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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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

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