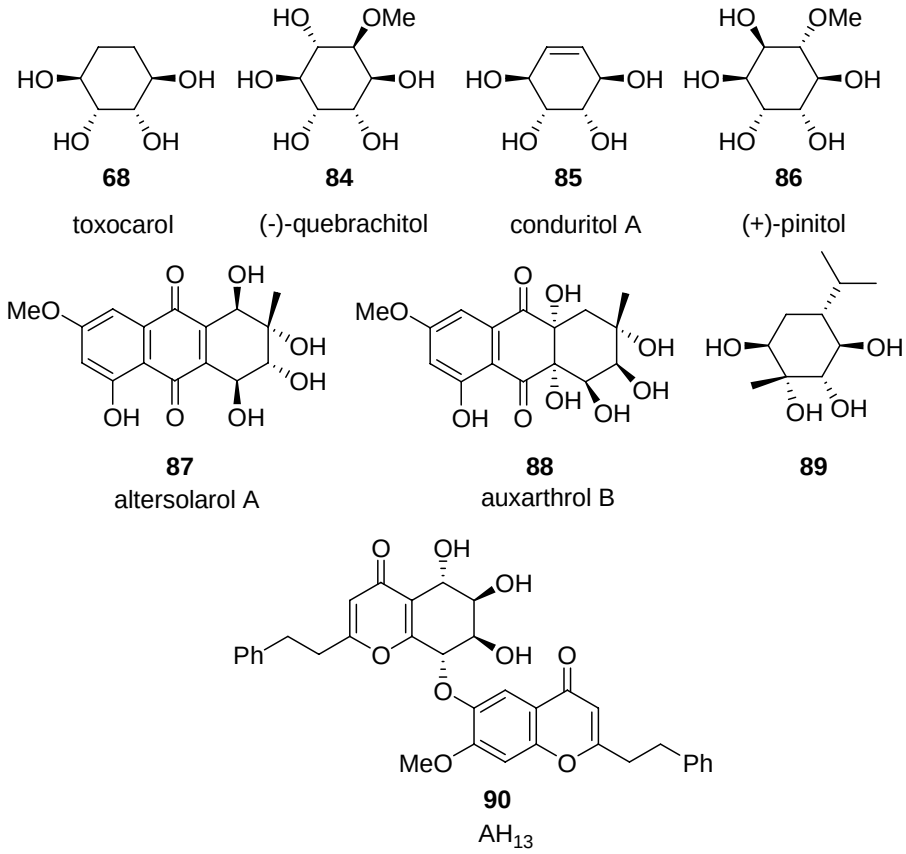


Figure 7. Natural products containing the toxocarol relationship of hydroxyl groups.

Other, more complex natural products also exhibit this relative stereochemistry, such as altersolarol A (**87**),[71] auxarthrol B (**88**),[72] the monoterpene **89**[73, 74] and AH_{13} (**90**),[75] many of which have yet to be synthesized (Figure 7). The toxocarol configuration has also appeared in several pharmacologically active compounds[76, 77] and within synthons in the synthetic routes to several natural products, such as ottelione A (**91**)[78] and zeylenone (**92**) (Figure 8).[79]

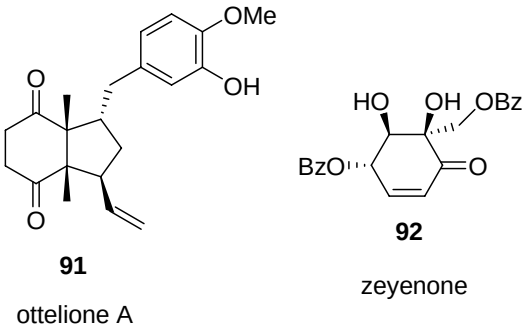
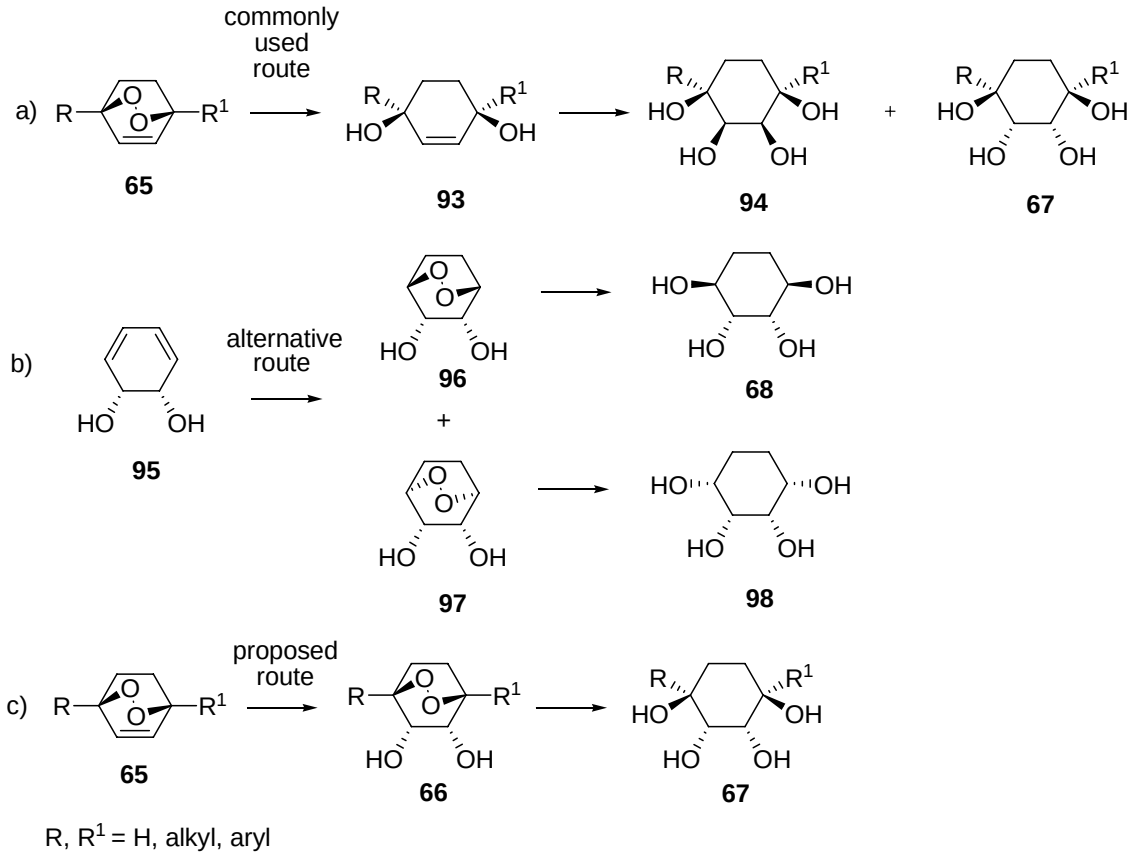


Figure 8.

Of the compounds that have been synthesized, the general approach has been to prepare them by reduction of the peroxide linkage of an appropriate 2,3-dioxabicyclo[2.2.2]oct-5-ene **65**, followed by dihydroxylation of the alkene **93** (Pathway a, Scheme 30).[80-84] In some cases extra synthetic steps for protection and deprotection of the initial diol **93** are employed to simplify aqueous workup after dihydroxylation.[76, 80, 82-84] Alternatively, photooxygenation of 3,5-cyclohexadiene-1,2-diol **95** and subsequent reduction of the peroxide linkage represents another route into the toxocarol configuration, (Pathway b, Scheme 30).[80, 81, 85]

Scheme 30.



It has been found that facial selectivity of the dihydroxylation for the previous common route (Pathway a, Scheme 30) is highly dependant on the steric environment of the alkene **93**, with mixtures sometimes observed.[76,77] High selectivity of dihydroxylation was observed when R and R^1 = H (for compound **93**, Scheme 30). In this case one of the hydroxyl groups will sit axial in the lowest energy half-chair conformation thus always directing dihydroxylation '*trans*' to the existing hydroxyl groups (Figure 7a), giving the stereochemistry of tetraol **67** (Pathway a, Scheme 30). When R and R^1 = alkyl or aryl substituents it was expected that both faces would be similarly hindered (Figure 7b) and a mixture of tetraols **94** and **67** would be observed (pathway a, Scheme 30). This outcome was found experimentally to be true (see Chapter 3.3). The proposed methodology (Pathway c, Scheme 30) should offer higher and in some instances alternate facial selectivity for dihydroxylation in an approach to cyclohexane-1,2,3,4-tetraols of toxocarol stereochemistry.

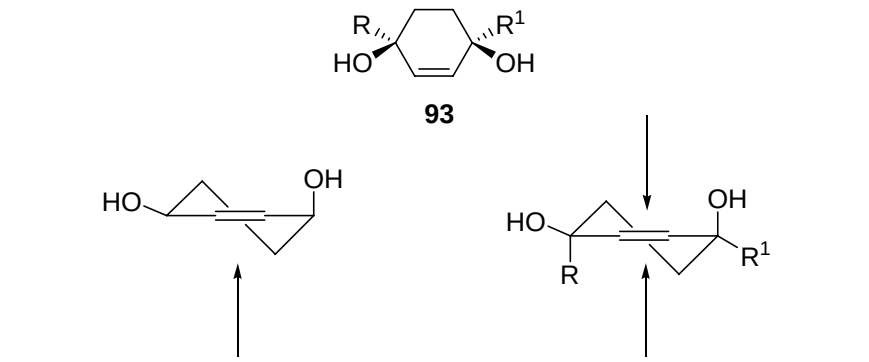
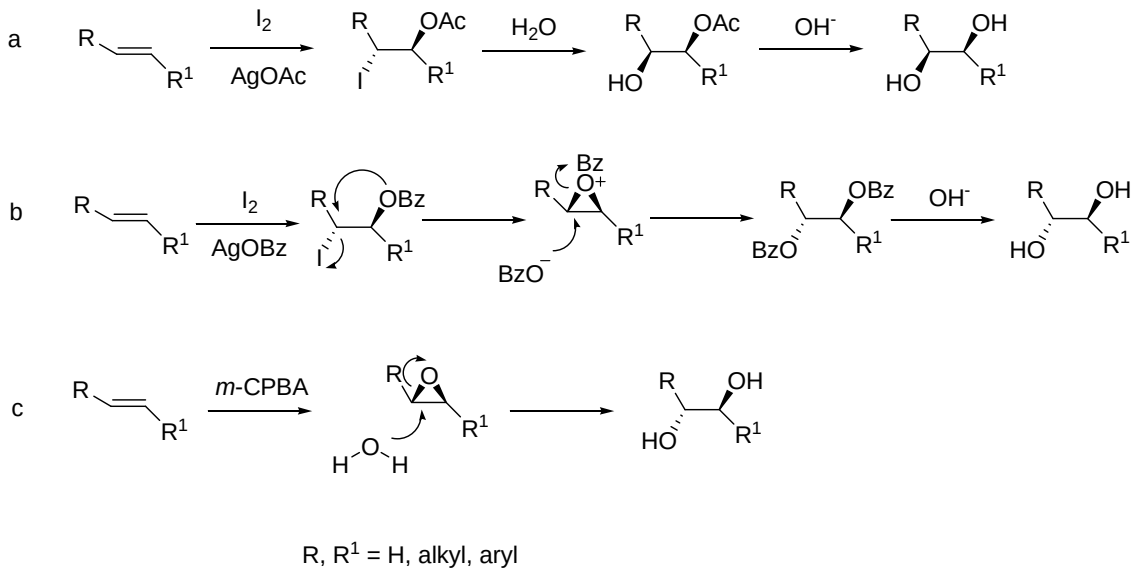


Figure 7. Selectivity for dihydroxylation in cyclic alkenes

3.2 General dihydroxylation of alkenes.

The catalytic dihydroxylation of alkenes represents a method for the preparation of 1,2-diols with defined relative configuration. There are many reagents that add two hydroxy groups to a double bond.[86] OsO_4 or $KMnO_4$ give *syn* addition, from the least hindered side of the alkene.[87, 88] The *syn* hydroxylation from the more hindered π face can be effected using the procedure of Woodward[89] (Pathway a, Scheme 31). In this method the alkene is treated with I_2-AgOAc in AcOH containing water. On the other hand, *anti* dihydroxylation can be achieved by reaction with I_2-AgOBz in the absence of water (Prevost Reaction).[90] This is a nucleophilic substitution reaction, and it operates by the neighboring-group mechanism, as shown in Pathway b, Scheme 31. Another route to the preparation of *anti* diols is by oxidation of an alkene with a peroxy acid[90] such as *m*-chloroperbenzoic acid (*m*-CPBA), followed by S_N2 ring-opening of the resultant epoxide (Pathway c, Scheme 31).

Scheme 31.



Given the Taylor group's success at dihydroxylation of monocyclic systems[29] it was decided to employ the same methodology in the dihydroxylation of bicyclic systems. The conditions employed for the reaction, which utilised catalytic osmium tetroxide as the active species (generated *in situ* from K_2OsO_4), NMO, citric acid and *t*-butanol/H_2O, is based on the so-called "Upjohn process"[91] for dihydroxylation of olefins. A mechanism for this reaction, as proposed by Sharpless *et al.*[92] is given in Figure 8.

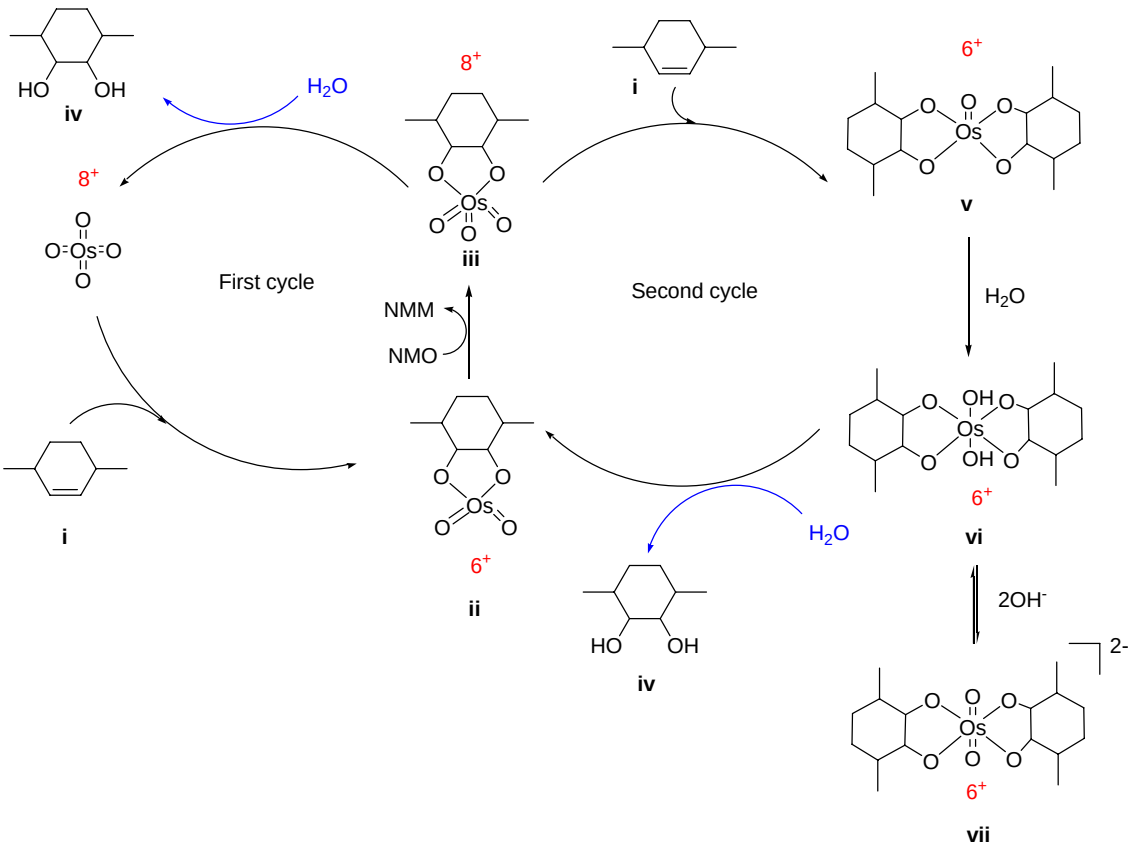


Figure 8. Proposed mechanism for the Os(VII)-catalysed dihydroxylation of olefins with NMO as re-oxidant, as shown in ref.[92]

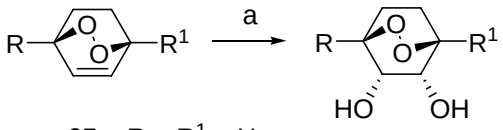
In the first step the olefin **i** is oxidized by osmium tetroxide to form the complex **ii** in which osmium has been reduced to Os^{6+}. The NMO then re-oxidizes the osmium complex to the Os^{8+} species **iii**, which is then hydrolysed to give the product **iv**. It is

also believed that a second catalytic cycle operates: In this process the Os^{8+} complex **iii** reacts with another olefin molecule to give the *bis* complex **v**. The hydrolysis of this species (**v**) is initiated by addition of a water molecule, forming intermediate **vi**. It is here that the added citric acid aids in preventing the formation of the catalytically inert dioxoosmate dianion species **vii**, which arises from deprotonation of the hydrated species **vi** at higher pH.

3.3 Dihydroxylation of 2,3-dioxabicyclo[2.2.2]oct-5-enes

The naturally occurring bicyclic peroxide ascaridole (**65d**), (Scheme 29), was initially treated under the conditions discussed above, however the reaction proved to be very slow, with starting material still present after 7 days. It became apparent that the alkene portion of the bicyclic endoperoxide was less reactive than that of the monocyclic systems. Therefore it was decided to heat the mixture to 50 ^{o}C, and as a result the reaction went to completion in 16 hours in an excellent yield of 85%. Furthermore, treatment of compounds **65a-h** under the same modified conditions (Scheme 32) afforded diols **66b-h** in moderate to high yields as single diastereomers, Table 3.

Scheme 32.



65a: R = R^1 = H
65b: R = Ph, R^1 = H
65c: R = R^1 = Me
65d: R = Me, R^1 = *i*-Pr
65e: R = Me, R^1 = $CH_2CH_2CO_2Me$
65f: R = R^1 = CH_2CO_2Me
65g: R = R^1 = Ph
65h: R = R^1 = *p*-F-Ph

66a-h

(a) K_2OsO_4, citric acid, NMO, *t*-BuOH / H_2O, 50 ^{o}C.

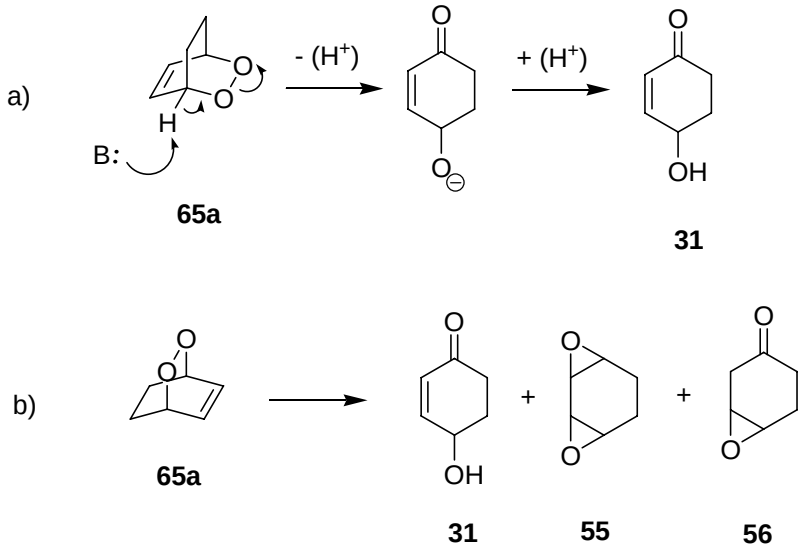
Table 3. Osmium catalysed dihydroxylation of 2,3-dioxabicyclo[2.2.2]oct-5-enes **65a-h**.

entry	Endoperoxide	**66** (% yield)
1	**65a**	0*
2	**65b**	63
3	**65c**	66
4	**65d**	85
5	**65e**	83
6	**65f**	55
7	**65g**	75
8	**65h**	68

* **65a** gave a complex mixture of products, none of which could be identified as **66a**

However, in the case of endoperoxide **65a** TLC showed multiple components which were difficult to isolate due to their water solubility. The reaction mixture was analysed by NMR prior to work-up and also subjected to column chromatography, but the only component that could be successfully identified was the known -hydroxycyclohexenone (**31**). This product was most likely to have arisen from a Kornblum-DeLaMare rearrangement of the peroxide (Pathway a, Scheme 33). The other possibility is that the rearrangement proceeded via a one electron redox process, catalysed by the osmium ions (Pathway b, Scheme 33). Although a [1,5] H-atom abstraction would also afford the product **31** this seems unlikely as there was no sign of the usual products of metal catalysed rearangment, i.e. *bis* epoxide **55** and epoxyketone **56** (see Chapter 1.2.5). These types of rearrangements were not possible for compounds **65c-h** due to the lack of a proton to the peroxide linkage.

Scheme 33.

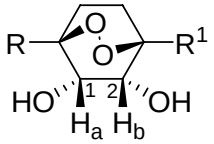


Yields of diols **66b-h** varied considerably due to their susceptibility to rearrangement to 1,4-dicarbonyl compounds and acetaldehyde (*vide infra*). 1,4-Dicarbonyls made up the bulk of the remaining isolable products from dihydroxylation. This previously unknown rearrangement will be discussed in detail in Chapter 5.

A summary of some of the characteristic spectroscopic data for the new diols **66b-f** is given in Table 4.

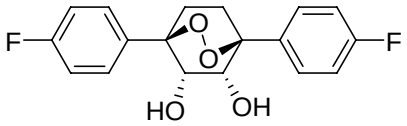
The orientation of the diols **66b-h** formed was, as anticipated *anti*, with respect to the peroxide linkage, in all cases. This stereochemistry was established through 2D NMR spectroscopy. Furthermore, single crystal X-ray analysis of compound **66h** (Figure 9), and tetraol **67d** (*vide infra*) (see Figure 10, Chapter 3.4) unambiguously confirmed the designated stereochemistry. No evidence for the formation of the *syn* product was observed in any example.

Table 4. Characteristic ^{1}H NMR and ^{13}C NMR for new 2,3-dioxabicyclo[2.2.2]octane-5,6-diols **66b-h**.



66b: R = Ph, R^1 = H
66c: R = R^1 = Me
66d: R = Me, R^1 = *i*-Pr
66e: R = Me, R^1 = $CH_2CH_2CO_2Me$
66f: R = R^1 = CH_2CO_2Me
66g: R = R^1 = Ph
66h: R = R^1 = *p*-F-Ph

Compound	δ H_a/H_b (J_{ab}) ppm	δ C_1/C_2 ppm
66b	4.28 and 4.47 (7.5Hz)	65.2 and 69.6
66c	3.92	77.5
66d	3.91 and 4.19 (7.8Hz)	76.8 and 80.6
66e	3.88 and 3.94 (8.2Hz)	77.7 and 78.0
66f	4.72	78.6
66g	4.47	70.7
66h	4.43	70.5



66h

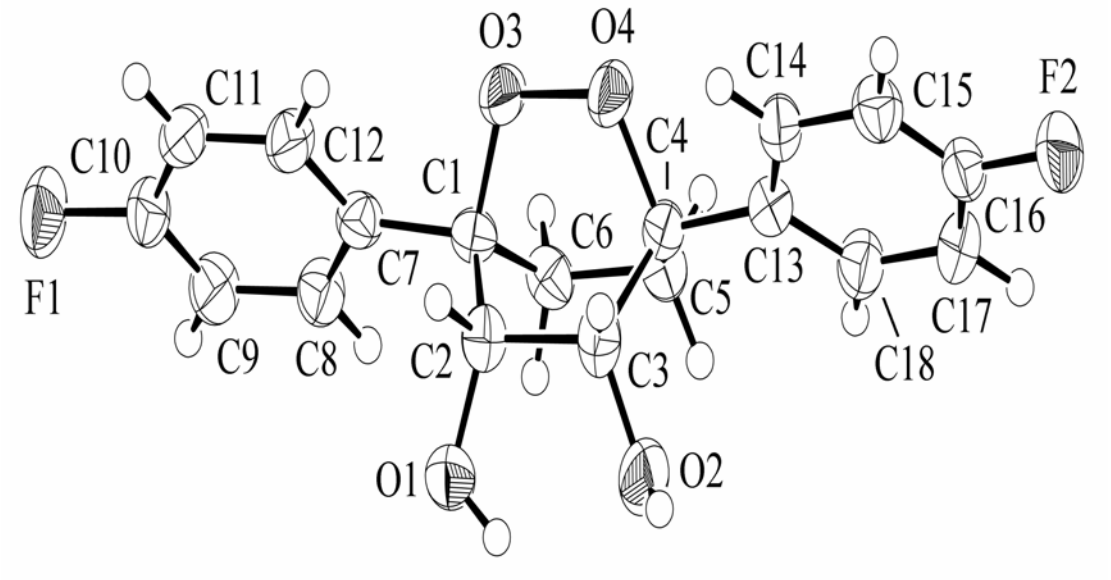


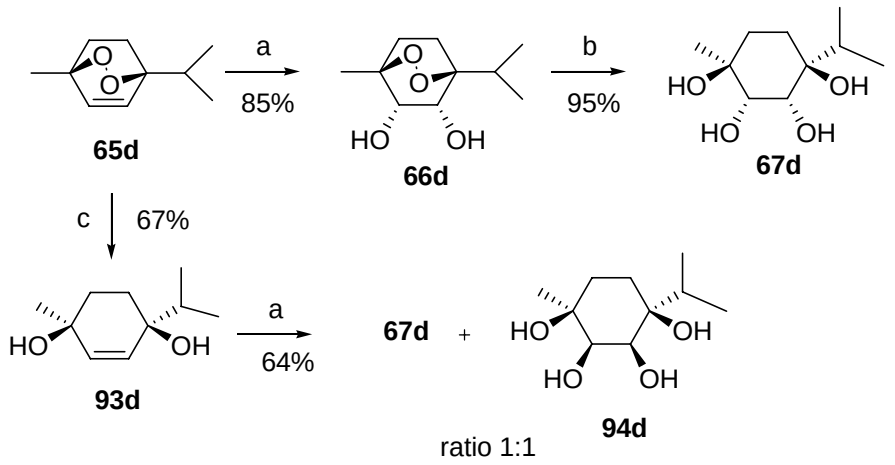
Figure 9. Molecular structure (50% probability ellipsoids) and crystallographic numbering scheme for compound (**66h**).

3.4 Synthesis of tetraols with toxocarol relative configuration

To directly compare the two synthetic routes to cyclohexane-1,2,3,4-tetraols outlined in Scheme 30 (pathway a and c), the easily synthesized ascaridole (**65d**) was chosen as a model system, Scheme 34.

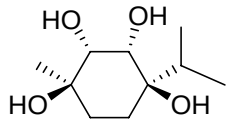
Given that dihydroxylation of ascaridole is completely facially selective it was expected that tetraol **67d** would be obtained in good yield after reduction of the peroxide linkage of **66d**. Different methods for the reduction of the peroxide linkage were discussed in Chapter 1.2.1. The two methods found to be of most value in the reduction of the O-O bond were Zn in acetic acid and catalytic Pd / C under an atmosphere of H_2. Both methods proved to be clean and high yielding.

Scheme 34.



(a) K_2OsO_4, citric acid, NMO, *t*-BuOH / H_2O. (b) Zn (dust), AcOH. (c) $LiAlH_4$, THF.

Using this methodology, tetraol **67d** was furnished in 95% purified yield from the reduction of diol **66d**. Furthermore, single crystal X-ray analysis of compound **67d** (Figure 10) unambiguously confirmed the structure and designated stereochemistry. The result of the model reaction by which the peroxide is dihydroxylated followed by reduction was in complete contrast to taking the alternative and commonly used method; peroxide reduction followed by dihydroxylation, (Scheme 34). The workup of the dihydroxylation of the 1,4-dihydroxy cyclohexenone **93d** resulted in a poor combined overall yield of 64% due, in part, to difficulty in separating the water-soluble tetraols from the aqueous phase. Tetraols **67d** and **93d** were isolated as a 1:1 mixture, suggesting no facial selectivity, and were inseparable by column chromatography. This demonstrates clearly that the approach to tetraols of type **67** using our new approach is superior in both yield and ease of workup.



67d

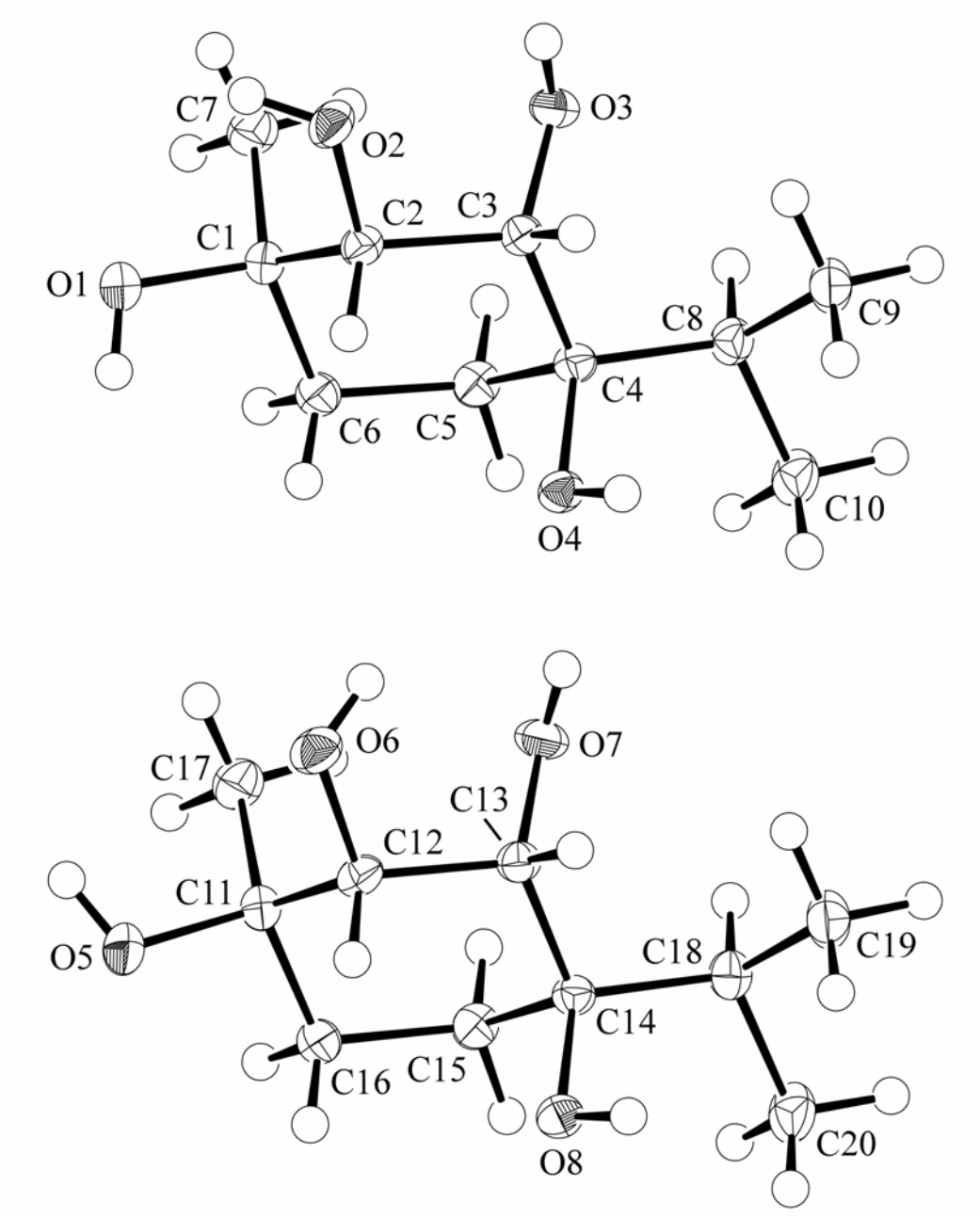
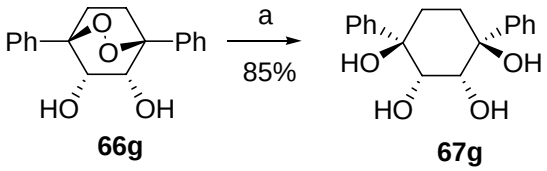


Figure 10. Molecular structure (50% probability ellipsoids) and crystallographic numbering scheme for the two independent conformations in compound **67d**. Note the different orientations for the O1- and O2-bound hydrogen atoms from the comparable O5- and O6-bound hydrogen atoms.

In order to demonstrate the synthetic scope of dihydroxylation of bicyclic endoperoxides followed by reduction of the peroxide linkage, tetraol formation from aryl substituted diol **66g** was examined**.** This compound was obtained from endoperoxide **65g** in 75% yield (Table 3) and subsequently reduced to give tetraol **67g** in 85% yield, Scheme 35, confirming that both alkyl and aryl substituents can be tolerated in the 1,4-positions.

Scheme 35.

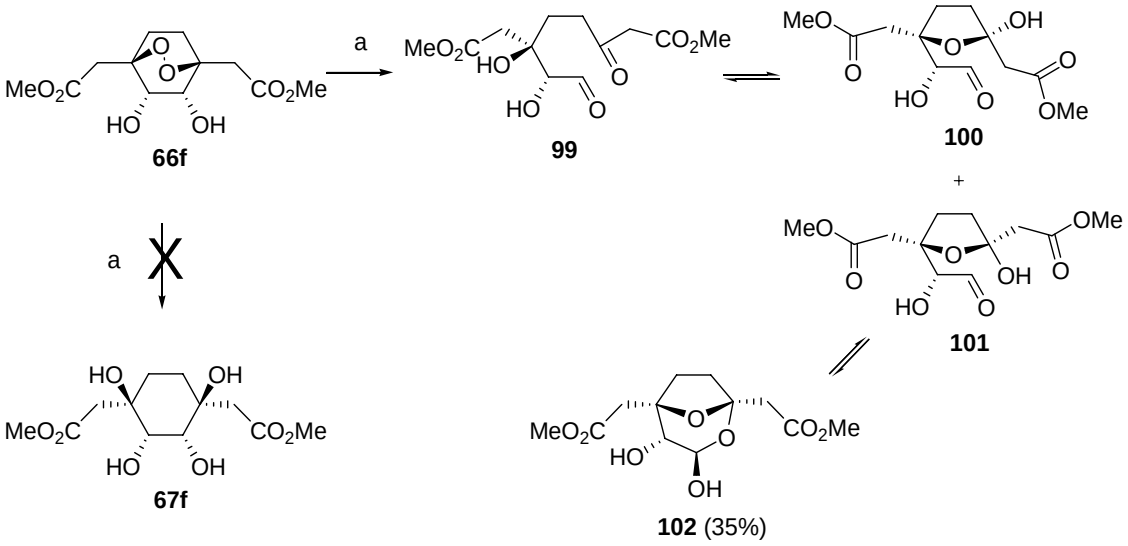


(a) H_2/Pd/C

Interestingly, attempted reduction of the diester **66f** with Pd/C 5% and hydrogen in methanol resulted in no formation of tetraol **67f**. Instead, bicyclic diol **102** was obtained in 35% yield and is rationalized through intermediates indicated in Scheme 36. This rearrangement was due solely to the Pd/C 5%, as the same major product was observed in the same yield when the reaction was repeated in the absence of hydrogen. Whilst the mechanism for the transformation of **66f** into **102** is unclear we can draw on the observation that Palladium(0) can induce fragmentation of the peroxide linkage in a free radical manner.[49] Thus it is proposed that homolytic cleavage of **66f** followed by β-scission and intramolecular hydrogen atom abstraction affords dicarbonyl **99**. Simple intramolecular cyclisation affords hemiacetals **100** and **101.** Further cyclisation of **101** leads to the observed hemiacetal **102**. The observed ROSEY cross peaks that confirm the stereochemistry of **102** are given in Figure 11. Coordination of Pd appears to be assisted by the proximal methyl ester groups, giving facile rearrangement in preference

to reduction. This hypothesis is supported by the fact that Pd induced reduction of **66d** and **66g** proceeded as expected. Reduction of the peroxide linkage of **66f** was also attempted using Zn in acetic acid. No evidence for the formation of diol **67f** was found; presumably due to ester hydrolysis and decomposition to dicarbonyl **103f** (see Chapter 5).

Scheme 36.



(a) Pd/C (5%), H_2, MeOH.

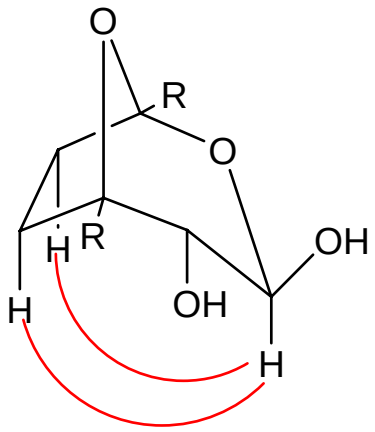
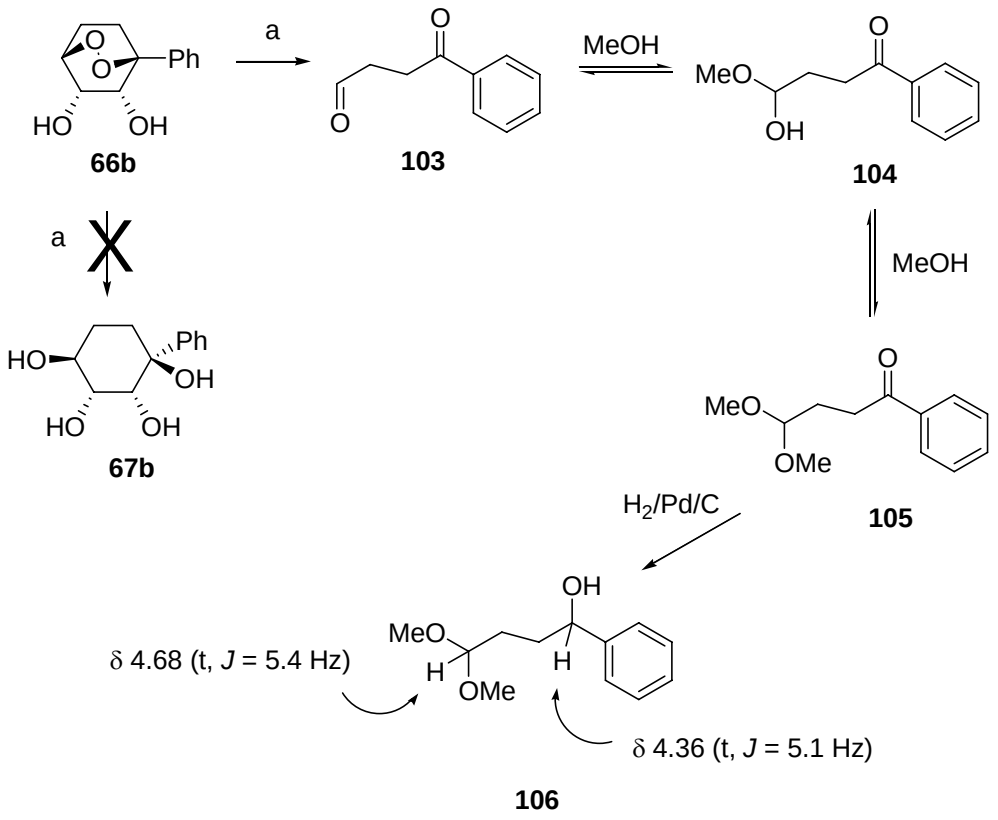


Figure 11. Through space interactions of protons in hemiacetal **102**.

Finally, reduction of the peroxide linkage of the mono-phenyl substituted diol **66b** was attempted. This diol was found to be particularly susceptible to decomposition; a finding which will be discussed in detail in Chapter 5. The acetal **106** was the only product isolated from the reaction of **66b** with hydrogen, Pd/C in methanol, and can be rationalized by the reactions outlined in Scheme 37. The keto-aldehyde **103**, which formed from the initial decomposition of diol **66b** reacts with the methanol solvent to form hemi-acetal **104**. Reaction with a second solvent molecule produces the acetal **105**. This compound is then reduced by the hydrogen, Pd/C under the reaction conditions to form the racemic alcohol **106**. The reaction was also carried out in the absence of H_2 and the only product obtained was the known acetal **105**,[93] confirmed by ^{1}H and ^{13}C NMR. This provides further evidence towards the mechanism proposed in Scheme 37.

Scheme 37.

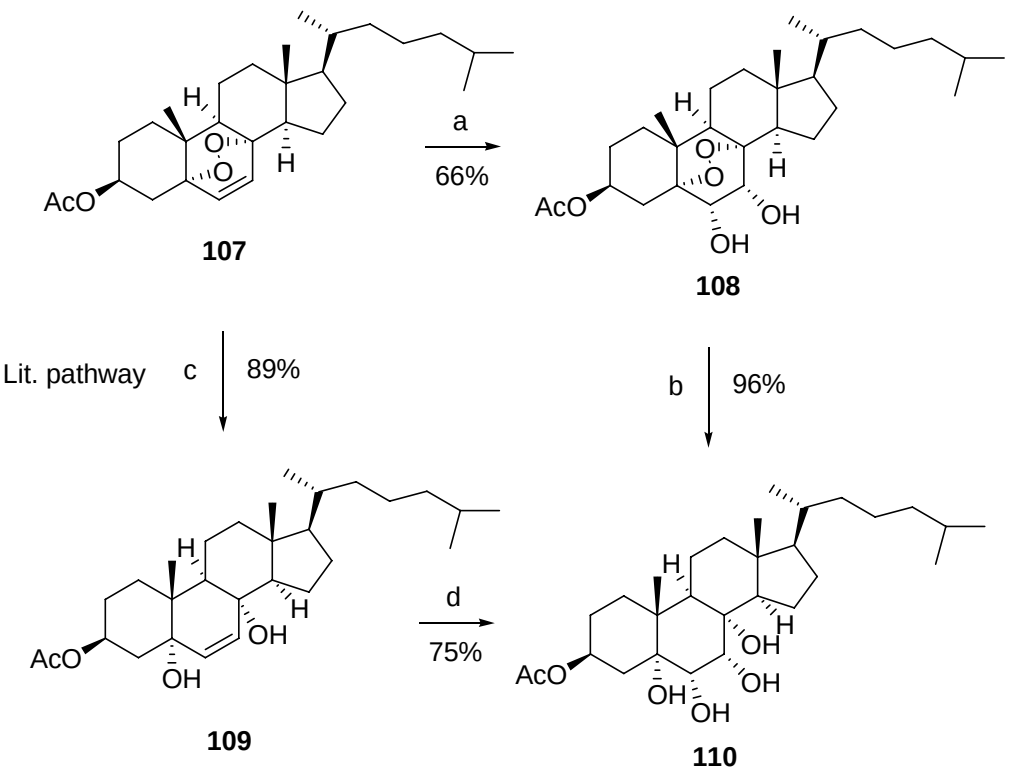


(a) Pd/C (5%), H_2, MeOH.

3.5 Dihydroxylation of heavily substituted 2,3-dioxabicyclo[2.2.2]oct-5-enes.

In order to investigate a highly sterically hindered system, 7-dehydrocholesterol acetate peroxide (**107**),[94] kindly donated by a colleague, was used as a model system for dihydroxylation and reduction, Scheme 38. In complete contrast to *anti* dihydroxylation observed for 1,4-disubsituted 2,3-dioxabicyclo[2.2.2]oct-5-enes, dihydroxylation of **107** proceeded in a *syn* fashion to afford diol **108**, and is most likely due to the sterically restricted environment of the steroid framework. Hydrogenation of **108** afforded the all *cis* tetraol **110** in excellent yield. The ^{1}H NMR and IR of tetraol **110**, which has been synthesized previously by the alternative method outlined in Scheme 38, matched that of the literature compound.[94]

Scheme 38.



107 **108** **109** **110**

(a) K_2OsO_4, citric acid, NMO, *t*-BuOH/H_2O. (b) Pd/C (5%), H_2, MeOH.
(b) Zn, KOH, EtOH. (d) OsO_4, pyridine.

Confirmation of the stereochemistry was made by 2D NMR, and the cross peaks from the ROESY spectrum are given in Figure 12.

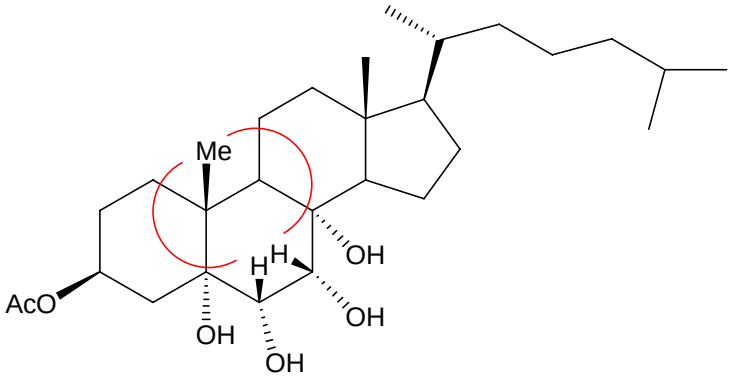


Figure 12. Through space interactions of protons in **110**.

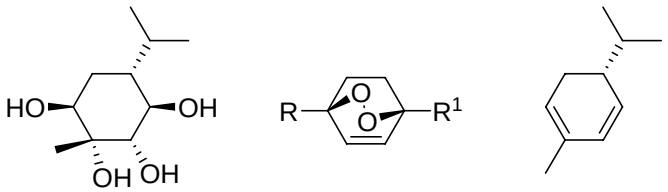
In this chapter a broad range of 1,4-disubstituted-2,3-dioxabicyclo[2.2.2]oct-5-enes were dihydroxylated with osmium tetroxide to yield diols *anti* to the peroxide linkage, as single diastereomers, in good to excellent yields. Reduction of the peroxide bond afforded cyclohexane-1,2,3,4-tetraols of toxocarol relative stereochemistry in excellent yield.

With there results in mind the focus of the next chapter will be to investigate the possibility of synthesis of a natural product using the same methodology.

Chapter 4: Dihydroxylation of 2,3-dioxabicyclo[2.2.2]oct-5-enes from α-phellandrene.

4.1 Introduction

The terpenoid **89** (Figure 13) has recently been reported as an isolate from *Eupatorium fortunei*, a herbal plant that has long been used as a traditional Chinese medicine.[74] This species has been used for the treatment of dropsical swelling, chills and fever, and as a diuretic and antipyretic.[95] In order to evaluate the dihydroxylation of compounds of type **65** where R and R^1 = H and to investigate the synthesis of reported natural product **89**, it was decided to look at the dihydroxylation of the 2,3-dioxabicyclo[2.2.2]oct-5-enes obtained from the photolysis of optically pure α-phellandrene (**111**),[57, 96] (Figure 13).



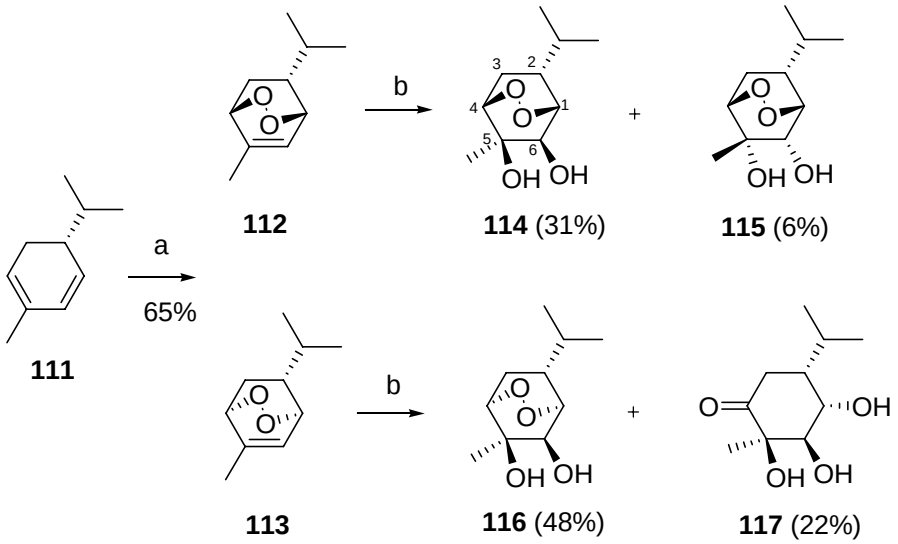
89 **65** **111**

Figure 13.

4.2 Dihydroxylation of 2,3-dioxabicyclo[2.2.2]oct-5-enes from α- phellandrene

The photolysis of optically pure α-phellandrene (**111**) in dichloromethane in the presence of singlet oxygen produced two diastereomeric peroxides in 67% overall yield; compound **112** with the peroxide linkage *trans* to the isopropyl group, and compound **113** with the peroxide linkage *cis* to the isopropyl group, (Scheme 39). The *trans* / *cis* ratio (2 : 1) was similar to that reported in the literature.[96] The *cis* and *trans* peroxides were easily separable by column chromatography.

Scheme 39.



(a) O_2, rose bengal *bis*(triethylammonium)salt, *hv*, DCM. (b) K_2OsO_4, citric acid, NMO, *t*-BuOH / H_2O

Dihydroxylation of the *trans* isomer **112** gave two diol isomers **114** and **115,** with the *syn* isomer **114** being favored, Scheme 39. Dihydroxylation of the *cis* isomer **113** gave only the *anti* diol **116** along with a significant amount of ketone **117** as the only other isolable product. ^{1}H and ^{13}C NMR data obtained for the three new diols **114-116** is collated in Table 5. The stereochemical outcome of the dihydroxylation of **112** and **113** is most likely explained by the overriding steric bulk of the isopropyl group, easily seen in Figure 14.

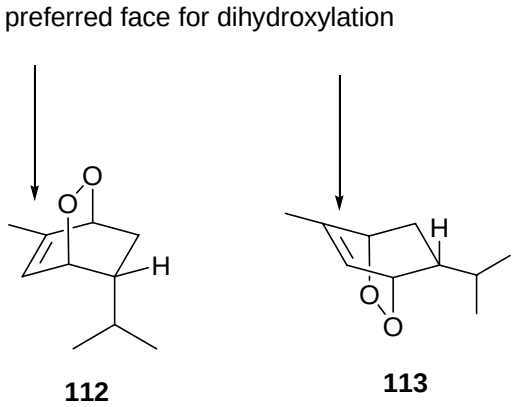
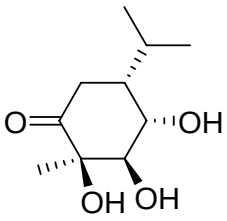


Figure 14. Illustration of the steric environment which directs the dihydroxylation of **112** and **113**.

The assigned stereochemistry of ketone **117**, which was confirmed by 2D NMR (Figure 15), shows that it must have been produced from a rearrangement of **116** and not from rearrangement of the other possible isomer (not observed) in which dihydroxylation would have been directed *syn* to the peroxide linkage. The formation of ketone **117** may have been initiated by a Kornblum-DeLaMare rearrangement, as discussed previously. This type of rearrangement is likely because of the presence of acidic H atoms to the peroxide linkage. It is also possible that ketone by-products, although not isolated, may be responsible for the relatively low yields of dihydroxylated compounds **114** and **115**.



117

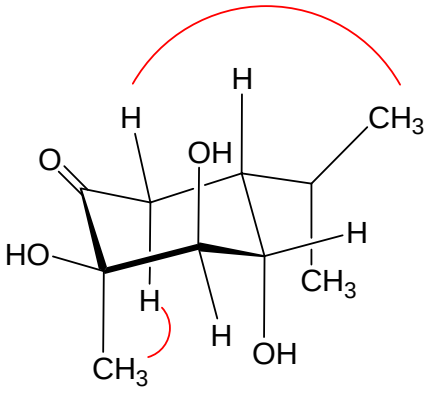
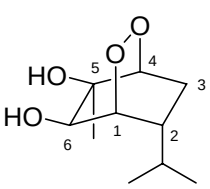
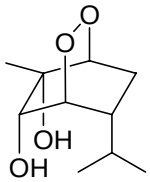


Figure 15. NOE interactions of protons in **117**.

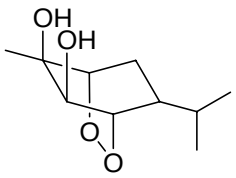
Table 5. ^{1}H and ^{13}C NMR data obtained for compounds **114, 115** and **116**.



114



115



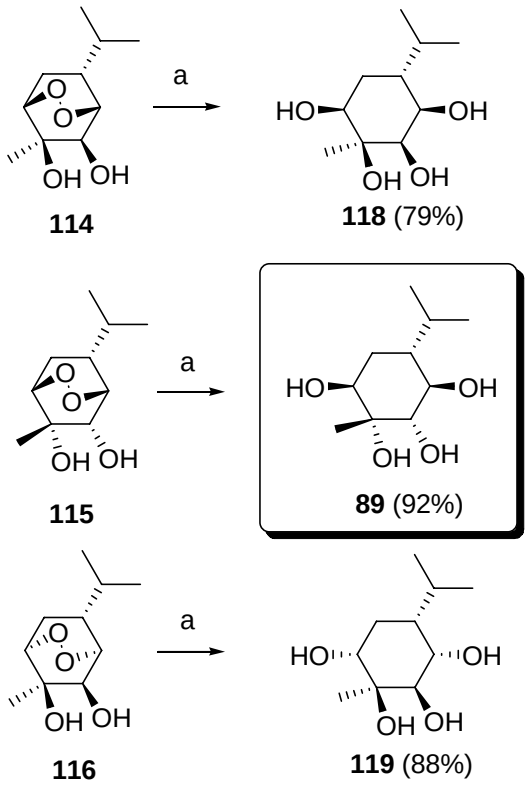
116

carbon	**114** ($CDCl_3$)		**115** ($CDCl_3$)		**116** ($CDCl_3$)	
	δ ^{1}H (*J*, Hz) ppm	δ ^{13}C ppm	δ ^{1}H (*J*, Hz) ppm	δ ^{13}C ppm	δ ^{1}H (*J*, Hz) ppm	δ ^{13}C ppm
1	4.08 (dd, 2.4, 1.8)	82.0	4.23 (ddd, 4.8 2.4, 2.4)	75.1	4.00 (dd, 3.6, 2.4)	76.9
2	1.91 (dddd, 10.8, 10.2, 8.4, 2.4)	40.8	1.77-1.91 (m)	40.5	1.60 (ddddd, 10.8, 9.6, 7.8, 3.0, 2.4)	33.7
3	1.30-1.35 (m)	27.1	1.77-1.91 (m)	24.8	1.71 (ddd, 13.8, 7.8, 3.0)	25.4
	2.40 (dddd, 14.4, 10.2, 6.0, 0.6)		2.15-2.32 (m)		2.27 (dddd, 13.8, 10.8, 3.0, 1.2)	
4	3.92 (dd, 6.0, 2.4)	78.7	3.88-3.95 (m)	78.8	3.89 (ddd, 3.0, 3.0, 3.0 Hz)	79.0
5		69.4		67.3		68.4
6	3.45-3.52 (m)	68.0	3.88-3.95 (m)	71.8	3.92 (d, 3.6)	70.6
Me	1.31 (s)	23.0	1.50 (s)	27.0	1.49 (s)	26.2
i-Pr	1.40 (dseptd, 10.8, 6.6, 0.6)	30.8	1.77-1.91 (m)	31.1	1.80 (dseptd, 9.6, 6.6, 1.2)	29.6
i-Pr	0.96 (d, 6.6)	20.3	0.91 (d, 6.0)	20.4	0.91 (d, 6.6)	20.0
i-Pr	0.97 (d, 6.6)	20.4	0.97 (d, 6.0)	21.2	0.98 (d, 6.6)	20.2

4.3 Reduction of diols of 2,3-dioxabicyclo[2.2.2]oct-5-enes from α-phellandrene

The peroxide bond of the new diols **114**, **115** and **116** was reduced with H_2/Pd/C in methanol (Scheme 40). The reductions proceeded smoothly in excellent yields providing the reported natural product **89** along with related isomers **118** and **119** (Scheme 40). The stereochemistry of the three tetraols was assigned by 2D NMR and the structure of **119** further confirmed by x-ray crystallography. The ROESY correlations used to assign the stereochemistry of compounds **118**, **119** and **89** are given in Figure 16. The crystal structure of tetraol **119** is shown in Figure 17.

Scheme 40.



(a) Pd/C (5%), H_2, MeOH.

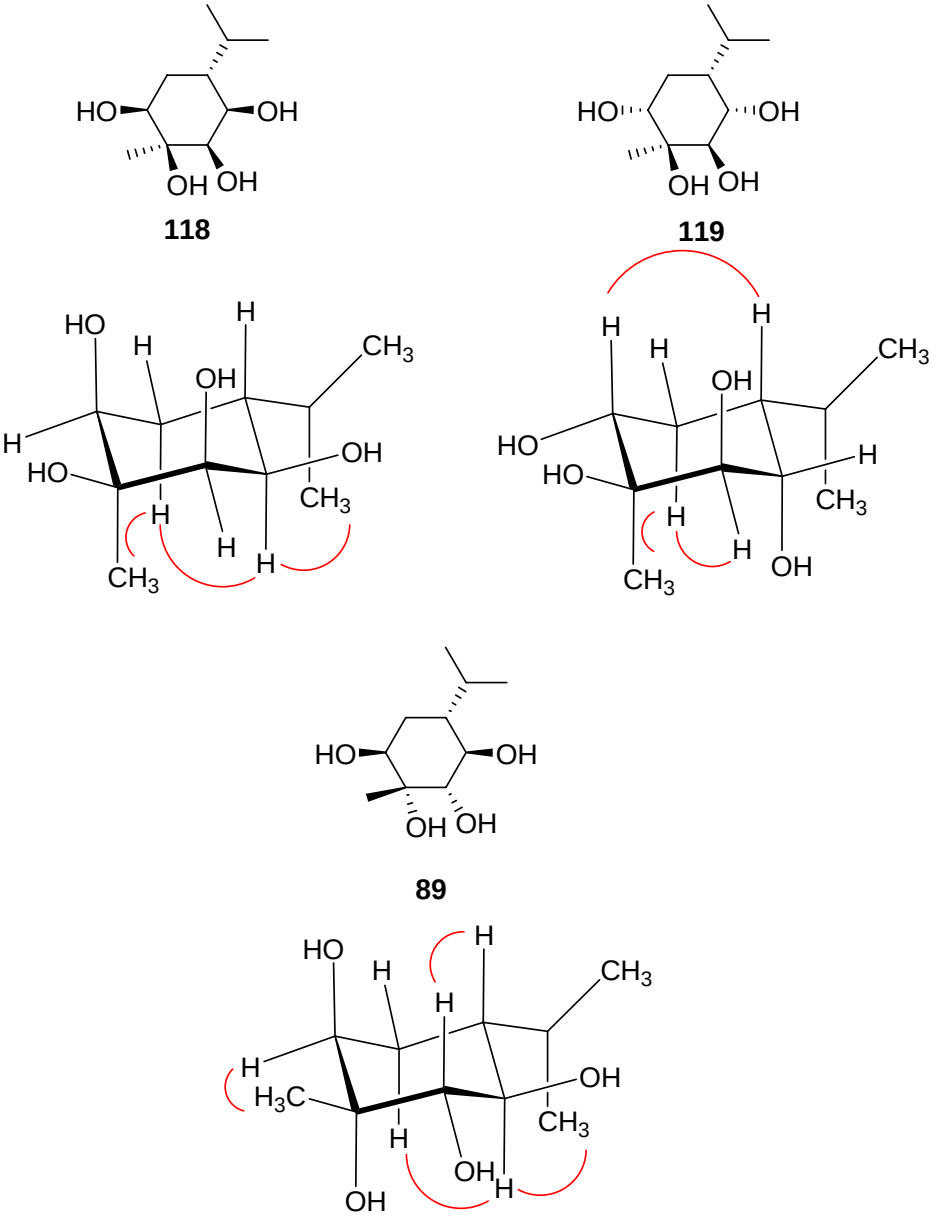
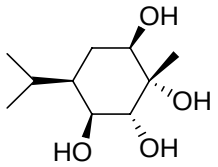


Figure 16. Through space interactions of protons in tetraols **118**, **119** and **89** showing the observed clear cross-peaks in the ROESY spectrum.



119

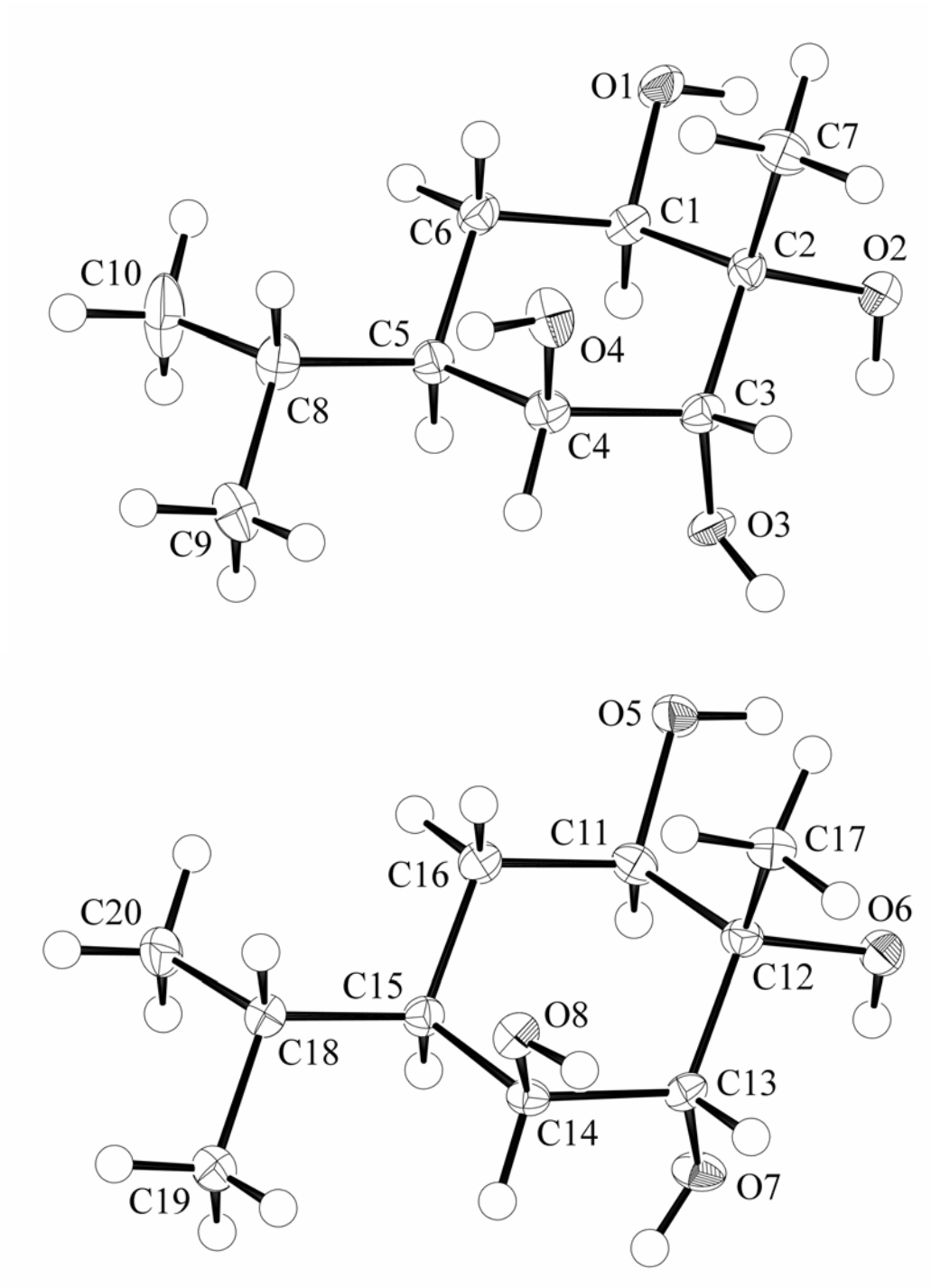
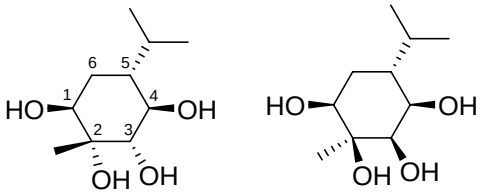


Figure 17. Molecular structure (50% probability ellipsoids) and crystallographic numbering scheme for the two conformations in tetraol **119**.

The synthesised tetraol **89**, however, did not match the data reported for this compound in the literature.[73, 74] Aside from reporting tetraol **89** as a new compound twice in the space of a year without referencing the first article in the second, there were a number of noticeable differences between synthesised tetraol **89** and that previously reported. It was observed that the melting point obtained for the synthetic tetraol **89** was 124-126 ºC whereas the compound reported in the literature was an oil. In addition, synthesised tetraol **89** was virtually insoluble in chloroform and dichloromethane, the solvents used to obtain NMR spectra and an optical rotation respectively for the reported literature compound. Obtaining an optical rotation in dichloromethane for comparison was therefore not possible. The High Resolution Single Ion Mass Spectrum (HRSIMS) obtained for $[M+H]^+$ of **89** by Gao *et al.*[74] was reported as 205.0536 for a calculated mass peak of $C_{10}H_{21}O_4^+$ 205.1434 (which actually should be 205.1440). This reported HRSIMS is outside the normal range for a match with the calculated mass, whilst the value for the synthetic compound **89** was within the acceptable limits. The authors also report an IR peak at 1705 cm^{-1} in the compound characterization data which is in contradiction to the proposed structure. Upon obtaining ^1H and ^{13}C NMR spectra of synthesised tetraol **89** and isomer **118** in $CDCl_3$ it was clear that the compound reported in the literature was not tetraol **89**, nor isomer **118**, Table 6. It proved impossible to obtain a satisfactory spectrum of **119** in $CDCl_3$ for comparison due to extremely poor solubility. Consequently it was concluded that the reported tetraol **89** is not the correct structural assignment for the compound isolated by Gao *et al*.

Table 6. Comparison of reported ^{1}H and ^{13}C NMR data for **89** with that obtained for synthesised **89** and **118**, in $CDCl_3$.



89 **118**

carbon	**89** (lit.)		**89** (synthesized)		**118** (synthesized)	
	δ ^{1}H (*J*, Hz) ppm	δ ^{13}C ppm	δ ^{1}H (*J*, Hz) ppm	δ ^{13}C ppm	δ ^{1}H (*J*, Hz) ppm	δ ^{13}C ppm
1	3.77 (t, 2.4)	72.9	3.77 (brs)	73.3	3.70 (brs)	78.1
2		74.6		74.3		73.0
3	3.69 (d, 9.3)	76.7	3.50 (d, 9.6)	77.3	3.62 (brd, 7.2)	70.6
4	3.96 (dd, 11.4, 9.3)	68.9	3.53 (dd, 9.6, 9.6)	73.8	3.67 (brs)	74.3
5	1.97 (ddt, 11.7, 11.4, 3.0)	41.4	1.76 (m)	40.6	1.77 (m)	37.9
6	1.78 (m)	26.8	1.78(m)	26.2	1.78 (m)	26.4
	1.70 (m)		1.56(m)		1.41 (brt, *J* = 7.2 Hz)	
Me	1.39 (s)	23.9	1.39 (s)	23.7	1.18 (s)	22.8
i-Pr	2.30 (m)	27.8	2.18 (dsept, 6.6, 1.8)	25.6	2.08 (brs)	25.5
i-Pr	0.92 (d, 7.2)	20.9	0.95 (d, 6.6)	20.8	0.96 (d, 7.2)	20.9
i-Pr	0.78 (d, 7.2)	14.9	0.86 (d, 6.6)	16.0	0.87 (d, 7.2)	16.9

It was shown in Chapter 3 that the stability of the synthesized 2,3-dioxabicyclo[2.2.2]octane-5,6-diols was found to be extremely variable. Therefore the next chapter will examine this phenomenon with a view to a possible new rearrangement.

Chapter 5: Facile Rearrangement of 2,3-Dioxabicyclo[2.2.2]octane-5,6-diols

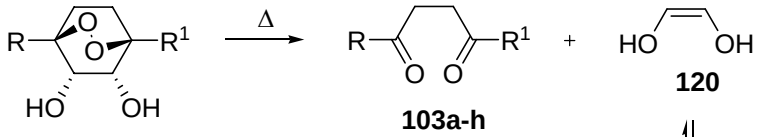
5.1 Introduction

The thermal, photochemical and metal-catalysed rearrangement of bicyclic endoperoxides has been extensively studied, and is summarised in Chapter 1.2.5. However, no such possible transformations have been investigated for 2,3-dioxabicyclo[2.2.2]octane-5,6-diol (**66,** Scheme 41) substrates. Consequently, studies on the thermal and photochemical decomposition of systems of type **66** are the focus of this chapter.

5.2 Rearrangement

As was previously mentioned in Chapter 3.3, the stability of diols of type **66** (Scheme 41) was found to be extremely variable during their formation and isolation. Upon closer examination it was discovered that these diols **66** undergo an extremely clean rearrangement to their 1,4-dicarbonyls **103** and glycoaldehyde (**121**), Scheme 41, a rearrangement not yet reported in the literature.

Scheme 41.



66b: R = Ph, R^1 = H
66c: R = R^1 = Me
66d: R = Me, R^1 = *i*-Pr
66e: R = Me, R^1 = $CH_2CH_2CO_2Me$
66f: R = R^1 = CH_2CO_2Me
66g: R = R^1 = Ph
66h: R = R^1 = *p*-F-Ph

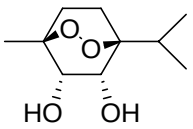
This rearrangement was examined for a range of peroxide diols **66b-h** under a variety of conditions as summarized in Table 7. It was found that the thermally induced rearrangement of diols **66b-h** to dicarbonyls **103b-h** proceeds quantitatively in acetonitrile and can tolerate a broad range of substituents R and R^1. Comparison of entries 2-8 or 10-12 clearly indicates that the reaction rate increases with solvent polarity.

Table 7. Thermal rearrangement of 2,3-dioxabicyclo[2.2.2]octane-5,6-diols **66b-h** to dicarbonyls **103b-h**.

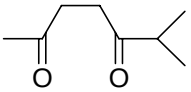
entry	diol	solvent/conditions	**103** (% conversion)
1	**66b**	Neat/4^{o}C 16hr	90
2	**66d**	Methanol/reflux 0.5hr	100
4	**66d**	Acetonitrile/reflux 2hr	100
5	**66d**	Ethylacetate/reflux 5.5hr	100
6	**66d**	THF/reflux 16hr	100
7	**66d**	Benzene/reflux 16hr	0
8	**66d**	DCM/Reflux 24hr	0
9	**66d**	Neat/4^{o}C 1 week	25
10	**66e**	Acetonitrile/reflux 16hr	100
11	**66e**	THF/reflux 16hr	50
12	**66e**	DCM/reflux 16hr	0
13	**66e**	Neat/4^{o}C 48hr	100
14	**66c**	Acetonitrile/reflux 16hr	100
15	**66f**	Acetonitrile/reflux 16hr	100
16	**66g**	Acetonitrile/reflux 16h	100
17	**66h**	Acetonitrile/reflux 16h	100

It has previously been reported that thermal decomposition of 2,3-dioxabicyclo[2.2.2]octane proceeds in a radical manner involving first the homolytic cleavage of the peroxide linkage followed by β-scission.[17] This process affords a range of products via a quite polar transition state, with the rate-determining step being accelerated with increasing solvent polarity and H-bonding. Moreover, it has been demonstrated that β-scission is the rate determining step in the decompositions of alkoxy radicals, generated from homolytic cleavage of dialkylperoxides, and is again accelerated with increasing solvent polarity and the ability for H-bonding, particularly in protic solvents.[97] To further demonstrate that the rearrangement was accelerated with increasing solvent polarity a preliminary study of the thermolysis kinetics of diol **66d** was made. The decomposition of **66d** in solvents of different polarity was monitored by following its disappearance by TLC. The results are collected in Table 8.

Table 8. Rate of thermal rearrangement of diol **66d** to dicarbonyl **103d** in solvents of increasing polarity.



66d



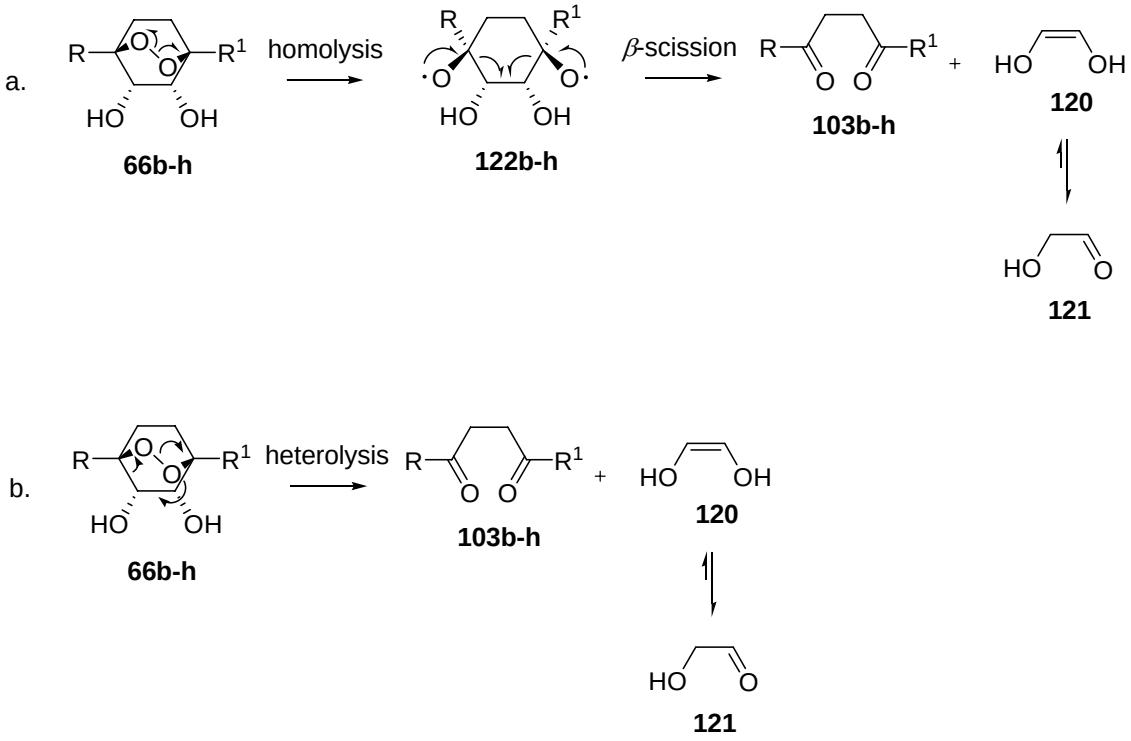
103d

Solvent	Polarity Index (p)	Boiling Point (^{o}C)	Completion time (Hr)
acetonitrile	5.8	82	2.0
methanol	5.1	65	0.5
ethyl acetate	4.4	77	5.5
THF	4.0	61.0	16
iso-propanol	3.9	82	24
DCM	3.1	41	-

It can be clearly seen that the rate of rearrangement is accelerated with solvents of increasing polarity, in particular the protic solvent methanol.

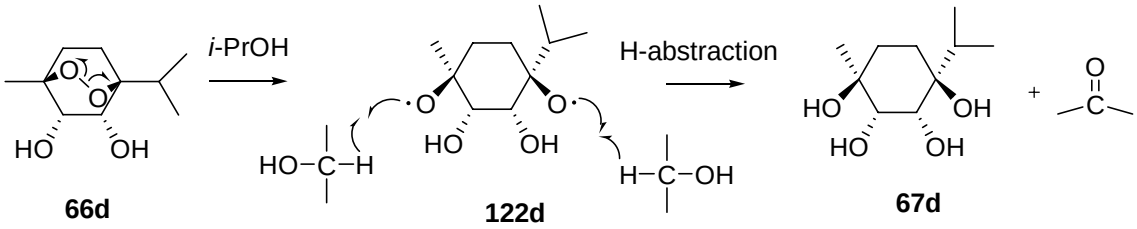
With the knowledge gained from these experiments it can be proposed that the rearrangement of 2,3-dioxabicyclo[2.2.2]octane-5,6-diols proceeds via the mechanism depicted in Scheme 42a, i.e. homolytic cleavage of the peroxide linkage followed by double *β*-scission. An alternative mechanism, which involves a concerted reorganisation of three bonds in a retrocycloaddition (Scheme 42b), appears not to be operative.

Scheme 42.



A further confirmation that decomposition was a radical process was made when diol **66d** was heated in isopropanol. This solvent is well known to inhibit free radical processes by competing radical abstraction of a hydrogen atom from isopropanol to afford acetone.[48, 59] Indeed, tetraol **67d** (Scheme 43) was isolated in 30% yield, with the remainder of the product being 1,4-diketone **103d**, confirming the free radical nature of these rearrangements.

Scheme 43.

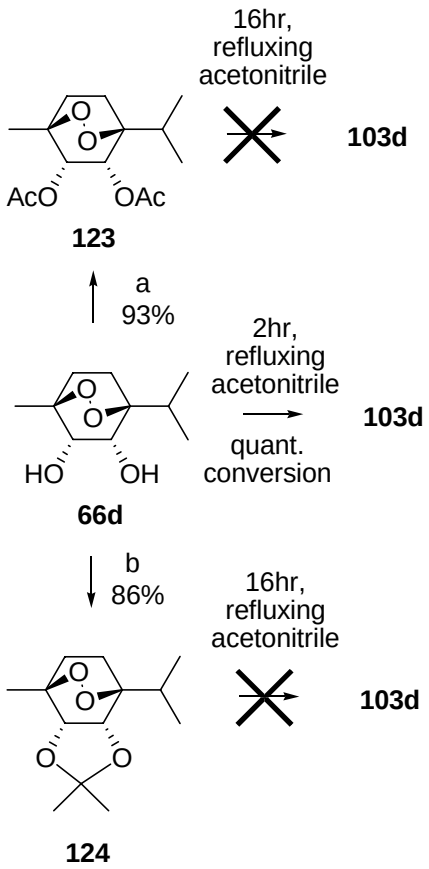


Because of the instability of the 2,3-dioxabicyclo[2.2.2]octane-5,6-diols **66b-h** it was decided to protect the diol moiety of **66d** as the acetonide. This technique has been utilised previously by Robinson *et al.*[29] for the stabilization of dihydroxylated 1,2-dioxines. Furthermore this would allow examination of the importance of the "free" hydroxyl groups within diol **66d** on the outcome of this rearrangement. It was also decided to protect the diol of **66d** as their acetates in order to gauge the effect of electron withdrawing groups.

The di-acetate **123** was synthesised from **66d** using acetic anhydride and pyridine in 93% yield, whilst the acetonide **124** was synthesised from **66d** using 2,2-dimethoxypropane and catalytic *p*-TSA in 86% yield, Scheme 44. Neither the di-acetate

123 nor the acetonide **124** showed any sign of decomposition in refluxing acetonitrile over 16hrs. In comparison, the unprotected diol **66d** was completely converted into diketone **103d** within 2 hours, Scheme 44. Thus it appears that under thermal conditions the presence of free hydroxyl groups increases the rate of rearrangement considerably. This tells us firstly that the hydroxy groups are a crucial feature in this rearrangement. Secondly, because we have introduced an electron withdrawing functionality with the acetyl group, and maintained an electron-donating functionality with the acetonide it seems likely that electronic factors play only a very minimal role.

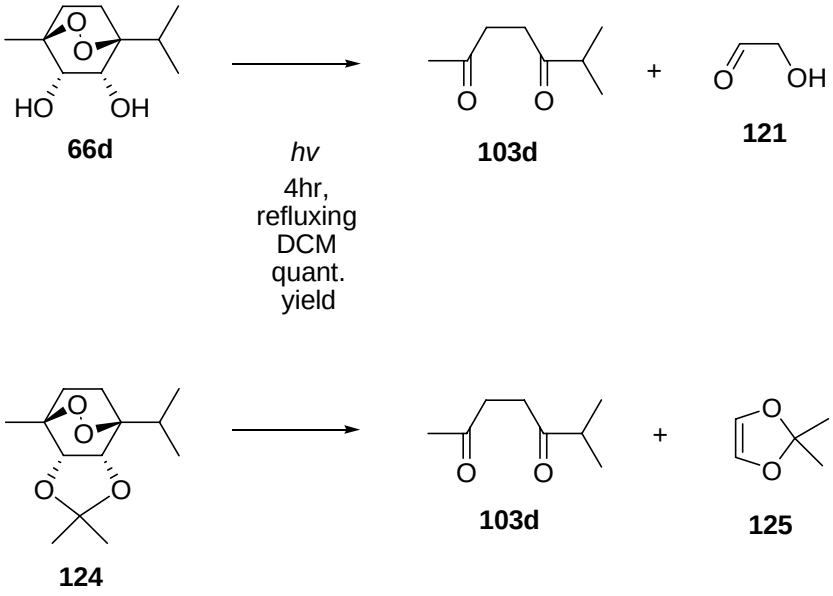
Scheme 44.



(a) acetic anhydride, pyridine
(b) 2,2-dimethoxypropane, *p*-TSA, DCM.

Interestingly, under photolytic conditions both the protected **124** and free **66d** diol underwent complete conversion to dicarbonyl **103d** in 4hrs in refluxing dichloromethane (Scheme 45); conditions within which **66d** is stable in the absence of light (compare with Table 7, Entry 8). The other by-product in the rearrangement of the acetonide **124** was 2,2-dimethyl-1,3-dioxole (**125**), which was detected by characteristic peaks in both the ^{1}H and ^{13}C NMR spectra.[98]

Scheme 45.

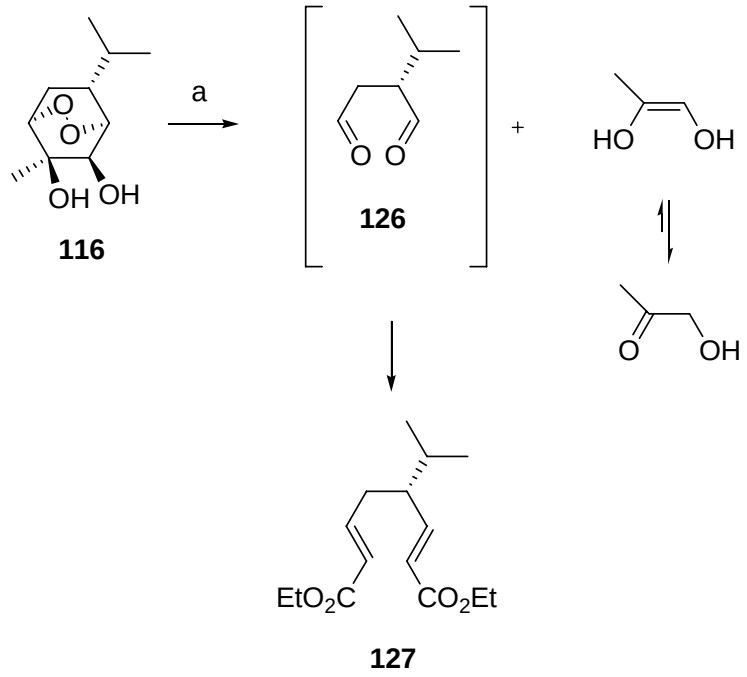


The fact that identical rates were obtained for photolytic decomposition of diol **66d** and acetonide **124** and different rates were determined for their thermal decomposition can be explained by the following: Photo-dissociation of the peroxide linkage initially affords an excited dialkoxy-radical, which undergoes decomposition, via β-scission, in an 'early vibration' as opposed to the thermal decomposition, which is reversible.[54]

5.3 Synthesis of optically pure 1,4-dicarbonyl compounds.

Formation of 1,4-dicarbonyl compounds in this fashion opens the opportunity for the synthesis of dicarbonyls containing other stereochemical features such as chiral centres. It was shown in Chapter 4.2 that photooxidation of *α*-phellandrene (**111**) followed by dihydroxylation provided compound **116**. As an example diol **116** was heated in acetonitrile under reflux, followed by *in situ* trapping of the subsequently formed dialdehyde **126** with ethyl (triphenyl-λ^5-phosphanylidene)acetate. This process afforded diester **127**, which contains a chiral carbon, in 90% yield, Scheme 46.

Scheme 46.

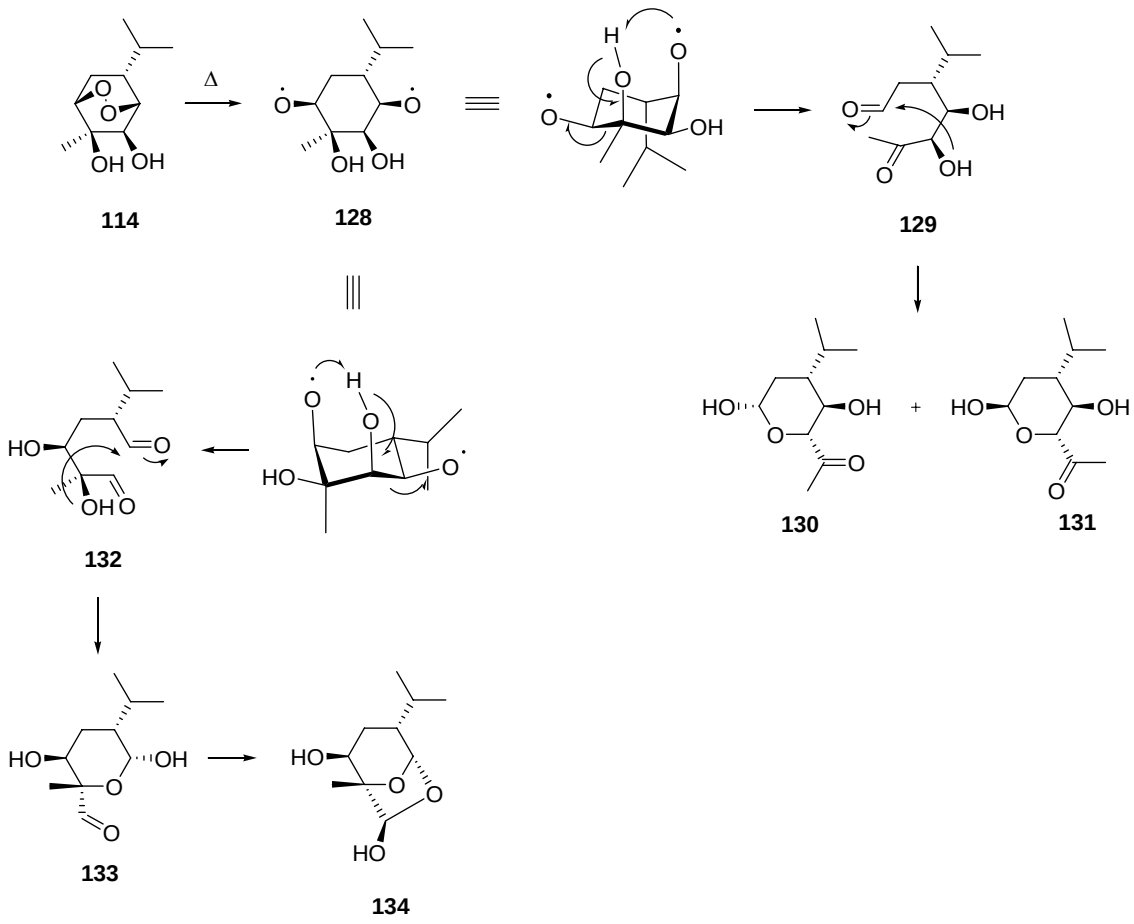


(a) acetonitrile, ethyl (triphenyl-λ^5-phosphanylidene)acetate, Δ.

5.4 Diol orientation with respect to peroxide bond and its influence on radical rearrangement.

It was shown in Chapter 5.3 that heating the *anti* diol **116** in acetonitrile afforded dicarbonyl **126**. The fact that the *syn* diastereomer of α-phellandrene derived diol (**114**) was also at hand provided a unique opportunity to examine the relationship of the peroxide bond to the diol on product outcome during thermolysis, Scheme 47.

Scheme 47.



Decomposition of **114** in acetonitrile under reflux resulted in the formation of a 1 : 1 mixture of anomers **130**, **131** and bicyclic hemiacetal **134**, with none of the dialdehyde **126** being formed. Anomers **130** and **131** were heated under the reaction conditions and did not give rise to compound **134**. The formation of the mixture of anomers (**130** and **131**) and **134** is rationalised from intramolecular hydrogen atom abstraction of different chair conformations of diradical **128**, Scheme 47. The formation of these compounds, as opposed to dialdehyde **126**, is due to the orientation of the hydroxyl group and its proximity to the oxygen-centred radical resulting from homolytic cleavage.

Confirmation of the structures was made by examining the clear cross-peaks in the ROESY spectrum and are given for compounds **130**, **131** and **134** in Figure 18.

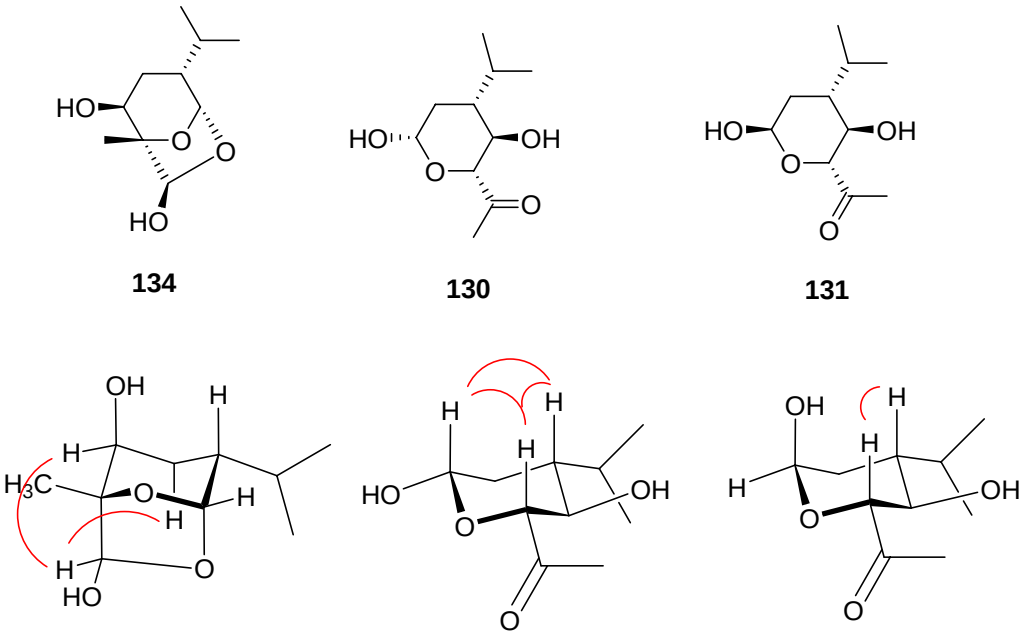


Figure 18. Through space interactions of protons in compounds **130**, **131** and **134** showing the observed clear cross-peaks in the ROESY spectrum.

5.5 Summary

This thesis has described the dihydroxylation of 2,3-dioxabicyclo[2.2.2]oct-5-enes and the utility of these products in synthesis.

Herein has been demonstrated an alternative route to cyclohexane-1,2,3,4-tetraols bearing the toxocarol relative stereochemistry. This method has higher selectivity in cases where the parent 2,3-dioxabicyclo[2.2.2]oct-5-enes contains functionality other than H at the bridgehead position(s). This alternative route also allows for a simplified workup and the necessity in some literature procedures for a protection / deprotection protocol has been removed. The application of this dihydroxylation procedure on 2,3-dioxabicyclo[2.2.2]oct-5-enes led to the synthesis of tetraols **89**, **118** and **119** and demonstrated that **89** was not the natural product isolated by Gao *et al*, nor was it the configuration of tetraols **118** or **119**.

A mechanistic explanation for the susceptibility of 2,3-dioxabicyclo[2.2.2]oct-5,6-diols to rearrange to 1,4-dicarbonyl compounds has been presented. It was proposed that homolytic cleavage of the peroxide bond followed by β-scission of the resulting alkoxy redicals results in the formation of 1,4-dicarbonyls and glycoaldehyde. The presence of the diol moiety appears to speed up the process by allowing hydrogen bonding to occur in the transition state.

Finally, a route towards optically pure substituted dicarbonyl compounds has been presented in a preliminary sense.

5.6 Conclusion

Having demonstrated that dihydroxylation at the double bond of 1,4-disubstituted endoperoxides is achievable it may be possible in future to perform further functionality at this position. This opens up the opportunity to synthesise a variety of natural products that contain specific stereochemistry.

Furthurmore, subjecting the functionalised endoperoxides to the newly discovered rearrangement would in turn produce a whole new variety of 1,4 dikertones, including those with optical activity.

Chapter 6: Experimental

6.1 General Methods

Reagents/solvents for anhydrous reactions were dried as follows: THF and ether were distilled from sodium wire with benzophenone as indicator. Dichloromethane, hexane, toluene, pyridine, *N*,*N*-dimethylformamide, triethylamine and dimethylsulfoxide were dried by appropriate methods[99] and stored over 4 Å molecular sieves. Methanol was dried and stored over 3 Å molecular sieves. *n*-Butyllithium was titrated against diphenylacetic acid before use. All organic extracts were dried over anhydrous magnesium sulphate.

All compounds were purified by column chromatography utilising *Merck* silica gel (230-400 mesh ASTM), unless otherwise stated. Thin layer chromatography (TLC) was carried out on commercially available pre-coated aluminium plates (Merck $60F_{254}$) and visualized under 254 nm light, or developed with vanillin dip.

Melting points were determined using a *Mel Temp* Electrothermal apparatus and are uncorrected.

Infrared spectra were recorded on an ATI Mattson Genesis Series FTIR spectrophotometer.

Microanalyses were carried out at the University of Otago, New Zealand.

Low and high resolution EI and ESI mass spectra were recorded by Central Science Laboratory at The University of Tasmania, Australia.

X-ray crystallography of compounds **66h**, **67d** and **119** was performed by Dr. Edward R. T. Tiekink, The University of Texas at San Antonio, U.S.A, using a Bruker AXS SMART CCD.

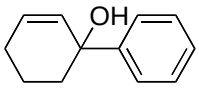
^{1}H, ^{13}C, HMBC, HSQC, COSY, and ROESY NMR spectra were recorded on Varian Gemini 200, Varian Gemini 300 or Varian Unity Inova 600 Fourier transform spectrometers using an internal deuterium lock. $CDCl_3$ (77.0 ppm) or TMS (0 ppm) were used as internal standards. NMR spectra recorded in CD_3OD were calibrated to CD_3OD (3.31 and 49.0 ppm). All resonances are given in parts per million (ppm). ^{1}H NMR multiplicities are given the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), pentet (p), sextet (sext), septet (sept), multiplet (m) and broad (br) referring to broadened signals. All coupling constants (*J*) are given in Hertz (Hz).

All yields reported refer to isolated material judged to be homogeneous by TLC and NMR spectroscopy.

The following compounds were purchased from *Sigma-Aldrich* chemical company and used without further purification: rose bengal *bis*(triethylammonium)salt, 2,2-dimethoxypropane, 1,4-cyclohexanedione (**57**), 1,3-cyclohexadiene (**68a**), 1-phenyl-1,3-cyclohexadiene (**68b**), α-terpinene (**68d**), 2,4-dinitro-benzenesulfenyl chloride (**72**), triethylphosphonoacetate (**76**) and α-phellandrene (**111**).

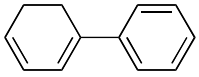
6.2 Compounds Described in Chapter 2

1-Phenyl-2-cyclohexen-1-ol (71)[62]



To a solution of bromobenzene (3.3 g, 21 mmol) in dry diethyl ether (10 mL) under nitrogen at 0 ^{o}C was slowly added 2.5M *n*-butyllithium (8.4 mL, 21 mmol)) in hexane. The solution was cooled to -78 ^{o}C and 2-cyclohexenone (**69**) (1.92 g, 20 mmol) in diethyl ether (20mL) was added dropwise. The solution was allowed to warm to 0 ^{o}C over 20 minutes and quenched with ice water (20 mL). The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography. Yield 2.5 g, 72%; White solid; mp: 42-44 °C (Lit.[62] 44-45 °C); R_f 0.48 (1:4 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54-1.63 (m, 1H), 1.72-1.82 (m, 1H), 1.85 (dd, 1H, *J* = 12.8, 2.8 Hz), 1.99-2.16 (m, 4H), 5.75 (d, 1H, *J* = 10.0), 6.00 (ddd, 1H, *J* = 10, 3.9, 3.7 Hz), 7.22 (tt, 1H, *J* = 7.4, 1.2 Hz), 7.31 (t, 2H, *J* = 7.8), 7.46 (d, 2H, *J* = 7.8) ^{13}C NMR (75 MHz, $CDCl_3$): 19.2, 25.0, 39.5, 72.1, 125.3, 126.6, 127.9, 130.4, 132.1, 147.7.

1-(Cyclohexa-1,3-dienyl) benzene (68b) [61]



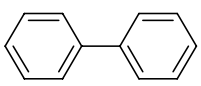
Method A

To a stirring solution 1-phenyl-2-cyclohexen-1-ol (**71**) (3.0 g, 17.2 mmol) and triethylamine (5.9 mL, 43mmol) in dicloromethane at 0 ^{o}C was added slowly 2,4-dinitrobenzenesulfenyl chloride (**72**) (8.1 g, 34.4 mmol). The mixture was allowed to warm to rt and stirred overnight. *n*-Pentane (120 mL) was added and the slurry filtered. The slurry was washed with a further 120 mL aliquot of *n*-pentane. The filtrate was concentrated *in vacuo* and the product purified by column chromatography. Yield 1.69 g, 63%; colourless solid; mp: 38-40 °C (Lit.[61] 38-39 °C); R_f 0.85 (DCM); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.25-2.40 (m, 2H), 2.60 (tt, 2H, *J* = 10.0, 2.6), 5.88 (dddd, 1H, *J* = 9.6, 4.5, 4.5, 0.8 Hz), 6.08 (ddt, 1H, *J* = 9.6, 5.4, 1.8 Hz), 6.32 (dd, 1H, *J* = 5.4, 0.8 Hz), 7.30-7.50 (m, 3H), 7.55-7.65 (m, 2H).

Method B

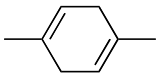
A solution of 1-phenyl-2-cyclohexen-1-ol (**71**) (1.0 g, 5.7 mmol) and *p*-toluenesulfonic acid (10 mg) in benzene (50 mL) was heated under reflux and the water formed driven off by azeotropic distillation (Dean-Stark). Removal of the solvent *in vacuo* and purification by column chromatography gave the desired product. Yield 125 mg, 14%.

Biphenyl (73).[100]



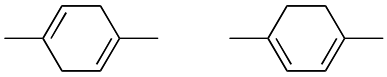
White solid; mp: 68-70 °C (Lit.[100] 69-71 °C); R_f 0.80 (DCM); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, 2H, *J* = 7.4 Hz), 7.43 (t, 4H, *J* = 7.4 Hz), 7.59 (d, 4H, *J* = 7.4 Hz).

1,4-Dimethyl-1,4-cyclohexadiene (75a).[101]



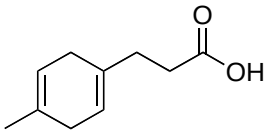
Ammonia (70ml) was condensed in a 250 mL flask at -78 ^{o}C under Nitrogen. *p*-xylene (**74a**) (10g, 94mmol) in dry THF (50 mL) was added slowly with stirring. Lithium (2.0 g) was added in small portions followed by absolute ethanol (15 g), and the mixture stirred at -78 ^{o}C for 3 hours. The reaction was allowed to heat up to room temperature overnight to evaporate the remaining ammonia. The mixture was poured into water (100 mL) and extracted with hexane (3 x 50 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The product was used without further purification. Yield 7.5 g, 74%; colourless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66 (s, 6H), 2.55 (s, 4H), 5.40 (m, 2H).

1,4-Dimethyl-1,4-cyclohexadiene (74a) / 1,4-dimethyl-1,3-cyclohexadiene (68c). [63]



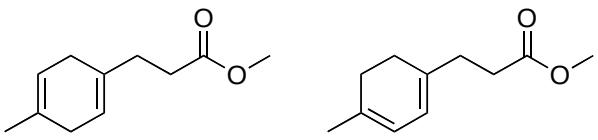
1,4-dimethyl-1,4-cyclohexadiene (**74a**) (10 g, 0.09 mmol) was refluxed in 10% HCl (100 mL) for 14h. After cooling to rt the mixture was extracted into ether (3 x 50 mL), washed with H_2O until neutral and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo gave a 30:70 mixture of 1,4-dimethyl-1,4-cyclohexadiene (**75a**) and 1,4-dimethyl-1,3-cyclohexadiene (**68c**). Combined yield 7.7 g, 89%; **68c** ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.75 (s, 6H), 2.10 (s, 4H), 5.57 (s, 2H).

3-(4-Methyl-cyclohexa-1,4-dienyl)-propanoic acid (75b)[102]



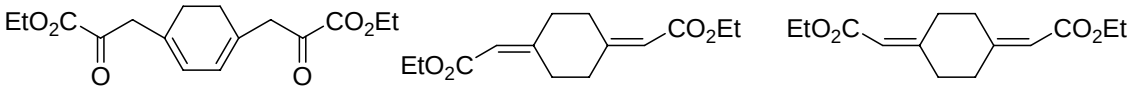
Ammonia (60 mL) was condensed in a 250 mL flask at -65 ^{o}C under Nitrogen. 3-*p*-tolylpropanoic acid (**74b**) (1.0 g, 6.1 mmol) in dry THF (20 mL) was added slowly with stirring. Lithium (1.5 g) was added in small portions over 30 minutes. The mixture was allowed to heat up to bring about evaporation of the ammonia. Ethanol (5 mL) was added over a 1 hour period. A further aliquot of ethanol was added and the remaining ammonia allowed to evaporate. The remaining solution was poured into water (100 mL) and extracted with hexane (3 x 50 mL). The aqueous layer was cooled to 0 ^{o}C and acidified. The product was extracted with diethyl ether and the combined organics were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The white solid obtained was used without further purification. Yield 0.89 g, 88%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69 (s, 3H), 2.26-2.35 (m, 2H), 2.46-2.54, (m, 2H), 2.56-2.64 (4H), 5.38-5.43 (m, 1H), 5.44-5.49 (m, 1H).

Methyl 3-(4-methyl-cyclohexa-1,4-dienyl)-propanoate (75c) / methyl 3-(4-methyl-cyclohexa-1,3-dienyl)-propanoate (68e).



A solution of 3-(4-methyl-cyclohexa-1,4-dienyl)-propanoic acid (**75b**) (0.5 g, 3 mmol) in dry methanol (20 mL) and H_2SO_4 (0.5 mL) was stirred under reflux for 16 hours under nitrogen. The methanol was removed *in vacuo* and water (30 mL) added. The product was extracted with diethyl ether (3 x 20 mL), washed with saturated $NaHCO_3$ and the combined organics were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The product, which was used without further purification, was a 30 : 70 mixture of the 1,3- and 1,4- isomers (0.50 g, 92%). **75c** ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.67 (s, 3H), 2.27-2.32 (m, 2H), 2.42-2.48, (m, 2H), 2.58 (brs, 4H), 3.67 (s, 3H), 5.40-5.44 (m, 2H); **68e** ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76 (s, 3H), 2.11 (brs, 4H), 2.35-2.49, (m, 4H), 3.67 (s, 3H), 5.59 (s, 2H).

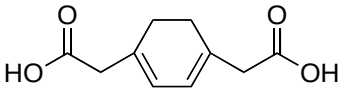
Diethyl 2,2'-cyclohexa-1,3-diene-1,4-diyldiacetate (68i), diethyl (2*E*,2'*E*)-2,2'-cyclohexane-1,4-diylidenediethanoate (77) and diethyl (2*Z*,2'*Z*)-2,2'-cyclohexane-1,4-diylidenediethanoate (78).[64]



To a dry, 300 mL, 3-necked, round-bottom flask, under N_2 was added 80% sodium hydride in mineral oil (2.58 g, 85 mmol). The mineral oil was removed by washing with *n*-hexane, and benzene (20 mL) added. The mixture was cooled in an ice-bath and triethyl phosphonoacetate (18.7 g, 83. 2mmol) added dropwise. The mixture was stirred for 0.5 hr, after the evolution of hydrogen had ceased. A solution of 1,4-cyclohexanedione (4.67 g, 41.6 mmol) was then added dropwise over 30 min. A sticky orange precipitate of sodium diethyl phosphate formed which made stirring difficult. The mixture was boiled under reflux for 30 min. After cooling to rt the benzene was

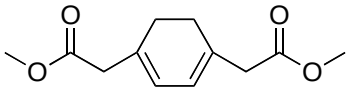
decanted and the residue washed with hot benzene (3 x 20 mL). The combined benzene solution was concentrated to dryness *in vacuo* to give a 60 : 20 : 20 mixture of 1,4-diene (**68i**), *E* (**77**) and *Z* (**78**) isomers (7.9 g, 75%), confirmed by ^{1}H NMR.[64] The mixture was used without further purification.

2,2'-Cyclohexa-1,3-diene-1,4-diyldiacetic acid (68j).[103]



To a solution containing a 60 : 20 : 20 mixture of 1,4-diene (**68i**), *E* (**77**) and *Z* (**78**) isomers (8.1 g, 32 mmol) in methanol (200 mL) was added KOH (18 g, 320 mmol), and the mixture was stirred under reflux for 1 hr. The methanol was removed under reduced pressure and H_2O (200 mL) was added. The solution was acidified with HCl, extracted with diethyl ether (3 x 100 mL), washed with H_2O and the combined organics were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The resulting solid was used without further purification. Yield 6.0 g, 95 %. White solid; mp: 184-188 °C (Lit.[103] 184-188 °C); ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 2.26 (s, 4H), 3.07 (s, 4H), 5.70 (s, 2H).

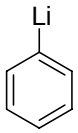
1,3-Cyclohexadiene-1,4-dimethylethanoate (68f).



A solution of 1,3-cyclohexadiene-1,4-diethanoic acid (**68j**) (6.0 g, 30.6 mmol) in dry methanol (100 mL) and concentrated H_2SO_4 (3 mL) was heated under reflux for 16

hours. The methanol was removed under reduced pressure and saturated $NaHCO_3$ (50 mL) was added. The product was extracted with diethyl ether (3 x 75 mL), washed with H_2O and the combined organics were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The resulting residue was purified by flash chromatography. Yield 4.93 g, 72 %; Colourless liquid; R_f 0.50 (DCM); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 4H), 3.09 (s, 4H), 3.68 (s, 6H), 5.76 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 26.9, 42.4, 52.0, 122.7, 130.6, 171.9; IR (solid): 2953, 1732, 1436, 1255, 1152, 1007 cm^{-1}.

Phenyllithium (70a).



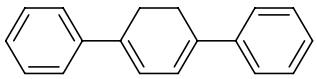
To a stirring solution of bromobenzene (11.2 g, 71.3 mmol) in dry ether (50 mL) was added drop-wise *n*-butyllithium (36.8 mL, 1.94 M in cyclohexane) under anhydrous nitrogen at -30 ^{o}C. After addition the reaction mixture was allowed to warm to room temperature. The mixture was used without further purification.

1,4-Diphenyl-1,3-cyclohexadiene (68g) and 1,4-diphenyl-1,4-cyclohexadiene (75d) (isomer mixture). [104]

To a solution of phenyllithium (**70a**) in anhydrous ether (87 mL, 71.3 mmol,) was added solid 1,4-cyclohexanedione (**57**) (2.0 g, 17.8 mmol) in anhydrous ether (50 mL) over 30

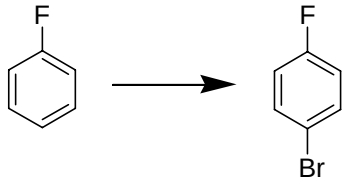
minutes. The reaction mixture was brought to reflux for 30 minutes, cooled in an ice bath and 50% sulphuric acid (100 mL) added slowly. The organic layer was separated and the aqueous layer extracted with ether (3 x 50 mL). The combined organics were washed with saturated Na_2CO_3, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The product was recrystallised from ethanol to give a mixture of the 1,3- and 1,4-isomers (70 : 30) as a yellow solid. Yield 1.9 g, 46%. (**68g**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.78 (s, 4H), 6.53 (s, 2H), 7.20-7.41 (m, 6H), 7.45-7.55 (m, 4H); (**75g**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.31 (s, 4H), 6.28 (s, 2H), 7.20-7.41 (m, 6H), 7.45-7.55 (m, 4H).

1,4-Diphenyl-1,3-cyclohexadiene 1c (68g). [65]



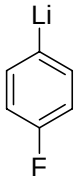
The isomeric mixture of 1,4-diphenylcyclohexadienes (**68g**, **75d**) (1.0 g, 4.3 mmol) was heated under reflux for 4 hours in *t*-butanol (250 mL) containing potassium *t*-butoxide (7.0 g). After cooling to rt most of the *t*-butanol was removed under reduced pressure and water (150mL) was added. The mixture was extracted with ethyl ether (3 x 100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude product was recrystallised from benzene to yield 1,4-diphenyl-1,3-cyclohexadiene (**68g**) as yellow flakes. Yield 0.75g, 75%; mp: 180-182 °C (lit[65] = 179-180 °C).

1-Bromo-4-fluorobenzene. [105]



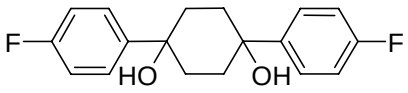
To a 2-necked round bottom flask equipped with a condenser and dropping funnel was added fluorobenzene (5 g, 52 mmol) and $FeCl_3$ (100 mg). The mixture was cooled to –8^{o}C with an ice/salt bath. Bromine (8.5 g, 53 mmol) was then added drop-wise over 2 hours. Following addition of bromine the reaction was heated to 60^{o}C for 1 hour. The crude product was distilled at atmospheric pressure to yield 1-bromo-4-fluorobenzene (6.37 g, 70%) as a colourless oil. bp: 148 -152 ^{o}C (Lit.[105] 150 ^{o}C).

4-Fluorophenyllithium (70b).



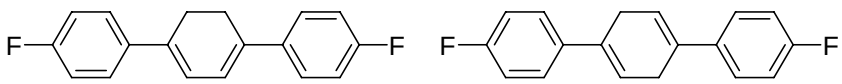
To a stirred solution of butyllithium (16 mL, 1.9 M in hexane) in dry ethyl ether (20 mL) under anhydrous nitrogen at -30 ^{o}C was added drop-wise 1-bromo-4-fluorobenzene (5.25 g, 30 mmol) in dry ethyl ether (20 mL). After addition the reaction mixture was allowed to warm to room temperature. The mixture was used without further purification.

1,4-Di-(4-fluorophenyl)-1,4-cyclohexadiol (79b).[104]



To a solution of 4-fluorophenyllithium (**70b**) (40 mL, 30 mmol) in ethyl ether was added a solution of 1,4-cyclohexanedione (**57**) (0.84 g, 7.5 mmol) in ethyl ether (30 mL) over 30 minutes. The reaction mixture was brought to reflux for 30 minutes, cooled in an ice bath and 10% hydrochloric acid (100 mL) added. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 75 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude product was purified by flash chromatography to yield 1,4-di-(4-fluorophenyl)-1,4-cyclohexadiol (1.25 g, 55%) as a colourless solid; R_f 0.6 (2:3 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (brs, 2OH), 1.69-1.82 (m, 4H), 2.31-2.45 (m, 4H), 7.08-7.03 (m, 4H), 7.57-7.53.

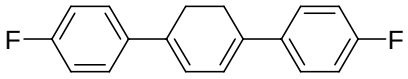
1,4-Di-(4-fluorophenyl)-1,3-cyclohexadiene (68h) and 1,4-di-(4-fluorophenyl)-1,4-cyclohexadiene (75e) (isomer mixture). [104]



To a solution of 1,4-di-(4-fluorophenyl)-1,4-cyclohexadiol (**79b**) (1.1 g, 3.6 mmol) in benzene (50 ml) was added *p*-toluenesulfonic acid (20 mg). The resulting reaction mixture was heated under reflux for 15 minutes while the water formed was removed by azeotropic distillation. The crystalline product that formed on cooling was

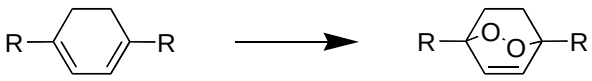
recrystallised from ethanol to give a mixture of the 1,3- and 1,4- isomers (70 : 30) as a yellow solid. Yield 0.84 mg, 87%. (**68h**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.75 (s, 4H), 6.44 (s, 2H), 7.08-7.01 (m, 4H), 7.45-7.42 (m, 4H). (**75e**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (s, 4H), 6.20 (s, 2H), 7.08-7.01 (m, 4H), 7.45-7.42 (m, 4H).

1,4-Di-(4-fluorophenyl)-1,3-cyclohexadiene (68h). [104]



The isomeric mixture of 1,3- and 1,4- isomers (0.2 g, 0.75 mmol) was heated under reflux for 4 hours in *t*-butanol (50 mL) containing potassium *t*-butoxide (1.4 g). After cooling to room temperature most of the *t*-butanol was removed and water (30 mL) was added. The mixture was extracted with ethyl ether (3 x 50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude product was recrystallised from benzene to yield 1,4-di-(4-fluorophenyl)-1,3-cyclohexadiene (**68h**) as a pale yellow solid. Yield 0.19 g, 95%.

General procedure for the synthesis of endoperoxides.



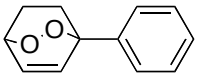
A solution of the appropriate 1,3-cyclohexadiene (**68a-h**) (~1g) in CH_2Cl_2 (60 mL / g) was photolysed with 3 x 500W halogen lamps in the presence of rose bengal *bis*(triethylammonium) salt (100 mg) and a stream of oxygen until reaction was

complete by TLC. The reaction was performed in a flask fitted with an external cooling jacket. The solution was concentrated *in vacuo* and the resulting residue purified by flash chromatography.

2,3-Dioxabicyclo[2.2.2]oct-5-ene (65a). [106]

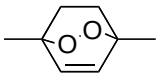
Yield 54 %; White solid; R_f 0.50 (DCM); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (d, 2H, *J* = 10.0 Hz), 2.30 (d, 2H, *J* = 10.0 Hz), 4.65 (m, 2H), 6.68 (t, 2H, *J* = 3.0 Hz).

(±)-(1*R*,4*S*)-1-Phenyl-2,3-dioxabicyclo[2.2.2]oct-5-ene (65b)



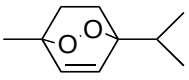
Yield 27 %; Colourless solid; mp: 50-52 °C; R_f 0.48 (1:4 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55-1.69 (m, 1H), 1.76-1.90 (m, 1H), 2.38-2.49, (m, 2H), 4.71-4.82 (m, 1H), 6.74 (dd, 1H, *J* = 8.5, 1.8 Hz), 6.82 (dd, 1H, *J* = 8.5, 5.6 Hz), 7.30-7.49 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): 23.4, 27.9, 71.3, 78.0, 126.2, 128.5, 128.7, 132.9, 136.1, 140.0; IR (solid): 2932, 1493, 1447, 1016, 919, 695 cm^{-1}; MS m/z (+EI): 188 (M^+, 4), 115 (15), 105 (100), 77 (33); HRMS (+EI) $(M+Na)^+_{found}$ 211.0723; $(M+Na)^+_{calcd}$ for $C_{12}H_{12}O_2Na$ 211.0735.

1,4-Dimethyl-2,3-dioxa-bicyclo[2.2.2]oct-7-ene (65c)



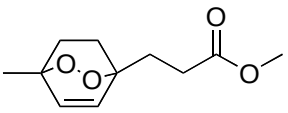
Yield 70 %; Pale yellow oil; R_f 0.44 (1:4 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 6H), 1.47-1.59 (m, 2H), 1.97-2.13 (m, 2H), 6.38 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 21.6, 30.0, 74.8, 136.0; IR (neat): 2932, 1452, 1380, 1052, 874, 699 cm^{-1}; HRMS (+EI) $(M)^+_{found}$ 140.0839; $(M)^+_{calcd}$ for $C_{10}H_{12}O_2$ 140.0837.

(±)-1-Isopropyl-4-methyl-2,3-dioxa-bicyclo[2.2.2]oct-7-ene (65d). [69]



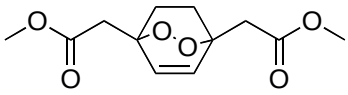
Yield 85 %; Pale yellow oil; R_f 0.69 (3:7 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (d, 3H, *J* = 6.9 Hz), 1.37 (s, 3H), 1.50-1.63 (m, 2H), 1.93 (sept, 1H, *J* = 6.9 Hz), 2.00-2.10 (m, 2H), 6.41 (d, 1H, *J* = 8.7 Hz), 6.50 (d, 1H, *J* = 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 17.1, 17.2, 21.4, 25.6, 29.5, 32.1, 74.3, 79.8, 133.0, 136.4.

(±)-Methyl 3-(4-methyl-2,3-dioxa-bicyclo[2.2.2]oct-7-en-1-yl)propanoate (65e).



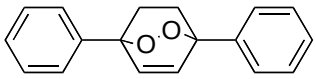
Yield 65%; Colourless oil; R_f 0.29 (1:4 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.44-1.57 (m, 2H), 1.97-2.17, (m, 4H), 2.39-2.57 (m, 2H), 3.69 (s, 3H), 6.42 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 21.3, 28.1, 28.2, 29.5, 30.2, 51.7, 74.8, 76.2, 133.8, 136.6, 173.5; IR (neat): 1737, 1637, 1438, 1378, 1197, 1172, 883, cm^{-1}; MS m/z (+EI): 211 (M^+, 4), 181 (100), 148 (38), 123 (60), 106 (46); HRMS (+EI) $(M+Na)^+_{found}$ 235.0948; $(M+Na)^+_{calcd}$ for $C_{11}H_{16}O_4Na$ 235.0946.

Dimethyl 2,2'-[(1*R*,4*S*)-2,3-dioxabicyclo[2.2.2]oct-5-ene-1,4-diyl]diacetate (65f).



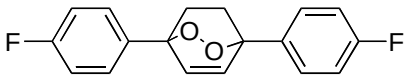
Yield 89 %; Colourless solid; mp: 32-34 °C R_f 0.50 (1:1 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66-1.82 (m, 2H), 2.06-2.22 (m, 2H), 2.65 (d, 2H, J = 15.0Hz), 2.73 (d, 2H, *J* = 15.0Hz), 3.71 (s, 6H), 6.70 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 27.9, 39.5, 52.1, 75.7, 134.0, 169.4; IR (solid): 2955, 1725, 1436, 1295, 1151, 1006, 698 cm^{-1}; HRMS (+EI) $(M+Na)^+_{found}$ 279.0853; $(M+Na)^+_{calcd}$ for $C_{12}H_{16}O_6Na$ 279.0853.

1,4-Diphenyl-2,3-dioxa-bicyclo[2.2.2]oct-7-ene (65g).[48]



Yield: 73%; White solid; mp:130-132°C (lit =131-132°C[48]); *R_f* 0.53 (1:4 ethylacetate : hexane); ^{1}H NMR (300MHz) δ 1.94-2.10 (m, 2H), 2.56-2.73 (m, 2H), 6.88 (s, 2H), 7.20-7.68 (m, 10H).

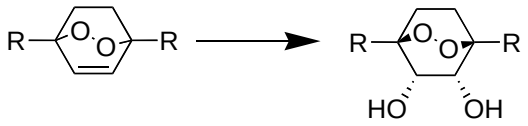
1,4-Di-(4-Fluorophenyl)-2,3-dioxa-bicyclo[2.2.2]oct-7-ene (65h). [104]



Yield: 51%; White solid; mp: 152-153 °C; R_f 0.57 (1:4 ethylacetate : hexane); ^{1}H NMR (300 MHz) δ 1.92-2.28 (m, 2H), 2.55-2.71 (m, 2H), 6.84 (s, 2H), 7.18-7.08 (m, 4H), 7.54 – 7.50 (m, 4H).

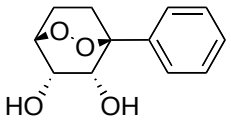
6.3 Compounds Described in Chapter 3

General procedure for the synthesis of *syn* diols.



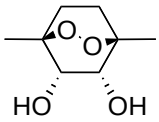
To a solution of endoperoxide (3 mmol) and citric acid (6 mmol) in *t*-butanol/H_2O (1:1) was added potassium osmate dihydrate (0.03 mmol) followed by 4-methylmorpholine *N*-oxide (3.3 mmol). The mixture was stirred at 50 ^{o}C until complete by TLC. The *t*-butanol was removed *in vacuo* and the aqueous layer extracted with ethyl acetate. The combined organics were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude product was purified by flash chromatography.

(±)- (1*S*,4*S*,5*S*,6*R*)-1-Phenyl-2,3-dioxabicyclo[2.2.2]octane-5,6-diol (66b)



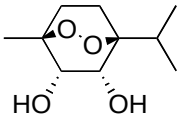
Yield 63 %; Colourless solid; R_f 0.14 (3:7 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.06-2.29 (m, 3H), 2.46-2.57 (m, 1H), 2.68, (br, 1OH), 3.13 (br, 1OH), 4.28 (m, 2H), 4.47 (dd, 1H, *J* = 7.5, 4.8 Hz), 7.30-7.50 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): 18.9, 22.4, 65.2, 69.6, 75.0, 80.3, 126.0, 128.3, 128.6, 128.8.

(1*R*,4*S*,5*S*,6*R*)-1,4-Dimethyl-2,3-dioxabicyclo[2.2.2]octane-5,6-diol (66c)



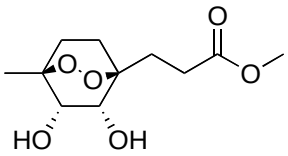
Yield 66 %; White needles; mp: 38-40°C; R_f 0.3 (2:3 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (s, 6H), 1.72 (dd, 2H, *J* = 13.5, 5.4 Hz), 2.00 (dd, 2H, *J* = 13.2, 5.4 Hz), 2.99 (br, 2OH), 3.92 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 21.7, 24.5, 69.5, 77.5. IR (neat): 3415, 3266, 2934, 1453, 1370, 1062, 980, 864, 652 cm^{-1}; HRMS (+EI) $(M-H)^-_{found}$ 173.0821; $(M-H)^-_{calcd}$ for $C_8H_{13}O_4$ 173.0819.

(±)(1*R*,4*R*,5*S*,6*R*)-1-Isopropyl-4-methyl-2,3-dioxa-bicyclo[2.2.2]octane-5,6-diol (66d)



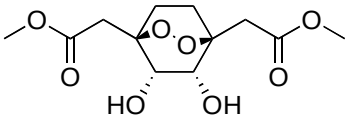
Yield 85 %; Colourless oil; R_f 0.25 (3:7 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (d, 3H, *J* = 6.9 Hz), 0.99 (d, 3H, *J* = 6.9 Hz), 1.17 (s, 3H), 1.66-1.74 (m, 1H), 1.80 (sept, 1H, *J* = 6.9 Hz), 1.85-2.05 (m, 3H), 3.00 (br s, 2OH), 3.91 (dd, 1H, *J* = 7.8, 1.5 Hz), 4.19 (dd, 1H, *J* = 7.8, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 16.6, 16.9, 20.9, 21.2, 24.6, 33.1, 67.0, 69.8, 76.8, 80.6; IR (neat): 3437, 1454, 1388, 1371, 1085, 1019 cm^{-1}; HRMS (+EI) $(M+Na)^+_{found}$ 225.1102; $(M+Na)^+_{calcd}$ for $C_{10}H_{18}O_4Na$ 225.1103.

(±)-Methyl 3-[(1*S*,4*S*,5*R*,6*S*)-5,6-dihydroxy-4-methyl-2,3-dioxa-bicyclo[2.2.2]octan-1-yl]propanoate (66e)



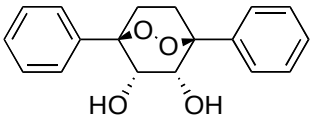
Yield 83 %; Colourless oil; R_f 0.30 (1:1 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (s, 3H), 1.62-1.83 (m, 3H), 1.91-2.09, (m, 3H), 2.34-2.58 (m, 2H), 3.65 (br, 2OH), 3.70 (s, 3H), 3.88 (dd, 1H, *J* = 8.2, 1.5 Hz) 3.94 (dd, 1H, *J* = 8.2, 1.5 Hz) ; ^{13}C NMR (75 MHz, $CDCl_3$): 21.4, 23.2, 24.3, 27.1, 29.4, 52.0, 66.4, 69.1, 77.7, 78.0, 175.1; IR (neat): 3468, 2936, 1731, 1441, 1105 cm^{-1}; MS m/z (+EI): 248 (M^+, 5), 230 (19), 178 (39), 167 (53), 133 (65), 118 (42), 65 (39), 48 (100).

Dimethyl 2,2'-[(1*R*,4*S*,5*R*,6*S*)-5,6-dihydroxy-2,3-dioxabicyclo[2.2.2]octane-1,4-diyl]diacetate (66f)



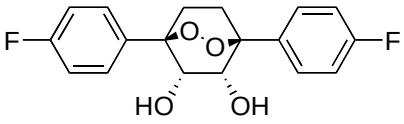
Yield 55 %; White solid; mp: 92-94 °C; R_f 0.45 (4:1 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.82-1.98 (m, 2H), 2.09-2.26 (m, 2H), 2.55 (d, 2H, J = 14.7Hz), 2.59 (d, 2H, J = 14.7Hz), 3.71 (s, 6H), 4.22 (s, 2H), 4.72 (br, 2OH); ^{13}C NMR (75 MHz, $CDCl_3$): 23.4, 40.3, 52.4, 68.0, 78.6, 170.6; IR (solid): 3394, 3251, 2957, 2938, 1729, 1440, 1348, 1299, 1212, 1172, 1090, 1014, 955, 714 cm^{-1}; MS m/z (+EI): 290 (M^+, <1), 193 (15), 183 (60), 151 (58), 145 (100), 91 (39), 85 (35); HRMS (+EI) $(M+Na)^+_{found}$ 313.0901; $(M+Na)^+_{calcd}$ for $C_{12}H_{18}O_8Na$ 313.0899.

(1*R*,4*S*,5*R*,6*S*)-1,4-Diphenyl-2,3-dioxabicyclo[2.2.2]octane-5,6-diol (66g)



Yield 65 %; White solid; mp: 138-140 °C; R_f 0.48 (2:3 ethylacetate : hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.24-2.35 (m, 2H), 2.63-2.73 (m, 2H), 2.76 (br, 2OH), 4.47 (s, 2H), 7.35-7.46 (m, 6H), 7.51-7.57 (m, 4H) ; ^{13}C NMR (75 MHz, $CDCl_3$): 24.7, 70.7, 81.1, 126.3, 128.8, 139.7, 199.0; IR (solid): 3366, 2943, 1497, 1447, 1100, 748, 695 cm^{-1}; MS m/z (+EI): 296 (M^+, <1), 238 (30), 133 (24), 105 (100), 77 (37); HRMS (+EI) $(M+Na)^+_{found}$ 321.1109; $(M+Na)^+_{calcd}$ for $C_{18}H_{18}O_4Na$ 321.1103.

(1*R*,4*S*,5*R*,6*S*)- 1,4-*Bis*(4-fluorophenyl)-2,3-dioxabicyclo[2.2.2]octane-5,6-diol (66h)

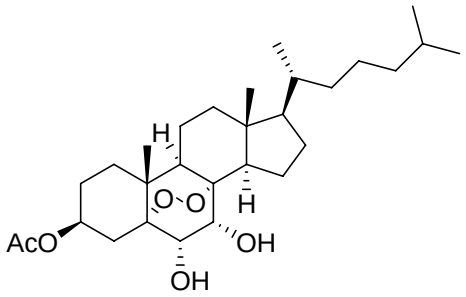


Yield 68 %; White solid; mp: 120-122 °C; R_f 0.54 (2:3 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26-2.34 (m, 2H), 2.55-2.71 (m, 2H), 2.72 (br, 2OH), 4.43 (s, 2H), 7.06-7.11 (m, 4H), 7.48-7.53 (m, 4H) ; ^{13}C NMR (75 MHz, $CDCl_3$): 24.7, 70.5, 80.8, 115.7 (d, J = 21.0 Hz), 128.2 (d, J = 8.3 Hz), 135.4, 163.0 (d, J = 246.4 Hz); IR (nujol): 3484, 3379, 1598, 1505, 1462, 1377, 1230, 1160, 1107, 1092, 1005, 957, 837, 814 cm^{-1}; Anal. Calcd for $C_{18}H_{16}F_2O_4$: C, 64.67; H, 4.82; Found: C, 64.66; H 4.96.

Details of crystal structure determination of 66h

Crystal data for $C_{18}H_{16}F_2O_4$: M = 334.31, T = 173(2) K, monoclinic, $C2/c$, a = 26.372(5), b = 5.6563(11), c = 20.652(4) Å, β = 108.83(3)º, V = 2915.7(10) Å^3, Z = 8, D_x = 1.523 g cm^{-3}, $F(000)$ = 1392, μ = 0.123 mm^{-1}, no. of unique data (AFC12κ/SATURN724 using Mo Kα radiation so that θ_{max} = 25.0°) = 2417, no. of parameters = 219, R (1986 data with $I \geq 2\sigma(I)$) = 0.065, wR (all data) = 0.161. The structure was solved by direct-methods (SIR92) and refined (anisotropic displacement parameters, H atoms in the riding model approximation and a weighting scheme $w = 1/[\sigma^2(F_o^2) + 0.064P^2 + 2.711P]$ where $P = (F_o^2 + 2F_c^2)/3)$ with SHELXL-97 on F^2. CCDC deposition number: 688503.

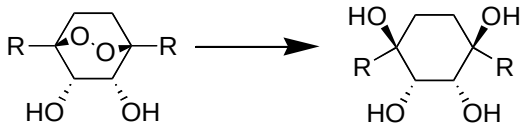
(3β,5α,6α,7α,8α)-6,7-Dihydroxycholestan-3-yl acetate (14)



Yield 66%; White crystals; mp: 174-176 °C (Ethanol); R_f 0.70 (1:1 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (d, 3H, J = 0.9 Hz), 0.87 (d, 3H, J = 0.9 Hz), 0.90 (d, 3H, J = 6.6 Hz), 0.91 (s, 3H), 1.03 (s, 3H), 1.04-1.96 (m, 24H), 2.0 (s, 3H), 2.13-2.30 (m, 1H), 2.92 (brs, 2OH), 3.76 (d, 1H, J = 7.8 Hz), 4.21 (d, 1H, J = 7.8 Hz), 4.76 (tt, 1H, J = 4.5, 11.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 12.6, 17.5, 18.6, 20.4, 21.2, 22.0, 22.5, 22.8, 23.7, 25.9, 27.9, 28.2, 33.4, 33.8, 35.4, 35.9, 36.0, 39.4, 39.8, 44.2, 51.8, 55.7, 56.5, 66.9, 68.9, 69.3, 82.7, 83.4, 170.1; IR (solid): 3476, 2930, 1726, 1366, 1244,

1115, 1058, 1029 cm^{-1}; Anal. Calcd for $C_{29}H_{48}O_6$: C, 70.70; H, 9.82; Found: C, 70.75; H 9.79.

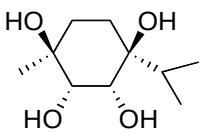
General methods for peroxide reduction.



Method A. To a stirred solution of endoperoxide (1 mmol) in methanol (5mL) was added 10% w/w of 5% palladium on carbon, and the mixture stirred under a hydrogen atmosphere until complete by TLC. The suspension was then filtered through kenite washing with methanol, and the solvent removed *in vacuo* to give the crude tetraol. The crude product was purified by flash column chromatography or recrystallisation.

Method B. To a stirred solution of endoperoxide (1 mmol) in acetic acid (5 mL) was added zinc dust (5 mmol), and the mixture stirred for 24 h. The acetic acid was removed *in vacuo*, and the solids triturated with THF to give the crude tetraol. The crude product was purified by flash column chromatography or recrystallisation.

(1*S*,2*S*,3*R*,4*S*)-1-Methyl-4-(propan-2-yl)cyclohexane-1,2,3,4-tetrol (67d)



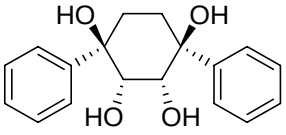
Yield 95%; White solid; mp: 122-124 °C (DCM); ^{1}H NMR (300 MHz, CD_3OD): δ 0.88 (d, 3H, *J* = 6.9 Hz), 0.93 (d, 3H, *J* = 6.9 Hz), 1.26 (s, 3H), 1.42-1.55 (m, 2H), 1.58-1.70 (m, 1H), 1.75-2.0 (m, 2H), 3.71-3.73 (m, 1H), 3.78 (d, 1H, *J* = 3.6 Hz), 4.88 (s, 4OH); ^{13}C NMR (75 MHz, CD_3OD): 16.6, 16.7, 21.9, 29.5, 34.1, 35.3, 74.3, 75.0, 76.2, 76.6; IR (solid): 3482, 3375, 2959, 1454, 1368, 1164, 1088, 989, 694 cm^{-1}; Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87 Found: C, 58.66; H 9.65.

Details of crystal structure determination of 67d.

Crystal data for $C_{10}H_{20}O_4$: *M* = 204.26, *T* = 153(2) K, triclinic, *P*-1, *a* = 9.3219(5), *b* = 10.5827(19), *c* = 11.9459(16) Å, α = 83.63(2), β = 68.448(13), γ = 73.18(2)º, *V* = 1049.2(2) $Å^3$, *Z* = 4, D_x = 1.293 g cm^{-3}, *F*(000) = 448, μ = 0.098 mm^{-1}, no. of unique data (AFC12κ/SATURN724 using Mo Kα radiation so that θ_{max} = 25.0°) = 3599, no. of parameters = 276, *R* (3402 data with $I \geq 2\sigma(I)$) = 0.043, *wR* (all data) = 0.129. The structure, having two independent but similar molecules in the asymmetric unit (but, see below) was solved by direct-methods (SIR92) and refined (anisotropic displacement parameters, H atoms in the riding model approximation and a weighting scheme $w = 1/[\sigma^2(F_o^2) + 0.061P^2 + 0.285P]$ where $P = (F_o^2 + 2F_c^2)/3$) with SHELXL-97 on F^2. Metrically, a unit cell of half the volume, i.e. with *Z* = 2 (i.e. one molecule comprises the asymmetric unit) can be obtained with the following transformation matrix: -1 0 -2, -1 0 0, 0 1 0. While a satisfactory refinement was obtained, the resultant model has two, i.e. the O1- and O2-bound, hydrogen atoms disordered over two positions. In any one given snapshot of the structure, 0.5 + 0.5 hydrogen atoms are not involved in a stabilising hydrogen bonding interaction. This contrasts the larger unit cell and the

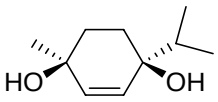
ordered structure which was adopted as a better representation of the crystal structure. CCDC deposition number: 688504.

(1*R*,2*S*,3*R*,4*S*)-1,4-Diphenylcyclohexane-1,2,3,4-tetrol (67g).



Yield 85%; White solid; mp: 162-164 °C (DCM); ^{1}H NMR (200 MHz, CD_3OD): δ 2.04-2.20 (m, 2H), 2.53-2.69 (m, 2H), 4.15 (s, 2H), 7.15-7.36 (m, 6H), 7.69-7.7.76 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD): 33.1, 76.3, 78.3, 127.9, 128.7, 146.7; IR (nujol): 3581, 3541, 3469, 3434, 1308, 1234, 787, 700 cm^{-1}; HRMS (+EI) $(M-H)^{+}_{found}$ 299.1281; $(M-H)^{+}_{calcd}$ for $C_{18}H_{19}O_4$ 299.1283.

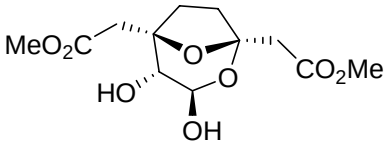
(1*S*,4*S*)-1-Methyl-4-(propan-2-yl)cyclohex-2-ene-1,4-diol (91d). [107]



To a stirring solution of ascaridole (**65d**) (500 mg, 3.0 mmol) in dry THF (20 ml) under nitrogen at 0^{o}C was added solid $LiAlH_4$ (230 mg, 6.1 mmol) over 5 minutes. The reaction mixture was stirred at rt for 10 minutes and then boiled under reflux for 4 hours. The reaction was then cooled with ice, quenched with a saturated solution of Na_2SO_4, and filtered through a pad of Kenite. The crude product was purified by column chromatography to furnish a white solid. Yield 340 mg, 67%; R_f 0.44 (ethylacetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (d, 3H, *J* = 6.9 Hz), 0.93 (d, 3H, *J* =

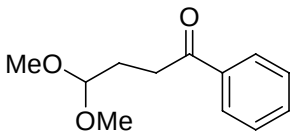
6.9 Hz), 1.23 (s, 3H), 1.62-1.88 (m, 5H), 5.53 (d, 1H, *J* = 10.0 Hz), 5.70 (d, 1H, *J* = 10.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 16.72, 18.74, 27.38, 35.19, 37.52, 69.88, 72.18, 132.36, 137.54.

Dimethyl 2,2'-[(3*R*,4*R*)-3,4-dihydroxy-2,8-dioxabicyclo[3.2.1]octane-1,5-diyl]diacetate (102).



Yield 35 %; Colourless oil; R_f 0.40 (4:1 ethylacetate : hexane); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.60-1.68 (m, 1H), 1.69-1.75 (m, 2H), 1.84-1.90 (m, 1H), 2.57 (d, 1H, *J* = 16.2 Hz), 2.86 (d, 1H, J = 16.2Hz), 2.88 (d, 1H, *J* = 16.2 Hz), 2.90 (d, 1H, *J* = 16.2 Hz), 3.71 (s, 3H), 3.72 (s, 3H), 4.06 (s, 1OH), 4.15 (s, 1H), 4.32 (d, 1OH, *J* = 9.6 Hz), 5.65 (d, 1H, *J* = 9.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 30.1, 31.7, 40.0, 40.4, 51.7, 66.9, 84.4, 95.6, 107.1, 169.5, 173.1; IR (solid): 3465, 2955, 1728, 1439, 1348, 1206, 1167, 1042 cm^{-1}; HRMS (+EI) $(M+Na)^+_{found}$ 313.0887; $(M+Na)^+_{calcd}$ for $C_{12}H_{18}O_8Na$ 313.0899.

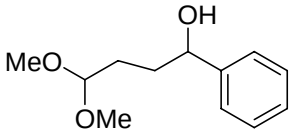
4,4-Dimethoxy-1-phenylbutan-1-one (105).[93]



Yield 83 %; Colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.06 (dt, 2H, *J* = 7.5, 5.7 Hz), 3.07 (t, 2H, *J* = 7.5 Hz), 3.35 (s, 6H), 4.48 (t, 1H, *J* = 5.7 Hz), 7.43-7.48 (m, 2H), 7.53-

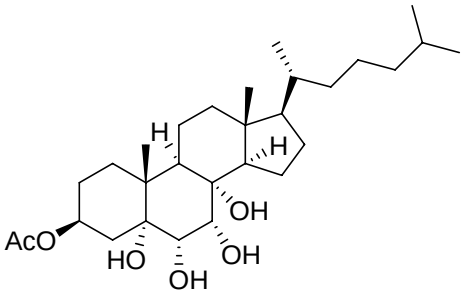
7.58 (m, 1H), 7.96-7.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 26.9, 33.2, 53.2, 103.9, 128.0, 128.5, 133.0, 136.8, 199.5.

(±)-4,4-Dimethoxy-1-phenylbutan-1-ol (106).



Yield 76 %; Colourless oil; R_f 0.42 (1:1 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63-1.83 (m, 4H), 2.62 (brs, 1OH), 3.25 (s, 6H), 4.36 (t, 1H, *J* = 5.1 Hz), 4.68 (t, 1H, *J* = 5.4 Hz), 7.24-7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): 28.8, 33.9, 52.8, 52.9, 74.0, 104.4, 125.8, 127.4, 128.4, 144.6.

(3β,5α,6α,7α,8α)-5,6,7,8-Tetrahydroxycholestan-3-yl acetate (110).

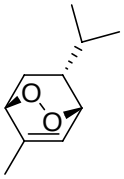


Yield 96%; White crystals; mp: 218-220 °C (Ethanol) R_f 0.50 (1:1 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78 (s, 3H), 0.85 (d, 3H, *J* = 1.2 Hz), 0.88 (d, 3H, *J* = 1.2 Hz), 0.92 (d, 3H, *J* = 6.6 Hz), 1.08 (s, 3H), 1.04-1.96 (m, 24H), 2.03 (s, 3H), 2.13-2.30 (m, 1H), 3.40 (brs, 4OH), 3.70 (d, 1H, *J* = 7.8 Hz), 4.04 (d, 1H, *J* = 7.8 Hz), 5.08-5.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 11.7, 18.8, 20.8, 21.4, 22.5, 22.8, 23.2,

23.3, 23.8, 26.7, 27.5, 28.0, 33.7, 35.7, 35.9, 38.0, 38.8, 39.1, 39.4, 42.5, 48.0, 56.0, 60.2, 69.0, 70.1, 70.3, 74.8, 78.2, 170.6; IR (solid): 3445, 3335, 3145, 2929, 1717, 1462, 1380, 1264, 1243, 1100, 1039, 992 cm^{-1}; Anal. Calcd for $C_{29}H_{50}O_6$: C, 70.41; H, 10.19; Found: C, 70.21; H, 10.16.

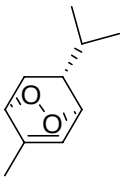
6.4 Compounds Described in Chapter 4

(1*R*,4*S*,7*R*)-5-Methyl-7-(propan-2-yl)-2,3-dioxabicyclo[2.2.2]oct-5-ene (112).[96]



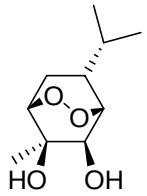
Yield 45%; Colourless oil; R_f 0.30 (4:1 DCM : hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.84 (d, 3H, *J* = 6.0 Hz), 0.89 (d, 3H, *J* = 6.0 Hz), 1.61-1.96 (m, 4H), 1.94 (d, 3H, 2.0 Hz), 4.43 (dd, 1H, *J* = 4.2, 1.8 Hz), 4.60 (dd, *J* = 6.4, 1.8 Hz), 6.19 (dt, 1H, *J* = 6.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 18.4, 19.9, 20.4, 28.7, 32.7, 41.9, 74.1, 75.8, 123.1, 142.6.

(1*S*,4*R*,7*R*)-5-Methyl-7-(propan-2-yl)-2,3-dioxabicyclo[2.2.2]oct-5-ene (113).[96]



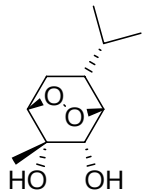
Yield 22%; Colourless oil R_f 0.40 (4:1 DCM : hexane); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.97 (d, 3H, *J* = 6.8 Hz), 0.99 (d, 3H, *J* = 6.8 Hz), 1.61-1.96 (m, 4H), 1.93 (d, 3H, 1.8 Hz), 4.37 (td, 1H, *J* = 3.8, 1.8 Hz), 4.56 (dd, *J* = 6.4, 1.8 Hz), 6.10 (dt, 1H, *J* = 6.6, 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 18.4, 20.7, 21.1, 27.8, 30.4, 41.6, 73.0, 76.1, 125.9, 141.2.

(1*R*,4*S*,5*R*,6*R*,7*R*)-5-Methyl-7-(propan-2-yl)-2,3-dioxabicyclo[2.2.2]octane-5,6-diol (114).



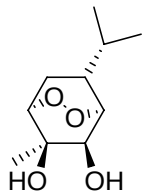
Yield 31%; Colourless oil; R_f 0.30 (2:3 ethylacetate : hexane); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.96 (d, 3H, *J* = 6.6 Hz), 0.97 (d, 3H, *J* = 6.6 Hz), 1.30-1.35 (m, 4H), 1.40 (ddsept, 1H, *J* = 10.8, 6.6, 0.6, Hz), 1.91 (dddd, 1H, *J* = 10.8, 10.2, 8.4, 2.4 Hz), 2.40 (dddd, 1H, *J* = 14.4, 10.2, 6.0, 0.6 Hz), 3.45-3.52 (m, 3H), 3.92 (dd, 1H, *J* = 6.0, 2.4 Hz) 4.08 (dd, 1H, *J* = 2.4, 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 20.3, 20.4, 23.0, 27.1, 30.8, 40.8, 68.0, 69.4, 78.7, 82.0; IR (neat): 3431, 2960, 1387, 1370, 1094, 963, 733 cm^{-1}; HRMS (+EI) $(M+H)^+_{found}$ 203.1287; $(M+H)^+_{calcd}$ for $C_{10}H_{19}O_4$ 203.1283.

(1*R*,4*S*,5*S*,6*S*,7*R*)-5-Methyl-7-(propan-2-yl)-2,3-dioxabicyclo[2.2.2]octane-5,6-diol (115).



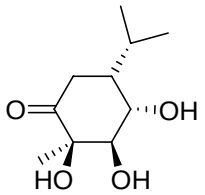
Yield 6%; Colourless oil; R_f 0.50 (2:3 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (d, 3H, *J* = 6.0 Hz), 0.97 (d, 3H, *J* = 6.0 Hz), 1.50 (s, 3H), 1.77-1.91 (m, 3H), 2.15-2.32 (m, 1H), 3.07 (s, 1OH), 3.20 (d, 1OH, *J* = 6.0 Hz), 3.88-3.95 (m, 2H), 4.23 (ddd, 1H, *J* = 2.4, 2.4, 4.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 20.4, 21.2, 24.8, 27.0, 31.1, 40.5, 67.3, 71.8, 75.1, 78.8; HRMS (+EI) $(M+H)^+_{found}$ 203.1288; $(M+H)^+_{calcd}$ for $C_{10}H_{19}O_4$ 203.1285.

(1*S*,4*R*,5*R*,6*R*,7*R*)-5-Methyl-7-(propan-2-yl)-2,3-dioxabicyclo[2.2.2]octane-5,6-diol (116).



Yield 48%; Colourless oil; R_f 0.44 (2:3 ethylacetate : hexane); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.91 (d, 3H, *J* = 6.6 Hz), 0.98 (d, 3H, *J* = 6.6 Hz), 1.49 (s, 3H), 1.60 (ddddd, 1H, *J* = 10.8, 9.6, 7.8, 3.0, 2.4 Hz), 1.71 (ddd, 1H, *J* = 13.8, 7.8, 3.0, Hz), 1.80 (ddsept, 1H, *J* = 9.6, 6.6, 1.2 Hz), 2.27 (dddd, 1H, *J* = 13.8, 10.8, 3.0, 1.2 Hz), 2.52 (br, 1OH), 2.95 (br, 1OH), 3.89 (ddd, 1H, *J* = 3.0, 3.0, 3.0 Hz), 3.92 (d, 1H, *J* = 3.6 Hz) 4.00 (dd, 1H, *J* = 3.6, 2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 20.0, 20.2, 25.4, 26.2, 29.6, 33.7, 68.4, 70.6, 76.9, 79.0; IR (neat): 3415, 2961, 1370, 1078, 980, 940, 735 cm^{-1}; HRMS (+EI) $(M+H)^+_{found}$ 203.1283; $(M+H)^+_{calcd}$ for $C_{10}H_{19}O_4$ 203.1285.

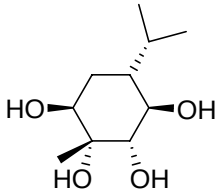
(2*R*,3*R*,4*S*,5*R*)-2,3,4-Trihydroxy-2-methyl-5-(propan-2-yl)cyclohexanone – methane (117).



Yield 22%; Pale yellow solid; mp: 72-74 °C; R_f 0.30 (1:1 ethylacetate : hexane); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.94 (d, 3H, *J* = 6.0 Hz), 1.01 (d, 3H, *J* = 6.0 Hz), 1.52 (s, 3H), 1.80 (m, 1H), 1.85 (m, 1H), 2.44 (dd, 1H, *J* = 13.2, 3.6 Hz), 2.70 (t, 1H, *J* = 13.2

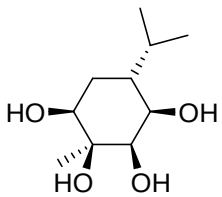
Hz), 3.93 (d, 1H, *J* = 2.4 Hz), 4.27 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 20.6, 20.7, 24.1, 28.8, 36.1, 45.6, 69.3, 77.5, 79.4, 213.8.; IR (nujol): 3436, 1715, 1135, 1040, 948, 736 cm^{-1}; HRMS (+EI) $(M+H)^+_{found}$ 203.1283; $(M+H)^+_{calcd}$ for $C_{10}H_{19}O_4$ 203.1283.

(1*S*,2*R*,3*S*,4*R*,5*R*)-2-Methyl-5-(propan-2-yl)cyclohexane-1,2,3,4-tetrol (89)



Yield 92%; White solid; mp: 124-126°C (DCM); R_f 0.40 (1:9 methanol : ethylacetate); ^{1}H NMR (600 MHz, CD_3OD): δ 0.82 (d, 3H, *J* = 6.6 Hz), 0.92 (d, 3H, *J* = 6.6 Hz), 1.30 (s, 3H), 1.43-1.50 (m, 1H), 1.66-1.74 (m, 2H), 2.19 (dsept, 1H, *J* = 6.6, 1.8 Hz), 3.35 (d, 1H, *J* = 9.0 Hz), 3.46 (dd, 1H, *J* = 9.0, 9.0 Hz), 3.59 (brt, 1H); ^{13}C NMR (75 MHz, CD_3OD): 16.7, 21.9, 24.4, 27.1, 27.2, 42.7, 74.2, 75.5, 76.2, 78.6; IR (solid): 3374, 2954, 1363, 1225, 1031 cm^{-1}; HRMS (+EI) $(M-H)^-_{found}$ 203.1289; $(M-H)^-_{calcd}$ for $C_{10}H_{19}O_4$ 203.1289.

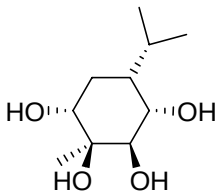
(1*S*,2*S*,3*R*,4*R*,5*R*)-2-Methyl-5-(propan-2-yl)cyclohexane-1,2,3,4-tetrol (118)



Yield 79%; White solid; mp: 48-50°C (DCM); R_f 0.26 (1:9 methanol : ethylacetate); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.87 (d, 3H, *J* = 7.2 Hz), 0.96 (d, 3H, *J* = 7.2 Hz), 1.18 (s,

3H), 1.41 (brt, 1H, *J* = 12.6, Hz), 1.77-1.81 (m, 2H), 2.08 (brs, 1H), 3.53 (br, 1OH), 3.62 (brd, 1H, *J* = 7.2 Hz), 3.67 (brs, 1H), 3.70 (brs, 1H), 4.16 (br, 1OH), 4.55 (br, 1OH), 4.65 (br, 1OH); ^{13}C NMR (75 MHz, $CDCl_3$): 16.9, 20.9, 22.8, 25.5, 26.4, 37.9, 70.6, 73.0, 74.3, 78.1; IR (solid): 3364, 2956, 1442, 1386, 1142, 1039, 930 cm^{-1}; HRMS (+EI) $(M+H)^+_{found}$ 205.1440; $(M+H)^+_{calcd}$ for $C_{10}H_{21}O_4$ 205.1440.

(1*R*,2*S*,3*R*,4*S*,5*R*)-2-Methyl-5-(propan-2-yl)cyclohexane-1,2,3,4-tetrol (119)



Yield 88%; White solid; mp: 176-178°C (ethylacetate); R_f 0.48 (1:9 methanol : ethylacetate); ^{1}H NMR (300 MHz, CD_3OD): δ 1.68 (d, 6H, *J* = 6.6 Hz), 1.90 (s, 3H), 1.93-2.17 (m, 2H), 2.24-2.46 (m, 2H), 4.08-4.21 (m, 1H), 4.29 (ddd, 1H, *J* = 11.4, 4.2, 4.2 Hz), 4.51-4.58 (m, 1H), 4.71 (s, 1OH), 4.93 (d, 1OH, *J* = 4.5 Hz), 5.14 (d, 1OH, *J* = 2.7 Hz), 5.31 (d, 1OH, *J* = 4.2 Hz); ^{13}C NMR (75 MHz, CD_3OD): 28.7, 30.5, 31.0, 37.1, 40.4, 51.4, 79.7, 81.9, 83.4, 87.4; IR (Solid): 3368, 2892, 1340, 1282, 1068, 1022, 973, 734, 693, 617 cm^{-1}; HRMS (+EI) $(M+H)^+_{found}$ 409.2811; $(M+H)^+_{calcd}$ for $(C_{10}H_{20}O_4)_2H$ (dimer) 409.2801.

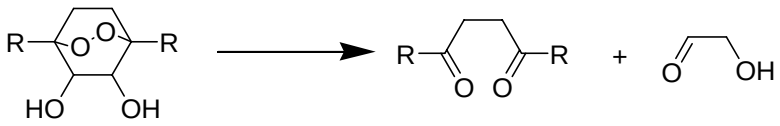
Details of crystal structure determination of 119.

Crystal data for $C_{10}H_{20}O_4$: *M* = 204.26, *T* = 98(2) K, monoclinic, $P2_1$, *a* = 6.600(3), *b* = 9.507(4), *c* = 17.683(7) Å, β = 93.003(7)º, *V* = 1108.0(7) Å^3, *Z* = 4, D_x = 1.225 g cm^{-3}, *F*(000) = 448, μ = 0.093 mm^{-1}, no. of unique data (AFC12κ/SATURN724 using Mo Kα radiation so that θ_{max} = 27.5°) = 4174, no. of parameters = 278, *R* (3928 data with *I* ≥

$2\sigma(I)) = 0.046$, *wR* (all data) = 0.099. The structure, with two independent but similar molecules in the asymmetric unit, was solved by direct-methods (SIR92) and refined (anisotropic displacement parameters, H atoms in the riding model approximation and a weighting scheme $w = 1/[\sigma^2(F_o^2) + 0.038P^2 + 0.236P]$ where $P = (F_o^2 + 2F_c^2)/3)$ as a twin with SHELXL-97 on F^2. CCDC deposition number: 688505.

6.5 Compounds Described in Chapter 5

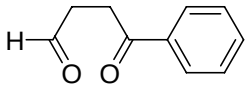
General methods for the thermal and photochemical decomposition of endoperoxides.



Thermal. A stirred solution of endoperoxide (1 mmol) was boiled under reflux in the appropriate solvent (5 mL) until decomposition was complete by TLC. The crude product(s) were purified by flash column chromatography.

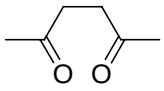
Photochemical. A solution of endoperoxide (1 mmol) in DCM (5 mL) was irradiated with a sun lamp under reflux until decomposition was complete by TLC. The crude product(s) were purified by flash column chromatography.

4-oxo-4-Phenylbutanal (103b). [108]



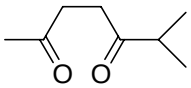
^{1}H NMR (300 MHz, $CDCl_3$): δ 2.95 (t, 2H, *J* = 6.6 Hz), 3.34 (t, 2H, *J* = 6.6 Hz), 7.50 (m, 3H), 8.00 (m, 2H), 9.91 (s, 1H).

Hexane-2,5-dione (103c).[109]



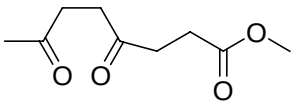
^{1}H NMR (300 MHz, $CDCl_3$): δ 2.15 (s, 6H), 2.62 (s, 4H).

6-Methylheptane-2,5-dione (103d).[110]



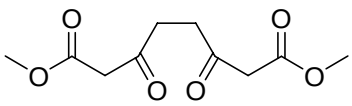
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (d, 6H, *J* = 6.9 Hz), 2.20 (s, 3H), 2.67 (sept, 1H, *J* = 6.9 Hz), 2.71 (s, 4H).

Methyl 4,7-dioxooctanoate (103e).[111]



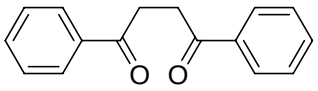
^{1}H NMR (600 MHz, $CDCl_3$): δ 2.18 (s, 3H), 2.60 (t, 2H, *J* = 6.6 Hz), 2.73, (dt, 4H, *J* = 4.2, 1.8 Hz), 2.78 (t, 2H, *J* = 6.6 Hz), 3.67 (s, 3H).

Dimethyl 3,6-dioxooctanedioate (103f).[112]



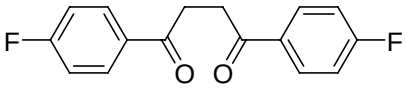
^{1}H NMR (300 MHz, $CDCl_3$): δ 2.83 (s, 4H), 3.50 (s, 4H), 3.72, (s, 6H).

1,4-Diphenylbutane-1,4-dione (103g).[113]



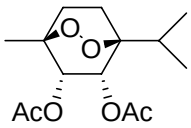
^{1}H NMR (200MHz, $CDCl_3$): δ 3.48 (s, 4H), 7.48-7.52 (m, 6H), 8.02-8.06 (m, 4H).

1,4-*Bis*(4-fluorophenyl)butane-1,4-dione (103h).[113]



^{1}H NMR (200MHz, $CDCl_3$): δ 3.43 (s, 4H), 7.16 (t, 4H, *J* = 8.8 Hz), 8.07 (dd, 4H, *J* = 8.8, 5.4 Hz).

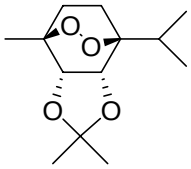
(±)-(1*S*,4*S*,5*R*,6*S*)-1-Methyl-4-(propan-2-yl)-2,3-dioxabicyclo[2.2.2]octane-5,6-diyl diacetate (123).



A solution of **66d** (0.3 g, 1.5 mmol) in pyridine (10 mL) and acetic anhydride (10 mL) was stirred at ambient temperature for 16 hours. The reaction mixture was diluted with $CHCl_3$ (100 mL), washed with water (3 x 50 mL), then brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by flash

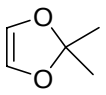
chromatography. Yield 0.39 g, 93%; Colourless oil; R_f 0.48 (3:7 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (d, 6H, *J* = 7.2 Hz), 1.09 (s, 3H), 1.73 (sept, 1H, *J* = 7.2 Hz), 1.78-1.83 (m, 1H), 1.95-2.05 (m, 3H), 2.06 (m, 3H), 2.07 (m, 3H), 5.25 (dd, 1H, *J* = 7.8, 1.8 Hz), 5.37 (dd, 1H, *J* = 7.8, 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 16.4, 16.7, 20.5, 20.6, 22.3, 25.8, 32.9, 67.4, 69.5, 75.8, 79.6, 169.2, 169.4; IR (neat): 1754, 1454, 1372, 1239, 1084, 1062 cm^1; HRMS (+EI) $(M+Na)^+_{found}$ 309.1313; $(M+Na)^+_{calcd}$ for $C_{14}H_{22}O_6Na$ 309.1314.

(±)-(3a*S*,4*S*,7*S*,7a*R*)-2,2,4-Trimethyl-7-(propan-2-yl)hexahydro-4,7-epidioxy-1,3-benzodioxole (124).



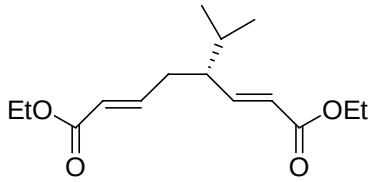
To a stirring solution of **66d** (0.5 g, 2.5 mmol) in dry CH_2Cl_2 (25 mL) was added 2,2-dimethoxypropane (1.3 g, 12.4 mmol) followed by *p*-toluenesulfonic acid (10 mol%), and the solution was stirred under nitrogen overnight. The reaction mixture was washed with saturated $NaHCO_3$ (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by flash chromatography. Yield 0.51 g, 86%; Colourless oil; R_f 0.69 (3:7 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (d, 3H, *J* = 9.0 Hz), 0.97 (d, 3H, *J* = 9.0 Hz), 1.17 (s, 3H), 1.37 (s, 3H), 1.50 (s, 3H), 1.58-1.80 (m, 1H), 1.90-2.05 (m, 3H), 4.10 (dd, 1H, *J* = 7.8, 1.5 Hz), 4.30 (dd, 1H, *J* = 7.8, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 17.1, 17.2, 19.6, 21.9, 23.9, 24.6, 26.4, 34.3, 74.5, 76.3, 77.1, 80.6, 110.2; IR (nujol): 1267, 1209, 1179, 1161, 1076, 1023, 874 cm^1; (+EI) $(M+Na)^+_{found}$ 265.1414; $(M+Na)^+_{calcd}$ for $C_{13}H_{22}O_4Na$ 265.1416.

2,2-Dimethyl-1,3-dioxole (125).[98]



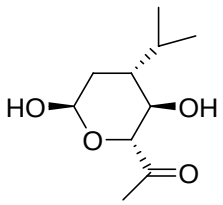
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (s, 6H), 6.17 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.8, 114.1, 126.6.

Diethyl (2*E*,4*R*,6*E*)-4-(propan-2-yl)octa-2,6-dienedioate (127)

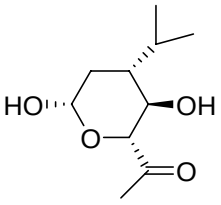


The dialdehyde decomposition product **126** was trapped by the addition of ethyl (triphenyl-λ^5-phosphanylidene) acetate (1.0 g, 2.9 mmol) to a solution of **116** (140 mg, 0.69 mmol) in acetonilrile (10 mL). The solution was boiled under reflux for 30 minutes. The resulting product was purified by flash chromatography. Yield 90%; Slightly yellow oil; R_f 0.25 (1:9 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (d, 3H, *J* = 6.6 Hz), 0.93 (d, 3H, *J* = 6.6 Hz), 1.28 (t, 3H, *J* = 7.2 Hz), 1.30 (t, 3H, *J* = 7.2 Hz), 1.74 (septd, 1H, *J* = 6.6, 1.2 Hz), 2.12-2.46 (m, 3H), 4.18 (q, 2H, *J* = 7.2 Hz), 4.19 (q, 2H, *J* = 7.2 Hz), 5.75-5.86 (m, 2H), 6.73-6.92 (m, 2H,); ^{13}C NMR (75 MHz, $CDCl_3$): 14.2, 18.6, 20.5, 31.1, 34.3, 47.9, 60.2, 60.3, 122.8, 122.9, 146.5, 149.4, 166.2; IR (neat): 2961, 1715, 1652, 1368, 1240, 1154, 1038, 984 cm^{-1}; HRMS (+EI) $(M)^{+}_{found}$ 268.1681; $(M)^{+}_{calcd}$ for $C_{15}H_{24}O_4$ 268.1675.

2,3,7-Trideoxy-3-propan-2-yl-L-*arabino*-heptopyranos-6-ulose (130,131)



α **130**

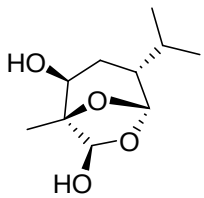


β **131**

Yield 65%; Yellow oil; R_f 0.40 (1 : 1 ethylacetate : hexane); ***α*** ^{1}H NMR (600 MHz, $CDCl_3$): 0.82 (d, 3H, *J* = 6.6 Hz), 0.93 (d, 3H, *J* = 6.6 Hz), 1.44 (ddd, 1H, *J* = 13.2, 13.2, 3.0 Hz), 1.71 (dd, 1H, *J* = 13.2, 3.0 Hz), 1.98 (dddd, 1H, *J* = 13.2, 9.0, 3.0, 3.0 Hz), 2.21-2.28 (m, 1H), 2.27 (s, 3H), 3.53 (dd, 1H, *J* = 9.0, 9.0 Hz), 4.10 (d, 1H, *J* = 9.0 Hz), 5.42 (d, 1H, *J* = 3.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 15.8, 20.3, 24.9, 27.1, 28.1, 39.6, 68.8, 76.4, 91.7, 212.9; IR (neat): 3415, 2958, 1709, 1357, 1244, 1068, 1016, 736 cm^{-1}; HRMS (+EI) $(M)^+_{found}$ 202.1201; $(M)^+_{calcd}$ for $C_{10}H_{18}O_4$ 202.1205.

β ^{1}H NMR (600 MHz, $CDCl_3$): 0.82 (d, 3H, *J* = 7.2 Hz), 0.93 (d, 3H, *J* = 7.2 Hz), 1.25 (ddd, 1H, *J* = 13.8, 12.6, 9.0 Hz), 1.59 (dddd, 1H, *J* = 13.8, 10.2, 3.6, 3.6 Hz), 1.86 (ddd, 1H, *J* = 12.6, 3.6, 1.2 Hz), 2.21-2.28 (m, 1H), 2.32 (s, 3H), 3.48 (dd, 1H, *J* = 10.2, 9.0 Hz), 3.62 (d, 1H, *J* = 9.0 Hz), 4.90 (dd, 1H, *J* = 9.0, 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 15.9, 20.5, 25.1, 27.0, 30.7, 45.1, 68.0, 81.8, 96.7, 211.7.

(1*S*,2*S*,4*R*)-1-Methyl-4-(propan-2-yl)-6,8-dioxabicyclo[3.2.1]octane-2,7-diol (134)



Yield 25%; White Solid; mp: 110-112 °C (Hexane/DCM) R_f 0.20 (1:1 ethylacetate : hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (d, 3H, *J* = 6.6 Hz), 0.95 (d, 3H, *J* = 6.6 Hz), 1.38 (s, 3H), 1.41 (m, 1H), 1.46 (m, 1H), 1.50 (m, 1H), 1.85 (ddd, 1H, *J* = 6.6, 6.6, 3.6 Hz), 2.16 (brs, 1OH), 2.74 (brs, 1OH), 3.53 (s, 1H), 5.02 (s, 1H), 5.63 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 15.6, 19.8, 20.3, 28.7, 30.1, 41.1, 67.7, 84.5, 96.2, 103.9 cm^{-1}; HRMS (+EI) $(M-H)^-_{found}$ 201.1132; $(M-H)^-_{calcd}$ for $C_{10}H_{17}O_4$ 201.1132.

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Publications arising from this work

1. Valente, P; Avery, T. D.; Taylor, D. K.; Tiekink, E.R.T., Synthesis and Chemistry of 2,3-Dioxabicyclo[2.2.2]octane-5,6-diols. *Journal of Organic Chemistry*. **2009,** 74, (1), 274-282.

2. del Pilar Crespo, M.; Avery, T. D.; Hanssen, E.; Fox, E.; Robinson, T. V.; Valente, P.; Taylor, D. K.; Tilley, L., Artemisinin and a series of novel endoperoxide antimalarials exert early effects on digestive vacuole morphology. *Antimicrobial Agents and Chemotherapy*. **2008,** 52, (1), 98-109.