Synthetic Studies towards Griseusin A

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ABSTRACT

This thesis presents the synthesis and attempted functionalization of the unsaturated ring system of the naturally occurring pyranonaphthoquinone antibiotic griseusin A **88**. Unsaturated spiroketals **333,334** were constructed *via* the addition of 2-trimethylsilyloxyfuran **189** to quinone **328**. Initial work using acetylenic quinone **321** afforded a pentacyclic product **323**, wherein an unanticipated third Michael reaction occurred due to the phenolic hydroxyl group cyclizing onto the α,β-unsaturated ketone moiety. Altering the reaction conditions gave trimethylsilyl analogue **325**, where the final Michael reaction abstracted not a proton (**323**) but a trimethylsilyl cation liberated from **189**. Naphthoquinone **328**, bearing a 2-alkenyl side chain rather than an acetylene, was synthesized using similar methodology to **321** and subsequently converted to furonaphthofuran adduct **330**. Ceric ammonium nitrate oxidative rearrangement of **330** produced diol **332**, which was then cyclized to spiroketals **333,334** under a variety of conditions. The isomer ratio **333:334** resulting from these conditions was determined by high field ^{1}H nmr spectroscopy.

With the two spiroketals **333,334** in hand, efforts were directed towards the functionalization of the C3'-C4' double bond. Osmium tetraoxide catalytic dihydroxylation of model olefin **345** gave diol **353**, where approach of the reagent was from the opposite face to that required for griseusin A **88**. Selective acetylation of the less hindered hydroxyl group was however achieved, giving **354**.

The Woodward-Prevost reaction of olefin **345** formed the iodoacetates **367-369**. Attempts to displace the iodine from the major diaxial iodoacetate **368** gave a complex mixture. Iodoacetate **387** was then prepared wherein the iodine and acetate positions were reversed, treatment of which with silver acetate afforded the fragmentation products **401** and **402**. The minor diequatorial iodoacetate **367** gave, like its stereoisomer **368**, a complex mixture when subjected to displacement conditions. Only iodoacetate **410**, formed from **367**, produced spiroketal hydroxyacetates as hoped for, however both of these had the opposite stereochemistry at C-4 and C-5 to that desired. One of these two hydroxyacetates (**354**) had also been isolated from the selective acetylation of diol **353**.

Several attempts using a variety of reaction conditions were made in an effort to force **333,334** to react with osmium tetraoxide. It was found that the functional groups present in **333**, **334**, **336**, **330** and **323** were incompatible with this reagent. Ketone **327** was the only compound that successfully underwent *syn*-hydroxylation, affording diols **419** and **420**. Use of cetyltrimethylammonium permanganate as an hydroxylation reagent for **333,334** afforded **423** and **421** rather than **343** and **344**, where reaction had occurred at the C5a-C11a double bond.

The difficulty in introducing the oxygenated substituents onto the O1'-C6' spiroketal ring was proposed to be overcome by synthesizing naphthoquinone **430**. The protected hydroxyl groups at C-2' and C-3' in this compound would possess the correct stereochemistry for elaboration to the hydroxyl and acetate groups at C-3' and C-4' respectively in griseusin A **88**.

Towards this end, the synthesis of the required naphthalene precursor (**432**) was undertaken *via* an enantioselective aldol condensation of imide **435** with (*R*)-aldehyde **437**. **435** was formed from (*R*)-phenylalanine and 2-(benzyloxy)acetyl chloride **439** and reacted with **437** using stannous triflate and tetramethylethylenediamine. The major product **452**, possessing the desired 2',3'-*anti* stereochemistry, was protected and the auxiliary reductively removed to give alcohol **459**. Oxidation of **459** using *tetra-n*-propylammonium perruthenate gave aldehyde **434**, ready to be coupled to the Grignard reagent (**498**) of trimethoxybromide **433**.

Trials using heptanal and various organometallic reagents found *n*-butyllithium to be the reagent of choice for generating the anion (in this case the lithiate, **500**) of **433**. With the optimum time determined, the coupling of **500** with **434** was undertaken but yielded only the debrominated compound **499**. The basicity of **500** and the hindrance at the carbonyl group of **434** were cited as possible reasons for this result, and attempts were made to "soften" the anion. Unfortunately both magnesium bromide and ceric chloride failed to produce the desired products **503**,**504**.

CONTENTS

ABBREVIATIONS

2D	=	two dimensional
aq.	=	aqueous
amu	=	atomic mass units
av	=	average
ax	=	axial
BINAP	=	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
b.p.	=	boiling point
n-Bu, Bu^n	=	*n*-butyl
Bu^t	=	*tert*-butyl
Bz	=	benzyl
CAN	=	ceric ammonium nitrate
cat.	=	catalytic
CD	=	circular dichroism
cm^3	=	cubic centimetres (ml)
CoA	=	coenzyme A
conc.	=	concentrated
COSY	=	correlation spectroscopy
CSA	=	camphor sulphonic acid
CTAP	=	cetyltrimethylammonium permanganate
D	=	deuterium
DBN	=	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
decomp.	=	decomposed
deg	=	degree
DEPT	=	distortionless enhancement by polarization transfer
DIBAL	=	diisobutylaluminium hydride
dil.	=	dilute
DMAP	=	4-dimethylaminopyridine
DME	=	dimethoxyethane/ethylene glycol dimethyl ether
DMF	=	*N*,*N*-dimethylformamide
DMSO	=	dimethyl sulphoxide
ds	=	diastereoselection
ee	=	enantiomeric excess

18C6	=	1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6 ether)
eq	=	equatorial
equiv.	=	equivalents
FAB	=	fast atom bombardment
h	=	hour
[H]	=	reduction
HETCOR	=	heteronuclear correlation spectroscopy
hplc	=	high pressure liquid chromatography
hrms	=	high resolution mass spectrometry
imid	=	imidazole
IR	=	infra-red
J	=	nmr coupling constant (hertz)
LDA	=	lithium diisopropylamide
MCPBA	=	*meta*-chloroperbenzoic acid
mg	=	milligrams
min	=	minutes
mm^3	=	cubic millimetres (µl)
mmol	=	millimoles
mol	=	moles
MOM	=	methoxymethyl
m.p.	=	melting point
ms	=	mass spectrometry
NADH	=	reduced nicotinamide adenine dinucleotide
NADPH	=	reduced nicotinamide adenine dinucleotide phosphate
NBA	=	*N*-bromoacetamide
NMO	=	4-methylmorpholine *N*-oxide
nmr	=	nuclear magnetic resonance
NOE	=	nuclear Overhauser effect
[O]	=	oxidation
OAc	=	acetate
ORD	=	optical rotatory dispersion
PCC	=	pyridinium chlorochromate
PDC	=	pyridinium dichromate
PMB	=	*p*-methoxybenzyl
PPTS	=	pyridinium *p*-toluenesulphonate
Pr^i	=	isopropyl

PTC	=	phase transfer catalyst
py	=	pyridine
R_f	=	distance travelled by compound÷distance travelled by solvent on TLC plate
RT	=	room temperature
s	=	seconds
t	=	time
TBAF	=	tetrabutylammonium fluoride
TBDMS	=	*tert*-butyldimethylsilyl
TES	=	triethylsilyl
Tf	=	trifluoromethanesulphonyl
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
THP	=	tetrahydropyranyl
TLC	=	thin layer chromatography
TMEDA	=	*N,N,N',N'*-tetramethylethylenediamine
TMS	=	trimethylsilyl
TPAP	=	*tetra-n*-propylammonium perruthenate
Tr	=	trityl (Ph_3C)
TsOH	=	*p*-toluene sulphonic acid (tosic acid)
UV	=	ultra-violet
var.	=	variety
wt.	=	weight