Synthetic Studies Towards Berkelic Acid

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requirements for the degree of Doctor of Philosophy

by

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Abstract

This thesis describes the synthetic endeavours towards berkelic acid, an extremophile derived bioactive natural product. *Penicillium* sp. Pitna 4 is a fungus isolated from Berkeley Pit Lake, a metal laden, pH 2.5 lake which formed when an abandoned copper mine in Butte, Montana filled with infiltrating ground water. Berkelic acid is one of several bioactive natural products isolated from this unlikely source and has been found to have desirable selective activity against the ovarian cancer cell line OVCAR-3, as well as inhibitory activity against caspase-1 and matrix metalloprotease-3. Synthetic access to this molecule is highly desirable due to its bioactivity and novel tetracyclic structure as well as the fact that the planned bioremediation of Berkeley Pit Lake may eliminate its natural source.

The synthetic studies undertaken have focused on developing a flexible strategy for the synthesis of berkelic acid that allows for future modification to structure to allow investigation of biological activity. The strategy is based on the use of a novel one-pot Horner-Wadsworth-Emmons/oxa-Michael cascade to couple two advanced intermediates – a phosphonate and a lactol. A final deprotection/spiroketalisation step then furnishes the spiroketal moiety. Careful functional group manipulations and key introduction of chirality were pivotal in the successful synthesis of a series of coupling partners which allowed the successful synthesis of a series of tricyclic analogues of berkelic acid as well as the entire tetracyclic core, with and without full substitution on the aromatic ring. The formal total synthesis of berkelic acid faltered at the penultimate step, but this project has none the less established a sound approach to this molecule which will build the foundations for a future total synthesis.

Preface

All the work described in this thesis was carried out by the author in the Department of Chemistry at the University of Auckland, except where due reference to the work of others has been made in the text.

Some parts of this work have been previously published:

Jonathan Sperry, Zoe E. Wilson, Dominea C. K. Rathwell and Margaret A. Brimble, "Isolation, biological activity and synthesis of benzannulated spiroketal natural products", *Nat. Prod. Rep.*, 2010, 27, 1117 – 1137, DOI: 10.1039/b911514p

Zoe E. Wilson and Margaret A. Brimble, "A flexible asymmetric synthesis of the tetracyclic core of berkelic acid using a novel Horner-Wadsworth-Emmons/oxa-Michael cascade", *Org. Biomol. Chem.,* 2010, 8, 1284-1286, DOI: 10.1039/B927219B

Zoe E. Wilson and Margaret A. Brimble, "Molecules derived from the extremes of life", *Nat. Prod. Rep.*, 2009, **26**, 44–71, DOI: 10.1039/b800164m

- Featured as an **Instant insight** article in *Chemical Biology* ("Life at the extremes", *Chemical Biology*, 2008, **3**, B95)

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Chapter 3: Experimental Procedures

Abbreviations

λ	wavelength
δ	chemical shift
μ	micro
°C	degrees celcius
1D	one dimensional
2D	two dimensional
Å	angstrom
Ac	acetyl
aq.	aqueous
atm	atmosphere(s)
b.p.	boiling point
Bn	benzyl
br	broad
cat.	catalytic
CBS	Corey-Bakshii-Shibata
CSA	camphorsulfonic acid
d	doublet
d.r.	diastereomeric ratio
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
dd	double of doublet
ddd	double of double of doublet
ddt	double of double of triplet
DEAD	diethyl azodicarboxylate

DIBAL-H	diisobutylaluminium hydride
4-DMAP	*N,N*-dimethyl-4-aminopyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
e.e.	enantiomeric excess
EI	electron impact
ent	enantiomer
epi	epimer
eq.	equivalent
ESI	electrospray ionisation
et al.	*et alii* (and others)
Et	ethyl
FAB	fast atom bombardment
g	gram(s)
h	hour(s)
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectroscopy
HSQC	heteronuclear single quantum correlation
HWE	Horner-Wadsworth-Emmons
HWE/oxa-M	Horner-Wadsworth-Emmons/oxa-Michael
Hz	hertz
i.d.	internal diameter
*i*Pr	isopropyl

IR	infra-red
J	coupling constant
KHMDS	potassium hexamethyldisilazide
LiHMDS	lithium hexamethyldisilazide
L	litre
IC_{50}	concentration to inhibit 50% of activity
LDA	lithium diisopropylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
lit.	literature
m	*meta*
M	molar
m	multiplet
m.p.	melting point
m/z	mass to charge ratio
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MHz	megahertz
min	minute(s)
mmHg	millimeters mercury
MMP	matrix metalloprotease
mmol	millimole(s)
mol	mole(s)
Ms	methanesulfonyl
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
n	*normal*

NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
p	*para*
Ph	phenyl
PHAL	phthalazine
PIFA	bis(trifluoroacetoxy)iodobenzene
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
q	quartet
quant.	quantitative
R	unspecified alkyl group
rt	room temperature
RCM	ring closing metathesis
R_F	retention factor
s	singlet
sat.	saturated
t	*tert* (tertiary)
t	triplet
TA	tricyclic analogue
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide

TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
*t*Bu	*tert*-butyl
TES	triethylsilyl
temp.	temperature
Tf	triflic
TFA	trifluroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine
TMS	trimethylsilyl
Ts	toluenesulfonyl
v	flow rate
v	wavenember (cm^{-1})
Val	Valine
vol	volume