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

Julia S. Crossman
B.Sc. (Hons), B.Tech. (Forensic and Analytical Chemistry)

at
Flinders University

The Faculty of Science and Engineering
School of Chemistry, Physics and Earth Sciences

September 2007
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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 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 \textbf{114} were achieved by employing highly diastereoselective substrate-controlled aldol reactions; an \textit{anti}-boron aldol reaction, controlled by the facial preference of (\textit{R})-2-benzoyloxypentan-3-one (\textbf{(R)-39}), and a \textit{syn}-titanium aldol reaction, under the control of chiral N-acylthiazolidinethione (\textbf{(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 \textit{(2E,5S)-114} produced a cycloadduct \textbf{232} with stereochemistry analogous to the natural products in 94 \% diastereoselectivity. Thus, a synthetic approach to the spiculoic acids \textit{via} synthesis of a linear precursor \textbf{285} possessing a TBS ether at C5 in the \textit{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.
OTBS

\( \text{CO}_2\text{Et} \)

94 % ds

(2E,5S)-114

\( \text{CO}_2\text{Et} \)

OTBS

H

H

(2)

E

S

\(-114 \quad 232 \)

R3

R2

R1

O

CO2H

spiculoic acids

\( \text{OTBS} \)

P = suitable carboxylic acid precursor

R3

R2

R1

\( \text{CO}_2\text{H} \)

285

\( \text{P} = \text{suitable carboxylic acid precursor} \)

spiculoic acids

R3

R2

R1

\( \text{CO}_2\text{H} \)
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
Acknowledgements

I would like to acknowledge the support and guidance provided by my supervisor, Dr. Michael Perkins, throughout my research projects. His advice, suggestions and unyielding enthusiasm were much appreciated, reigniting my passion in the wake of setbacks and keeping me focused on the targets.

The efforts of the academic and technical staff in the School of Chemistry, Physics and Earth Sciences at Flinders University in keeping the equipment in working order and laboratories stocked with chemicals and glassware cannot be overlooked. The staff of the chemical store deserve individual mention for placing extra orders when I required chemicals urgently. Dr. Martin Johnston and Mr. Phil Clements (University of Adelaide) also warrant special mention for their tireless efforts in maintaining the NMR spectrometers and for their assistance in acquiring the large numbers of spectra of all of my isomers!

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.

For financial support, I would like acknowledge the Australian Government for providing me with an Australian Postgraduate Award, the Australian Research Council for project funding and Flinders University for an Elaine Martin Fund Travel Scholarship.

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


Presentations


*(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)
Ac₂O  acetic anhydride
apt  apparent
9-BBN  9-borabicyclo[3.3.1]nonane
BF₃.OEt₂  boron trifluoride-diethyl ether complex
BH₃.SMe₂  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
Bu₂BOTf  dibutylboron triflate
°BuLi  butyllithium
¹BuLi  tert-butyllithium
Bz  benzoyl
c  concentration (g/100 mL)
cat.  catalytic
CH₂Cl₂  dichloromethane
COSY  homonuclear CORrelation Spectroscopy
Cp₂ZrCl₂  bis(cyclopentadienyl)zirconium(IV) dichloride
m-CPBA  meta-chloroperbenzoic acid
CuBr.DMS  copper(I) bromide dimethylsulfide complex
δ  chemical shift
dba  dibenzylideneacetone
DCE  1,2-dichloroethane
DDQ  2,3-dichloro-5,6-dicyano-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
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dppe</td>
<td>diphenylphosphino ethane</td>
</tr>
<tr>
<td>dppf</td>
<td>diphenylphosphino ferrocene</td>
</tr>
<tr>
<td>ds</td>
<td>diastereoselectivity</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>EIMS</td>
<td>electron impact mass spectroscopy (spectrum)</td>
</tr>
<tr>
<td>eq.</td>
<td>equivalent (s)</td>
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<td>ESI</td>
<td>electrospray ionisation</td>
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<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>EtCOCl</td>
<td>propionyl chloride</td>
</tr>
<tr>
<td>Et2O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>(EtO)2CO</td>
<td>diethyl carbonate</td>
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<td>EtOH</td>
<td>ethanol</td>
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<tr>
<td>HMBC</td>
<td>Heteronuclear Multiple Bond Connectivity</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HMQC</td>
<td>Heteronuclear Multiple Quantum Coherence</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest Occupied Molecular Orbital</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectroscopy (spectrum)</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>Icp</td>
<td>isopinocamphenyl</td>
</tr>
<tr>
<td>IBX</td>
<td>2-iodoxybenzoic acid</td>
</tr>
<tr>
<td>IMDA</td>
<td>intramolecular Diels-Alder</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>$J$</td>
<td>coupling constant (Hz)</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest Unoccupied Molecular Orbital</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
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<tr>
<td>MeCN</td>
<td>acetonitrile</td>
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<td>methanol</td>
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<tr>
<td>mol</td>
<td>mole</td>
</tr>
<tr>
<td>m.p.</td>
<td>melting point</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>MPM</td>
<td>methoxyphenylmethyl</td>
</tr>
<tr>
<td>m/z</td>
<td>mass-to-charge ratio</td>
</tr>
<tr>
<td>NIS</td>
<td>N-iodosuccinimide</td>
</tr>
<tr>
<td>NMO</td>
<td>N-methylmorpholine-N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOESY</td>
<td>Nuclear Overhauser and Exchange Spectroscopy</td>
</tr>
<tr>
<td>OAc</td>
<td>acetate</td>
</tr>
<tr>
<td>OTf</td>
<td>trifluoromethanesulfonate (trilate)</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PMB</td>
<td>para-methoxybenzyl</td>
</tr>
<tr>
<td>PPh₃</td>
<td>triphenylphosphine</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium para-toluenesulfonic acid</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
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<tr>
<td>iPrOH</td>
<td>isopropanol</td>
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<td>1-phenyl-1H-tetrazole-5-yl</td>
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<td>pyridine</td>
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<td>PYR</td>
<td>pyridin-2-yl</td>
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<tr>
<td>Rₚ</td>
<td>retention factor</td>
</tr>
<tr>
<td>ROESY</td>
<td>Rotating frame Overhauser Effect Spectroscopy</td>
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<tr>
<td>R.T. or RT</td>
<td>room temperature</td>
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<td>sat.</td>
<td>saturated</td>
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<tr>
<td>SM</td>
<td>starting material</td>
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<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
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<td>TBAI</td>
<td>tetrabutylammonium iodide</td>
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<tr>
<td>TBATFA</td>
<td>tetrabutylammonium trifluoroacetate</td>
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<tr>
<td>TBDPS</td>
<td>tert-butylidiphenylsilyl</td>
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<td>TBS</td>
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<td>TFA</td>
<td>trifluoroacetic acid</td>
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<td>triisopropylsilyl</td>
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<td>Abbreviation</td>
<td>Definition</td>
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<td>----------------------------------</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
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<td>TMEDA</td>
<td>trimethylethlenediamine</td>
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<td>TMS</td>
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<td>TOtal Correlation SpectroscopY</td>
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<td>TPAP</td>
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<td>p-TsOH</td>
<td>para-toluenesulfonic acid</td>
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