Synthetic studies towards polyketide derived biologically active natural products

A thesis submitted in fulfilment

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Doctor of Philosophy

by

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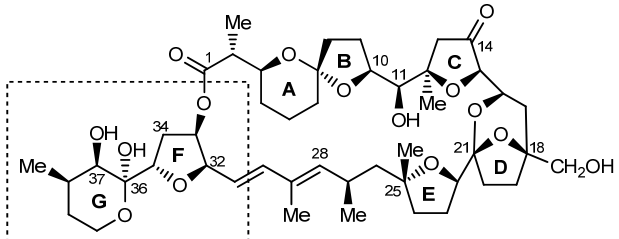
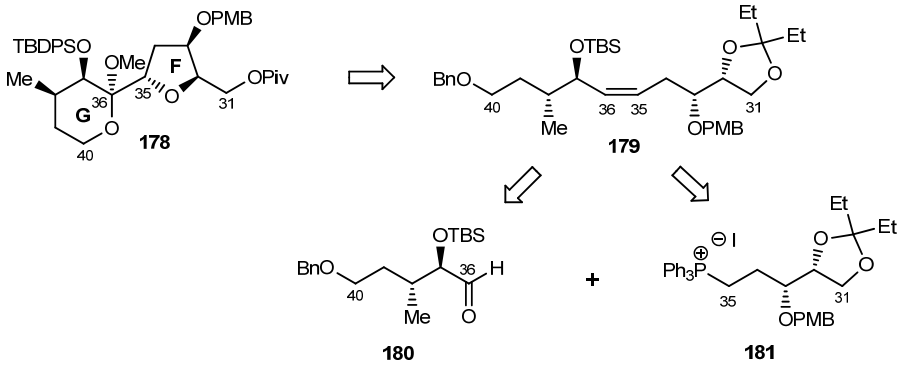
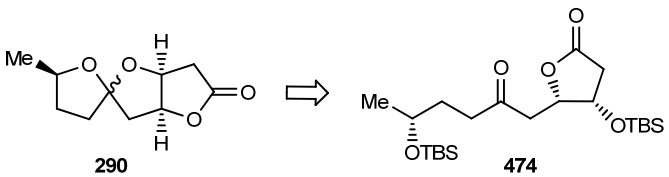
Abstract

The first part of this thesis describes the successful synthesis of the FG ring fragment **178** of the structurally complex marine toxins, the pectenotoxins. The synthesis hinges on functional group manipulations of the advanced olefin-(*Z*) **179** to install the tetrahydrofuran and tetrahydropyran ring systems. Olefin-(*Z*) **179** is itself obtained by the *cis* selective Wittig olefination of aldehyde **180** and the phosphorus ylide derived from phosphonium salt **181**. Key stereocentres of these two fragments are installed using a Katsuki-Sharpless asymmetric epoxidation and a Sharpless asymmetric dihydroxylation reaction, respectively.





The second part of this research presents synthetic attempts to access the fungal metabolites cephalosporolides E and F (**290**). These compounds contain the small but interesting *β*,*γ*-fused-[4.4]-spiroacetal-*γ*-lactone moiety which is a functional group found in seven known natural products, and has until recently eluded the synthetic chemist.



A Fukuyama coupling reaction was initially proposed to prepare advanced precursor ketone **474** but proved to be unsuccessful in our hands. A variant of the original Fukuyama reaction was successfully employed to obtain the same advanced ketone **474** but low yielding reactions combined with the delicate nature of this structure posed an insurmountable bottleneck in the planned synthetic strategy. Based on results of the research presented herein, the synthetic strategy towards this family of natural products was revised.

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Abbreviations

Á	angstrom (1.0×10^{-10} m)
δ	chemical shift
Δ	reflux
°	degrees
μ	micro
μλ	microwave
μm	micrometer (1.0×10^{-6} m)
μL	microlitre
Ac	acetyl
acac	acetoacetate
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	aromatic
Atm	atmosphere
ax	axial
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOMCl	benzyl chloromethyl ether
BORSM	based on recovered starting material
b.p.	boiling point
br	broad
BSA	bovine serum albumin
Bt	benzotriazole
Bu	butyl
Bz	benzoate
c	concentration
C	celcius
ca.	approximately
CAL-B	*Candida antarctica* lipase B
cat.	catalytic
CCE	constant current electrode
cm	centimetre
conc	concentrated
CSA	camphorsulfonic acid
d	doublet
DBI	*N*,*N*'-dicyclohexyl-*O*-benzylisourea
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide

dd	doublet of doublets
ddd	doublet of doublets of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzo-quinone
DEPT	distortionless enhancement by polarisation transfer
DET	diethyl tartrate
DHQ	dihydroquinine
DHQD	dihydroquinidine
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIC	diisopropylcarbodiimide
DIPA	diisopropylamine
DIPEA	diisopropylethylamine (Hünig's Base)
DMAP	4-dimethylaminopyridine
DMB	3,4-dimethoxybenzyl
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane [1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one]
DMPU	*N*,*N*'dimethylpropyleneurea
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
DST	diarrhetic shellfish toxin
DTX	dinophysistoxin
E	energy
E1cB	conjugate base unimolecular elimination reaction
ED_{50}	effective dose to produce desired effect in 50% of the test population
EDC	1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride
EE	ethoxyethyl
ELISA	enzyme-linked immunosorbent assay
EM	ethoxymethyl ether
ent	enantiomeric
Et	ethyl
eq	equatorial or equivalents
F	Faraday
FA	fatty acid
FAB	fast atom bombardment
g	gram(s)
h	hour(s)
HBTU	*O*-benzotriazol-1-yl-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilazide

HMPA	hexamethylphosphoric triamide
HOBt	1-hydroxy-1*H*-benzotriazole
HPLC	high pressure liquid chromatography
hv	photon energy
Hz	hertz
i-Bu	isobutyl
IBX	2-iodoxybenzoic acid
IDCP	iodonium dicollidine perchlorate
im	imidazole
IMHA	intramolecular hydrogen abstraction
i-Pr	isopropyl
IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
J	joule(s)
K	Kelvin
kcal	kilocalorie(s)
LC_{50}	lethal concentration to kill 50% of the test population
LD_{50}	lethal dose to kill 50% of the test population
LiDBB	lithium di-*tert*-butylbiphenylide
lit	literature
lut	2,6-lutidine
m	multiplet or milli
M	molar
mbar	millibar
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	millilitre(s)
mm	millimetre(s)
mmol	millimole(s)
MOM	methoxymethyl
Ms	mesylate
MS	molecular sieves
MTM	methylthiomethyl
n	nano (1.0×10^{-9})
n-BuLi	*n*-butyllithium
NIS	*N*-iodosuccinimide

NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
OA	okadaic acid
p	pico (1.0×10^{-12})
P	probability
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PEG	poly(ethylene glycol)
Ph	phenyl
Phal	phthalazine
Piv	pivalate
PMB	*para*-methoxybenzyl
PMBOMCl	*p*-methoxybenzyl chloromethyl ether
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
psi	pounds per square inch
PTX	pectenotoxin
py	pyridine
q	quartet
R	ideal gas constant (8.314 J K^{-1} mol^{-1})
RCM	ring closing metathesis
R_F	retention factor
rt	room temperature
rxn	reaction
s	singlet
SA	seco acid
sat	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
t	triplet
t	*tert*
T	temperature
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBHP	*tert*-butylhydrogen peroxide
TBDPS	*tert*-butyldiphenylsilyl
TBODPS	*tert*-butoxydiphenylsilyl
TBS	*tert*-butyldimethylsilyl

t-Bu	*tert*-butyl
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonate (triflate)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
t.l.c.	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
TPS	triphenylsilyl
Ts	*p*-toluenesulfonyl (tosyl)
tt	triplet of triplets
v/v	volume to volume ratio
W	watt(s)
w/w	weight to weight ratio

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