Synthetic Studies Towards Spirangien A and Total Synthesis of (+)-Ascosalipyrone and ent-Micropyrone

A thesis submitted for the fulfilment of the degree of

Doctor of Philosophy

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Declaration

I certify that this thesis does not incorporate without acknowledgment 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.

Claire Gregg
13\textsuperscript{th} May 2011
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Abstract

Polyketides are considered not only the largest class of secondary metabolites that share a common biosynthesis, but are also one of the most interesting classes of natural products due to their enormous structural diversity and broad spectrum biological activities. Chapter one introduces the reader to polyketide natural products, including their origin, structure and activity. This is followed by an overview of the aldol reaction, a highly useful synthetic tool in the biomimetic construction of polyketide motifs. The aldol reaction will feature extensively in the studies to follow.

Chapter two describes studies towards the synthesis of spirangien A (1), a highly cytotoxic and antifungal polyketide metabolite, isolated from the myxobacterium Sorangium cellulosum. The synthetic approach to spirangien A exploited the obvious C22-C23 acetate aldol disconnection in linear precursor 158. Model studies were conducted which showed that the diastereoselectivity of this aldol reaction is highly substrate controlled and depends heavily on the hydroxyl protecting group strategy. This model system lacked the C17 stereocentre of the natural product, which evidently exhibited strong 1,7-stereinduction, therefore the model was concluded to be an inadequate representation of the natural product system.

The aldehyde coupling partner 150 was synthesised in 10 steps (10% yield), utilising a highly efficient cross-coupling of zinc homoenolate 144 with (E)-2-bromo-2-
butene (48) to install the C28 stereocentre and two successive Evans syn aldol reactions to give the desired C24-27 stereotetrad and differential protection of the resulting hydroxyl groups. Ketone coupling partner 130 was synthesised from (R)-Roche ester (R)-32 in 16 steps (22% yield), using a mercury catalysed hydration of the terminal alkynyl functionality derived from ethynylmagnesium bromide (35) to afford the methyl ketone, and a syn,syn selective aldol reaction with (S)-Roche ester derived dipropionate equivalent (S)-10 to give the C14-17 stereotetrad. Coupling of the resulting aldehyde 150 and ketone 130 was achieved using a LiHMDS aldol to give 1.2-2.5:1 ds in favour of the desired product 158. The stereochemistry of aldol adduct 158 was assigned by conversion to the corresponding hemiacetal and subsequent nOe analysis. Spirocyclisation of the major product hemiacetal gave 165, from which stereochemical assignment was confirmed. Further manipulation of 165 in 3 steps (removal of the TBS groups, re-protecting with TES groups and finally cleavage of the PMB ether) would result in a formal synthesis of spirangien A, however limited availability of material prevented completion of the total synthesis.
Chapter three details the total synthesis of (+)-ascosalipyrone [(6S,8S)-4] and ent-micropyrene [(6S,8S)-5]. Ascosalipyrone (4), isolated from the obligate marine fungus A. salicorniae, and micropyrone (5), isolated from the plant H. italicum, are two novel, structurally related polyketide natural products. Both compounds have the same 4-hydroxy-α-pyrone containing core structure, differing only by an extra methyl group at C4 in micropyrene (5). Ascosalipyrone was reported as an inseparable mixture of diastereomers, while micropyrone was reported as a single isomer with a non-zero specific rotation.

The synthesis of two potential diastereomers of each natural product from a common intermediate was achieved. A highly diastereoselective syn aldol reaction between both the (R)-77 and (S)-77 enantiomers of Evans’ auxiliary and chiral aldehyde 178 was exploited to produce aldehydes (6R,7S,8S)-177 and (6S,7R,8S)-177. The linear precursors (6R,7S,8S)-193 and (6R,7S,8S)-194 were constructed by addition of β-ketoesters 175 or 176 respectively to aldehyde (6R,7S,8S)-177, with DBU promoted cyclisation to install the 4-hydroxy-α-pyrone ring system. Removal of the protecting groups and Jones oxidation gave two possible isomers of each ascosalipyrone and micropyrone. No epimerisation of the α-stereocentre was observed for the micropyrone isomers but partial epimerisation (3:1) was seen for ascosalipyrone isomers. This was attributed to less steric congestion for ascosalipyrone, which lacks one pyrone methyl. Comparison of the NMR and specific rotation assigned the structure of (+)-ascosalipyrone [(6S,8S)-4] and micropyrone [(6R,8R)-5].
## Glossary

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>Å</td>
<td>angstroms</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid (glacial)</td>
</tr>
<tr>
<td>Ac₂O</td>
<td>acetic anhydride</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>AR</td>
<td>analytical reagent</td>
</tr>
<tr>
<td>Ar</td>
<td>aromatic</td>
</tr>
<tr>
<td>atm</td>
<td>atmospheres</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>bp.</td>
<td>boiling point</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>Bz₂O</td>
<td>benzoic anhydride</td>
</tr>
<tr>
<td>c</td>
<td>concentration (g/100 mL)</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic</td>
</tr>
<tr>
<td>CAN</td>
<td>cerium ammonium nitrate</td>
</tr>
<tr>
<td>CDCl₃</td>
<td>deuterated chloroform</td>
</tr>
<tr>
<td>C₆D₆</td>
<td>deuterated benzene</td>
</tr>
<tr>
<td>CD₃OD</td>
<td>deuterated methanol</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>CSA</td>
<td>10-camphorsulfonic acid</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift (parts per million)</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>(c-Hex)₂BCl</td>
<td>dicyclohexylboron chloride</td>
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<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DMA</td>
<td>N,N-dimethylacetamide</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(N,N-dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>(Sia)$_2$BH</td>
<td>disiamylborane</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin Periodinane</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>ds</td>
<td>diastereoselectivity</td>
</tr>
<tr>
<td>E</td>
<td>entgegen (opposite)</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>eq.</td>
<td>equivalents</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionisation</td>
</tr>
<tr>
<td>et al.</td>
<td>et alia (and others)</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>FGI</td>
<td>Functional Group Interconversions</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>HF</td>
<td>hydrofluoric acid</td>
</tr>
<tr>
<td>HMBC</td>
<td>heteronuclear multiple bond connectivity</td>
</tr>
<tr>
<td>HMQC</td>
<td>heteronuclear multiple quantum coherence</td>
</tr>
<tr>
<td>HRESIMS</td>
<td>high resolution electrospray ionization mass spectroscopy (spectrum)</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>ie.</td>
<td>id est (that is)</td>
</tr>
<tr>
<td>i-</td>
<td>iso-</td>
</tr>
<tr>
<td>Ipc</td>
<td>diisopinocampheyl</td>
</tr>
<tr>
<td>IBX</td>
<td>2-iodobenzoic acid</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 hexamethyldisilaside</td>
</tr>
<tr>
<td>LC</td>
<td>liquid chromatography</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamine</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium hexamethyldisilazide</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
<tr>
<td>mmol</td>
<td>millimole</td>
</tr>
</tbody>
</table>
mol    mole
mp.    melting point
MS     mass spectrum
NMR    nuclear magnetic resonance
nOe    nuclear Overhauser effect
NOESY nuclear Overhauser and exchange spectroscopy
OTf    trifluoromethanesulfonate (triflate)
[O]    oxidation
Ph     phenyl
PMB    para-methoxybenzyl
PMP    para-methoxyphenyl
ppm    parts per million
PPTS   pyridinium para-toluenesulfonate
Pr     propyl
pyr    pyridine
Rf     retention factor
rt     room temperature
sat.   saturated
TBAF   tetrabutylammonium fluoride
TBS    tert-butyldimethylsilyl
t-      tertiary
(Thex)BH₂ thexylborane
TES    triethylsilyl
TfOH   trifluoromethanesulfonic acid (triflic acid)
THF    tetrahydrofuran
TLC    thin layer chromatography
TMS    trimethylsilyl
p-TsOH para-toluenesulfonic acid
p-TsCl para-toluenesulfonyl chloride
Ts     toluene sulfonyl (tosyl)
UV     ultraviolet
X4     hexanes
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>Xp</td>
<td>Evans auxiliary</td>
</tr>
<tr>
<td>μmol</td>
<td>micromole</td>
</tr>
<tr>
<td>Z</td>
<td>zusammen (together)</td>
</tr>
<tr>
<td>&lt;</td>
<td>less than</td>
</tr>
<tr>
<td>&gt;</td>
<td>greater than</td>
</tr>
</tbody>
</table>
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