Synthetic Studies Towards Aromatic Polyketide Derived Natural Products

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Doctor of Philosophy

by

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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:

"Synthesis of 6,6-bisbenzannulated spiroketals related to the rubromycins using a double intramolecular hetero-Michael addition (DIHMA)" Peter J. Choi, Dominea C. K. Rathwell, Margaret A. Brimble. *Tetrahedron Letters,* **2009**, *50*, 3245-3248, Special Edition to Celebrate 50th Anniversary

"Heteroatom-directed reverse Wacker oxidations. Synthesis of the reported structure of (−)-herbaric acid" Peter J. Choi, Jonathan Sperry, Margaret A. Brimble. *Journal of Organic Chemistry*, **2010**, *75*, 7388-7392.

Abstract

The first part of this thesis describes the successful synthesis of a series of 6,6-bisbenzannulated spiroketal analogues of the rubromycin family. The synthesis of spiroketals **183a-183e** and spiroaminal **237** were successfully executed using a novel microwave-assisted DIHMA approach. Coupling of an aryl acetylene and an aryl aldehyde via acetylide anion addition resulted in the formation of an alkynol which was followed by oxidation to the desired ynone. Spirocyclisation using the DIHMA protocol afforded the desired bisbenzannulated spiroketals **183a-183e** and spiroaminal **237** in good yields. Hydroxy-substituted 6,6-bisbenzannulated spiroketal **182** was successfully furnished by the reduction of keto-substituted 6,6-bisbenzannulated spiroketal **183a** with sodium borohydride.

The second part of this research presents synthetic attempts to access the chiral 3-substituted phthalide containing natural products; aigialospirol (**256**) and herbaric acid (**255**). The synthesis of chiral vinylphthalide **406** proved challenging and was overcome by the use of a microwave-assisted chemoenzymatic resolution to install the C3 stereocenter of phthalide **406**. Despite various attempts to functionalise vinylphthalide **406** towards the synthesis of aigialospirol, results were unsuccessful. With chiral vinylphthalide **406** in hand, the first synthesis and the structural assignment of (−)-herbaric acid (**255**) was accomplished. This was achieved *via* heteroatom-directed Wacker oxidation on vinylphthalide **406** to form aldehyde **460**. Aldehyde **460** underwent smooth oxidation with Oxone® affording acid **488** which underwent facile methyl ester formation to facilitate purification, thus delivering enantioenriched lactone ester **489**. Smooth demethylation with concomitant ester hydrolysis was effected by boron tribromide to give (−)-herbaric acid (**255**). The realisation of this entirely regioselective anti-Markovnikov addition of water during the Wacker oxidation provides a mild alternative to hydroboration/oxidation protocols that are traditionally used for terminal alkenes.

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Peter Jaein Choi

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Abbreviations

δ	chemical shift, parts per million downfield from tetramethylsilane
Å	Angstrom
Δ	reflux
°	degrees
µ	micro
Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
aq.	aqueous
atm	atmosphere(s)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOP	benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate
br	broad (spectral)
c	concentration
C	celcious
Ca.	approximately
calc.	calculated

CAN	cerium(IV) ammonium nitrate
cat.	catalytic
CDI	*N*-*N*'-carbonyl diimidazole
CDMT	2-chloro-4,6-dimethoxy-[1,3,5]triazine
CI	chemical ionization
cm^{-1}	wavenumber(s)
conc.	concentrated
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarisation transformation
DEAD	diethyl azodicarboxylate
DMAP	4-*N,N*-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid

dr	diastereomeric ratio
EI	electron impact
EOM	ethoxymethyl
Et	ethyl
eq.	equivalent(s)
FAB	fast atom bombardment
g	grams
h	hours
HIV	human immunodeficiency virus
HL	human leukemia
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazide
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	hertz
IBX	2-iodobenzoic acid
IC_{50}	half maximal inhibitory concentration
^{i}Pr	isopropyl
IR	infrared
J	coupling constant

L	liters
LDA	lithium diisopropylamide
m	multiplet (spectral)
m-	*meta*
M	molar
M^+	parent molecular ion
max	maximum
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
mg	milligrams
MHz	megahertz
min	minutes
mL	milliliters
mmol	millimoles
mol	moles
MOM	methoxymethyl
mp	melting point
MS	molecular sieves
MTPA	α-methoxy-α-trifluoromethylphenylacetic acid
MW	microwave

m/z	mass to charge ratio
NBS	*N*-bromosuccinimide
n-Bu	*n*-butyl
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
o-	*ortho*-
p-	*para*-
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
PhH	benzene
PMB	*p*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
i-Pr	*iso*-propyl
q	quartet (spectral)
R_f	retention factor
RNA	ribonucleic acid

r.t.	room temperature
RT	reverse transcriptase
SAR	structure activity relationship
s	singlet (spectral)
sat.	saturated
s-Bu	*sec*-butyl
t	triplet (spectral)
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBHP	*tert*-butylhydrogen peroxide
TBDPS	*tert*-butyldiphenylsilyl
TBDMS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TES	triethylsilyl
TFA	trifluoroacetic Acid
TFAA	trifluoroacetic anhydride
Tf	trifluoromethanesulfonate (triflate)
Tf_2O	triflic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine

TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TsOH	*p*-toluenesulfonic acid
UV	ultraviolet

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