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

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Claire Gregg

B. Tech. (Forensic & Analytical Chemistry), B. Sc. (Hons)

Flinders University

Faculty of Science and Engineering

School of Chemical and Physical Sciences

Adelaide, Australia

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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

13th May 2011

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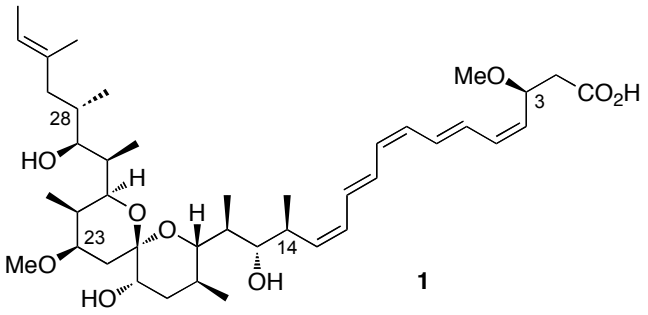
Abstract

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.

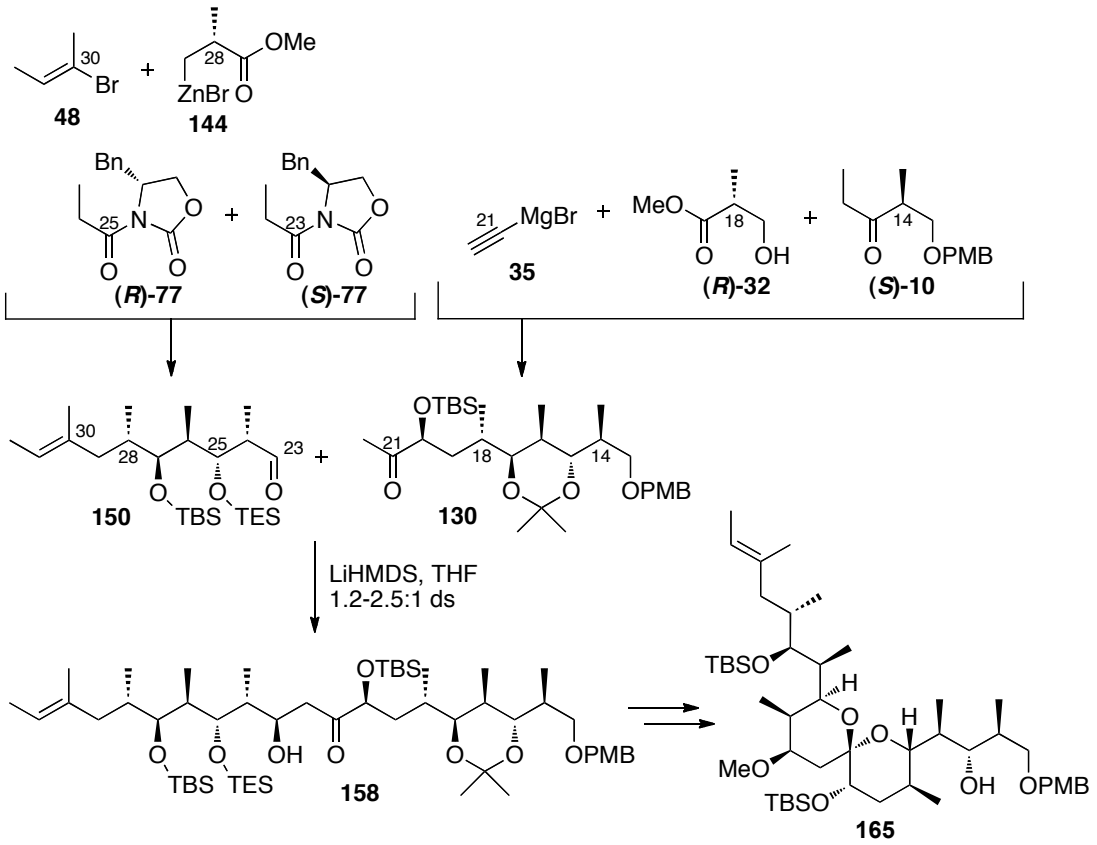
Chapter two describes studies towards the synthesis of spirangien A (**1**), a highly cytotoxic and antifungal polyketide metabolite, isolated from the myxobacterium *Sorangium cellulosum*. The synthetic approach to spirangien A exploited the obvious C22-C23 acetate aldol disconnection in linear precursor **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-stereoinduction, therefore the model was concluded to be an inadequate representation of the natural product system.



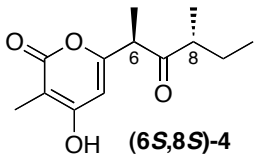
1

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-

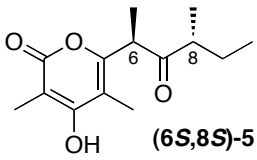
butene (**48**) to install the C28 stereocentre and two successive Evans *syn* aldol reactions to give the desired C24-27 stereotetrad and differential protection of the resulting hyroxyl groups. Ketone coupling partner **130** was synthesised from (*R*)-Roche ester **(*R*)-32** in 16 steps (22% yield), 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 [**(6*S*,8*S*)-4**] and *ent*-micropyrone [**(6*S*,8*S*)-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 micropyrone (**5**). Ascosalipyrone was reported as an inseparable mixture of diastereomers, while micropyrone was reported as a single isomer with a non-zero specific rotation.

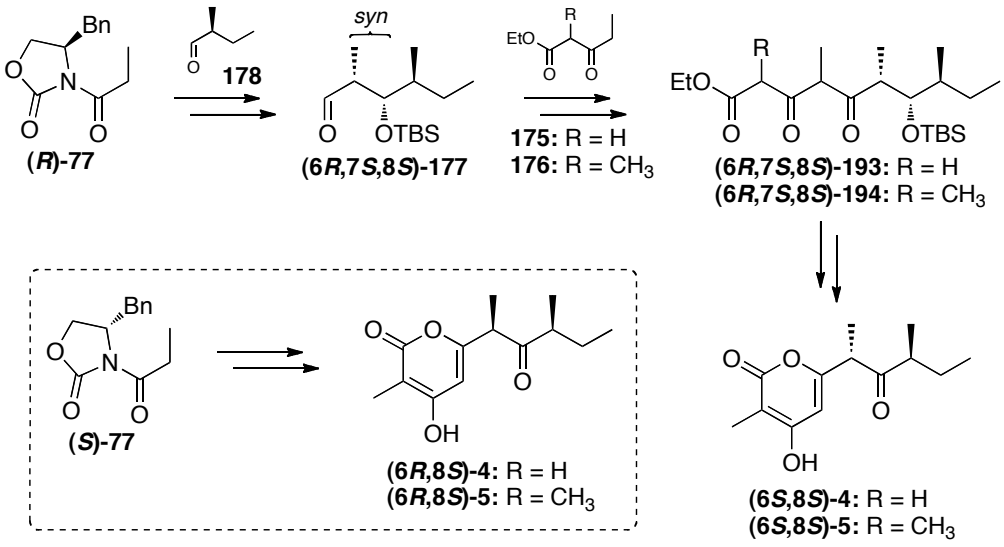


(6*S*,8*S*)-4



(6*S*,8*S*)-5

The synthesis of two potential diastereomers of each natural product from a common intermediate was achieved. A highly diastereoslective *syn* aldol reaction between both the **(*R*)-77** and **(*S*)-77** enantiomers of Evans' auxiliary and chiral aldehyde **178** was exploited to produce aldehydes **(6*R*,7*S*,8*S*)-177** and **(6*S*,7*R*,8*S*)-177**. The linear precursors **(6*R*,7*S*,8*S*)-193** and **(6*R*,7*S*,8*S*)-194** were constructed by addition of β-ketoesters **175** or **176** respectively to aldehyde **(6*R*,7*S*,8*S*)-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 epimerisastion (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 [**(6*S*,8*S*)-4**] and micropyrone [**(6*R*,8*R*)-5**].


Bn
O
N
O
O
(R)-77
178
syn
O
OTBS
(6R,7S,8S)-177
R
EtO
O
O
175: R = H
176: R = CH3
EtO
R
O
O
O
OTBS
(6R,7S,8S)-193: R = H
(6R,7S,8S)-194: R = CH3
Bn
O
N
O
O
(S)-77
O
O
O
OH
(6R,8S)-4: R = H
(6R,8S)-5: R = CH3
O
O
O
OH
(6S,8S)-4: R = H
(6S,8S)-5: R = CH3

Glossary

°C	degrees Celsius
Å	angstroms
AcOH	acetic acid (glacial)
Ac_2O	acetic anhydride
aq.	aqueous
AR	analytical reagent
Ar	aromatic
atm	atmospheres
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Bz	benzoyl
bp.	boiling point
Bu	butyl
Bz_2O	benzoic anhydride
c	concentration (g/100 mL)
cat.	catalytic
CAN	cerium ammonium nitrate
$CDCl_3$	deuterated chloroform
C_6D_6	deuterated benzene
CD_3OD	deuterated methanol
COSY	correlation spectroscopy
CSA	10-camphorsulfonic acid
δ	chemical shift (parts per million)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
$(c\text{-Hex})_2BCl$	dicyclohexylboron chloride
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminium hydride
DMA	*N*,*N*-dimethylacetamide
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide

$(Sia)_2BH$	disiamylborane
DMP	Dess-Martin Periodinane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ds	diastereoselectivity
E	*entgegen* (opposite)
ee	enantiomeric excess
eq.	equivalents
ESI	electrospray ionisation
et al.	*et alia* (and others)
Et	ethyl
FGI	Functional Group Interconversions
GC	gas chromatography
HF	hydrofluoric acid
HMBC	heteronuclear multiple bond connectivity
HMQC	heteronuclear multiple quantum coherence
HRESIMS	high resolution electrospray ionization mass spectroscopy (spectrum)
Hz	hertz
ie.	id est (that is)
i-	*iso-*
Ipc	diisopinocampheyl
IBX	2-iodobenzoic acid
IR	infrared
J	coupling constant (Hz)
KHMDS	potassium hexamethyldisilaside
LC	liquid chromatography
LDA	lithium diisopropylamine
LiHMDS	lithium hexamethyldisilazide
Me	methyl
MHz	megahertz
mmol	millimole

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
R*f*	retention factor
rt	room temperature
sat.	saturated
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
t-	*tertiary*
$(Thex)BH_2$	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

Xp	Evans auxiliary
μmol	micromole
Z	*zusammen* (together)
<	less than
>	greater than

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