Studies Directed Towards the Synthesis of (–)-Ebelactone-A

Colin Foster

Magdalene College

Cambridge

January 1999

A Dissertation Submitted to the University of Cambridge in partial fulfilment of the requirements for the degree of Doctor of Philosophy

Acknowledgements

The work described in this thesis was carried out at the University Chemical Laboratory, Cambridge, between October 1995 and October 1998 and, except where indicated otherwise, is the original work of the author. No part of this thesis has been, or is being, submitted for a degree or any other qualification at this, or any other university.

Firstly, I would like to thank my supervisor, Prof. Ian Fleming, for his encouragement, endless patience and eagerness to help throughout my PhD. Thanks also to him and several Directors of Studies in the department for providing me with a large amount of undergraduate supervision work, which I have greatly enjoyed. I would also like to thank all the members (past and present) of the Fleming group for their friendship and help, which has made my three years extremely enjoyable. Many thanks also to Melvyn & co. for technical help, to David Blakemore for getting me started with the basics of practical work in my first year, and to the Mass Spectrometry and NMR staff. I would also like to thank the EPSRC for funding this work and Zeneca for additional money. Finally, thanks to Mum and Dad for their support, and to Mum for proof-reading this entire thesis!

Colin Foster

Cambridge

January 1999

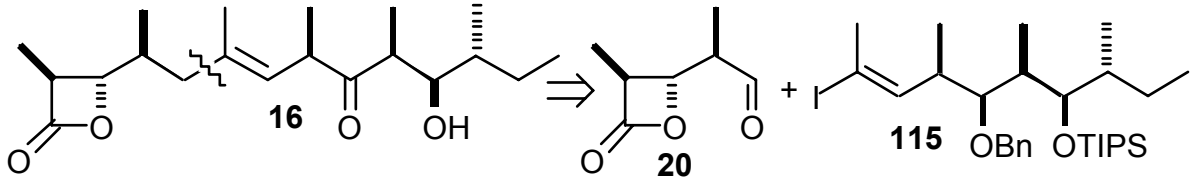
To my parents

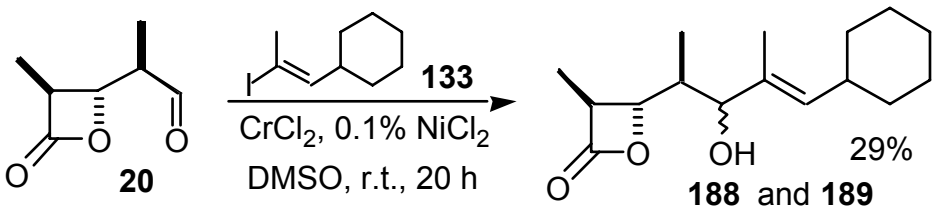
Studies Directed Towards the Synthesis of (–)-Ebelactone-A

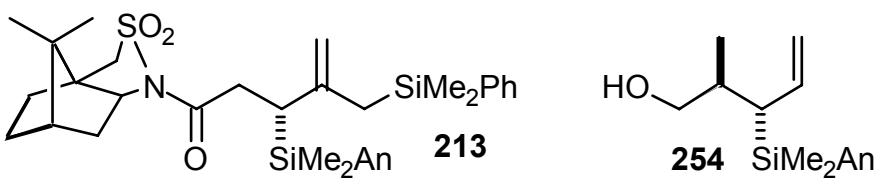
Colin Foster, Magdalene College, 1999

This thesis describes work concerning the total synthesis of ebelactone-a **16**, and in particular the synthesis of one of the retrosynthetic fragments (fragment A **20**) and its coupling to the combined fragment BC **115** formed from the other two. We repeated the synthesis of enantiomerically enriched **20** devised by Williams, employing a Mukaiyama aldol reaction directed by Oppolzer's sultam to establish the *anti-anti* stereotriad of the fragment. We modelled the coupling of this to **115** using isobutyraldehyde in place of **20** and vinyl iodide **133** in place of **115**, and verified that the Nozaki-Kishi method using chromium(II) chloride and catalytic nickel(II) chloride was effective. By this method, we successfully coupled **133** to **20**. Model work was unsuccessful in establishing a methodology for removing the hydroxy group from alcohols **188**/**189** without disrupting either the position or geometry of the adjacent C=C bond.

We also established a completely new route to fragment A, utilising the features of organosilicon chemistry to control the stereochemistry. An intermediate **213** containing two different silyl groups, in which we hoped to transform one selectively into a hydroxy group with retention of configuration by Fleming's method, proved too unstable for synthesis, but we were able to modify the route and produce alcohol **254** in enantiomerically pure form (Oppolzer's sultam was once again used as the chiral auxiliary), and we expect future workers to be able to take this through to fragment A.







Abbreviations

The following abbreviations are used in this thesis.

A^*	chiral auxiliary
Ac	acetyl
An	anisyl (4-methoxyphenyl)
Ar	aryl
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
bp	boiling point
br	broad
Bu	n-butyl
^{i}Bu	i-butyl
^{t}Bu	t-butyl
°C	degrees Celsius
cat.	catalytic
cm	centimetre
COSY	correlated spectroscopy
Cp	cyclopentadienyl
Cy	cyclohexyl
d	doublet or day
DCM	dichloromethane
d.e.	diastereoisomeric excess
DIBAL	diisobutylaluminium hydride
dm	decimetre
DMAD	dimethyl azodicarboxylate

DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
E^+	electrophile
e.e.	enantiomeric excess
eq	equivalent
Et	ethyl
g	gram
GC	gas chromatography
GLC	gas-liquid chromatography
[H]	reduction
h	hour
HPLC	high pressure liquid chromatography
Hz	hertz
Ipc	isopinocampheyl
IR	infra-red
kJ	kilojoule
L	ligand
LDA	lithium diisopropylamide
lit.	literature
M	metal
m	multiplet
Me	methyl
mg	milligram
MHz	megahertz
min	minute
mm	millimetre
mmol	millimole
mol	mole

mp	melting point
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	NOE spectroscopy
Nu^-	nucleophile
[O]	oxidation
oct	octet
P	protecting group
p.	page
PCC	pyridinium chlorochromate
Ph	phenyl
Pr	n-propyl
^{i}Pr	i-propyl
q	quartet
qn	quintet
R	alkyl
r.t.	room temperature
S	solvent
s	singlet
S_E	electrophilic substitution
sept	septet
sex	sextet
S_N	nucleophilic substitution
T	temperature
t	triplet
TBAF	t-butylammonium fluoride
TBDMS	t-butyldimethylsilyl

Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	tolyl (4-methylphenyl)
X	unspecified heteroatom