



<http://researchspace.auckland.ac.nz>

ResearchSpace@Auckland

Copyright Statement

The digital copy of this thesis is protected by the Copyright Act 1994 (New Zealand).

This thesis may be consulted by you, provided you comply with the provisions of the Act and the following conditions of use:

- Any use you make of these documents or images must be for research or private study purposes only, and you may not make them available to any other person.
- Authors control the copyright of their thesis. You will recognise the author's right to be identified as the author of this thesis, and due acknowledgement will be made to the author where appropriate.
- You will obtain the author's permission before publishing any material from their thesis.

To request permissions please use the Feedback form on our webpage.

<http://researchspace.auckland.ac.nz/feedback>

General copyright and disclaimer

In addition to the above conditions, authors give their consent for the digital copy of their work to be used subject to the conditions specified on the [Library Thesis Consent Form](#) and [Deposit Licence](#).

**Synthetic studies towards polyketide derived
biologically active natural products**

**A thesis submitted in fulfilment
of the requirements for the degree of**

Doctor of Philosophy

by

Amanda Heapy

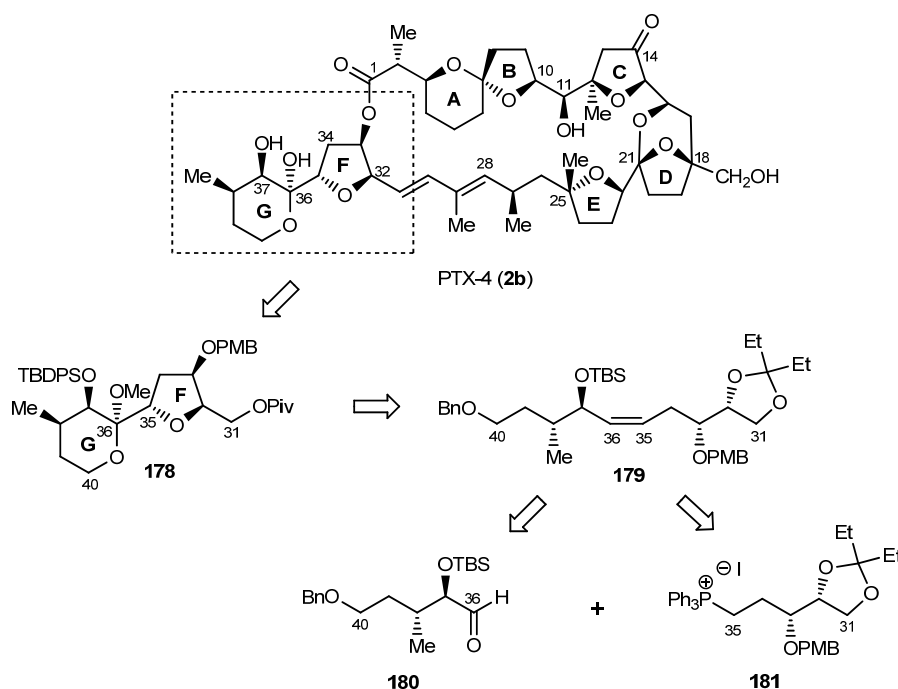
Department of Chemistry

The University of Auckland

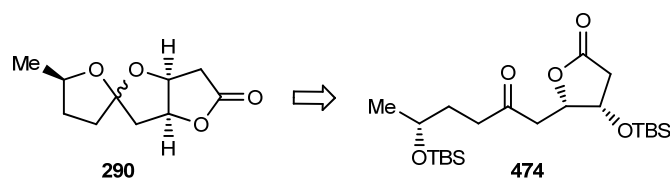
October 2009

Abstract

The first part of this thesis describes the successful synthesis of the FG ring fragment **178** of the structurally complex marine toxins, the pectenotoxins. The synthesis hinges on functional group manipulations of the advanced olefin-(Z) **179** to install the tetrahydrofuran and tetrahydropyran ring systems. Olefin-(Z) **179** is itself obtained by the *cis* selective Wittig olefination of aldehyde **180** and the phosphorus ylide derived from phosphonium salt **181**. Key stereocentres of these two fragments are installed using a Katsuki-Sharless asymmetric epoxidation and a Sharpless asymmetric dihydroxylation reaction, respectively.



The second part of this research presents synthetic attempts to access the fungal metabolites cephalosporolides E and F (**290**). These compounds contain the small but interesting β,γ -fused-[4.4]-spiroacetal- γ -lactone moiety which is a functional group found in seven known natural products, and has until recently eluded the synthetic chemist.



A Fukuyama coupling reaction was initially proposed to prepare advanced precursor ketone **474** but proved to be unsuccessful in our hands. A variant of the original Fukuyama reaction was successfully employed to obtain the same advanced ketone **474** but low yielding reactions combined with the delicate nature of this structure posed an insurmountable bottleneck in the planned synthetic strategy. Based on results of the research presented herein, the synthetic strategy towards this family of natural products was revised.

Acknowledgements

First and foremost I would like to thank Professor Margaret Brimble for taking me on as a postgraduate student. The opportunity to work in a world class synthetic organic chemistry research group has been an invaluable experience that I have thoroughly enjoyed. The confidence that you have had in me as a student has been unbelievable and encouraging, and without which I don't think I would have reached this point. I also thank you for the numerous hours you have spent helping with this thesis.

Thank-you Dr Patrick O'Connor for all your assistance and useful discussions relating to every aspect of this work.

I would also like to thank those, that because of your passion and enthusiasm for chemistry are responsible for inspiring me to take up, and continue on with the discipline; Of course, Professor Margaret Brimble but also, Associate Professor Brent Copp (also for useful discussions relating to NMR analysis), Dr David Barker, Dr Vittorio Caprio and Dr Judy Brittain.

Also thank-you to Michael Schmitz and Michael Walker for NMR assistance, Raisa Imatdieva for mass spectral analysis and Anoma Ratnayake for the general day to day organization of the lab.

Thank-you to all my friends and labmates on the 7th floor for your help, support, the fun times, and above all, making this an enjoyable place to work; especially Tsz Yuen (also for proof reading), Isabell Haym, Jack Chen, Olivia Laita, Suzy Chan, Rhys Finlayson, Danny Lee, Louise Stubbing (also for proof reading), Ubin Kim, Darcy Atkinson, Dominea Rathwell, Greg Hung, Kevin Sparrow, William Liu, Andrew Wadsworth, Stephanie Gueret, Dr Renata Kowalczyk, Dr Dave Rennison, Dr Janice Choi, Dr Paul Harris and Dr Geoff Williams.

A special big thanks to Dr Anna Giddens who has been an incredible friend over the past year or two.

Last but not least I would like to thank Mum and Dad for being great parents. There is not enough room here to acknowledge all the ways in which you have supported me. This thesis is dedicated entirely to you both.

Amanda Heapy
27th October 2009

Abbreviations

Å	angstrom (1.0×10^{-10} m)
δ	chemical shift
Δ	reflux
°	degrees
μ	micro
μλ	microwave
μm	micrometer (1.0×10^{-6} m)
μL	microlitre
Ac	acetyl
acac	acetoacetate
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	aromatic
Atm	atmosphere
ax	axial
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
BOMCl	benzyl chloromethyl ether
BORSM	based on recovered starting material
b.p.	boiling point
br	broad
BSA	bovine serum albumin
Bt	benzotriazole
Bu	butyl
Bz	benzoate
c	concentration
C	celcius
ca.	approximately
CAL-B	<i>Candida antarctica</i> lipase B
cat.	catalytic
CCE	constant current electrode
cm	centimetre
conc	concentrated
CSA	camphorsulfonic acid
d	doublet
DBI	<i>N,N'</i> -dicyclohexyl- <i>O</i> -benzylisourea
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide

Abbreviations

dd	doublet of doublets
ddd	doublet of doublets of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzo-quinone
DEPT	distortionless enhancement by polarisation transfer
DET	diethyl tartrate
DHQ	dihydroquinine
DHQD	dihydroquinidine
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIC	diisopropylcarbodiimide
DIPA	diisopropylamine
DIPEA	diisopropylethylamine (Hünig's Base)
DMAP	4-dimethylaminopyridine
DMB	3,4-dimethoxybenzyl
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane [1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1 <i>H</i>)-one]
DMPU	<i>N,N'</i> -dimethylpropyleneurea
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
DST	diarrhetic shellfish toxin
DTX	dinophysistoxin
E	energy
E1cB	conjugate base unimolecular elimination reaction
ED ₅₀	effective dose to produce desired effect in 50% of the test population
EDC	1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride
EE	ethoxyethyl
ELISA	enzyme-linked immunosorbent assay
EM	ethoxymethyl ether
ent	enantiomeric
Et	ethyl
eq	equatorial or equivalent
F	Faraday
FA	fatty acid
FAB	fast atom bombardment
g	gram(s)
h	hour(s)
HBTU	<i>O</i> -benzotriazol-1-yl- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilazide

HMPA	hexamethylphosphoric triamide
HOBt	1-hydroxy-1 <i>H</i> -benzotriazole
HPLC	high pressure liquid chromatography
<i>hν</i>	photon energy
Hz	hertz
<i>i</i> -Bu	isobutyl
IBX	2-iodoxybenzoic acid
IDCP	iodonium dicollidine perchlorate
im	imidazole
IMHA	intramolecular hydrogen abstraction
<i>i</i> -Pr	isopropyl
IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
<i>J</i>	coupling constant
J	joule(s)
K	Kelvin
kcal	kilocalorie(s)
LC ₅₀	lethal concentration to kill 50% of the test population
LD ₅₀	lethal dose to kill 50% of the test population
LiDBB	lithium di- <i>tert</i> -butylbiphenylide
lit	literature
lut	2,6-lutidine
m	multiplet or milli
M	molar
mbar	millibar
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	millilitre(s)
mm	millimetre(s)
mmol	millimole(s)
MOM	methoxymethyl
Ms	mesylate
MS	molecular sieves
MTM	methylthiomethyl
n	nano (1.0 × 10 ⁻⁹)
<i>n</i> -BuLi	<i>n</i> -butyllithium
NIS	<i>N</i> -iodosuccinimide

Abbreviations

NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NMP	<i>N</i> -methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
OA	okadaic acid
p	pico (1.0×10^{-12})
P	probability
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PEG	poly(ethylene glycol)
Ph	phenyl
Phal	phthalazine
Piv	pivalate
PMB	<i>para</i> -methoxybenzyl
PMBOMCl	<i>p</i> -methoxybenzyl chloromethyl ether
ppm	parts per million
PPTS	pyridinium <i>para</i> -toluenesulfonate
psi	pounds per square inch
PTX	pectenotoxin
py	pyridine
q	quartet
R	ideal gas constant ($8.314 \text{ J K}^{-1} \text{ mol}^{-1}$)
RCM	ring closing metathesis
R _F	retention factor
rt	room temperature
rxn	reaction
s	singlet
SA	seco acid
sat	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
t	triplet
<i>t</i>	<i>tert</i>
T	temperature
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBHP	<i>tert</i> -butylhydrogen peroxide
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBODPS	<i>tert</i> -butoxydiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl

<i>t</i> -Bu	<i>tert</i> -butyl
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonate (triflate)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
t.l.c.	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetra- <i>n</i> -propylammonium perruthenate
TPS	triphenylsilyl
Ts	<i>p</i> -toluenesulfonyl (tosyl)
tt	triplet of triplets
v/v	volume to volume ratio
W	watt(s)
w/w	weight to weight ratio

Table of Contents

Abstract	ii
Acknowledgements	iii
Abbreviations	iv

PART ONE: THE SYNTHESIS OF THE FG RING FRAGMENT OF THE PECTENOTOXINS

Chapter One: Introduction – Pectenotoxin

1.1	Pectenotoxins; an overview	1
1.1.1	The pectenotoxin family: Isolation and structural elucidation	2
1.1.2	Pectenotoxin metabolism	6
1.1.3	Pectenotoxins: Biological activity and mechanism of action	7
1.2	Previous synthetic studies towards the pectenotoxins	9
1.2.1	Evans' total synthesis of PTX-4 (2b) and PTX-8 (13)	9
1.2.2	Murai and Fujiwara's approach to PTX-2 (1a)	17
	1.2.2.1 Murai and Fujiwara's 1997 synthesis of <i>ent</i> -FG ring fragment 72	18
	1.2.2.2 Murai and Fujiwara's 2005 synthesis of FG ring fragment 71	20
	1.2.2.3 Murai and Fujiwara's 2007 synthesis of C ring fragment 73	22
1.2.3	Paquette's approach to PTX-2b (1b)	23
	1.2.3.1 Paquette's synthesis of F ring fragment 99	24
	1.2.3.2 Paquette's synthesis of AB ring fragment 97	25
	1.2.3.3 Paquette's synthesis of E ring fragment 98	26
	1.2.3.4 Paquette's coupling of ABC ring fragment 97 to E ring fragment 98	26
1.2.4	Pihko's approach to PTX-2 (1)	27
	1.2.4.1 Pihko's synthesis of the AB spiroketal fragment 116	27
	1.2.4.2 Pihko's synthesis of CDE ring fragment 118	27
1.2.5	Williams' approach to PTX-2b (1b)	28
	1.2.5.1 Williams' synthesis of the AB ring fragment 124	28
	1.2.5.2 Williams' synthesis of the E ring fragment 126	28
1.2.6	Rychnovsky's synthesis of the AB ring system of PTX-2 (1a)	29
1.2.7	Roush's synthesis of the CDE ring fragment 131	29
1.2.8	Brimble's approach to PTX-4 (2b)	30
	1.2.8.1 Brimble's synthesis of the ABC ring fragment 144	31
	1.2.8.2 Brimble's synthesis of the CDE ring fragment 157	32
1.3	Aim of the current research	34

Chapter Two: Discussion – Pectenotoxin

2.1	Overview	36
2.2	Synthesis of aldehyde 180	37
2.2.1	Synthesis of allyl alcohol 183	37
2.2.2	Conversion of allyl alcohol 183 to aldehyde 180	38
2.2.2.1	The Katsuki-Sharpless asymmetric epoxidation	39
2.3	Synthesis of phosphonium salt 181	41
2.3.1	Synthesis of olefin-(<i>E</i>) 205	41
2.3.2	Conversion of olefin-(<i>E</i>) 205 to diol intermediate 209	42
2.3.2.1	The Sharpless asymmetric dihydroxylation	43
2.3.3	Conversion of intermediate diol 209 to phosphonium salt 181	47
2.4	Synthesis of advanced olefin-(<i>Z</i>) 179	48
2.5	Elaboration of olefin-(<i>Z</i>) 179 : Substrate directed epoxidation	50
2.6	Installation of the F ring	51
2.7	Installation of the G ring and completion of target fragment 178	54
2.8	Summary of the synthesis of the FG ring target fragment 178	56
2.9	Pectenotoxin hapten synthesis	57
2.9.1	What is a hapten and why generate haptens towards pectenotoxin?	57
2.9.2	Proposed hapten structure of pectenotoxin	58
2.9.3	Oxidation of diol 250 to dicarbonyl 258	59
2.9.4	Modified Takai olefination	59
2.9.5	Wittig reaction	61
2.9.6	Rhodium catalyzed olefination	61
2.9.7	Horner-Wadsworth-Emmons olefination	62

Chapter Three: Experimental – Pectenotoxin

3.1	General Details	66
3.2	Synthesis of aldehyde 180	67
3.3	Synthesis of phosphonium salt 181	74
3.4	Synthesis of advanced olefin-(<i>Z</i>) 179	85
3.5	Elaboration of olefin-(<i>Z</i>) 179	86
3.6	Installation of F ring tetrahydrofuran 250	89
3.7	Installation of G ring tetrahydropyran 256	92
3.8	Towards target hapten structure 257	94

PART TWO SYNTHETIC STUDIES TOWARDS CEPHALOSPOROLIDES E AND F (290)

Chapter Four: Introduction – Cephalosporolide E 290a and cephalosporolide F 290b

4.1	Overview	100
4.2	Natural products with β,γ -fused-[4.4]-spiroacetal- γ -lactone core	101
4.2.1	Cephalosporolide E 290a and cephalosporolide F 290b	101
4.2.2	Ascospiroketal A 308 and ascospiroketal B 291	104
4.2.3	Penisporolide A 292 and penisporolide B 293	105
4.2.4	Cephalosporolide H 294 and cephalosporolide I 295	105
4.3	Spiroacetals	106
4.3.1	Spiroacetal structure	106
4.3.2	Spiroacetal conformation	107
4.3.2.1	The anomeric effect	107
4.3.2.2	Hydrogen bonding and chelation effects	109
4.3.2.3	Steric effects	111
4.3.2.4	Chiral substituents	112
4.4	Biologically active natural products possessing 5,5-spiroacetals	113
4.4.1	Cephalostatins and Ritterazines	113
4.4.2	CJ-12,954 (334a) and CJ-13,014 (335a)	114
4.4.3	Pyrenolide D 336	114
4.4.4	Insect pheromones	115
4.4.5	Hippurin-1 (345)	115
4.4.6	Halichondrins	116
4.5	Methods for the construction of spiroacetals	117
4.5.1	Acid catalyzed spirocyclization of dihydroxyketones	118
4.5.1.1	Exposure of the diol moiety promoting cyclization	118
4.5.1.2	Exposure of the ketone moiety promoting cyclization	118
4.5.2	Metal-mediated double intramolecular hydroalkoxylation of internal alkynes	120
4.5.3	Ring closing metathesis	122
4.5.4	Reaction of cyclic enol ethers	124
4.5.5	Oxidative methods	125
4.5.5.1	Intramolecular hydrogen abstraction (IMHA)	125
4.5.5.2	Oxidative cyclization	127
4.5.5.3	Oxidative ring contraction	128
4.5.5.4	Oxidative ring expansion	128
4.5.5.5	Oxidation of furan by singlet oxygen	129
4.5.6	Reductive methods	129
4.5.7	Hetero-Diels-Alder reactions	130
4.5.8	Intramolecular conjugate (Michael) addition to unsaturated C-C bonds	131

4.5.9	Carbonyl cascade reactions	132
4.6	Ramana <i>et al.</i> total synthesis of <i>ent</i> -cephalosporolide E 296a and F 296b	133
4.7	Aim of the current research	136

Chapter Five: Discussion – Cephalosporolide E 290a and Cephalosporolide F 290b

5.1	Overview	137
5.2	The Fukuyama coupling reaction	138
5.2.1	Literature precedence for the Fukuyama coupling reaction	139
5.2.2	Organozinc reagents	140
5.2.2.1	Preparation of organozinc reagents	141
5.2.2.2	Reactivity of organozinc reagents	141
5.2.3	Model study of the Fukuyama coupling reaction	142
5.2.3.1	Synthesis of model thioester 500	142
5.2.3.2	Synthesis of model iodide 507	143
5.2.3.3	Synthesis of model ketone 499	143
5.2.4	Synthesis of thioester 475	145
5.2.4.1	Synthesis of lactone 509	146
5.2.4.2	Conversion of lactone intermediate 509 with thioester 475	151
5.2.4.3	Aside –K.C. Nicolaou and the structural reassignment of Vannusal B	154
5.2.5	Synthesis of alkyl iodide 157 and attempted Fukuyama coupling reaction	157
5.3	Revised synthesis incorporating the <i>modified</i> Fukuyama coupling reaction	159
5.3.1	Literature precedence for the use of the modified Fukuyama coupling reaction	160
5.3.2	Synthesis of protected alkyne 551	161
5.3.3	Modified Fukuyama coupling reaction of alkyne 551 to thioester 475a	161
5.3.4	Synthesis of alkane 474	162
5.3.5	Spirocyclization attempts	162
5.3.6	Methoxymethyl protecting group strategy	165
5.3.6.1	Synthesis of methoxymethyl protected compounds	166
5.3.7	Triethylsilyl ether protecting group strategy	169
5.3.8	Modification of protecting group strategy	170
5.3.8.1	Literature precedence for planned debenzoylation sequence	171
5.3.8.2	Synthesis of benzyl protected alkyne 593	171
5.3.8.3	Overview of the synthesis of benzyl protected lactone intermediates	172
5.3.8.4	Acid mediated benzylation of base sensitive lactone 509	172
5.3.8.5	Selective removal of primary benzyl protecting groups	174
5.3.8.6	Oxidation of primary alcohol to carboxylic acid	175
5.4	Investigation into the synthesis of the ascospiroketal B backbone	176
5.5	Future work	180

Chapter Six: Experimental – Cephalosporolide E 290a and cephalosporolide F 290b

6.1	General Details.	183
6.2	Synthesis of model ketone 499	184
6.3	Synthesis of <i>bis</i> silyl protected (+)-bassianolone 474	189
6.4	Synthesis of <i>bis</i> methoxymethyl protected (+)-bassianolone 576	204
6.5	Synthesis of orthogonally protected (+)-bassianolone 587	211
6.6	Triethylsilyl protecting group strategy	213
6.7	Benzyl protecting group strategy	215
6.8	Towards the synthesis of the ascospiroketal B backbone	221

Chapter Seven: Appendix

7.1	¹³ C NMR spectra of novel compounds produced during the course of this research.	A-1
7.2	The first total synthesis of (+)-Cephalosporolide E and (-)-Cephalosporolide F.	A-50

Chapter Eight: References B-1