

New Methods for the Construction of Novel Heterocycles from 1,2-Dioxines

A thesis submitted for the
degree of Doctor of Philosophy

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October 2009

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Abstract

Cyclic peroxides are abundant in Nature and synthetic manipulation of the peroxide linkage and alkene portion of 1,2-dioxines has established 1,2-dioxines as important compounds as both chemical building blocks and bioactive compounds. Much of the chemistry performed thus far utilizing 1,2-dioxines involves the initial rearrangement of 1,2-dioxines to γ -hydroxyenones allowing for the generation of structural motifs such as cyclopropanes, THF's, THP's, 1,4-diketones and natural sugars.

Herein describes the synthesis of novel 1,2-dioxines with a variety of tethered functionalities and their transformations to afford novel cyclic compounds whilst maintaining the peroxide linkage intact. Chapter two outlines the intramolecular cyclisations of tethered hydroxyl and carboxylic acid moieties onto the olefin of 1,2-dioxines to generate both tetrahydrofurans and dihydrofuran-2(3*H*)-ones, whilst maintaining the peroxide linkage. This work presents the first examples of *syn* fused cyclic peroxide furans through intramolecular cyclisation of tethered hydroxyl groups. Improved methods for the oxidation of hydroxyl tethered 1,2-dioxines to carboxylic acid moieties are also reported.

In addition, improved methods for intramolecular cyclisation of carboxylic acid moieties were developed to afford *syn* fused cyclic peroxide lactones. Furthermore, reduction of the peroxide bond enabled generation of functionalized tetrahydrofurans and dihydrofuran-2(3*H*)-ones which have previously been utilized as synthetic building blocks for several natural products.

Chapter three reports the first examples of carbenoid insertion into the peroxide linkage of 1,2-dioxines allowing for the generation of novel bicyclic hemiacetals. Alternatively novel tricyclic cyclopropyl peroxides were generated through insertion into the olefin whilst maintaining the peroxide linkage intact. Additionally, the attempted intramolecular cyclisation of diazoketone tethered bicyclic 1,2-dioxines was also probed. Furthermore, the attempted intermolecular insertion of diazoketones onto 1,2-dioxines are presented within this chapter.

Finally, Chapter four outlines the intramolecular cyclisations of bromo-alkyl tethered 1,2-dioxines to furnish novel cyclic cyclopentyl peroxides whilst maintaining the peroxide linkage intact. The work presented in this chapter represents the first examples of the synthesis of *syn* fused cyclic cyclopentyl peroxides.

In summary, this thesis outlines methodology towards the synthesis of novel cyclic peroxides from 1,2-dioxines containing tethered functional groups.

Declaration

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

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Ondrej John Zvarec

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Date

Acknowledgements

Firstly I would like to thank my supervisor Prof. Dennis K. Taylor for the opportunity to undertake a PhD under his guidance and supervision. I also appreciate the freedom given to me to explore very interesting chemistry and learn and develop new skills. I would also like to thank Dr. Tom Avery for his advice, guidance and teaching me useful skills both in and out of the laboratory.

Additionally, I must thank the past and present Taylor group members who have helped me throughout my postgraduate studies through friendship, advice and making the place more fun. In particular, Dr. Antony Robinson provided great advice and guidance and was particularly helpful while keeping the lab a fun place.

Furthermore, I would like to thank the technical staff, who have contributed to the work within my thesis, such as Phil Clements for 600MHz NMR's, Sally Duck for Mass spectrometry and Prof. Edward Tiekink for X-ray crystallography.

I must give thanks to friends who have kept me sane throughout my postgraduate studies through making the day's fun and pass easier. In particular I must thank my best mates Abdul, Fernando, Mansur and Ervine for the fun times and the support they have show me in the highs and lows.

Most importantly I would like to finally thank my mother and father who have always shown interest in my academic endeavours and have given encouragement and support throughout my studies and life. I'm in debt to them and would not be where I am today without their support.

Abbreviations

Ac	acetyl
AcOH	acetic acid
Ad	adamantly
AIBN	azobisisobutyronitrile
Anal. Calcd.	analysis calculated
BAIB	bis(Acetoxy)-iodo-benzene
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Cbz	carboxybenzyl
Co(II)(SALEN) ₂	<i>N,N'</i> -bis(salicylidene)-ethylenediamineocobalt(II)
COSY	correlated spectroscopy
¹³ C NMR	carbon nuclear magnetic resonance
Δ	heat
d	doublet
1D	1 Dimensional
2D	2 Dimensional
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
<i>de</i>	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMSO	dimethyl sulfoxide
4-DMAP	4-Dimethylaminopyridine
<i>dr</i>	diastereomeric ratio
<i>ee</i>	enantiomeric excess
ESI	Electrospray ionization
Et	ethyl
equiv.	equivalent (s)
eV	electron Volts
EI	electron impact
¹ H NMR	proton nuclear magnetic resonance

HRMS	high resolution mass spectrometry
g	gram (s)
hrs	hours
<i>hν</i>	light
Hz	hertz
IR	infrared
<i>J</i>	coupling constant
Lit.	literature
<i>m</i>	meta
M	moles per litre
<i>m</i> -CPBA	<i>m</i> -chloroperbenzoic acid
<i>m/z</i>	mass to charge ratio
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	megahertz
MIRC	Michael initiated ring closure
ml	milliliter (s)
mmol	millimole (s)
Mol	mole(s)
MOM	methoxymethyl
mp	melting point
NADH	nicotinamide adenine dinucleotide
<i>n</i> -Bu	<i>n</i> -butyl
NBS	<i>n</i> -bromosuccinimide
NEt ₃	triethylamine
NIS	<i>n</i> -iodosuccinimide
NMO	<i>N</i> -methyldmorphine- <i>N</i> -oxide
nm	nanometers
NMR	nuclear magnetic resonance
<i>o</i>	ortho
OEt	ethoxy
OMe	methoxy
OMIRC	oxy Michael initiated ring closure

<i>p</i>	para
PDC	pyridinium dichromate
Ph	phenyl
³¹ P NMR	phosphorus nuclear magnetic resonance
ppm	parts per million
<i>pr</i> ^{<i>i</i>}	isopropyl
PSI	pound per square inch
<i>p</i> -TSA	<i>p</i> -toluenesulfonic acid
q	quartet
quin	quintet
R _f	retention factor
ROESY	rotating frame overhauser effect spectroscopy
s	singlet
t	triplet
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
<i>t</i> -Bu	<i>t</i> -butyl
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPP	5,10,15,20-tetraphenyl-21 <i>H</i> ,23 <i>H</i> -porphine
TPPO	triphenylphosphine oxide
W	watt (s)