

Total Synthesis of Auripyrrone A and Related Metabolites

A thesis submitted for the fulfilment of the degree of

Doctor of Philosophy

Troy Lister BTech (Forens&AnalytChem), BSc (Hons)

Flinders University



Faculty of Science and Engineering
School of Chemistry, Physics and Earth Sciences
Adelaide, Australia

February, 2006

Declaration

I declare that the material presented in this thesis is the culmination of original work conducted by the author and that none has been previously submitted for any other degree at any university. To the best of my knowledge, this thesis does not contain any material previously published, or written, by any person except where acknowledgment by citation of the original publication is made in the text.

Troy Lister
24th February 2006

"We act as though comfort and luxury were the chief requirements of life, when all that we need to make us happy is something to be enthusiastic about."

Albert Einstein

Acknowledgements

I wish to first and foremost sincerely thank my supervisor, Dr. M.V. Perkins. After completing my honours degree under his guise, I had no hesitation in deciding to continue my education through research in his lab. The past few years have been tremendously enjoyable and fulfilling and I thank 'Dr. Mike' for the opportunity he has given me to grow and succeed in a field which I am passionate to be a part of. As a man of boundless wisdom and a contagious smile, Dr. Perkins was seemingly never short of advice and support when things went awry. I am very grateful for the freedom I have been given to explore and grasp the subtleties of organic synthesis, but also for the wealth of knowledge and ability that Dr. Mike has passed on to me. It is testament to his teachings, support and profound understanding of natural product synthesis that I am able to submit the dissertation that follows in under three years.

Many thankyou must also go to the various academic staff whose teachings and support during my years as an undergraduate student have given me the foundation and skills in chemistry that enabled my pursuit of a PhD. In particular, Prof. Rolf Prager, who has followed my research career closely and whose endless knowledge has been invaluable. Also, Dr. Martin Johnston, Dr. Gordon Elsey, Prof. Kevin Wainwright and Prof. Bill Adcock for their many contributions.

Thankyou also goes to Flinders University and the many technical and administrative staff in the SoCPES, whose ample facilities, skills, friendly faces and helpful support have made my time as a research student very enjoyable. I also wish to acknowledge the Australia government for financial support in the form of an Australian Postgraduate Award.

The long days as a graduate student were made easy with the companionship and assistance provided me by the many undergraduate and postgraduate students I have had the pleasure to work with. Many thanks to David Jeffery, Eric Dennis, Milena Kasprzyk, Julia Crossman, Rebecca and John Joannou, Dani Lyons, Simon Matthew and many others.

Acknowledgments

I wish to thank my loving family and friends for their boundless support and encouragement that has enabled me to pursue a dream. I especially wish to thank Mum and David, whose love and support have given me the opportunity and ability to make my dreams come true and Kate and Bryan for their love, friendship and smiling faces.

Publications and Presentations

The following list represents publications that have resulted from research outlined in this thesis and presentations that were given at various symposia.

Publications

1. Total Synthesis of a Hemiacetal Polypropionate from *Siphonaria australis*.
Lister, T.; Perkins, M. V. *Aust. J. Chem.* **2004**, 57(8), 787-797.
2. Total Synthesis of Auripyrone A
Lister, T.; Perkins, M. V. *Angew. Chem. Int. Ed.* **2006**, 45(16), 2560-2564.
3. A retro-Claisen Approach to Dolabriferol
Lister, T.; Perkins, M. V. *Org. Lett.* **2006**, 8(9), 1827-1830.

Presentations

The Synthesis of Two Marine Polypropionates from *Siphonaria australis*.

Poster presentation at the 19th RACI Organic Conference, Lorne, VIC, 6th-11th July, 2003.

Towards a Total Synthesis of Dolabriferol.


Oral presentation delivered at the Adelaide Organic Symposium, Adelaide, SA, December 2003.

Forays in Total Synthesis: The retro-Claisen Rearrangement of Marine Natural Products.

Poster presentation at the 39th National Organic Chemistry Symposium, Salt Lake City, Utah, 12th-16th June, 2005.

Adventures in the Synthesis of Polypropionate Natural Products

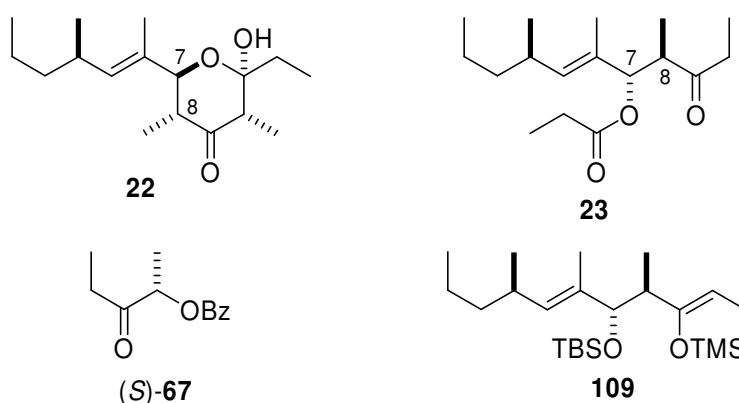
Oral presentation delivered at RACI Connect 2005, Sydney, NSW, 3rd-7th July, 2005.

 Reprints (and/or preprints) are contained within Appendix C.

Abstract

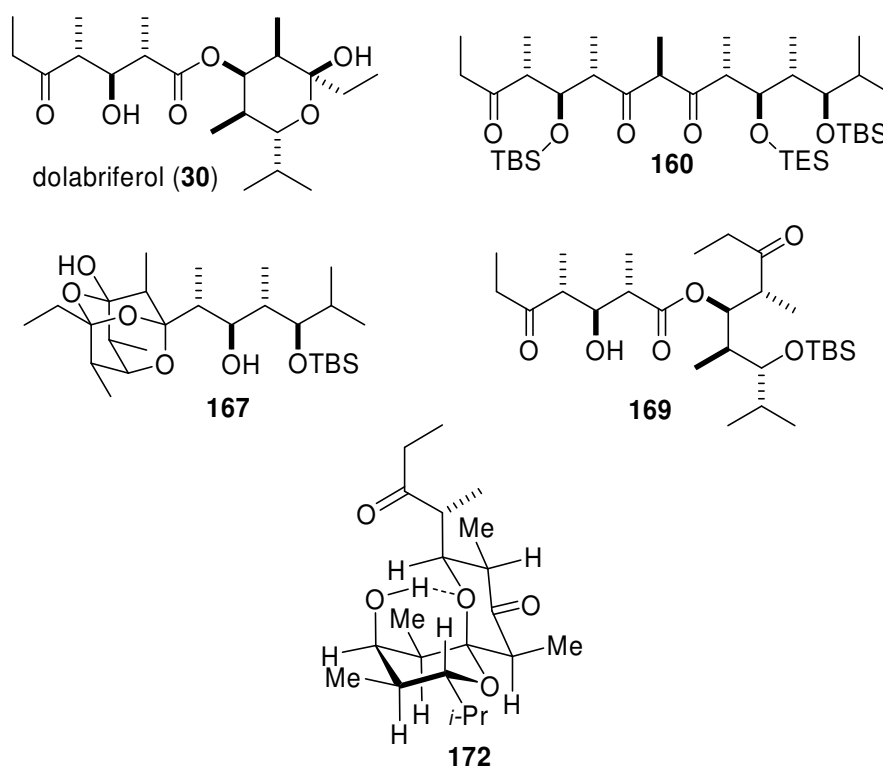
In recent decades the emergence of marine polypropionate natural products as compounds of diverse structural complexity and intriguing biological activity has influenced the advancement of asymmetric synthesis and predicated detailed studies of marine ecology. The introductory chapter of this thesis explores the nature of marine natural products, including their structure, biological activity and biosynthesis. Additionally, a brief review of the aldol reaction is presented. This well established biomimetic chemical transformation underpins polyketide synthesis and was utilised extensively in the research contributing to this dissertation.

Chapter Two describes the first asymmetric total synthesis of the two marine polypropionates isolated from specimens of *Siphonaria australis* by Hochlowski *et al.* in 1984. Spectroscopic analysis revealed hemiacetal **22** and ester **23** to be identical to the secondary metabolites extracted from the marine pulmonate. The synthetic approach to hemiacetal **22** utilised lactate derived ketone (*S*)-**67** to control the configuration of the C7 and C8 stereocentres and involved the discovery of a mild protocol for the synthesis of trimethylsilyl enol ether **109**, which was employed for a Mukaiyama aldol homologation reaction. Additionally, ester **23** was synthesised from hemiacetal **22** *via* a retro-Claisen fragmentation.



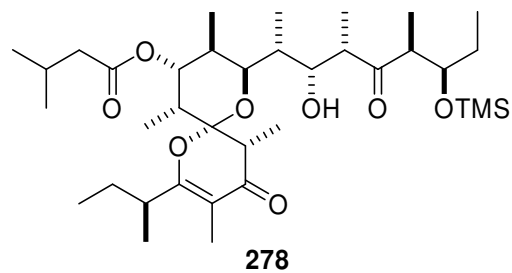
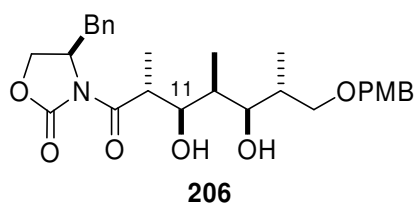
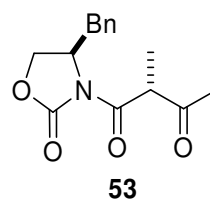
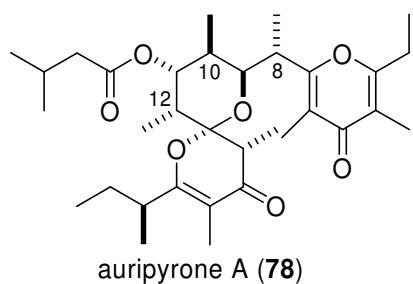
The retro-Claisen approach utilised in the synthesis of ester **23** was extended in Chapter Three to serve as the pivotal transformation in an attempted total synthesis of the unusual marine polypropionate dolabriferyl (**30**). The strategy toward

dolabriferol (**30**) involved an iterative homologation of chiral ketone (*S*)-**67** to install all but one of the requisite stereocentres in the natural product. Chemoselective deprotection of acyclic precursor **160** gave the elaborate 2,4,6-trioxaadamantane **167**, whose participation as a protecting group mimic lead to the formation of ester **169** after reaction of the polycycle **167** with base. The synthesis of ester **169**, which represents a direct precursor to dolabriferol (**30**), was achieved in 16 steps with an overall yield of 24%. Unfortunately, a robust protecting group on ester **169** prohibited a synthesis of dolabriferol (**30**), but intriguingly in one deprotection of ester **169** with aqueous hydrofluoric acid, spiroacetal **172** was isolated.



Chapter Four describes the first total synthesis of cytotoxic marine polypropionate auriopyrone A (**78**) and establishes the absolute configuration of this important natural product as that depicted for compound **78**. The requisite C8-C12 stereopentad of auriopyrone A (**78**) was formulated from Evans' dipropionate equivalent **53** in a double stereodifferentiating aldol reaction, followed by *syn*-reduction to give diol **206**. Differentiation of the secondary alcohols in compound **206** was achieved by migration of the PMB protecting group and protection at C11 with the requisite acyloxy group of auriopyrone A (**78**). Differential protection was critical to achieving

selective spiroacetalisation to afford the unique spiroacetal dihydropyrone core of the natural product. The utility of LiHMDS for highly selective double stereodifferentiating aldol homologations of sensitive fragments is also discussed. This mild aldol protocol was pivotal to forming the carbogenic skeleton of auripyronone A, in particular, elaborate adduct **278**.



Glossary

°C	degrees Celsius
Δ	heat
4Å	4 angstroms
AcOH	acetic acid (glacial)
Ac ₂ O	acetic anhydride
app	apparent (¹ H NMR spectra)
APT	attached proton test (¹³ C NMR spectroscopy)
aq	aqueous
atm	atmosphere
BF ₃ ·OEt ₂	boron trifluoride-diethyl ether complex
BH ₃ ·SMe ₂	borane-dimethyl sulfide complex
Bn	benzyl
bp	boiling point
Bu ₂ BOTf	dibutylboron triflate
<i>tert</i> -BuOH	<i>tertiary</i> -butanol
<i>n</i> -BuLi	butyllithium
Bz ₂ O	benzoic anhydride
<i>c</i>	concentration (g/100 mL)
<i>ca.</i>	<i>circa</i> (approximately)
Calcd.	calculated
cat.	catalytic
CCl ₄	carbon tetrachloride
CH ₂ Cl ₂	dichloromethane
COSY	correlation spectroscopy
δ	chemical shift (parts per million)
<i>de novo</i>	from the beginning
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
^c Hex ₂ BCl	dicyclohexylboron chloride
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

Glossary

DIBAL	diisobutylaluminium hydride
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
2,2-DMP	2,2-dimethoxypropane
DMP	Dess-Martin Periodinane
	1,1,1-triacetoxy-1,1-dihydro-1,1-benziodoxol-3(1 <i>H</i>)-one
DMSO	dimethylsulfoxide
ds	diastereoselectivity
<i>E</i>	<i>entgegen</i> (opposite)
e.e.	enantiomeric excess
<i>e.g.</i>	<i>exempli gratia</i> (for example)
EI	electron impact
EIMS	electron impact mass spectroscopy (spectrum)
eq	equivalents
ESI	electrospray ionisation
<i>et al.</i>	<i>et alia</i> (and others)
Et	ethyl
ether or Et ₂ O	diethyl ether
EtCOCl	propionyl chloride
EtMgBr	ethylmagnesium bromide
Et ₃ N	triethylamine
(EtO) ₂ CO	diethyl carbonate
EtOH	ethanol
FGI	Functional Group Interconversions
HF	hydrofluoric acid
HMBC	heteronuclear multiple bond connectivity
HMDS	hexamethyldisilazide
HMQC	heteronuclear multiple quantum coherence
HRMS	high resolution mass spectroscopy (spectrum)
Hünig's Base	<i>N,N</i> -diisopropylethylamine
Hz	hertz
<i>i.e.</i>	<i>id est</i> (that is)

Glossary

i Pr	<i>iso</i> -propyl
i -PrMgCl	<i>iso</i> -propylmagnesium chloride
IR	infrared
J	coupling constant (Hz)
KBrO ₃	potassium bromate
LDA	lithium diisopropylamine
LiHMDS	lithium hexamethyldisilazide
lit.	literature
LiAlH ₄	lithium aluminium hydride
LiBH ₄	lithium borohydride
LSI	liquid secondary ionisation
M ⁺	molecular ion (mass spectrum)
Me	methyl
MeCN	acetonitrile
Me ₂ NEt	dimethylethylamine
MeOH	methanol
MHz	megahertz
mmol	millimole
mol	mole
m.p.	melting point
MS	mass spectrum
m/z	mass-to-charge ratio
NaBH ₄	sodium borohydride
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser and exchange spectroscopy
ν_{\max}	infrared absorption maxima (cm ⁻¹)
OTf	trifluoromethanesulfonate (triflate)
PCC	pyridinium chlorochromate
Ph	phenyl
PMB	<i>para</i> -methoxybenzyl
PMBCl	<i>para</i> -methoxybenzyl chloride
PMP	<i>para</i> -methoxyphenyl

Glossary

PPh ₃	triphenylphosphine
ppm	part per million
PPTS	pyridinium <i>para</i> -toluenesulfonate
pyr	pyridine
R _f	retention factor
rt	room temperature
sat.	saturated
SiO ₂	silica gel
SmI ₂	samarium(II) iodide
SO ₃	sulfur trioxide
Sn(OTf) ₂	tin(II) trifluoromethanesulfonate
TAS-F	tris(dimethylamino)sulfur (trimethylsilyl)difluoride
TBAF	tetrabutylammonium fluoride
TBS	<i>tert</i> -butyldimethylsilyl
TBSOTf	<i>tert</i> -butyldimethylsilyl trifluoromethanesulfonate
TES	triethylsilyl
TESOTf	triethylsilyl trifluoromethanesulfonate
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid (triflic acid)
THF	tetrahydrofuran
TiCl ₄	titanium tetrachloride
tlc	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSOTf	trimethylsilyl trifluoromethanesulfonate
™	trade mark
<i>p</i> -TsOH	<i>para</i> -toluenesulfonic acid
<i>Z</i>	<i>zusammen</i> (together)
<	less than
>	greater than

Table of Contents

<i>Declaration</i>	i
<i>Acknowledgements</i>	v
<i>Publications and Presentations</i>	vii
<i>Abstract</i>	ix
<i>Glossary</i>	xiii

Chapter One

Introduction: Marine Natural Products: Biological Activity, Structure and Synthetic Approaches

1.1	Investigating Marine Natural Products	1
1.2	Biological Activity of Marine Natural Products	2
1.3	Biosynthesis of Marine Natural Products	4
1.4	Polypropionate Marine Natural Products	5
1.4.1	Polypropionate Biosynthesis	8
1.4.2	Cyclisation Modes of Polypropionates	8
1.4.3	The Fate of Cyclic Polypropionates	11
1.5	Methods for Polyketide Synthesis	13
1.5.1	The Aldol Reaction	14
1.5.2	Controlling Enolate Geometry	15
1.5.3	π -Facial selectivity	19
1.5.4	Determining the Stereochemistry of Aldol Products	29
1.6	Targets for Total Synthesis	30
1.7	References	33

Chapter Two

*An Asymmetric Total Synthesis of the Marine Polypropionates Isolated from *S. australis**

2.1	Introduction	39
2.1.1	<i>S. australis</i> and the Isolation of its Related Metabolites.....	39
2.1.2	Structural Elucidation	41
2.1.3	Previous Work	42
2.1.4	A Stereocontrolled Approach	43
2.2	Retro-Synthetic Analysis	44
2.3	Total Synthesis of Hemiacetal 22 and Ester 23	45
2.3.1	Acquisition of Aldehyde 84	45
2.3.2	The Synthesis of Lactate Derived Ketones (<i>S</i>)- and (<i>R</i>)- 67	48
2.3.3	Acquisition of Acyclic Precursor β -Diketone 96	49
2.3.4	Completion of the Synthesis of Hemiacetal 22	56
2.3.5	The Synthesis of Hemiacetal 87 for Spectral Comparison	56
2.3.6	Identifying the Stereochemistry of the Natural Products.....	62
2.4	Conclusion	64
2.5	References	65

Chapter Three

A Retro-Claisen Approach to the Marine Polypropionate Dolabriferyl

3.1	Introduction	67
3.1.1	<i>Dolabrifera dolabrifera</i> and the Isolation of Dolabriferyl	67
3.1.2	Structural Elucidation of Dolabriferyl	68
3.2	Previous Work	70
3.2.1	Overview.....	70
3.2.2	Goodman's Computational Studies.....	71
3.2.3	Chênevert's Synthesis of Ketoacid Fragment 119	73
3.2.4	Dias's Studies on Direct Esterification.....	74
3.3	Synthetic Strategy and Retro-Synthetic Analysis	75
3.4	Synthesis of Pivotal Acyclic Precursor 130	77

Table of Contents

3.4.1	Acquisition of Aldehyde 131	77
3.4.2	The Synthesis of Ketone Fragment 132	85
3.4.3	A Direct Approach to Esterification	89
3.4.4	Merger of the Aldol Fragments and Synthesis of Dione 130	90
3.5	Acquisition of Ester 169	97
3.6	Attempted Deprotection of Ester 169	104
3.7	Directions for a Synthesis of Dolabriferol (30)	109
3.8	Natural Product Status of Dolabriferol (30)	110
3.9	Conclusion	111
3.10	References	113

Chapter Four

Asymmetric Total Synthesis of Cytotoxic Marine Polypropionate

Auripyrone A

4.1	Introduction	117
4.1.1	Dolabella auricularia and the Isolation of the Auripyrones.....	117
4.1.2	Structural Elucidation	120
4.2	Previous Work	122
4.3	Strategies Towards a Synthesis of Auripyrone A	125
4.4	A First Approach to Auripyrone A	126
4.4.1	Retro-Synthetic Analysis	126
4.5	Model Studies	128
4.5.1	Acquisition of Model Diol 211	128
4.5.2	Lactonisation of Diol 211 as a Protecting Group Mimic.....	130
4.5.3	Addition of Enolates to Weinreb Amides.....	134
4.6	Pursuing the Lactone Approach to Auripyrone A	136
4.6.1	The Synthesis of Diol 206	136
4.6.2	Confirmation of the Relative Stereochemistry of Diol 206	139
4.6.3	The Synthesis of β -Triketide 203	142
4.6.4	The Synthesis of γ -Pyrone from β -Triketides	148
4.6.5	Investigating the Synthesis of γ -Pyrone 202	151

Table of Contents

4.7	A Revised Approach to Auripyronone A	152
4.7.1	Retro-Synthetic Analysis	152
4.8	Total Synthesis of Auripyronone A	153
4.8.1	Acquisition of Aldehyde 257	153
4.8.2	The Synthesis of Ketone 200 as a Single Stereoisomer.....	159
4.8.3	Aldol Extension and Formulation of β -Triketide 256	162
4.8.4	The Synthesis of Spiroacetal Dihydropyrone 274	165
4.8.5	Acquisition of β -Triketide 254	170
4.8.6	Completion of the Total Synthesis of Auripyronone A.....	173
4.9	Conclusion	179
4.10	References	181

Chapter Five

Experimental Procedures for Chapters Two to Four

5.1	General Procedures	187
5.2	Experimental Procedures for Chapter Two	190
5.3	Experimental Procedures for Chapter Three	214
5.4	Experimental Procedures for Chapter Four	251
5.5	References for Chapter Five	301

Appendices

Appendix A:	Additional Spectral Data for Chapter Three	303
Appendix B:	Additional Spectral Data for Chapter Four	308
Appendix C:	Copies of Publications Resulting from Research Conducted for the Thesis Presented Herein	311