Biomimetic Approaches to the Synthesis of Polyketide Derived Marine Natural Products; (-)-Maurenone and the Spiculoic Acids

A Thesis submitted for the fulfilment of the degree of

Doctor of Philosophy

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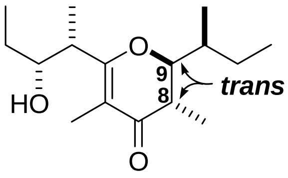
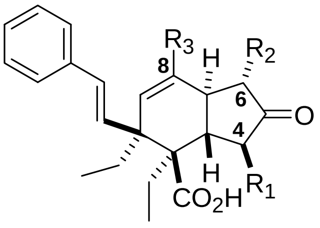
Contents

Abstract

This thesis describes the total synthesis of the polyketide derived marine natural product (-)-maurenone (**14**) and synthetic studies of a model system for the marine polyketides, the spiculoic acids (**20, 22-24**). A biomimetic approach involving cyclisation of linear polyketide precursors to install the complex chemical frameworks was employed.

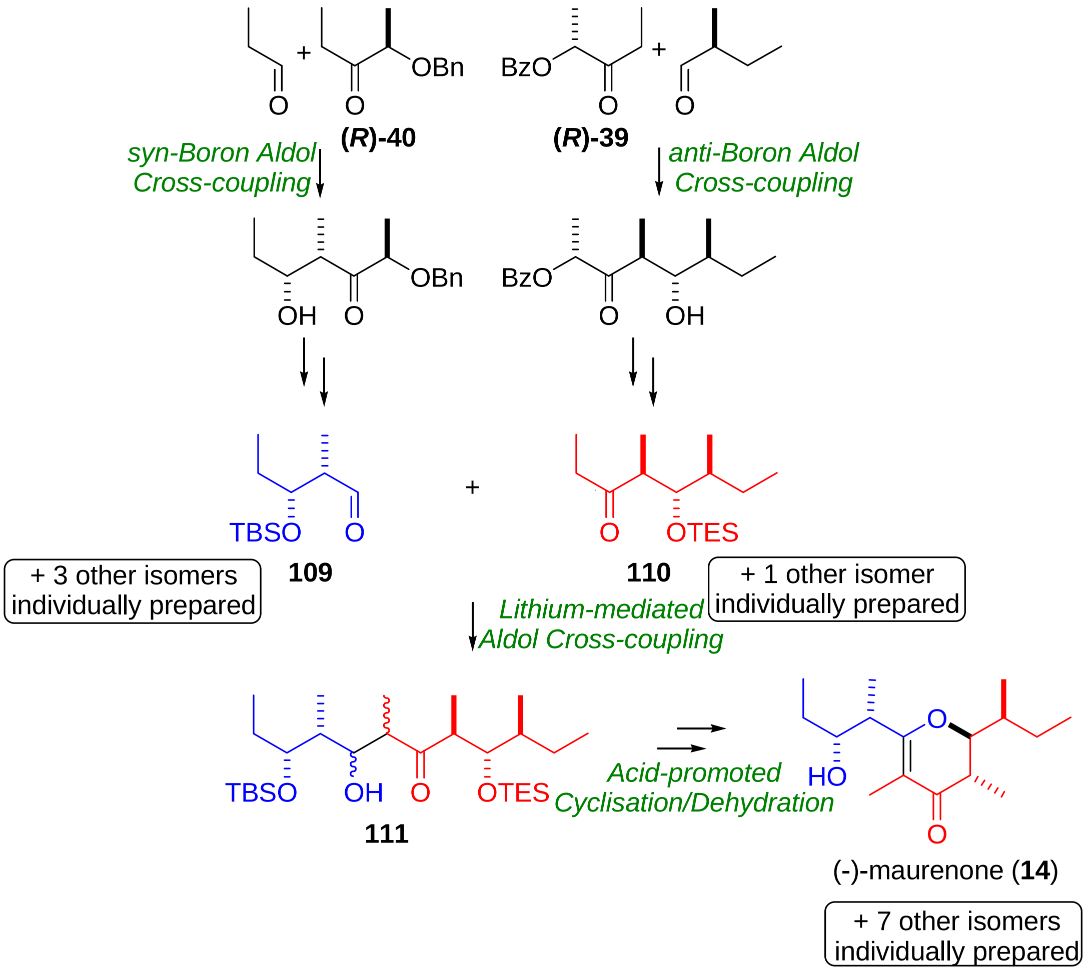


(-)-maurenone **(14)**

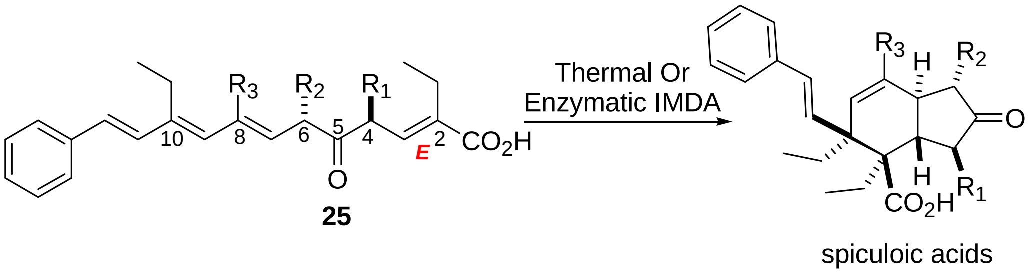


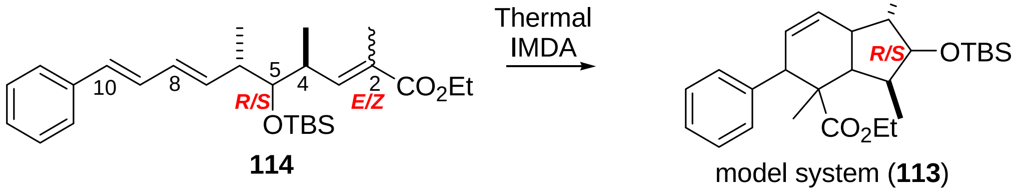
spiculoic acid A (**20**), R_1 = Et, R_2 = Me, R_3 = Et
isospiculoic acid A (**22**), R_1 = Me, R_2 = Et, R_3 = Et
nor-spiculoic acid A (**23**), R_1 = Me, R_2 = Et, R_3 = Me
dinor-spiculoic acid A (**24**), R_1 = Me, R_2 = Me, R_3 = Me

Maurenone is a polypropionate derived metabolite isolated from pulmonate molluscs collected off the coast of Costa Rica. While structural assignment following isolation revealed a relatively uncommon tetra-substituted dihydropyrone moiety the only stereochemical information deduced was the *trans*-relative relationship between the C8 and C9 protons. The total synthesis of a series of eight stereoisomeric putative structures was achieved in order to assign the stereochemistry of (-)-maurenone (**14**), as that depicted above. A time and cost efficient strategy was developed utilising common intermediates providing access to the eight stereoisomeric structures in a convergent manner. Six key fragments, four aldehydes (**109**) and two ketones (**110**), were synthesised using highly diastereoselective *syn-* and *anti*-boron aldol reactions and were coupled using a lithium-mediated aldol reaction. Trifluoroacetic acid-promoted cyclisation/dehydration enabled installation the γ-dihydropyrone ring. All eight isomers of one enantiomeric series were synthesised by coupling two ketones with each of four aldehydes. By comparison of the NMR data for the eight isomers with that reported for the natural product, the relative stereochemistry was established as shown. The (-)-enantiomer of maurenone was synthesised in nine linear steps (13 % overall yield) from (*R*)-2-benzylpentan-3-one (**(*R*)-40**) and (*R*)-2-benzoyloxypentan-3-one (**(*R*)-39**).

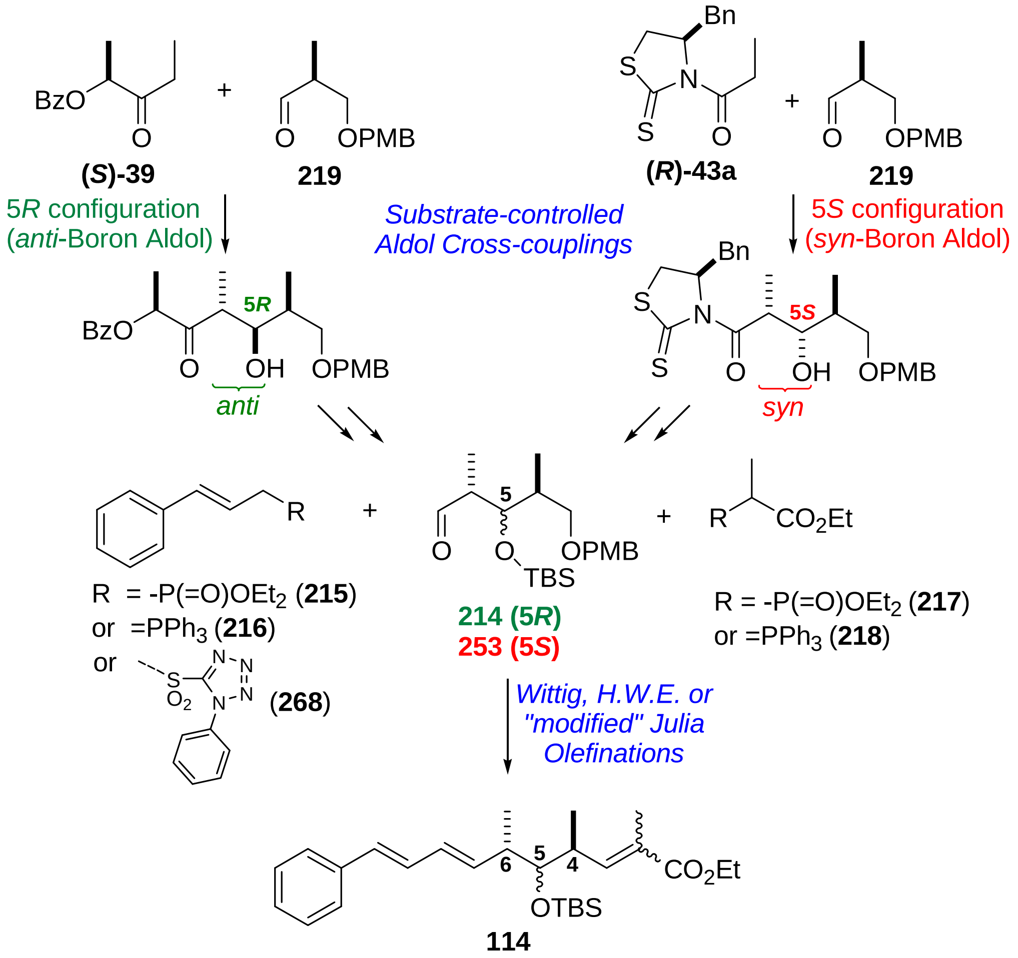


The spiculoic acid family of polyketide derived natural products, isolated from *plakortis* sponges, possess a unique [4.3.0]-bicyclic core which is proposed to be formed *via* an enzyme catalysed Intramolecular Diels-Alder (IMDA) cycloaddition reaction of linear polyene precursors **25**. Model linear precursors (**114**), possessing various olefin geometries at C2 and both stereochemical orientations of the C5 stereocentre, were synthesised in order to examine stereoselectivity of the thermally induced IMDA cycloaddition reaction.

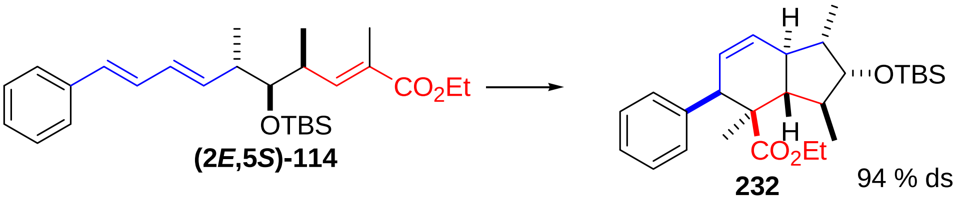




The two alternative C4-C6 stereotriads of the linear precursors **114** were achieved by employing highly diastereoselective substrate-controlled aldol reactions; an *anti*-boron aldol reaction, controlled by the facial preference of (*R*)-2-benzoyloxypentan-3-one (**(*R*)-39**), and a *syn*-titanium aldol reaction, under the control of chiral N-acylthiazolidinethione (**(*R*)-43a**). The diene and dienophile moieties were installed using either standard Wittig, H.W.E. or "modified" Julia olefination reactions.



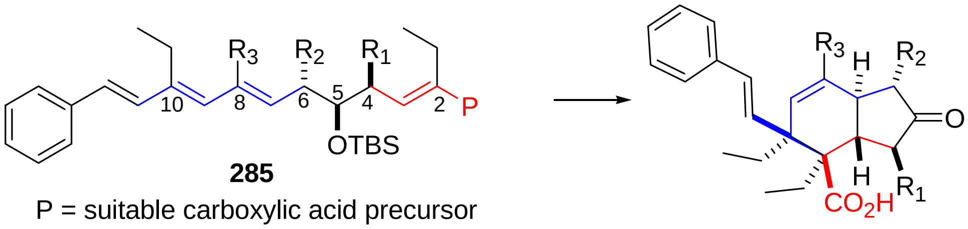
A thorough stereochemical assignment of the cycloadducts of the thermally induced IMDA reaction of each linear precursor was accomplished employing 2D NMR techniques. Comparison of the stereochemistry of each of the cycloadducts with the spiculoic acids revealed that the linear precursor **(2*E*,5*S*)-114** produced a cycloadduct **232** with stereochemistry analogous to the natural products in 94 % diastereoselectivity. Thus, a synthetic approach to the spiculoic acids *via* synthesis of a linear precursor **285** possessing a TBS ether at C5 in the *S* configuration was proposed. Unfortunately, problems encountered in the synthesis of the proposed linear precursors to the spiculoic acids ultimately prevented the total synthesis from being achieved.



(2*E*,5*S*)-114

232

94 % ds



285

P = suitable carboxylic acid precursor

spiculoic acids

Declaration

I certify that this thesis does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Julia S. Crossman
24th September, 2007

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The long and bumpy road towards a PhD would have been longer, bumpier and much less enjoyable without the support and friendship of my fellow students over the years. In particular thanks to my lab partners; Milena Kasprzyk, Helen Wray and Claire Gregg who made our lab an enjoyable place to come to work in each day. Thanks also to Rachel Brown, David Jeffery, Troy Lister, Eric Dennis, Simon Mathew, Dani Lyons and Jozef Hodel for their friendly faces, willingness to share chemicals, equipment and advice and for their idiosyncrasies which made the department an entertaining and unique place to work.

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Finally, I am indebted to my family and Damian for their endless love and support during this arduous journey. Their unwavering belief in my abilities kept me on track and helped me to survive the rollercoaster ride that is a PhD. Thank you for knowing intuitively when to provide distractions, laughs or a shoulder to cry on.

Publications and Presentations

The following is a list of publications that have resulted from research outlined in this thesis and presentations that were delivered at various symposia.

Publications

Total Synthesis and Structural Elucidation of (-)-Maurenone, Crossman, J.S. and Perkins, M.V. *Journal of Organic Chemistry* **2006**, 71 (1) 117-124.

Synthesis of a Model of the Spiculoic Acids by an Intramolecular Diels-Alder Reaction, Crossman, J.S. and Perkins, M.V. *Tetrahedron* **2008**, accepted for publication in a *Symposium in Print* on "Reseach in Natural Product Synthesis – A Vital and Dynamic Global Enterprise".

Presentations

Investigations of the Diels-Alder Reaction Towards the Synthesis of the Spiculoic Acids. Oral presentation delivered at the RACI Organic and Physical Chemistry Conference, Adelaide, S.A., January 2007.

Investigations of the Diels-Alder Reaction Towards the Synthesis of the Spiculoic Acids. Poster presentation delivered at the ICOB-5 and ISCNP IUPAC International Conference on Biodiversity and Natural Products, Kyoto, Japan, July 2006.

Total Synthesis and Structural Elucidation of (-)-Maurenone. Oral presentation delivered at the Adelaide Organic Synthesis Symposium, Adelaide, S.A., December 2005.

Total Synthesis and Structural Elucidation of (-)-Maurenone. Poster presentation delivered at the RACI Connect 2005 Conference, Sydney, N.S.W., July 2005.
(Awarded the IUPAC Poster Prize and the Geoffrey I. Feutrill Award for best student poster.)

Abbreviations

Δ	heat
AcCl	acetyl chloride
AcOH	acetic acid (glacial)
Ac_2O	acetic anhydride
apt	apparent
9-BBN	9-borabicyclo[3.3.1]nonane
$BF_3.OEt_2$	boron trifluoride-diethyl ether complex
$BH_3.SMe_2$	borane-dimethyl sulfide complex
BHT	butylated hydroxytoluene
binap	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
b.p.	boiling point
Bn	benzyl
BT	benzothiazole-2-yl
Bu_2BOTf	dibutylboron triflate
^{n}BuLi	butyllithium
^{t}BuLi	*tert*-butyllithium
Bz	benzoyl
c	concentration (g/100 mL)
cat.	catalytic
CH_2Cl_2	dichloromethane
COSY	homonuclear COrrelation SpectroscopY
Cp_2ZrCl_2	bis(cyclopentadienyl)zirconium(IV) dichloride
m-CPBA	*meta*-chloroperbenzoic acid
CuBr.DMS	copper(1) bromide dimethylsulfide complex
δ	chemical shift
dba	dibenzylidineacetone
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyanno-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DMAP	4-(N,N-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone

DMSO	dimethylsulfoxide
dppe	diphenylphosphino ethane
dppf	diphenylphosphino ferrocene
ds	diastereoselectivity
EI	electron impact
EIMS	electron impact mass spectroscopy (spectrum)
eq.	equivalent (s)
ESI	electrospray ionisation
Et	ethyl
EtCOCl	propionyl chloride
Et_2O	diethyl ether
$(EtO)_2CO$	diethyl carbonate
EtOH	ethanol
HMBC	Heteronuclear Multiple Bond Connectivity
HMPA	hexamethylphosphoramide
HMQC	Heteronuclear Multiple Quantum Coherence
HOMO	Highest Occupied Molecular Orbital
HRMS	high resolution mass spectroscopy (spectrum)
Hz	hertz
Icp	isopinocamphenyl
IBX	2-iodoxybenzoic acid
IMDA	intramolecular Diels-Alder
IR	infrared
J	coupling constant (Hz)
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
LUMO	Lowest Unoccupied Molecular Orbital
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	megahertz
mmol	millimole
mol	mole
m.p.	melting point

MPM	methoxyphenylmethyl
m/z	mass-to-charge ratio
NIS	N-iodosuccinimide
NMO	N-methylmorpholine-N-oxide
NMR	nuclear magnetic resonance
NOESY	Nuclear Overhauser and Exchange SpectroscopY
OAc	acetate
OTf	trifluoromethanesulfonate (triflate)
Ph	phenyl
PMB	*para*-methoxybenzyl
PPh_3	triphenylphosphine
PPTS	pyridinium *para*-toluenesulfonic acid
ppm	parts per million
^{i}PrOH	isopropanol
PT	1-phenyl-1H-tetrazole-5-yl
Pyr	pyridine
PYR	pyridin-2-yl
R_f	retention factor
ROESY	Rotating frame Overhauser Effect SpectroscopY
R.T. or RT	room temperature
sat.	saturated
SM	starting material
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBATFA	tetrabutylammonium trifluoroacetate
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
TBT	*tert*-butyl-1H-tetrazole-5-yl
TES	triethylsilyl
TESOTF	triethylsilyl trifluoromethanesulfonate
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl

TLC	thin layer chromatography
TMEDA	trimethylethylenediamine
TMS	trimethylsilyl
TOCSY	TOtal Correlation SpectroscopY
TPAP	tetrapropylammonium perruthenate
p-TsOH	*para*-toluenesulfonic acid