Biomimetic Synthesis of Natural Products via Reactions of *ortho*-Quinone Methides

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For My Family

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Date

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Abstract

In recent times, natural product synthesis has become central to many scientific fields; from chemistry, through to biology and pharmacology. As synthetic chemists, natural products are attractive targets due to their interesting and complex structures, combined with some intriguing biological properties. One field that is of particular interest is the use of a biomimetic approach towards the synthesis of complex natural products. This thesis will describe the use *ortho*-quinone methides and cascade reactions towards the biomimetic synthesis of the penilactones A and B, the peniphenones A-D, virgatolide B and epicolactone.

The total synthesis of *ent*-penilactone A and penilactone B has been achieved via biomimetic Michael reactions between tetronic acids and *o*-quinone methides. A five-component cascade reaction between a tetronic acid, formaldehyde, and a resorcinol derivative that generates four carbon-carbon bonds, one carbon-oxygen bond and two stereocenters in a one-pot synthesis of penilactone A is also reported.

The total synthesis of peniphenones A-D has been achieved via Michael reactions between appropriate nucleophiles and a common *ortho*-quinone methide intermediate. This strategy, which was based on a biosynthetic hypothesis, minimised the use of protecting groups and thus facilitated concise syntheses of the natural products. The most complex target, the benzannulated spiroketal peniphenone A, was synthesised enantioselectively in nine linear steps from commercially available starting materials.

A synthesis for the *ortho*-quinone methide precursor of virgatolide B has been developed. A simplified enol ether was employed for the biomimetic [4+2] cycloaddition reaction to afford a simplified virgatolide B analogue. An isomerised compound containing a *cis* fused ring junction, thought to arise via a [4+2] cycloaddition of an *ortho*-quinone methide and an endocyclic enol ether formed by acid catalysed tautomerisation *in situ* will also be reported.

Finally, preliminary studies towards the synthesis of epicolactone have been conducted. A synthesis of the proposed key proposed biosynthetic intermediate epicoccone B has been achieved in four steps. Efforts towards the synthesis of epicoccine via our proposed cycloetherification route proved to be challenging. Furthermore, the synthesis of epicolactone through our proposed biosynthesis was not viable, which was also observed by Trauner and co-workers in their 2014 synthesis of dibefurin.

List of Abbreviations

°C	degrees Celsius
^{13}C	Carbon-13
^{1}H	Hydrogen-1
Ac	acetyl, acetate
AcOH	acetic acid
aq.	aqueous
atm	atmosphere
Bn	benzyl
BnBr	benzyl bromide
br	broad
Bu	butyl
c	concentration for specific rotation measurements
CAN	ceric ammonium nitrate
CD	circular dichroism
cm^{-1}	wavenumbers
conc	concentrated
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
DBU	1,8-diazobicycloundec-7-ene
DIBAL-H	diisobutylaluminium hydride
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EI	electron impact
ent	enantiomer
epi	epimer
equiv	equivalents
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether

ESI	electrospray ionisation
EtOAc	ethyl acetate
g	grams
h	hours
HFIP	hexafluoroisopropanol
HMBC	heteronuclear multiple bond correlation spectroscopy
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation spectroscopy
Hz	Hertz
hν	light
i-Pr	isopropyl
i-Pr_2NH	diisopropylamine
IC_{50}	half maximal inhibitory concentration
IR	infrared
J	coupling constant
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisoproylamide
LiHMDS	lithium hexamethyldisilazide
LiTMP	lithium tetramethylpiperidide
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Mz	megahertz
Min	minutes
Mp	melting point
Ms	mesyl
n-Bu	*n*-butyl
n-BuLi	*n*-butyllithium
nm	nanometre
NMO	N-methylmorpholine
NMR	nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
Nu	nucleophile

o-QM	*ortho*-quinone methide
p-TsOH	*para*-toluenesulfonic acid
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Pd/C	palladium on activated carbon
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
Ph	phenyl
PhMe	toluene
PIDA	phenyliodine diacetate ((diacetoxy)iodobenzene)
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
R_f	retention factor
rt	room temperature
S_N2	substitution nucleophilic bimolecular
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	*p*-toluenesulfonyl (tosyl)
TsCl	tosyl chloride