Total Synthesis of Auripyrone 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

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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

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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.

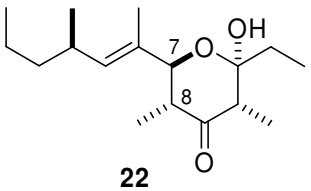
Adventures in the Synthesis of Polypropionate Natural Products
Oral presentation delivered at RACI Connect 2005, Sydney, NSW, 3rd-7th July, 2005.

📖 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.



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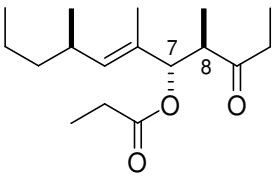

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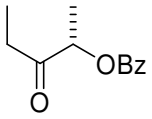
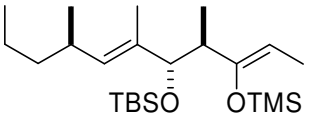


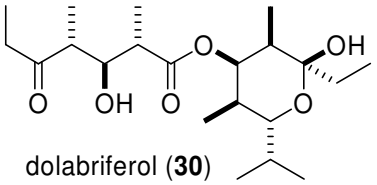
(*S*)-**67**



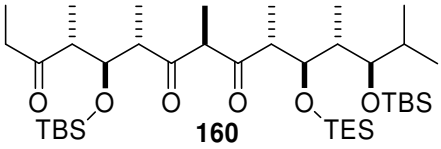
109

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 dolabriferol (**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.



dolabriferol (**30**)



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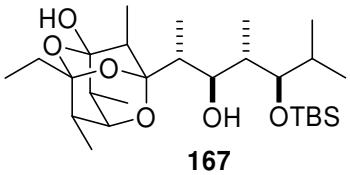
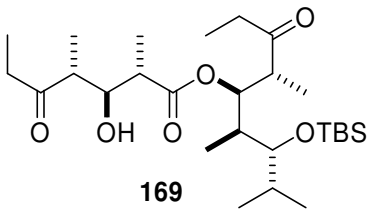


167



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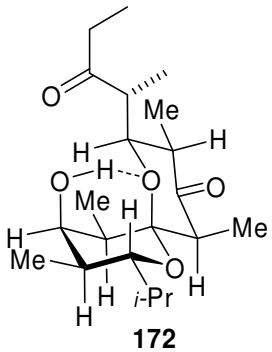
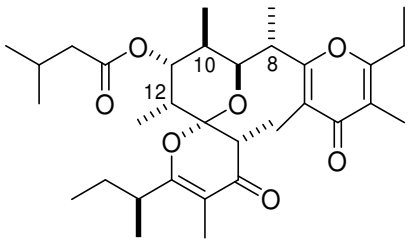


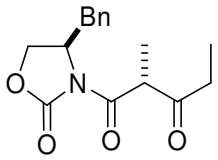
172

Chapter Four describes the first total synthesis of cytotoxic marine polypropionate auripyrone A (**78**) and establishes the absolute configuration of this important natural product as that depicted for compound **78**. The requisite C8-C12 stereopentad of auripyrone 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 auripyrone 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 auripyrone A, in particular, elaborate adduct **278**.



auripyrone A (**78**)



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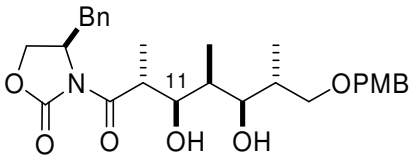
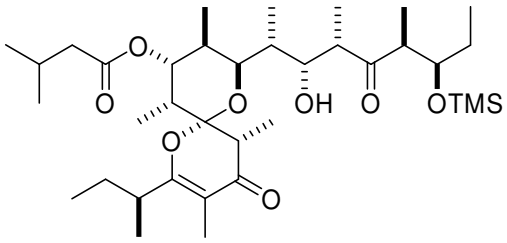


206



278

Glossary

°C	degrees Celsius
Δ	heat
4Å	4 angstroms
AcOH	acetic acid (glacial)
Ac_2O	acetic anhydride
app	apparent (^{1}H NMR spectra)
APT	attached proton test (^{13}C NMR spectroscopy)
aq	aqueous
atm	atmosphere
$BF_3{\cdot}OEt_2$	boron trifluoride-diethyl ether complex
$BH_3{\cdot}SMe_2$	borane-dimethyl sulfide complex
Bn	benzyl
bp	boiling point
Bu_2BOTf	dibutylboron triflate
tert-BuOH	*tertiary*-butanol
n-BuLi	butyllithium
Bz_2O	benzoic anhydride
c	concentration (g/100 mL)
ca.	*circa* (approximately)
Calcd.	calculated
cat.	catalytic
CCl_4	carbon tetrachloride
CH_2Cl_2	dichloromethane
COSY	correlation spectroscopy
δ	chemical shift (parts per million)
de novo	from the beginning
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
$^c Hex_2BCl$	dicyclohexylboron chloride
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DIBAL	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
2,2-DMP	2,2-dimethoxypropane
DMP	Dess-Martin Periodinane
	1,1,1-triacetoxy-1,1-dihydro-1,1-benziodoxol-3(1*H*)-one
DMSO	dimethylsulfoxide
ds	diastereoselectivity
E	*entgegen* (opposite)
e.e.	enantiomeric excess
e.g.	*exempli gratia* (for example)
EI	electron impact
EIMS	electron impact mass spectroscopy (spectrum)
eq	equivalents
ESI	electrospray ionisation
et al.	*et alia* (and others)
Et	ethyl
ether or Et_2O	diethyl ether
EtCOCl	propionyl chloride
EtMgBr	ethylmagnesium bromide
Et_3N	triethylamine
$(EtO)_2CO$	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	*N*,*N*-diisopropylethylamine
Hz	hertz
i.e.	*id est* (that is)

^{i}Pr	*iso*-propyl
^{i}PrMgCl	*iso*-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_2NEt	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	*para*-methoxybenzyl
PMBCl	*para*-methoxybenzyl chloride
PMP	*para*-methoxyphenyl

PPh_3	triphenylphosphine
ppm	part per million
PPTS	pyridinium *para*-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	*tert*-butyldimethylsilyl
TBSOTf	*tert*-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
p-TsOH	*para*-toluenesulfonic acid
Z	*zusammen* (together)
<	less than
>	greater than

Table of Contents

Chapter Two

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

Chapter Three

A Retro-Claisen Approach to the Marine Polypropionate Dolabriferol