Synthetic Studies Towards the Tridachione Family of Marine Natural Products

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

Doctor of Philosophy

by

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"Happy is he who gets to know the reasons for things"

- Virgil (70 – 19 BCE), Roman poet

Declaration

I declare that this thesis does not incorporate, without acknowledgement, any material previously submitted for any other degree or diploma at any university. To the best of my knowledge, this thesis does not contain any material previously published or written by another person, except where due reference of the original work has been made in the text.

Milena Kasprzyk

October 2008

For my mum, Gina

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Presentations and Publications

"Towards the Synthesis of the Tridachione Family of Marine Natural Products"
Poster presented at Connect 2005, Sydney, NSW, July 2005.

"Towards the Synthesis of Tridachiahydropyrone"
Poster presented at the ICOB-5 and ISCNP-25 IUPAC International Conference on Biodiversity and Natural Products, Kyoto, Japan, July 2006.

"Towards the Synthesis of Tridachiahydropyrone"
Seminar presented at the RACI Organic Chemistry Symposium, Adelaide, South Australia, December 2006.

"Towards the Synthesis of Tridachiahydropyrone: The Development of Cuprate Additions to Complex Enones"
Poster presented at the RACI Organic and Physical Chemistry Conference 2007, Adelaide, January 2007.

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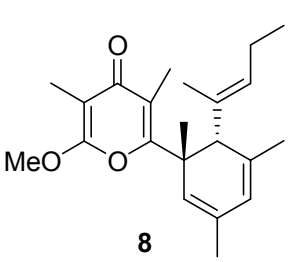
Abstract

Since the middle of the 20th century, significant interest has evolved from the scientific community towards the polypropionate family of marine natural products. A number of these compounds have been shown to possess significant biological activity, and this property, as well as their structural complexity, has driven numerous efforts towards their synthesis. The first chapter provides an introduction into the world of polypropionates, with a discussion on synthetic studies into a number of members of the tridachiapyrone family. Fundamental synthetic concepts utilised in this thesis towards the preparation of polyketides are also described, with a focus on their application towards the synthesis of 9,10-deoxytridachione (**8**), *anti* tridachiahydropyrone (**14**) and *syn* tridachiahydropyrone (**42**).



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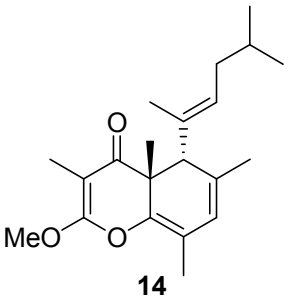

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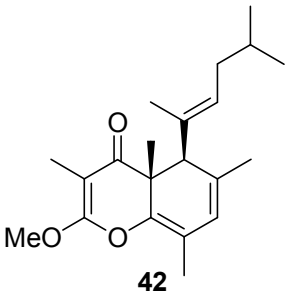

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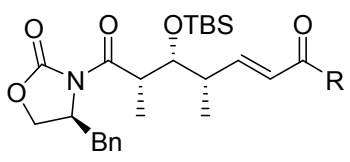
Chapter 2 describes the work undertaken towards the total synthesis of 9,10-deoxytridachione (**8**). The novel tandem conjugate addition-Dieckmann condensation of complex enones **118** and **109** developed previously in the Perkins group was used to generate *anti* methylated cyclohexenones **110** and **123** as key synthetic intermediates. The conversion of **110** and **123**, into the corresponding cyclohexadienes **111** and **197** *via* allylic alcohols **(*R*)-112** and **131**, was attempted, utilising a Grignard-mediated reaction to achieve the selective 1,2-reduction of cyclohexenones **110** and **123**. Studies into the Grignard-mediated reduction were also undertaken on seven additional cyclohexenones, in order to investigate the utility and scope of the reaction.



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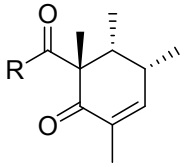
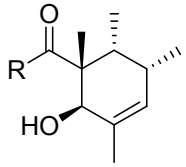
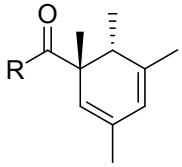
109 R = OEt



110 R = Me
123 R = OEt

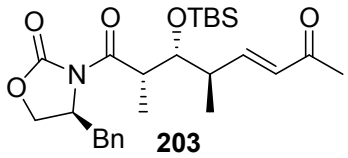


(*R*)-112 R = Me
131 R = OEt



111 R = Me
197 R = OEt

The extension of the methodology previously developed for the synthesis of cyclohexenones is the subject of Chapter 3. This section describes investigations into the synthesis of stereochemically-diverse cyclohexenones ***ent*-110** and **280**, from enones **203** and **278**, respectively. The conjugate addition-Dieckmann condensation strategy was extended successfully towards the synthesis of *syn* methylated cyclohexenone **280**, which allowed the synthesis of the proposed true structure of tridachiahydropyrone (**42**) to be pursued.



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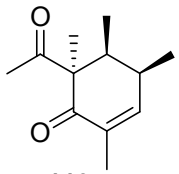
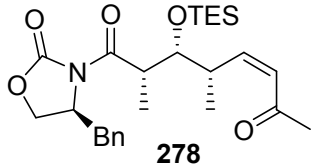


***ent*-110**



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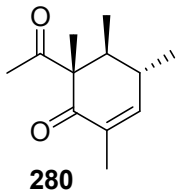

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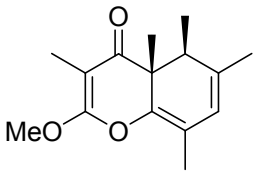
The methodology developed in Chapter 3 was utilised in Chapter 4 to synthesise model system **282** of *syn* tridachiahydropyrone (**42**). A comparative analysis of the NMR data of *syn* model **282**, *anti* model **306** and *anti* tridachiahydropyrone (**14**) with the natural product indicated that the true structure of tridachiahydropyrone may indeed be that depicted in **42**. The synthesis of *syn* tridachiahydropyrone (**42**) was attempted, and to this end cyclohexanone **307** was successfully synthesised. However, the subsequent methylation-elimination cascade failed to furnish the desired *syn* methylated cyclohexenone, producing only the *anti* methylated cyclohexanone **318**. The stereochemistry of the methylation was deduced using high and low VT NMR coupled with selective irradiation NOESY.



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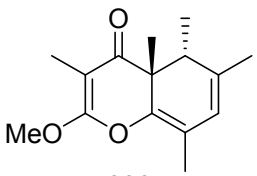

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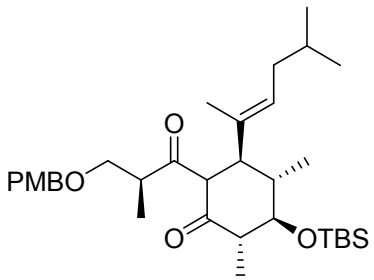

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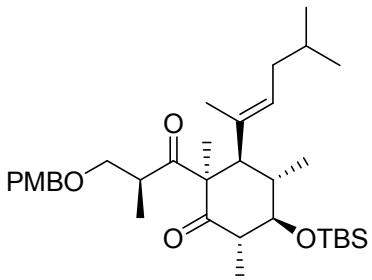

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Glossary

^{o}C	degrees Celcius
ab initio	from the beginning
AcOH	acetic acid
Ac_2O	acetic anhydride
APT	attached proton test
atm	atmosphere
$BF_3.OEt_2$	boron trifluoride-diethyl etherate
$BH_3.SMe_2$	borane-dimethyl sulphide complex
Bu_2BOTf	dibutylboron triflate
BPt	boiling point
c	concentration (g/100 mL)
CI-MS	chemical ionisation-mass spectrometry
conc.	concentration
COSY	^{1}H-^{1}H correlation spectroscopy
δ	chemical shift (parts per million)
dm	decimetre
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-*para*-benzoquinone
de novo	from the beginning
Diazald®	*N*-methyl-*N*-nitroso-*para*-toluenesulfonamide
DIBAL	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin Periodinane (1,1,1-triacetoxy-1,1-dihydro-1,1-benzodioxol-3(1*H*)-one)
DMSO	dimethylsulfoxide
ds	diastereomeric excess
E	engegen (opposite)
ee	enantiomeric excess

endo	inside
en route	on the way
ent	enantiomer
equiv	equivalents
ESI	electrospray ionisation
Et	ethyl
EtCOCl	propionyl chloride
EtOAc	ethyl acetate
$(EtO)_2CO$	diethyl carbonate
Et_2O	diethyl ether
EtOH	ethanol
Et_3N	triethylamine
exo	outside
g	gram
GC-MS	gas chromatography-mass spectrometry
HF-pyr/pyr	pyridinium hydrofluoride with excess pyridine
HMPA	hexamethylphosphoric acid triamide
HMPT	hexamethylphosphorous triamide
HMQC	heteronuclear multiple quantum coherence
hr	hour
HRESIMS	high resolution electrospray isonisation mass spectrometry
hν	light
Hz	Hertz
in situ	in the original position
in vacuo	in a vacuum
in vitro	in an artificial environment outside the living organism
in vivo	within a living organism
i-Pr	*iso*-propyl
IR	infrared
J	coupling constant (Hertz)
LC	liquid chromatography
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilylazide

lit.	literature
Ln	ligand
μ	micro
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MeON(H)Me.HCl	*N,O*-dimethylhydroxylamine hydrochloride
min	minute
mL	millilitre
MHz	mega Hertz
mmHg	millimetres of mercury
mmol	millimole
mol	mole
MTPI	methyltriphenoxyphosphonium iodide
nm	nanometre
n-Bu	*n*-butyl
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
OTf	triflate
PCC	pyridinium chlorochromate
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	parts per million
p-TsCl	*para*-toluenesulfonyl chloride
p-TsOH	*para*-toluenesulfonic acid
R_f	retention factor
RT	room temperature
sat.	saturated
sec	second
TBAF	tetrabutylammonium fluoride
t-Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl

TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF	time of flight
TS	transition state
UV	ultraviolet
VT	variable temperature
Z	zusammen (together)