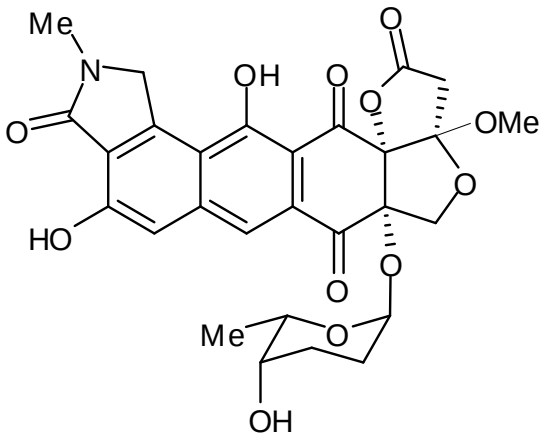
Studies Toward a Total Synthesis of Lactonamycin.



Lewis Preece

A Thesis Submitted for the Degree of Doctor of Philosophy

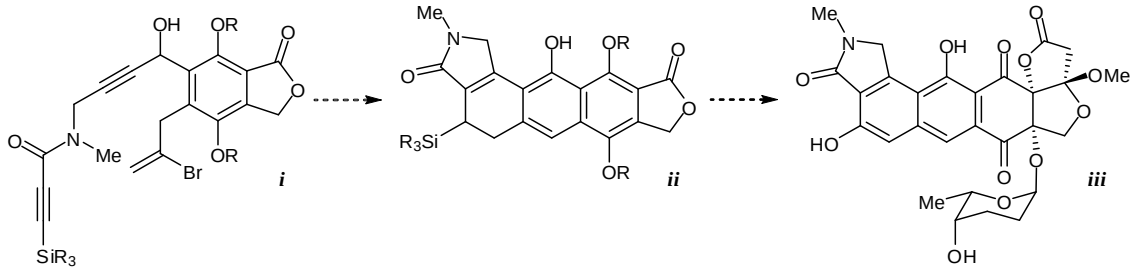
September 2011

University of Sussex

Abstract

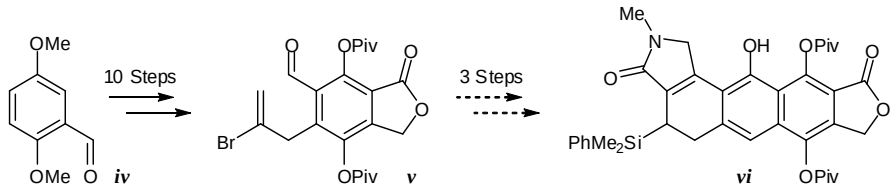
UNIVERSITY OF SUSSEX
LEWIS PREECE, DOCTOR OF PHILOSOPHY
STUDIES TOWARD A TOTAL SYNTHESIS OF LACTONAMYCIN
SUMMARY

Work was undertaken towards the synthesis of the promising antibiotic lactonamycin (***iii***). Following the work of Parsons *et al.* it was proposed that cyclisation of the ene-diyne (***i***) would give access to advanced pentacyclic intermediate (***ii***) and that from this a total synthesis of lactonamycin would be achieved (scheme I).



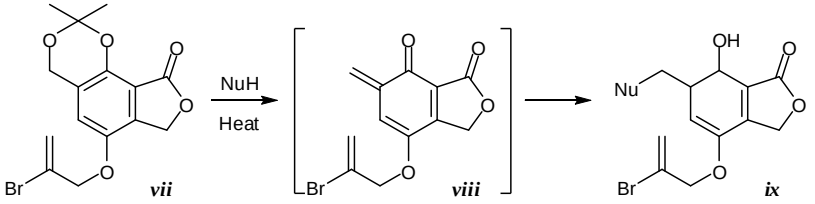
Scheme I : Proposed Parsons, Board, Waters cyclisation to form the pentacycle (iii)

A synthesis towards the cyclisation precursor (***i***) was carried out and a route to the key tetrasubstituted phthalide (***v***) established. Further chemistry was proposed to complete the synthesis of lactonamycin (scheme II).



Scheme II : Formation of a fully substituted benzolactone.

During attempts to introduce the β-bromoallyl group of key intermediate (***v***) using a high temperature Claisen rearrangement it was established that the benzodioxin (***vii***) underwent thermolysis to generate the reactive quinone methide intermediate (***viii***) and that in the presence of a nucleophilic solvent the adduct (***ix***) was formed (scheme III). Model studies showed the reaction to be both general and high-yielding.



Scheme III : Novel quinone methide methodology.

Contents

Dedication

Dedicated to the memory of my grandfather Ronald P. Lonsdale for fostering the intellectual curiosity that would one day lead me to this end.

Acknowledgements

I would be the first to confess that the past four years have not been my most carefree. From what I have observed, the most successful chemists are those able to draw sufficient enthusiasm from those fleeting moments of sublime success to sustain them through the long days of tedious chromatography and ever dwindling reserves of hard wrought intermediates. In this respect I have frequently fallen short. Fortunately the kind words and deeds of those noted below have helped to bridge that gap. They are the only reason I have come so far and for that they have my most sincere thanks and my enduring gratitude.

Foremost Prof. Phil Parsons for the friendship and support he's given over these long years. He's by far the most generous man I know with both his time and his hospitality and I've never felt a warmer welcome than I've received from him and his wife Sue. I look forward to collaborating on a number of good bottles in the future. Thanks are also due for the munificent provision of funding for this work.

Drs. Adrian Murray and Lewis Pennicott for their most capable supervision when I first joined the group and for enlightening me with their differing, yet complementary approaches to lab work! Dr. Clive Penkett for many an edifying chemical discussion. Drs. Iain Day, Peter Hitchcock and Alaa Abdul-Sada, for their provision of NMR, crystallography and mass spectrometry services respectively.

For their particularly noteworthy contribution to the preservation of my sanity: Noel Cooper for all our conversations and for always proving a willing donut co-conspirator. James 'Jimbob' Pryke for tolerating me so admirably in a bay that was half the size of any other in the lab. Richard Bouglas for his delightfully horrific sense of humour. Alex 'Gibbo' Waters for the many Ale Night pints we shared. Sarah 'Dutch' Holland for believing in me at just the right time. Juman Jarallah for allowing me to moisten her shoulder with salty salty tears when things were at their worst. Hannah Mattacks for always being there and never *ever* wanting to talk about chemistry. Tara Williams for being the one person to truly understand my pain and for sharing enough beer to drown it. Honourable mentions are also due to Crissy Gomes, Dana Jarallah, Matt Renshaw and Lee Walsh.

Members of the Parsons group past and present and the many Sussex chemists I've had the pleasure to meet over the last 7 years. The department would not have been such a pleasant place to work without you all.

My non-chemist friends for the respite they provided on numerous occasions, it was far more valuable than I think they realised.

All my family. With special thanks to my Mum and Dad whose unending support, both emotional and financial has been truly humbling. I could not have wished for more.

And lastly Katherine, for everything.

Abbreviations

Å	Ångstrom
Ac	acetyl
AIBN	azobisisobutyronitrile
aq	aqueous
Ar	aryl
atm	atmosphere
BBN	borabicyclo[3.3.1]nonane
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
b.p.	boiling point
Bu	butyl
^{i}Bu	isobutyl
^{n}Bu	butyl
^{s}Bu	*sec*-butyl
^{t}Bu	*tert*-butyl
Bz	benzoyl
°C	degrees Celsius
CAN	cerium (IV) ammonium nitrate
cat.	catalytic
Cbz	benzyloxycarbonyl
CDI	1,1'-carbonyldiimidazole
cm	centimetre
CoA	coenzyme A
conc.	concentrated
CSA	camphorsulphonic acid
Cy	cyclohexyl
D	debye
dba	dibenzylideneacetone
DCC	1,3-dicyclohexylcarbodimide
DCM	dichloromethane

DDQ	2,3-dichloro-5,6-dicyanoquinone
d.e.	diastereomeric excess
DIAD	diisopropyl azo dicarboxylate
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
Dmb	2,4-dimethoxybenzyl
DMB	3,4-dimethoxybenzyl
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPS	dimethylphenylsilyl
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dppa	diphenylphosphoryl azide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
E^+	electrophile
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
e.e.	enantiomeric excess
EI	electron impact
ESI	electrospray ionisation
Et	ethyl
eq.	equivalent(s)
g	gram(s)
Glc	glucosyl
hν	irradiation
HMDS	hexamethyldisilazide
HPLC	high performance liquid chromatography
hr(s)	hour(s)
HRMS	high resolution mass spectrum
Hz	hertz

IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
IR	infrared spectroscopy
KIE	kinetic isotope effect
LA	Lewis acid
LDA	lithium diisopropylamide
M	molar
MAO	methylaluminoxane
mbar	millibar
mCPBA	*meta*-chloroperbenzoic acid
Me	methyl
MIC	minimum inhibitory concentration
min(s)	minute(s)
mL	millilitre
mol(s)	mole(s)
mmol	millimole(s)
m.p.	melting point
MPO	4-methoxypyridine *N*-oxide
Ms	methanesulfonyl
MS	molecular sieve
MW	microwave heating
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NMO	*N*-methylmorpholine *N*-oxide
Nu	nucleophile
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
Phth	phthaloyl
PHPB	pyridinium hydrobromide perbromide
PIDA	phenyliodine(III)diacetate
PIFA	phenyliodine(III)bis(trifluoroacetate)
Piv	pivaloyl

PMB	*para*-methoxybenzyl
PPA	polyphosphoric acid
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
pTSA	*para*-toluenesulphonic acid
^{i}Pr	isopropyl
quant.	quantitative
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
R_f	retention factor
RM	reaction mixture
rt	room temperature
SM	starting material
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
Tcm	tetracenomycin
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFE	2,2,2-trifluoroethanol
TFA	trifluoroacetic acid
TFPAA	trifluoroperacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Tr	trityl
Ts	tosyl
UV	ultraviolet

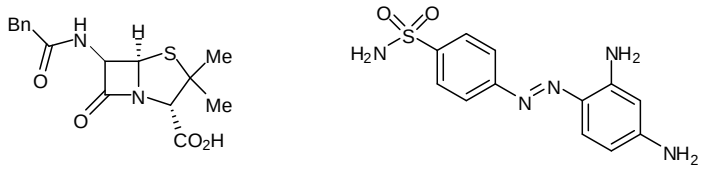
1. Introduction

"Lord, I fall upon my knees
And pray that all my syntheses
May no longer be inferior,
To those conducted by bacteria." [1]

1.1 The Need for New Antibiotics.

1.1.1 The Rise of Antibiotic Resistance.

Antimicrobial compounds have been one of the key medical developments of the past century. The introduction of the penicillins[2] and sulfonamides[3] (figure 1.1) of the 1930's and 40's changed the way in which physicians tackled bacterial infections forever. Once fatal or debilitating illnesses could be cured in near miraculous fashion. In the intervening years antibiotics have saved the lives of millions of people and alleviated the suffering of many more. In that time many more efficacious compounds would be discovered, with a vast array of structures and modes of action, a great number are natural products, some entirely synthetic creations of man and many more are the semi-synthetic results of chemists adapting and improving upon nature's good work.



Penicillin G Prontosil

Figure 1.1: The first commercial antimicrobials.

So successful were these miracle drugs that their usage expanded rapidly and whilst a great deal of good has come of this (and continues to), humanity has often wielded these potent biological tools recklessly. Antibiotics have frequently been misused by physicians, patients and those in the agricultural sector. Doctors have and indeed still do prescribe them inappropriately, patients frequently disregard their instructions for use and it is common practice in the rearing of livestock to use them indiscriminately in prophylaxis.

Antibiotic resistance arises as simple consequence of natural selection. When we apply a selection pressure in the form of antibiotics to a colony of bacteria we promote the survival of only those most able to tolerate that pressure. The sheer numbers (approximately 10^{14} bacterial cells in the human body)[4] and rate of reproduction (generation times of the order of minutes and hours)[5] of bacteria, mean that the evolution of resistance is a phenomenon we can observe over the course of months and years rather than millennia. Resistance is a natural consequence of antibiotic use, it would always occur. However our careless use can increase the rate at which resistance

develops substantially.

There are a number of ways that bacteria have been shown to adapt to avoid the deleterious effects of antimicrobial compounds to which they're exposed:

- Drug inactivation, whereby the bacterium gains the ability to destroy or bind the drug molecule so as to render it inert. For example the very many examples of β-lactamases, which actively cleave the β-lactam unit of the penicillins.[6]

- Alteration of target site, whereby the bacterium gains an alteration to the chemical binding target of the active compound either steric or chemical that prevents the active compound binding to that site, or decreases the rate at which it does so.[7]

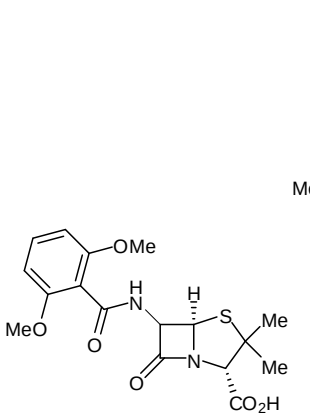
- Alteration of metabolic pathway, whereby the bacterium gains the ability to circumvent the elements of a metabolic pathway that are targeted by the active compound.[8]

- Reduced drug accumulation, whereby the bacterium gains the ability to lower the rate of influx (through a reduction in cell wall binding proteins for example)[9] and/or increase the rate of efflux (through active pumping proteins in the bacterial wall)[10] thus resulting in a lower cytoplasmic concentration of the active compound.

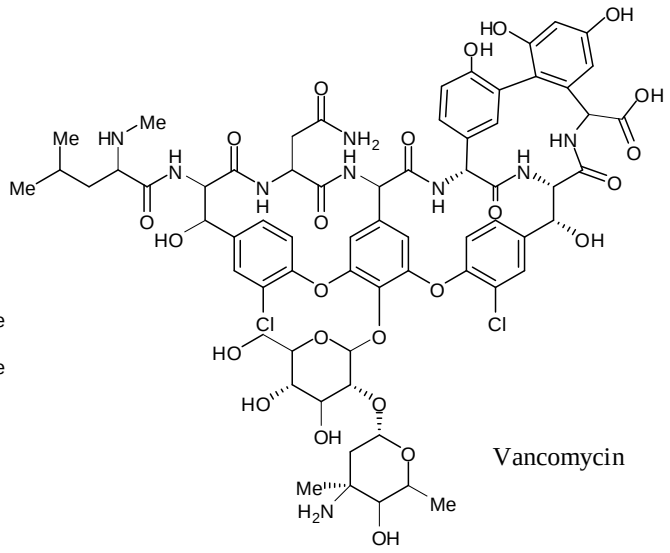
Of course the development of resistance by one strain of bacteria to a single antibiotic is of relatively little concern. Let us not forgot that bacteria tend to be immune to vast swathes of our antibacterial armoury entirely naturally. It is when through selection, we start to induce resistance to whole classes of antibiotics followed by multiple classes that we start to lack any effective means of fighting off such infections. Such multiply resistant strains, or 'superbugs' as they have become colloquially known are becoming more and more ubiquitous in both the healthcare and community environments.

Methicillin Resistant *Staphylococcus Aureus* (MRSA) is one of the most frequently cited examples of such a multiply resistant organism, particularly in the popular press. It was first identified in the UK in 1961,[11] approximately 2 years after the first clinical use of the newly developed penicillin derivative methicillin (figure 1.2). This resistance was notable at the time as methicillin itself had been introduced as an alternate treatment for

infections exhibiting resistance to penicillin G. MRSA is in fact resistant to not just the penicillins, but all other classes of β-lactam antibiotics including the cephalosporins, carbapenems, and penems.[12] This resistance arises from a change in one of the bacterial cell wall proteins, to which β-lactam antibiotics bind, inhibiting growth.[13] MRSA strains are also frequently resistant to erythromycin, fusidic acid, tetracycline, minocycline, streptomycin, spectinomycin, and the sulphonamides.[12] In a distressing example of quite how rapidly such resistance can develop one study found that a single year after the introduction of ciprofloxacin (a fluoroquinolone antibiotic) incidences of resistance in MRSA increased from 5% to over 80%.[14] Throughout the emergence of ever more resistant strains and over the course of almost 40 years the drug vancomycin (figure 1.2) persisted as the drug of choice for nearly all cases of MRSA,[15] leading some to optimistically suggest that it may even be impossible for resistance to develop. In 2002 the first case of Vancomycin Resistant *S.Aureus* (VRSA) was identified in a hospital in Michigan.[16]



Methicillin



Vancomycin

Figure 1.2 : Methicillin and Vancomycin.

Many commentators have noted that the continuing trend of ever greater numbers of multiply drug resistant organisms and ever decreasing supplies of novel drugs with which to fight them may well be leading us to disaster; the waning of an unheralded golden age, in which man's mastery over the microbial was unquestioned. It is against this backdrop that we synthetic chemists are charged with both synthesising new antimicrobial compounds and completing artificial syntheses of natural products with the aim of developing methodology to allow the creation of efficacious analogues.

1.1.2 The Lactonamycins.

Lactonamycin **(1.1)** (figure 1.3) was isolated in 1996 by Matsumoto *et al.*[17] from a culture broth of the bacterium *Streptomyces Rishiriensis* which was in turn isolated from a soil sample (as more than half of all known antibiotics are)[18] collected in Yokohama city within the Greater Tokyo Area. Isolated as part of a routine screening process attempting to identify new antibiotics, initial results suggested this compound showed potent activity against gram-positive bacteria. Significantly this included MRSA. The fully elucidated structure including stereochemistry was published in 1999,[19] an accompanying publication also contained further details of the biological activities observed.[20] MIC's of between 0.39-1.56 μg/mL were noted for MRSA strains and 0.20-0.78 μg/mL for various strains of Vancomycin Resistant *Enterococcus* (VRE). In addition inhibitory behaviour was observed against a number of human tumour cell lines. It was these results that fuelled the initial interest in lactonamycin as a molecule of potential pharmaceutical interest.

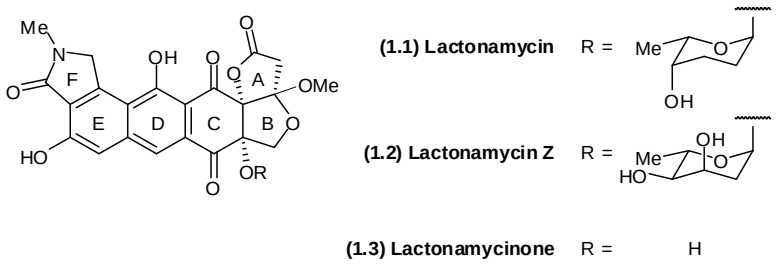
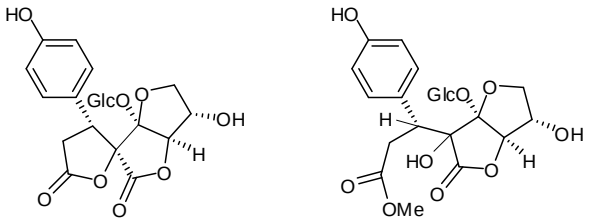


Figure 1.3 : Lactonamycin and its analogues.

The first natural analogue of lactonamycin **(1.2)** was discovered in 2003, it was identified as a metabolite of another soil-borne bacterium *Streptomyces Sanglieri*, which was itself found in pine wood soil samples from County Durham, UK.[21] This compound was found to be structurally very similar to lactonamycin and as such was dubbed lactonamycin Z by its discoverers. Biological screening of this new compound showed disappointing levels of efficacy with respect to gram-positive bacteria however the material did exhibit notable inhibition of human gastric adenocarcinoma cell lines (IC_{50}: 0.19 μg/mL).

Lactonamycin and its analogue differ only by the sugar moiety linked through the *O*-glycosidic bond, the core structure being coupled with α-rhodinose and α-2,6-dideoxyribohexose saccharides respectively. The range of biological activities brought about by relatively minor structural changes suggests an interesting target for total

synthesis and synthetic analogue development. In addition it was noted by the discoverers of lactonamycin that the naptha[e]isoindole structure that comprises the DEF ring system is unique among natural products. In addition the chiral fused perhydrofuran-furanone structure of the AB ring system has been seen only in the natural products derived from *Viburnum Wrightii*,[22] and in these systems (figure 1.4) the substituents differ significantly.

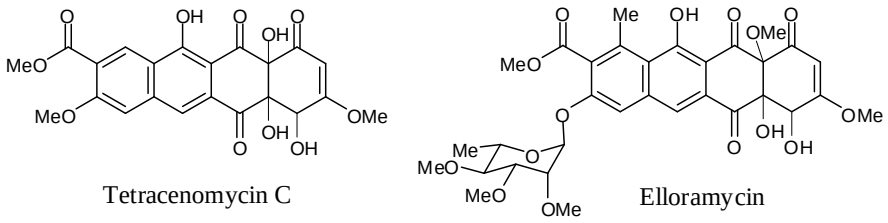


Viburnolide A Viburnolide B

Figure 1.4 : Perhydrofuran-furanone containing compounds from *V.Wrightii*.

1.1.3 Biosynthesis.

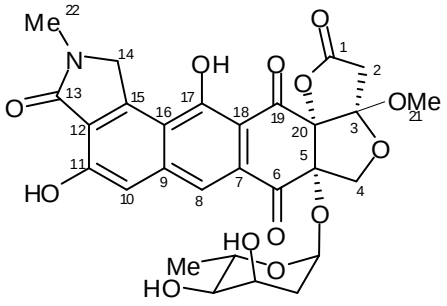
The biosynthesis of the hexacyclic core of the Lactonamycins has been investigated by Parry *et al.*[23] They initially noted the structural similarities between the aglycone lactonamycinone **(1.3)** and the napthacenequinone antibiotics Tetracenomycin C (TcmC) and Elloramycin (figure 1.5) and postulated that it too is a type II polyketide. Investigations into the biosynthesis of TcmC have previously revealed some novel chemistry involved in the formation of the *cis*-diol unit which it was thought may also result in the formation of the corresponding *cis* oxygen functionality in lactonamycinone.[24]



Tetracenomycin C Elloramycin

Figure 1.5 : Napthacenequinone Antiobiotics.

It was proposed that lactonamycin was a decaketide formed by a similar pathway to TcmC, which is formed by the head to tail incorporation of ten acetate units to synthesise the polycyclic core. Parry conducted a number of labelling experiments to investigate this hypothesis (figure 1.6).

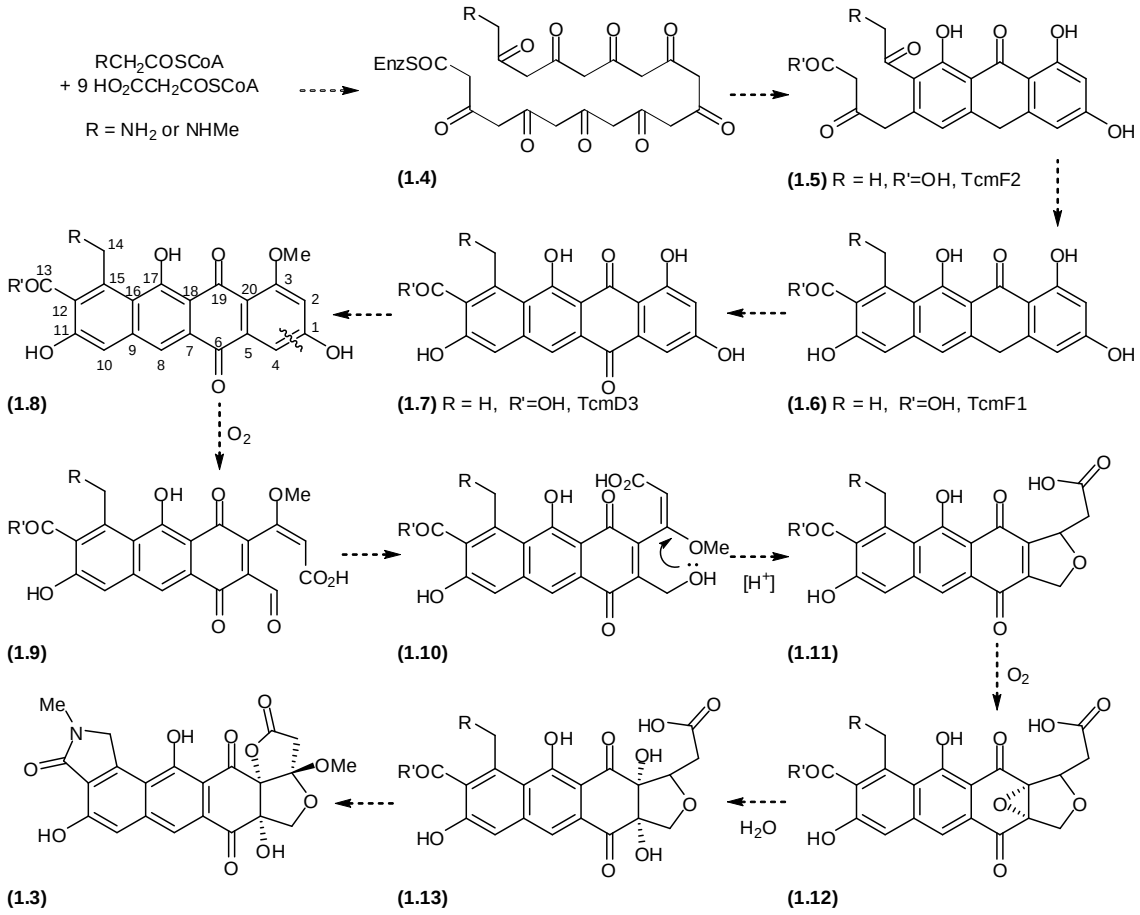


Precursor	Labelling pattern
Sodium Acetate [1-^{13}C]	C1, C3, C5, C7, C9, C11, C13, C17, C19.
Sodium Acetate [2-^{13}C]	C2, C4, C6, C8, C10, C12, C16, C18, C20.
Sodium Acetate [1,2-$^{13}C_2$]	C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13, C16, C17, C18, C19, C20.
Glycine [1,2-^{13}C]	C14, C15, C21, C22.
Glycine [1-^{13}C]	C15.
Glycine [2-^{13}C, ^{15}N]	C14, C21, C22, N1.

Figure 1.6 : Results of *in vivo* radiolabeled precursor incorporation in lactonamycin Z.

Their results seemed to partly confirm the hypothesis with the labelling patterns consistent with the head to tail inclusion of 9 acetate units with a proposed oxidative cleavage of an initial linkage between C1 and C4. It was also noted that the presence of labelled acetate failed to produce any enrichment of C14 or C15. It was suggested that this may be due to the use of a nitrogen-containing starter unit for the polyketide chain. Experimentation with labelled glycine seemed to confirm that this was the source of both C14 and C15 as well as the nitrogen of the lactam.

The results of the labelling experiments, especially when viewed with reference to the studies of TcmC biosynthesis,[25] led them to propose the following biosynthetic pathway (scheme 1.1). Starting from 9 units of malonyl-CoA and 1 unit of glycinyl-CoA, it seemed reasonable to propose that this would follow an analogous route to the production of TcmD3 **(1.7)** as shown. From that structure it was proposed the AB ring system would be formed from the oxidative cleavage of the double bond indicated. Reduction of the resulting aldehyde **(1.9)** would allow a conjugate addition of the primary alcohol onto the adjacent double bond to form the tetrahydrofuran **(1.11)**. Formation of the epoxide **(1.12)** would then allow either opening with a sulfur based enzyme followed by displacement with water[26] or straight displacement with water followed by enzymatic epimerisation.[24] Closing of the lactone and *post facto* installation of the lactam and the methoxy group would furnish a lactonamycinone type compound.



Scheme 1.1 : Biosynthetic pathway proposed by Parry *et al.*

1.2 Previous Synthetic Approaches.

The following is a concise analysis of the work published towards the synthesis of the Lactonamycins, in chronological order, with further detail following.

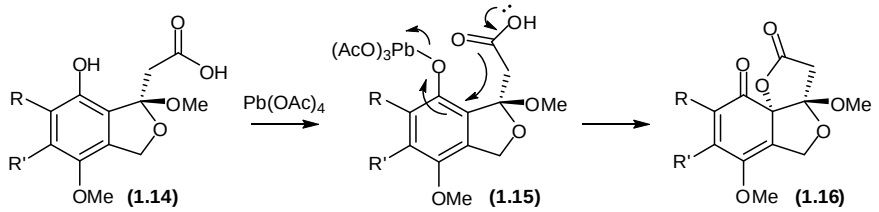
Group	Year	Summary
Danishefsky	2000	Model synthesis of the ABC system.
Danishefsky	2001	Improved synthesis of the ABC system.
Behar	2002	Model synthesis of CDEF system.
Kelly	2002	Model synthesis of CDEF system.
Danishefsky	2003	Total synthesis of racemic lactonamycinone.
Kelly	2004	Asymmetric model synthesis of AB system.
Barrett	2005	(L)-α-rhodinosylation methodology.
Barrett	2006	Model synthesis of the ABC system.
Barrett	2006	Model synthesis of the CDEF system.
Barrett	2006	Failed attempts at the CDEF system.
Nakata	2010	Model synthesis of the ABCD system.
Tatsuta	2010	Total asymmetric synthesis of lactonamycin.

Figure 1.7 : Summary of previous synthetic approaches to the Lactonamycins.

It is readily apparent from these publications that lactonamycin can be thought of as a 3-part challenge, with distinct strategies required for the synthesis of the asymmetric AB system, the planar fused CDEF system and the formation and attachment of the sugar residue. With this wide variety of synthetic challenges and as yet only one synthesis of lactonamycinone and one of lactonamycin it is clear that there is still a great deal to learn through the attempted synthesis of this molecule. No synthesis of lactonamycin Z has been reported at the time of publication.

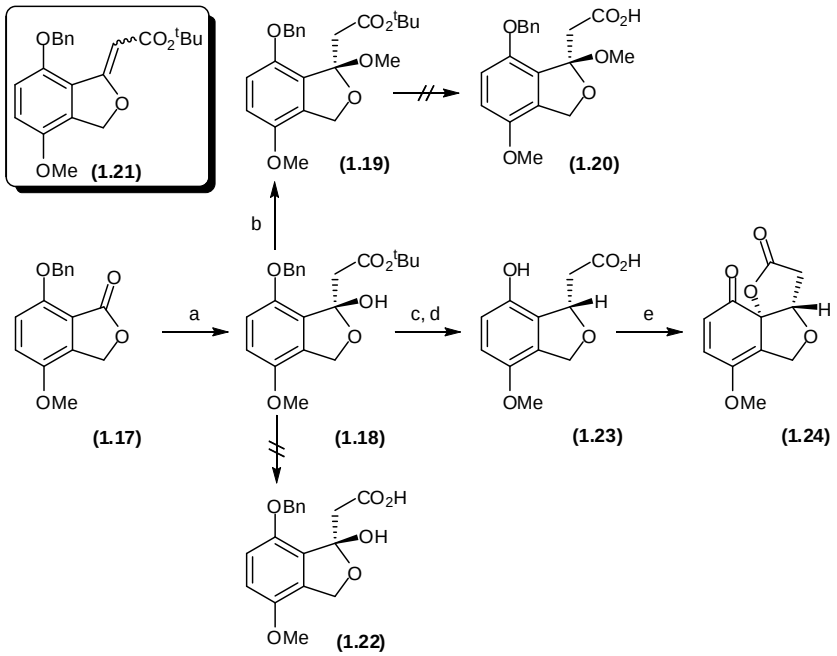
1.2.1 Danishefsky *et al.*

Danishefsky was the first author to publish details of his synthetic attempts toward lactonamycin and his further contributions have been the most extensive of any author. His first publication in collaboration with Cox concerned his proposed synthesis of the ABC ring system.[27] A Wessely oxidation[28] would be utilised to trap a carboxylic acid[29] in an intramolecular fashion to form the A ring lactone (scheme 1.2).



Scheme 1.2 : Proposed Wessely oxidation route toward the AB ring system.

Work on a model system however proved this route to be somewhat less simple than anticipated (scheme 1.3). Starting from lactone **(1.17)** introduction of the ester was accomplished simply enough with the addition of the enolate of *tert*-butyl acetate to give the hemiacetal **(1.18)**, this in turn could be converted to the corresponding methyl acetal **(1.19)** by treatment with methanol over a catalytic acid resin. However what Danishefsky had not anticipated was how labile both the acetal and the hemiacetal would be in the presence of either acid or base, with elimination to form the α,β-unsaturated ester **(1.21)** occurring rapidly.

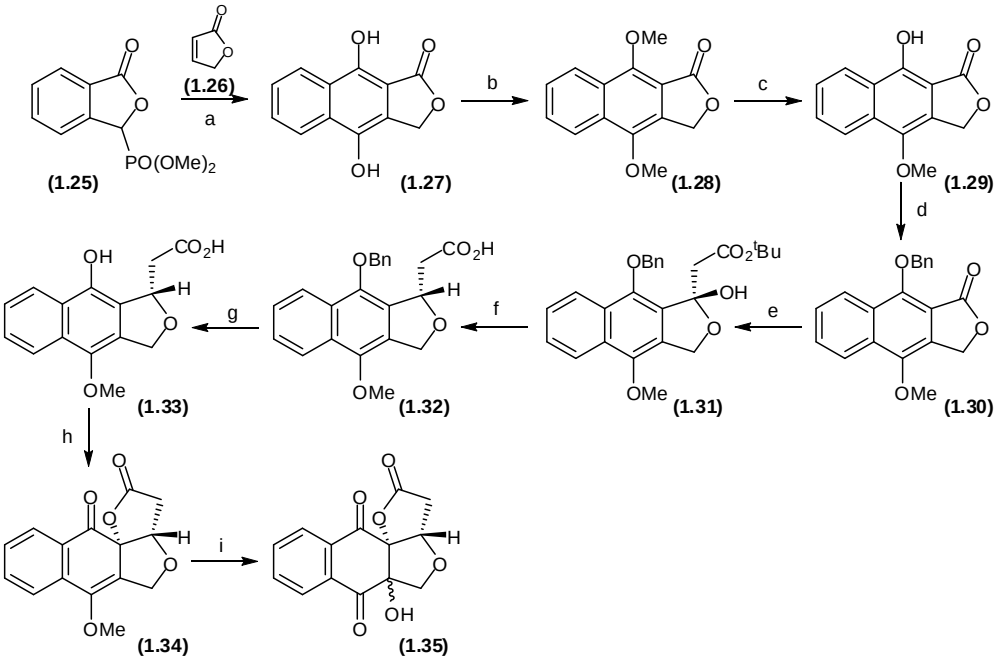


Scheme 1.3 : Reagents and Conditions: (a) LDA, ^{t}BuOAc then **(1.17)** (85%); (b) Amberlite IR 120+, MeOH (88%); (c) Triethylsilane, TFA, CH_2Cl_2 (95%); (d) H_2, Pd/C, MeOH (99%); (e) $Pb(OAc)_4$, CH_2Cl_2 (20%).

While attempts were made to allow cleavage of the ester without this undesired collapse of the acetal, ultimately none were successful. Danishefsky therefore elected to simply reduce out the acetal hoping that the required oxygen functionality could be installed later in the synthesis. Treatment of hemiacetal **(1.18)** with triethylsilane and TFA achieved both reduction of the acetal and cleavage of the ester in the same step. After standard hydrogenolytic cleavage of the benzyl protecting group, treatment of the

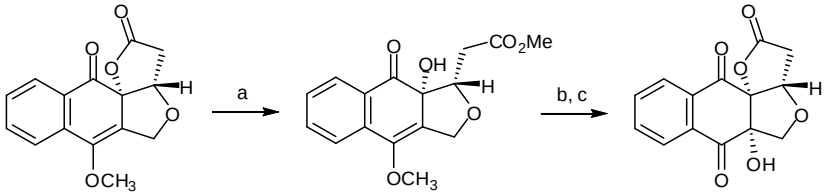
resulting phenol **(1.23)** with lead (IV) acetate led to the formation of desired tricycle **(1.24)**. Sadly this product was only isolable in relatively low yield due to decomposition on silica, Florisil and alumina complicating its purification.

Confident that their methodology was at least somewhat viable Danishefsky decided to proceed with a more complex synthesis in the hope that the tetracyclic Wessely product **(1.34)** would display greater stability than model **(1.24)** (scheme 1.4). The synthesis began with the known phosphonate **(1.25)**[30] which when deprotonated underwent a Michael addition with butenolide **(1.26)** the product of which cyclises to give hydroquinone **(1.27)**. Standard protecting group chemistry was used to differentiate the phenols and the ester side chain was inserted by the established method to give Wessely precursor **(1.33)** in 7 steps. This compound underwent a clean and efficient cyclisation upon exposure to lead (IV) acetate to give lactone **(1.34)** with the additional ring appearing to confer the anticipated stability. Sadly when the epoxidation of this product was attempted with DMDO the undesired *trans* diastereoisomer of alcohol **(1.35)** was obtained in 95% d.e. Despite their best efforts to optimise the epoxidation it did not prove possible to achieve better than a diastereomeric ratio of 1:1 which itself came at the cost of a poor overall yield.



Scheme 1.4 : Reagents and Conditions: (a) LiO^tBu, THF then **(1.26)** (80%); (b) Me_2SO_4, K_2CO_3, acetone, reflux (91%); (c) *B*-Iodo-9-BBN, CH_2Cl_2, reflux (79%); (d) BnBr, K_2CO_3, acetone, reflux (97%); (e) ^tBuOAc, LDA then **(1.30)**; (f) Triethylsilane, TFA, CH_2Cl_2 (70% over 2 steps); (g) 1,4-Cyclohexadiene, Pd/C, EtOH (97%); (h) $Pb(OAc)_4$, CH_2Cl_2 (74%); (i) DMDO, CH_2Cl_2 (80%).

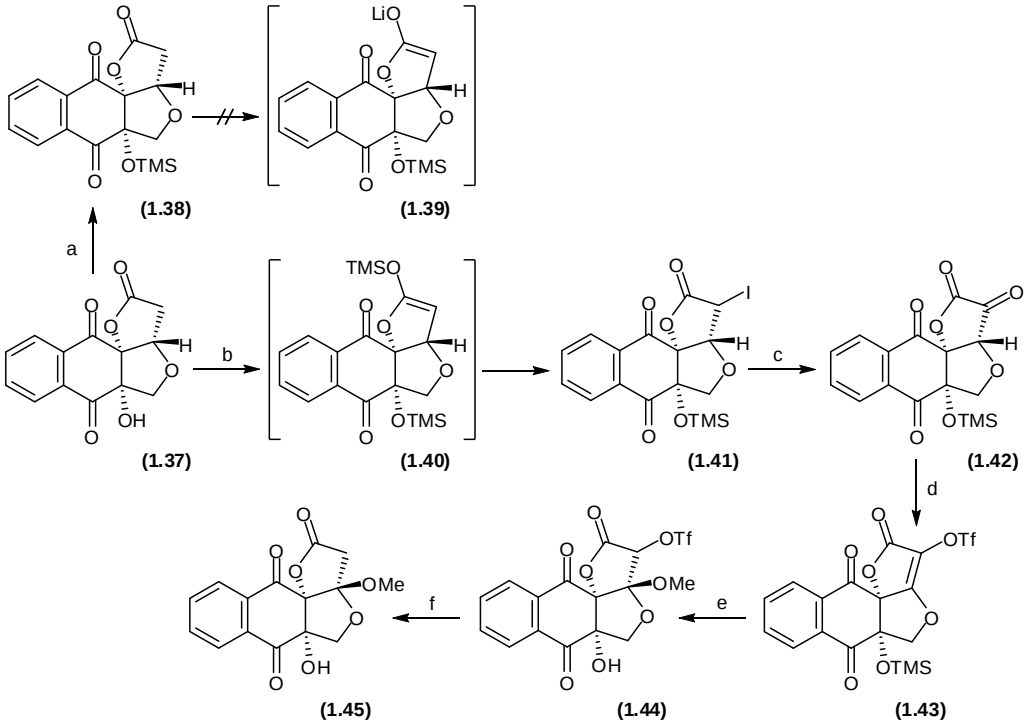
It was decided that the best strategy would be to open the lactone ring and then use the exposed hydroxyl group to direct the epoxidation to the desired face. With the correct stereochemistry installed the lactone could then be closed again. This was a strategy that Danishefsky had used previously in his synthesis of Vernolepin.[31] This approach proved to be successful with lactone **(1.34)** undergoing a methoxide mediated opening to give the alcohol **(1.36)** (scheme 1.5). After some optimisation it was possible to obtain the desired epoxidation product in 95% d.e. with the use of TFPAA. Exposure to catalytic acid reclosed the lactone and recrystallisation gave quinone **(1.37)** as a single diastereoisomer.



(1.34) **(1.36)** **(1.37)**

Scheme 1.5 : Reagents and Conditions: (a) LiHMDS, MeOH, CH_2Cl_2, -35 °C (91% based on recovered SM); (b) TFPAA, Na_2CO_3, CH_2Cl_2, 0 °C; (c) pTSA, benzene, reflux (51% over 2 steps).

Whilst Danishefsky was disappointed that it had not been possible to integrate the desired methoxy unit at an earlier stage (and this would remain a long-term goal) it was felt that the strain of the lactone ring should allow addition of the required functionality in a Michael fashion (scheme 1.6).



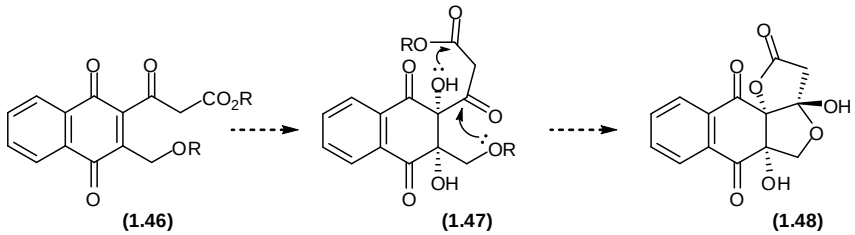
Scheme 1.6 : Reagents and Conditions: (a) HMDS-H, imidazole, TMSCl, CH_2Cl_2 (84%); (b) TMSCl, THF then LiHMDS then NIS (86%); (c) DMDO, CH_2Cl_2 (88% based on recovered SM); (d) Tf_2O, DIPEA, CH_2Cl_2 (60%); (e) CSA, MeOH (88%); (f) LiI, THF, AcOH, reflux (55%).

Initial attempts to enolise protected lactone **(1.38)** led only to β-elimination and opening of the hydrofuran ring. However when enolisation of unprotected lactone **(1.37)** was attempted in the presence of TMSCl the silyl ketene acetal **(1.40)** resulted and it proved possible to use this intermediate to form the α-iodolactone **(1.41)** through reaction with NIS. It was initially planned that the iodine be oxidised to an iodosyl intermediate which would then undergo elimination to give the necessary strained double bond.[32] Oxidation with DMDO however gave exclusively the α-ketolactone **(1.42)** through what Danishefsky suggested to be a Pummerer-like reaction. While this ketolactone was not the intended product it did enable the synthesis to be continued, trapping of the enolate of the newly formed ketone as the triflate **(1.43)** allowed Michael addition of methanol as predicted. Reductive removal of the triflate residue with lithium iodide gave target **(1.45)** with all of the ABC ring system functionality in place.

Whilst this synthesis was a significant first step along the road towards a total synthesis, Danishefsky was disappointed. Despite the Wessely oxidation route working largely as planned there was substantial frustration that it had proved impossible to incorporate the angular methoxy group from an early stage, *post facto* installation of which greatly elongated the route. The epoxidation step was also felt to be somewhat inefficient. The

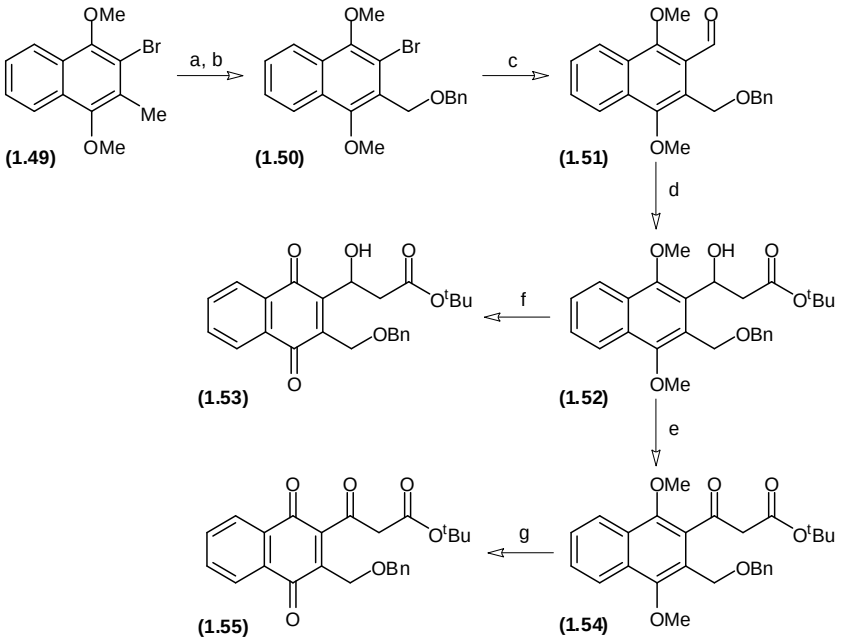
main concern however was the apparent inability to utilise this route to install the absolute stereochemistry required.

As a result of these problems Danishefsky opted to reevaluate his approach, hoping to circumvent some of the issues established in the earlier work. This re-evaluation led to the 2001 publication of an alternate route to the same ABC ring system (scheme 1.7).[33] The proposed route would involve the early installation of a quinone, with the key step a dihydroxylation, which would in theory allow access to an enantioselective synthesis in the future. Deprotection and cyclisation of the side chains would allow the completion of the model system.



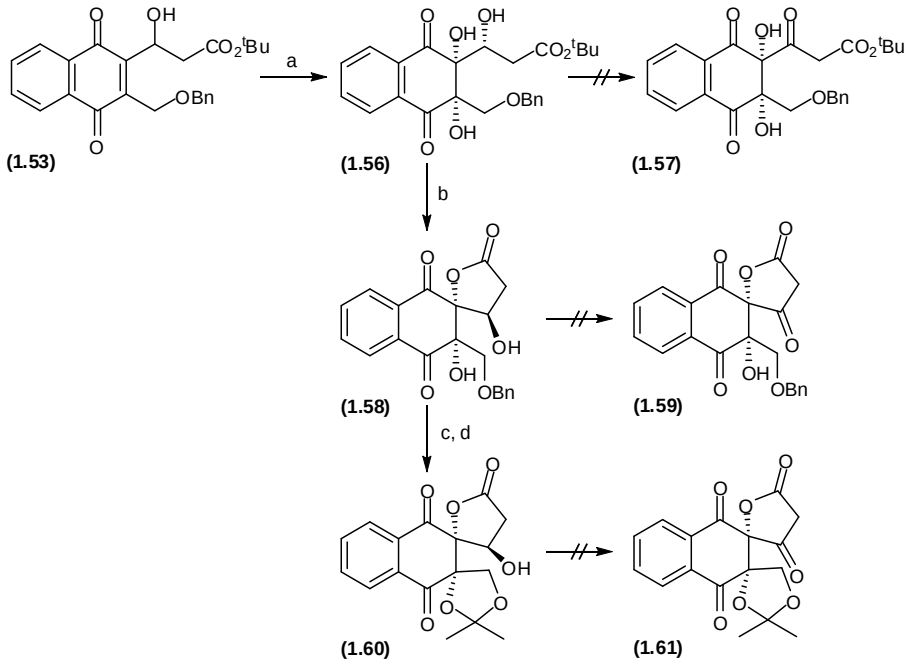
Scheme 1.7 : Proposed dihydroxylation route toward the AB ring system.

Work began with known bromonapthalene **(1.49)**[34] which was converted to napthaldehyde **(1.51)** through standard aromatic chemistry (scheme 1.8). Addition of the enolate of *tert*-butyl acetate to the aldehyde resulted in alcohol **(1.52)**. The carbon of this alcohol corresponds to the carbon of the troublesome methoxy group in the final product, it was therefore considered desirable to attain the correct oxidation level at this early stage. However it was acknowledged that introducing a ketone alpha to the quinone double bond may inhibit the later dihydroxylation of that bond, as such both alcohol **(1.52)** and ketone **(1.54)** were synthesised. The oxidation to give the hydroxyquinone **(1.53)** proceeded in excellent yield, but the contrasting oxidation to the β-ketoquinone **(1.55)** was low-yielding as predicted.



Scheme 1.8 : Reagents and Conditions: (a) NBS, benzoyl peroxide, CCl_4, reflux (quant.); (b) NaH, BnOH, TBAI, THF (81%); (c) ^{n}BuLi then EtOCHO, THF, -95 °C (80%); (d) LDA, ^{t}BuOAc, -78 °C, THF (quant.); (e) DMP, CH_2Cl_2 (76%); (f) CAN, MeCN, H_2O (97%); (g) CAN, MeCN, H_2O (20%).

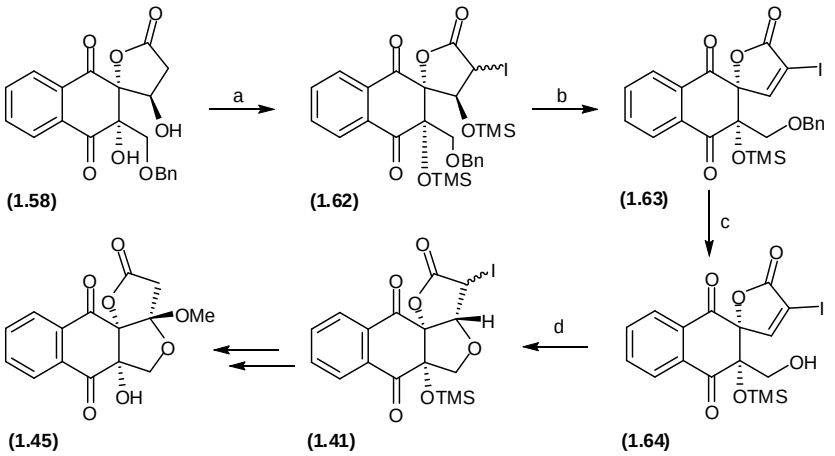
Sadly all efforts to dihydroxylate the electron deficient double bond of the α-ketoquinone **(1.55)** proved ineffectual. Whilst this was disappointing, it was not unexpected. Thankfully dihydroxylation of the alcohol **(1.53)** proceeded smoothly to give the 1,2-diol **(1.56)** as a single diastereoisomer (scheme 1.9). Danishefsky felt it important to elaborate on the nature of the stereoselectivity in this transformation and was keen to cite work by Kishi *et al.*[35] that explains that the allylic alcohol does not direct the osmium to the *anti* face of the alkene (examples of this seemingly reasonable hydrogen bonding effect are surprisingly rare)[36] it merely sets up a steric environment in which attack is most favourable from the *anti* face. Work by Duthaler *et al.* led Danishefsky to believe that using an aldol reaction to form the equivalent of alcohol **(1.53)** in a future total synthesis could be conducted in a highly stereoselective manner,[37] thus opening a route to an asymmetric synthesis.



Scheme 1.9 : Reagents and Conditions: (a) OsO_4, NMO, acetone, H_2O (71%); (b) TFA, H_2O, CH_2Cl_2 (83%); (c) BBr_3, CH_2Cl_2, -78 °C (85%); (d) Acetone, $AlCl_3$, Et_2O, 0 °C (79%).

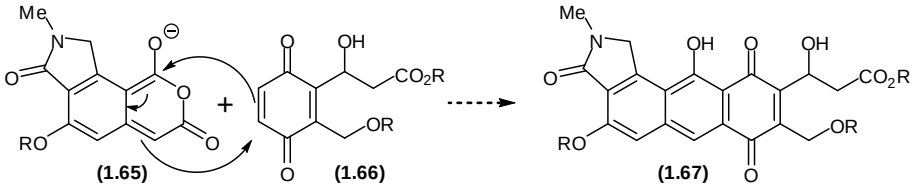
With the triol **(1.56)** in hand Danishefsky imagined that the synthesis should be completed relatively simply by an intramolecular transesterification and exposure of the open chain ester to acidic conditions did indeed promote a rapid cyclisation to the β-hydroxylactone **(1.58)**. Further efforts were made to attain the correct oxidation state at the beta carbon but oxidation of the hydroxyl group (or its equivalents in **(1.56)** & **(1.60)**) proved to be extremely challenging and a working protocol could not be developed. Crystallography suggested this apparent inertness towards oxidation may be due to a surprisingly hindered environment around the geminal proton.

Once again Danishefsky's plans to install the methoxy group were foiled, this necessitated yet another awkward revision of route (scheme 1.10), utilising an intramolecular addition of the deprotected alcohol in **(1.64)** onto the electron poor double bond to give known α-iodolactone **(1.41)**. Completion of the model system **(1.45)** then proceeded as demonstrated previously (*vide supra*, scheme 1.6). This completed the second synthesis of this system and with it Danishefsky managed to remedy the main problem of his initial Wessely oxidation route. The selectivity of the dihydroxylation and the potential to produce the precursor in enantiomerically pure form meant this route was far more suitable for a full asymmetric synthesis of lactonamycin.



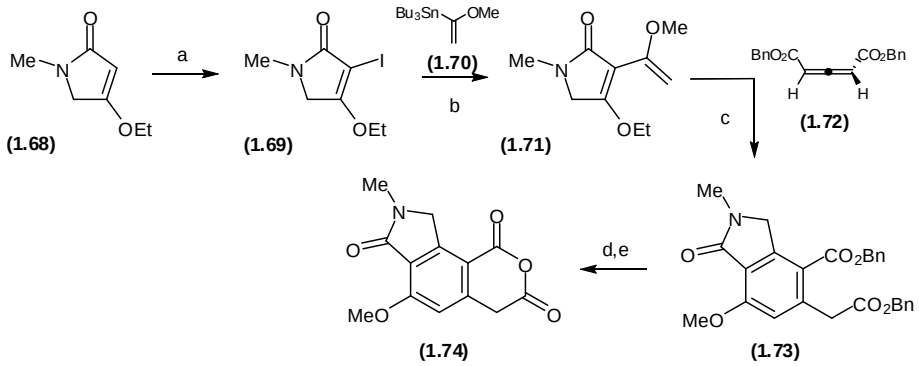
Scheme 1.10 : Reagents and Conditions: (a) TMSCl, THF then LiHMDS then NIS, -78 °C (85%); (b) DBU, THF (82%); (c) BBr_3, CH_2Cl_2, -78 °C; (d) SiO_2, $CHCl_3$ (84% over 2 steps).

Details of the completed synthesis of lactonamycinone were published 2 years later in two communications.[38] The first of these detailed the convergent synthesis of the CDEF ring system and the second the progression from this to the full hexacyclic construct. Danishefsky proposed to form the bulk of the structure by using his quinone dihydroxylation method of forming the ABC rings to give quinone **(1.66)** which would undergo a Tamura-Diels-Alder reaction with the enolate of a homophthalic anhydride **(1.65)** (scheme 1.11), the resulting advanced intermediate **(1.67)** would be converted to the target compound by the chemistry established in the model systems (*vide supra*, schemes 1.9 & 1.10).



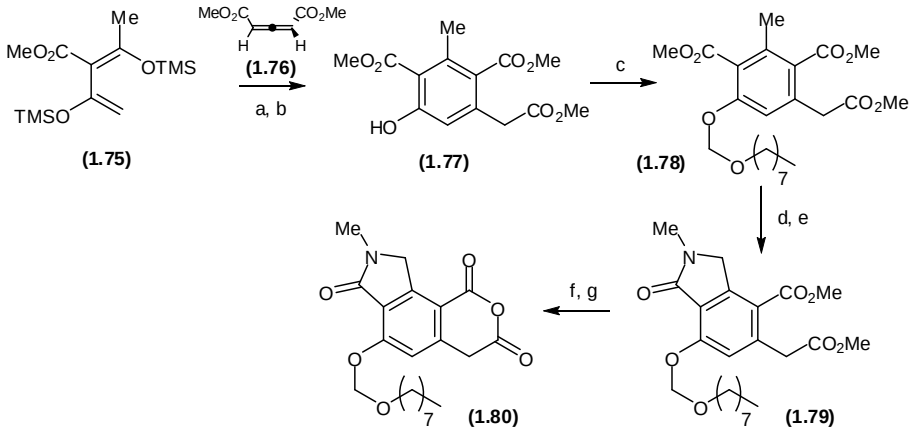
Scheme 1.11 : Proposed Tamura-Diels-Alder route toward the CDEF ring system.

Synthesis of the anhydride began with lactam **(1.68)**[39] which was converted to the diene **(1.71)** in two steps (scheme 1.12), it was Danishefsky's intention to react this diene with an allene in order to form what would become the E ring of lactonamycinone. The Diels-Alder reaction with 1,3-dicarbobenzyloxyallene **(1.72)** gave the diester **(1.73)** in low, but viable yield. However whilst cleavage of the esters proceeded smoothly, attempts to dehydrate the resulting diacid proved unsuccessful, this was thought to be largely due to solubility issues with the extremely polar intermediate.



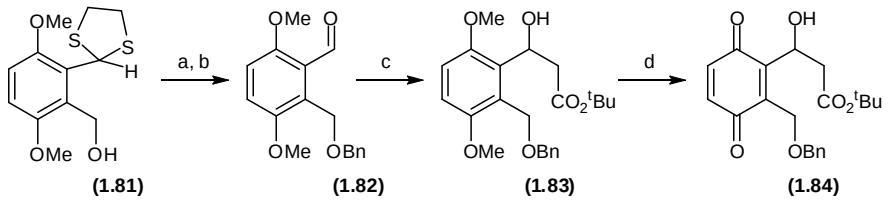
Scheme 1.12 : Reagents and Conditions: (a) I_2, PIFA, pyridine, (51%); (b) **(1.70)**, $PdCl_2(PPh_3)_2$, toluene, reflux (83%); (c) **(1.72)**, neat, 200°C, (15 -25%); (d) H_2, Pd/C (50%); (e) (Trimethylsilyl)ethoxyacetylene, MeCN, CH_2Cl_2 (trace).

An alternate route was initiated (scheme 1.13), starting with known silyl enol ether **(1.75)**[40] this underwent a similar cycloaddition reaction with allene **(1.76)** and the synthesis of the anhydride **(1.80)** proceeded without issue. The unusual choice of an octyloxymethyl protecting group was intended to counter the solubility issues experienced with the diacid in the previous synthesis and this appeared to work as intended with the dehydration proceeding in quantitative yield.



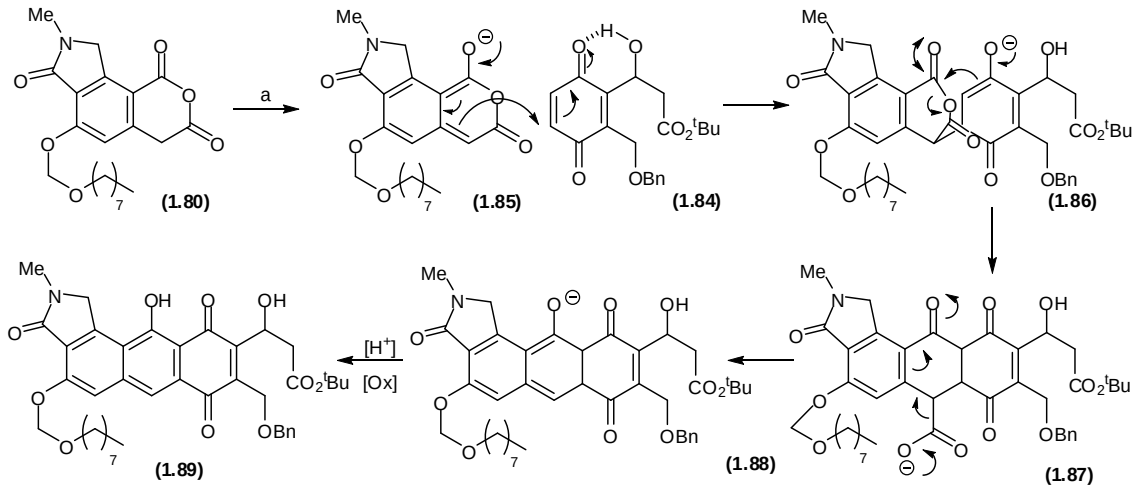
Scheme 1.13 : Reagents and Conditions: (a) **(1.76)**, neat, 105 °C; (b) NH_4F, MeOH, (75% over 2 steps); (c) $CH_3(CH_2)_7OCH_2Cl$, DIPEA, DMF (95%); (d) NBS, benzoyl peroxide, UV, benzene; (e) K_2CO_3, NH_2Me, MeOH/MeCN (1:2), (30% based on recovered SM, over two steps); (f) KOH, MeOH (98%); (g) (Trimethysilyl)ethoxyacetylene, MeCN, CH_2Cl_2 (quant.).

Synthesis of the Tamura-Diels-Alder coupling partner **(1.84)** was completed in 4 steps from known dithiane **(1.81)**[41] using standard chemistry. The previous ambition[33] of installing chirality at the secondary alcohol carbon was seemingly abandoned, there is no mention of any attempts to this end and one can only speculate that this proved substantially more challenging than originally anticipated. The racemic β-hydroxyquinone **(1.84)** was therefore carried through.



Scheme 1.14 : Reagents and Conditions: (a) NaH, BnBr, TBAI, THF (86%); (b) PIFA, MeCN/H_2O (1:1) (86%); (c) LDA, ^{t}BuOAc, -78 °C, THF (99%); (d) CAN, 0 °C, MeCN/H_2O (9:1) (96%).

No attempt was made to oxidise the secondary alcohol to the ketone as whilst this oxidation state may have still been desirable in terms of installing the methoxy group later in the synthesis, the β-hydroxyl group was now essential to the selectivity of the Tamura-Diels-Alder (scheme 1.15). Hydrogen bonding between the alcohol and the β-carbonyl of the quinone activated it, making 1,4-addition to that carbonyl significantly more favourable than addition to the opposite end of the quinone system.

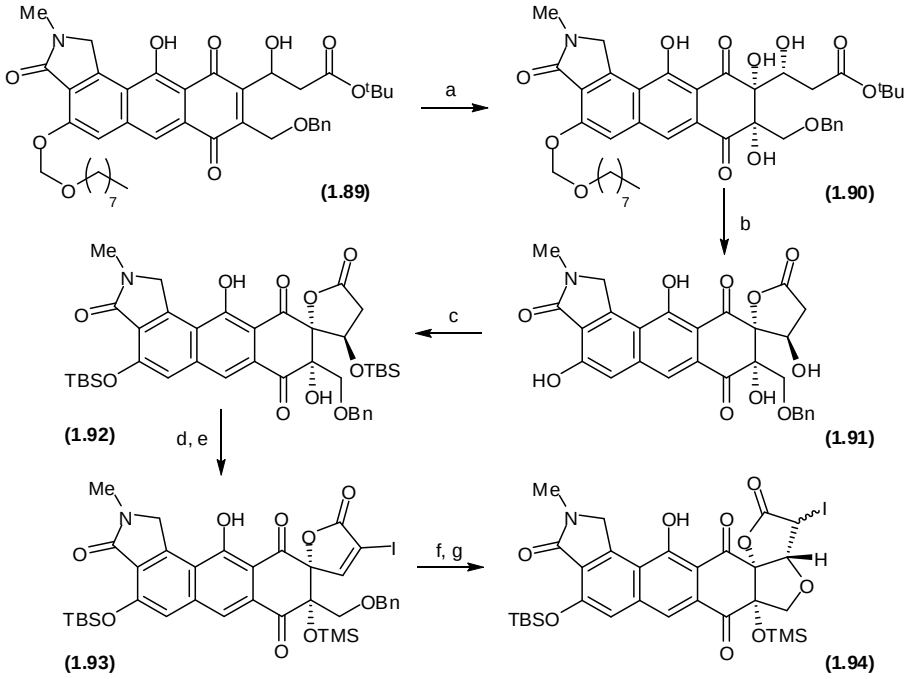


Scheme 1.15 : Reagents and Conditions: (a) NaH, THF, -78 °C to 0 °C (40%).

The directing effect of the alcohol was further elaborated by the preparation of the TBS ether, when this was exposed to the Tamura-Diels-Alder conditions, no selectivity was observed, the product being a 1:1 ratio of the two possible stereoadducts. Preparation of a sodium chelate *via* pre-treatment of alcohol **(1.84)** with NaH demonstrated a similar mode of selectivity, yields were not improved however.

Tetracyclic intermediate **(1.89)** was converted to the *cis*-diol **(1.90)** as expected with osmium tetroxide (scheme 1.16) and subsequent treatment with TFA allowed the formation of the lactone with concomitant deprotection of the octyloxymethyl ether giving spirocycle **(1.91)**. Once again exhaustive efforts were made to oxidise the secondary alcohol to the desired ketone, but this target continued to prove elusive. This

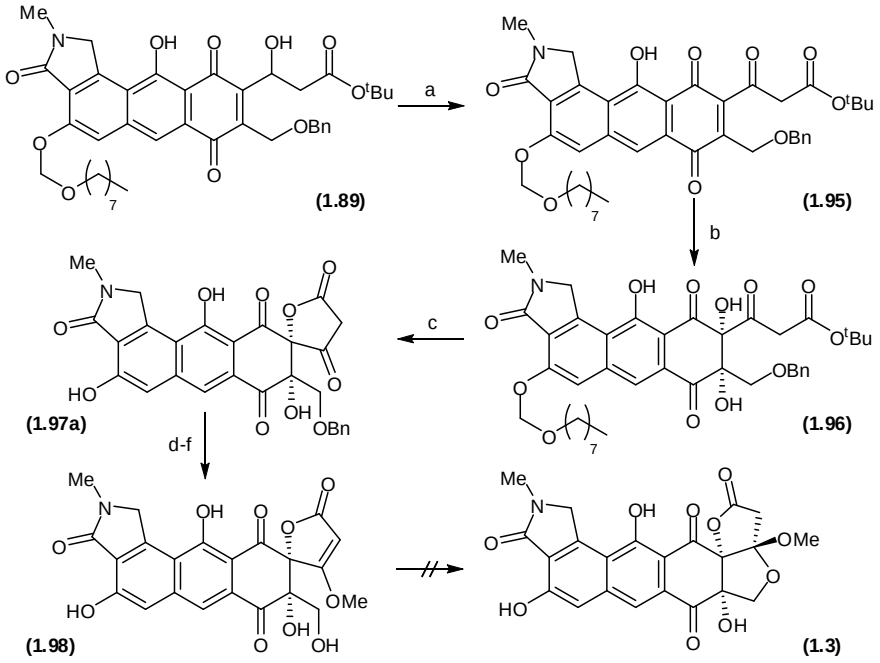
resulted in a retreat to the previously described chemistry (*vide supra*, scheme 1.10) to integrate the angular methoxy group leading to iodolactone **(1.94)**, this at least was a very encouraging development for Danishefsky as the analogous iodolactone **(1.41)** had been converted into the desired AB ring structure in both of the model studies of that system. In the case of the hexacyclic construct however it proved impossible to gain access to the required analog of vinyl triflate **(1.43)**. It also proved impossible to close the B ring without the activating effect of iodine on the alkene.



Scheme 1.16 : Reagents and Conditions: (a) OsO_4, pyridine, THF then $NaHSO_3$ (90%); (b) TFA, CH_2Cl_2, H_2O (97%); (c) TBSOTf, 2,6-lutidine (73%); (d) LDA, TMSCl, NIS, THF, -78 °C (61%); (e) Cs_2CO_3, THF (83%); (f) BBr_3, CH_2Cl_2, -78 °C; (g) Al_2O_3, $CHCl_3$, (65% over 2 steps).

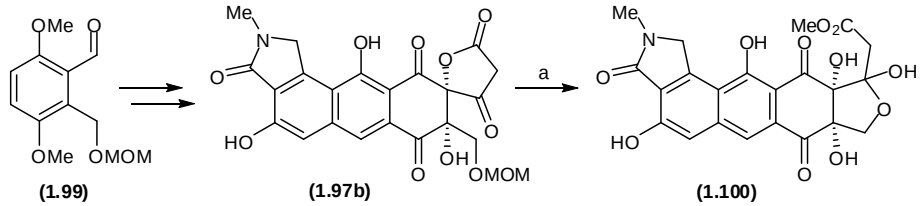
A different approach to the AB system was therefore required and so it was decided to attempt the oxidation of alcohol **(1.89)** (scheme 1.17). This was converted to ketone **(1.95)** with DMP. This ketone was not an ideal intermediate, as it would make the following dihydroxylation of the now deactivated alkene somewhat more complicated. It also ruled out the application of this route to a chiral synthesis, as the stereoselectivity imbued by the alcohol is removed. Whilst the conjugated ketoquinone did indeed prove resistant to dihydroxylation by OsO_4, the use of a bidentate amine ligand (TMEDA) as described by Corey *et al.*[42] increased the reactivity of the osmium significantly, allowing conversion to the diol **(1.96)** in surprisingly high yield. Treatment with acid once again allowed simultaneous deprotection of the octyloxymethyl group and formation of the spirolactone **(1.97a)**, this reaction did however prove prone to decarboxylation, giving somewhat erratic yields. The ketolactone (or analogous

compounds) had been an elusive target for some time, unfortunately the deprotection of the *O*-benzyl group proved impossible without also causing significant decomposition of the labile ketolactone. Further triage of this route allowed conversion of the ketolactone into methyl tetronate **(1.98)**, this proved sufficiently resilient for the benzyl ether to be cleaved. Work by Murphy *et al.*[43] had shown how methyl tetronate had proved almost completely inert to Michael additions and the intramolecular closing of the primary alcohol proved to be just as resistant.



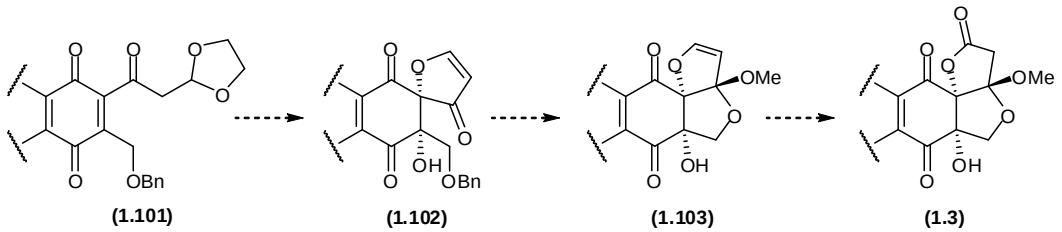
Scheme 1.17 : Reagents and Conditions: (a) DMP, CH_2Cl_2 (96%); (b) OsO_4, TMEDA, CH_2Cl_2 then HCl, $NaHSO_3$, THF (77%); (c) TFA, CH_2Cl_2, (20-55%); (d) TBSOTf, 2,6-lutidine, -78 °C, CH_2Cl_2; (e) $TMSCHN_2$, DIPEA, MeCN, CH_2Cl_2, (22% over 2 steps); (f) BBr_3, CH_2Cl_2, -78 °C (95%).

This difficulty proved impossible to evade and this route too reached a dead end. It was felt however that a simple adjustment of the protecting group strategy (scheme 1.18), introducing a more labile protecting group instead of the benzyl ether would allow the route to proceed. Methoxymethyl-protected analog **(1.97b)** was prepared through the same methodology as the corresponding benzyl compound **(1.97a)**.



Scheme 1.18 : Reagents and Conditions: (a) AcCl, MeOH, 65 °C (32%).

The protecting group in this compound was readily cleaved under acidic conditions without the decomposition previously observed, but these conditions also led to the methanolysis of the lactone, presumably leading to stereo randomisation of the hemiacetal centre in the ring open compound **(1.99)**. No mention was made of attempts to reclose the lactone. The abandonment of this modification marked the end of attempts at this route and a further revision of strategy (scheme 1.19). A strategy was proposed that would utilise masked aldehyde **(1.101)** to form the A ring as a butenolide, which would undergo conversion to the lactone only after the B ring had been closed and the methoxy group installed.



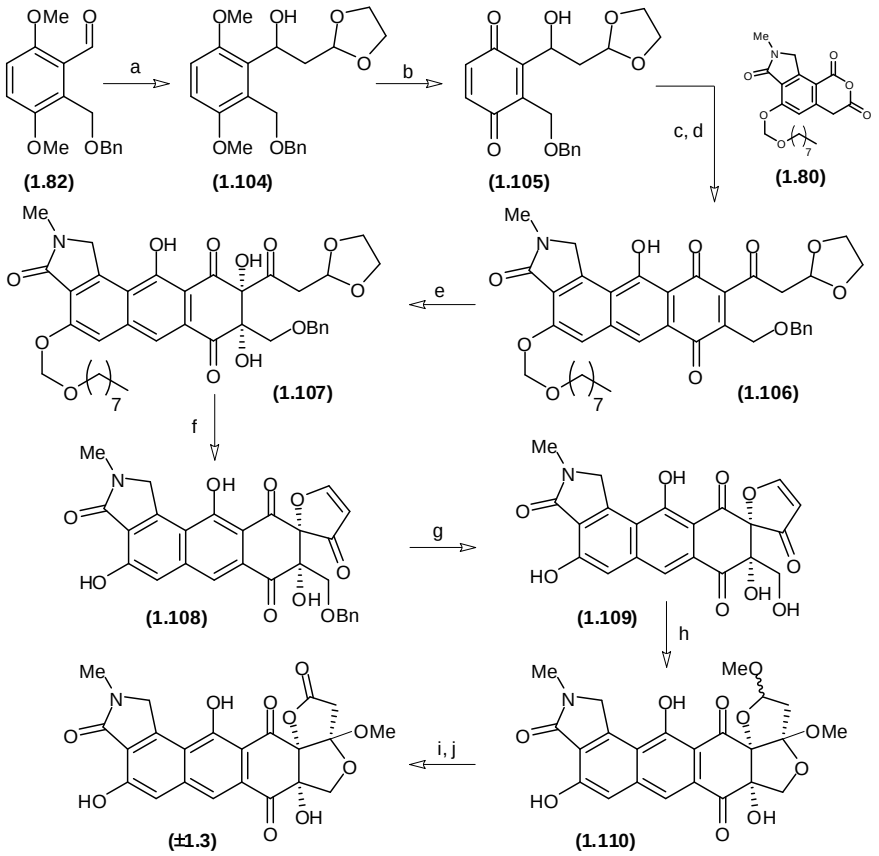
(1.101) **(1.102)** **(1.103)** **(1.3)**

Scheme 1.19 : Revised strategy for AB ring formation.

Regressing to benzaldehyde **(1.82)** (scheme 1.20) the synthesis proceeded by the addition of a methyl dioxolane Grignard reagent, subsequent Tatsuta-Diels-Alder cyclisation, oxidation and dihydroxylation steps worked as per the model precedent to give diol **(1.107)**. When this was exposed to acid, the anticipated deprotection/cyclisation step occurred to give the butenolide **(1.108)**, which proved suitably stable to allow deprotection of the benzyl ether; the newly exposed primary alcohol **(1.109)** then underwent a methanol induced cyclisation to give the acetal **(1.110)** with the required methoxy group in place. The acetal was readily cleaved to the corresponding lactol with acid. Oxidation to furnish the lactone of (±)-lactonamycinone **(1.3)** was not quite as simple as anticipated, requiring a quite specific oxidant. The presence of catalytic TEMPO and the use of PIDA as a stoichiometric oxidant[44] proving to be the only efficacious combination.

The completion of this compound was a substantial achievement for Danishefsky *et al.* with the target molecule being finished by what ultimately proved to be a very concise route. Persistence proved to be a valuable asset in the synthesis as the model chemistry that has been so well established failed to be replicated on the full hexacyclic construct. The failure of such reasonable model systems to faithfully replicate the chemistry of the AB-ring systems is certainly a warning sign to any chemist intent on tackling this

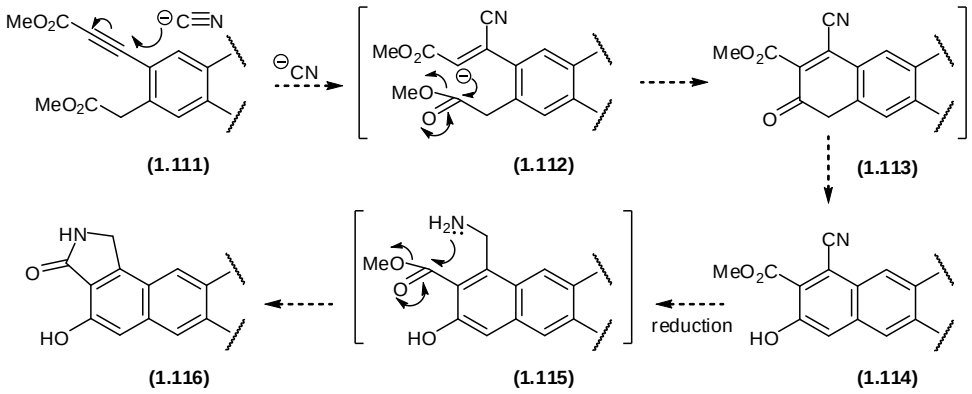
problem. It was also most unfortunate that the planned route to an asymmetric synthesis was nullified through necessity, whether such an opportunity can be reintegrated at a future point remains to be seen.



Scheme 1.20 : Reagents and Conditions: (a) (1,3-Dioxolan-2-ylmethyl)magnesium bromide, LiBr, THF, reflux (69%); (b) CAN, 0 °C, MeCN/H_2O (1:1) (80%); (c) NaH, **(1.80)** THF, (42%); (d) DMP, CH_2Cl_2 (quant.); (e) OsO_4, TMEDA, CH_2Cl_2 then HCl, $NaHSO_3$, THF (89%); (f) HCl, acetone, THF, reflux, (82% based on recovered SM); (g) BBr_3, CH_2Cl_2, -78 °C; (h) HCl, dioxane, MeOH, 65 °C (51% based on recovered SM, over 2 steps); (i) HCl, THF, (quant.); (j) TEMPO, PIDA, CH_2Cl_2 (58%).

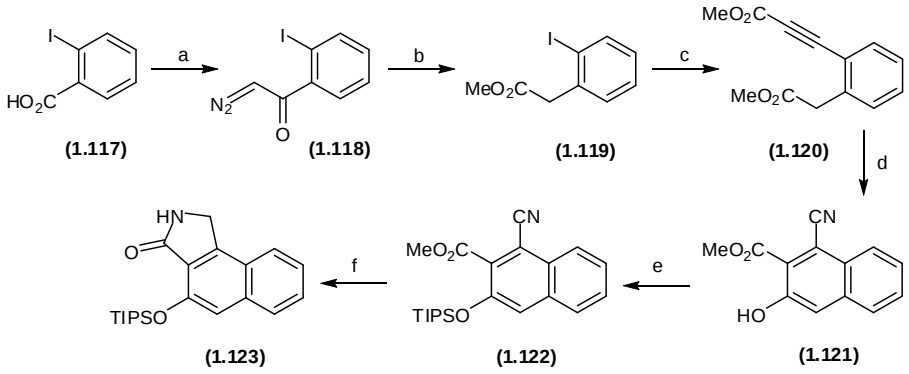
1.2.2 Behar and Deville.

Behar and Deville, reporting shortly after Danishefky's initial work, proposed a route to the CDEF ring system of lactonamycin (scheme 1.21).[45] This route would utilise a tandem conjugate addition of cyanide to alkyne **(1.111)** with a subsequent Dieckmann-type condensation of the intermediate anion **(1.112)**, this would give enone **(1.113)** which would rapidly tautomerise to napthol **(1.114)**. Reduction of the nitrile would give the free amine **(1.115)** that should rapidly cyclise onto the nearby ester, giving lactam **(1.116)**.



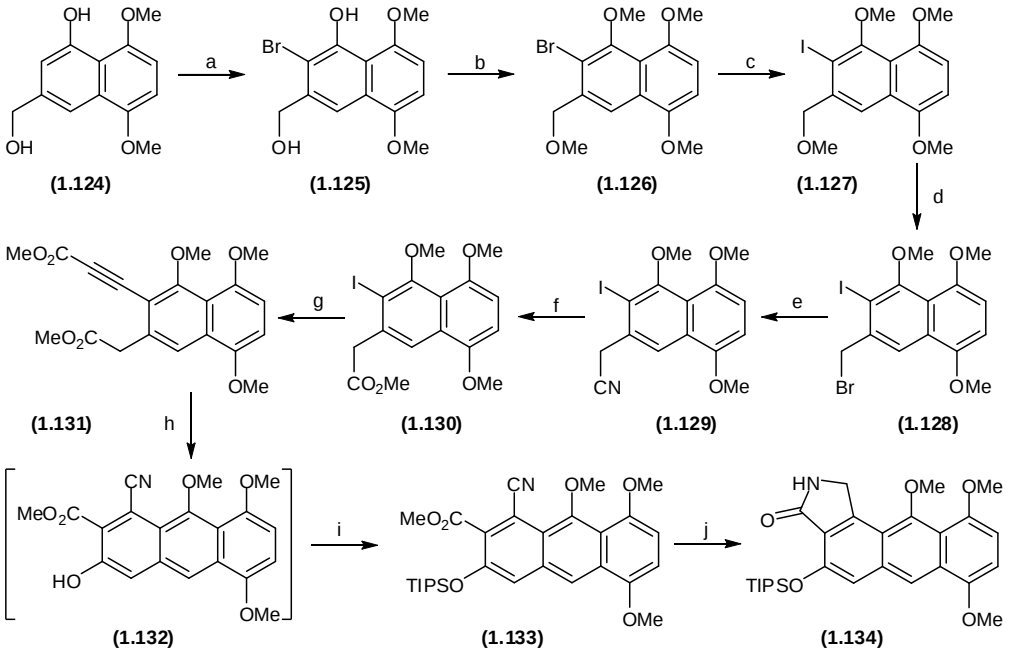
Scheme 1.21 : Proposed tandem conjugate addition/ Dieckmann condensation route.

A model system was prepared to test the hypothesis and this would prove to be most successful (scheme 1.22). Commercially available iodobenzoic acid **(1.117)** was first converted to the acid chloride by the action of oxalyl chloride, before reaction with diazomethane gave diazoketone **(1.118)**. Treatment with silver benzoate effected a Wolff rearrangement and in the presence of methanol the intermediate ketene reacted to give methyl ester **(1.119)**. A Sonogashira coupling with triethylorthopropynoate, followed by reaction with methanol and acid gave the diester **(1.120)**. This compound was then treated with a number of different cyanides (NaCN, KCN, $[Bu_4N]CN$) in DMSO. Whilst all effected the required addition-condensation to give benzonitrile **(1.121)** NaCN was found to be the most consistently high-yielding and this protocol was adopted as standard. The phenol was incompatible with the reaction conditions of the reduction and so this was quantitatively protected as the TIPS ether **(1.122)**. Treatment of the aryl cyanide with sodium borohydride in the presence of cobaltous chloride allowed selective reduction of the nitrile.[46] This gave the expected lactam **(1.123)** after cyclisation of the intermediate amine.



Scheme 1.22 : Reagents and Conditions: (a) $(COCl)_2$, DMF, THF, benzene, 0 °C then CH_2N_2, Et_2O, 0 °C (79%); (b) AgOBz, NEt_3, MeOH, 0 °C (86%); (c) $HCCC(OEt)_3$, $PdCl_2(PPh_3)_2$, CuI, NEt_3, MeCN, 0 °C to rt then pTSA, MeOH (85%); (d) NaCN, DMSO, rt (88%); (e) NaH, TIPSCl, DMF (quant.); (f) $NaBH_4$, $CoCl_2$, MeOH, THF (71%).

Now confident in their methodology the authors elected to attempt the synthesis of a more elaborate model that would more closely replicate the functionality needed for a total synthesis of lactonamycin (scheme 1.23). Known napthol **(1.124)**[47] was selected and this underwent bromination *ortho* to the phenol with pyridinium bromide perbromide to give napthyl bromide **(1.125)**. Standard methylation conditions protected both the phenol and the secondary alcohol as their methyl ethers giving methyl ether **(1.126)**. The aryl bromide was converted to the corresponding iodide **(1.127)** *via* a lithiated intermediate. The benzylic methoxy group was then converted to the corresponding benzyl bromide **(1.128)** by treatment with HBr in acetic acid. The bromide was displaced with KCN to give the nitrile **(1.129)** and this underwent methanolysis to give the methyl ester **(1.130)**. An analogous Sonogashira coupling and subsequent hydrolysis gave diester **(1.131)**, it was noted that Sonogashira conditions were tried on the equivalent bromo compound but were found to be ineffective. This necessitated the slightly less elegant conversion to the iodide.



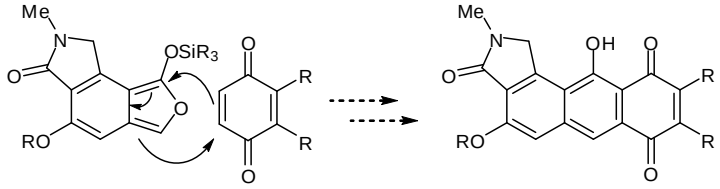
Scheme 1.23 : Reagents and Conditions: (a) PHPB, THF, 0 °C (99%); (b) NaH, MeI, DMF (84%); (c) ^{n}BuLi, THF, I_2, -78 °C (91%); (d) HBr, AcOH, 50 °C (65-79%); (e) KCN, EtOH, H_2O, reflux (82%); (f) TfOH, MeOH, reflux (86%); (g) $HCCC(OEt)_3$, $PdCl_2(PPh_3)_2$, CuI, NEt_3, MeCN, 0 °C to rt then pTSA, MeOH (97%); (h) NaCN, DMSO; (i) NaH, TIPSCl, DMF (68% two steps); (j) $NaBH_4$, $CoCl_2$, MeOH, THF, 50 °C (52%).

Exposure of diester **(1.131)** to the previously optimised cyclisation conditions gave the desired product, although the reaction was significantly slower than that of the model. Concerns over the stability of intermediate phenol **(1.132)** led them to TIPS protect the crude material to give silyl ether **(1.133)**. This material was reduced using the same

borohydride-cobalt chloride system and whilst requiring longer reaction times and heating, the lactam **(1.134)** was successfully obtained. This sluggishness seems reasonable given the large amount of oxygen functionality in this system.

1.2.3 Kelly *et al.*

Published only shortly after the effort of Behar and Deville was a second model study of the CDEF ring system from the Kelly laboratory.[48] They proposed to make the key step of their synthesis a Diels-Alder reaction between a quinone and the silyl enolate of a tricyclic phthalide system (scheme 1.24).

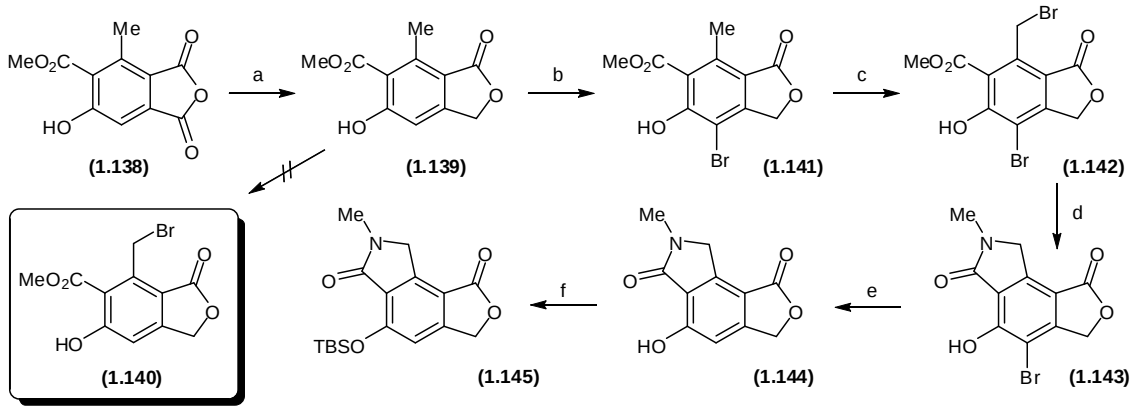


(1.135) **(1.136)** **(1.137)**

Scheme 1.24 : Proposed Diels-Alder formation of C&D rings.

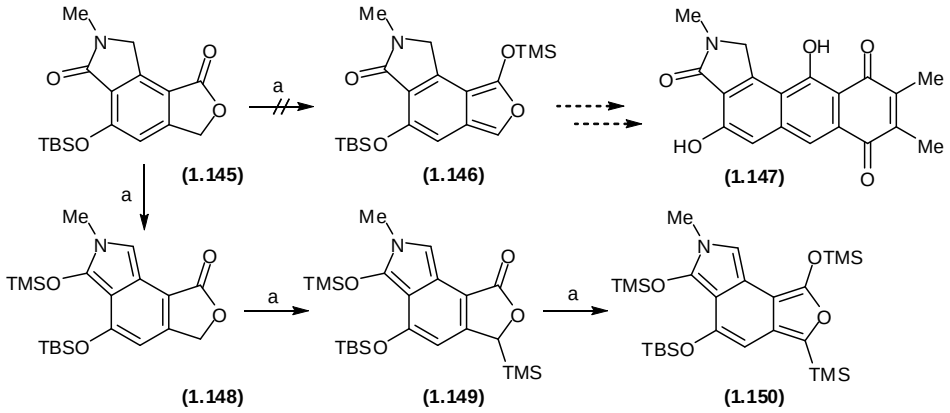
The route began with the formation of the known anhydride **(1.138)**[49] (scheme 1.25), this was selectively reduced to the desired lactone **(1.139)** with L-Selectride®, the work of Makhlouf and Rickborn suggesting that the observed selectivity (≥95%) is a result predominantly of sterics,[50] though the electronics of this particular system are also favourable for reduction at the more electron poor carbonyl. It was intended that this phthalide system would then undergo bromination on the methyl group *via* a radical reaction pathway to give benzyl bromide **(1.140)**, however even under very strong radical conditions (AIBN as an initiator and performed under an intense light source) the only observed bromination product was the ring-substituted product **(1.141)**. This reactivity was driven by the strong activation of the aryl position by the *ortho*-phenol, this could be counteracted by the protection of the phenol as its acetate ester, however this compound still did not undergo the desired transformation, instead undergoing bromination at the methylene position of the lactone. Treatment of aryl bromide **(1.141)** with a further equivalent of NBS under free radical conditions allowed advancement to the corresponding benzyl bromide **(1.142)** albeit as one of a mixture of competing bromination products, the mild selectivity towards the methyl rather than methylene position was attributed to hindrance from the bromine on the ring. The lactam **(1.143)** was formed through reaction with methylamine, displacing the benzyl bromide and then closing onto the adjacent ester. The aryl bromide was then removed and the phenol

protected as its TBS ether **(1.145)**.



Scheme 1.25 : Reagents and Conditions: (a) L-Selectride, THF, -78 °C to rt (87%); (b) NBS, CCl_4, H_2O, rt (91%); (c) NBS, AIBN, P_2O_5, CCl_4, H_2O, reflux (32% based on recovered SM); (d) NEt_3, $MeNH_2$, MeOH; reflux; (e) Zn, NaOH, H_2O, reflux; (f) TBSCl, imidazole, DMF, rt (51% over 3 steps).

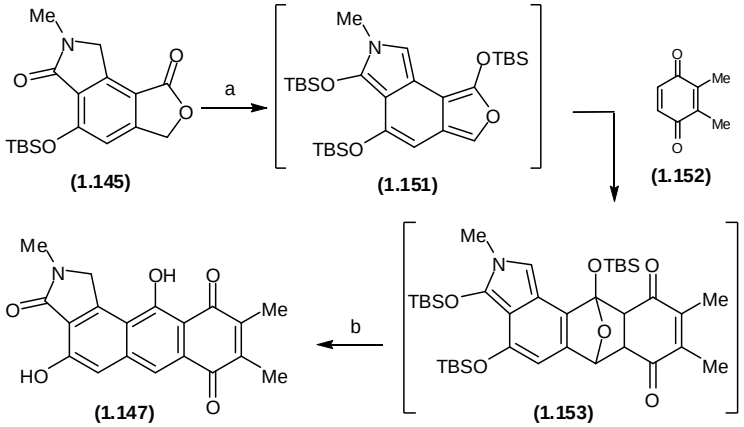
With phthalide system **(1.145)** in hand, it was thought that treatment with a single equivalent of base would be sufficient to deprotonate at the lactone methylene, this would generate the enolate, which could then be trapped with TMSCl to give the isobenzofuran **(1.146)**. However what actually occurred was that the first equivalent of base instead deprotonated the lactam, generating the isoindole **(1.148)**. Unfortunately, a second deprotonation/trapping resulted in the *C*-silylated product **(1.149)** and only with a third equivalent of base was the isobenzofuran **(1.150)** generated.



Scheme 1.26 : Reagents and Conditions: (a) LDA then TMSCl.

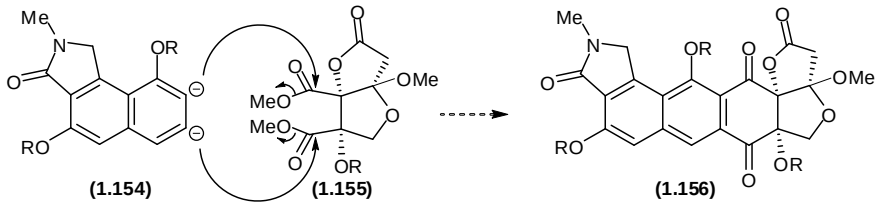
Fortunately it was found that if TBSCl was substituted for TMSCl then it was possible to avoid *C*-silylation entirely (scheme 1.27) and that 2 equivalents of base with an excess of silylating agent would allow direct access to furoisoindole system **(1.151)** *in situ*. The generation of two dienes did briefly raise the issue of selectivity in the reaction with a dienophile, however addition of quinone **(1.152)**[51] to the highly reactive furoisoindole resulted in rapid reaction of the furan diene. Fragmentation of the bridged

intermediate **(1.153)** was achieved by stirring with TFA for 5 days, giving the model CDEF ring system **(1.147)**.



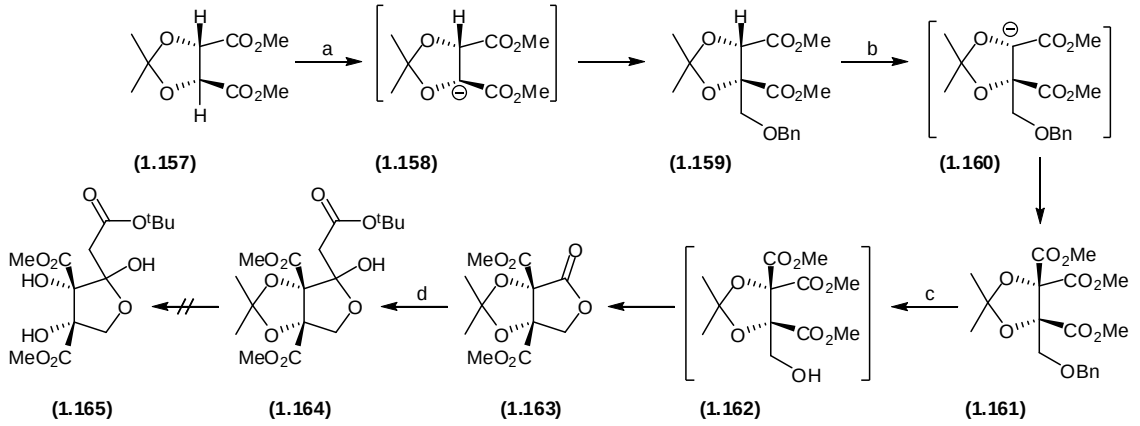
Scheme 1.27 : Reagents and Conditions: (a) KHMDS, TBSCl, THF, -78 °C to rt then **(1.152)**, $CHCl_3$, -60 °C to rt; (b) TFA, 5 days (74% over 2 steps).

This was a remarkably concise synthesis of the tetracyclic ring system and would have been even more so if not for the unfortunate complication with the bromination which added an additional two steps. However it serves only as a proof of concept that the *in situ* use of the furan was viable as a Diels-Alder partner, no methodology was suggested for a reasonable coupling partner for a full synthesis and it was not indicated how stereocontrol would be exerted in the case of an addition to a non-symmetric quinone. In his second publication two years later Kelly seemed to acknowledge this issue and instead proposed an alternate means of forming the quinone with the chiral AB ring already intact (scheme 1.28).[52]



Scheme 1.28 : Proposed coupling strategy with fully formed asymmetric AB rings.

It was thought that the core of the AB ring system could be synthesised starting from a readily available tartrate ester (scheme 1.29). Use of enantiomerically pure tartrate would then allow configuration of the later stereochemistry from the very beginning. D-Tartrate was chosen, with the intention of inverting one of the stereocentres during the synthesis. The synthesis started from readily available D-tartaric acid, which was readily converted to the known acetonide diester **(1.157)**.[53]



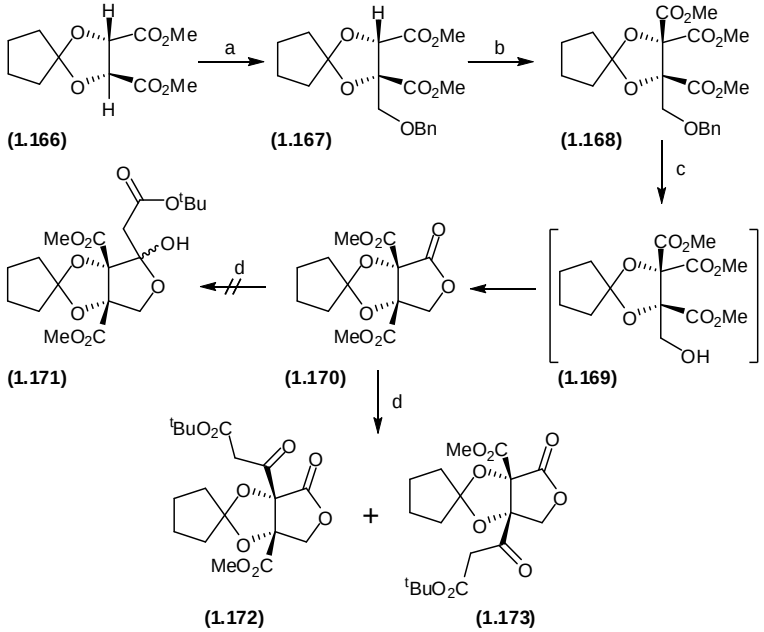
Scheme 1.29 : Reagents and Conditions: (a) LDA, THF, HMPA, -78 °C then BOMCl (60%); (b) LDA, THF, -78 °C then MeO_2CCl (45%); (c) H_2, Pd/C, MeOH (89%); (d) $LiCH_2COO^tBu$, THF, -78 °C (46%).

This acetonide was selected due to the well established enolate chemistry associated with such systems; the cyclic acetal plays a crucial role in restricting the orbital overlap necessary for the system to undergo β-elimination.[54] As such treatment with LDA results in the formation of the anion **(1.158)**, treatment with BOMCl then installs the protected hydroxymethyl group required. Deprotonation of the remaining enolisable position in diester **(1.159)** then allows access to the triester **(1.161)** by the addition of methyl chloroformate. It should be noted that both of these substitutions proceeded with retention of stereochemistry, the adjacent stereocentre directing substitution as such. Most importantly the addition did not proceed with stereochemical randomisation, though an inversion would still have been acceptable, as the L-tartrate derivative could have been used as an alternative.

Hydrogenation of the benzyl group generated the primary alcohol **(1.162)** which rapidly cyclised to give the thermodynamically favourable *cis*-fused lactone **(1.163)** as confirmed by crystallography. Addition of the enolate of *tert*-butyl acetate to the lactone gave a single unspecified diastereomer of hemiacetal **(1.164)**. Attempts were then made to remove the acetonide, but this proved to be impossible under a broad range of conditions.

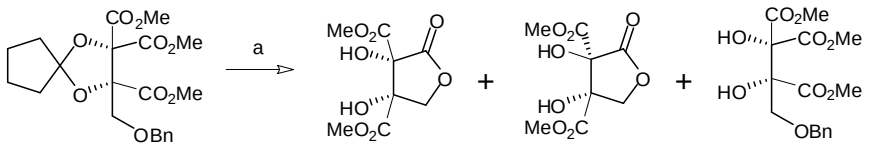
The failure to remove this led Kelly to search for an alternative acetal protecting group, whilst a diverse mixture of acetals were prepared, only the cyclopentylidene acetal **(1.166)** underwent the necessary substitution with BOMCl (scheme 1.30). Knowing that cyclopentylidene acetals had been shown to be more labile than the equivalent acetonides the synthesis was continued with the new protecting group in place.[55] Progression to the lactone **(1.170)** proceeded smoothly, however in this modified

sequence addition of the enolate to give the *tert*-butyl ester did not go as planned. Instead of adding at the lactone carbonyl as one might have anticipated, addition instead occurred at the ester carbonyls giving β-ketoesters **(1.172)** and **(1.173)**.



Scheme 1.30 : Reagents and Conditions: (a) LDA, BOMCl, THF, HMPA, -78 °C (60%); (b) LDA, THF, -78 °C then MeO_2CCl (66%); (c) H_2, Pd/C, MeOH, (quant.); (d) $LiCH_2COO^tBu$.

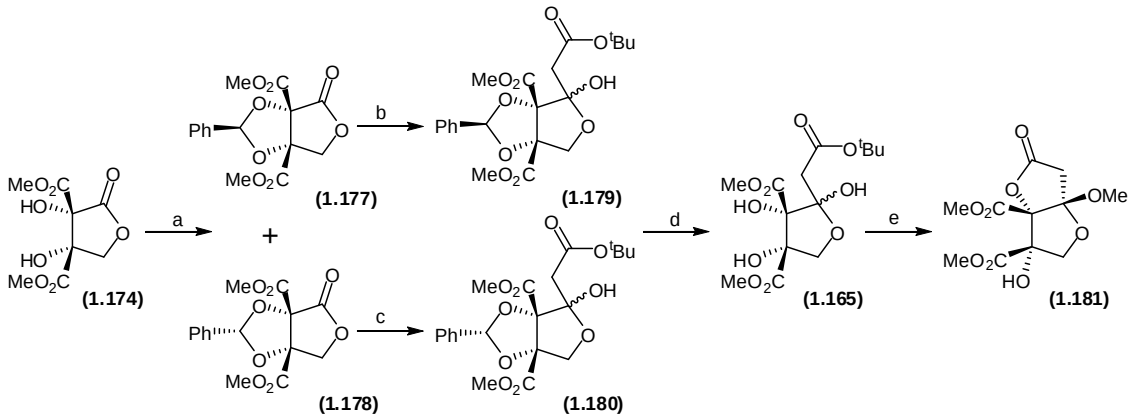
As the change in reactivity between lactones **(1.163)** and **(1.170)** can only be attributed to the altered protecting group it was hoped that a further revision to this acetal would restore the original mode of enolate addition. Lactone **(1.170)** was completely resilient to hydrolysis yet in a serendipitous turn of events attempting to deprotect uncyclised precursor **(1.168)** with TFA led not only to deprotection of the acetal, but also to the cleavage of the benzyl group, leading to formation of the desired lactone **(1.174)** as the major product (scheme 1.31).



Scheme 1.31 : Reagents and Conditions: (a) TFA, H_2O, CH_2Cl_2, sealed tube, 65 °C.

Numerous attempts were made to reprotect the diol as various acetals, esters and silyl ethers, the result was that either the formation of these would fail, or the addition of the enolate would be directed to the incorrect position. Work was also undertaken to

establish whether the action of a Lewis acid could be used to modify the site of enolate attack. The result of extensive work on optimising this sequence resulted in the following route (scheme 1.32); the diol **(1.174)** was first reprotected to give the pair of benzylidene acetals **(1.177)** and **(1.178)**, addition of the enolate proceeded at the desired position under the chelating influence of $TiCl_4$ to give the corresponding hemiacetals **(1.179)** and **(1.180)**. The benzylidene was removed by hydrogenation to give the diol **(1.165)** and this in turn underwent a relatively straightforward conversion to the lactone **(1.181)**, the stereochemistry being dictated by the thermodynamic imperative to form the favoured *cis*-fused ring system under the equilibration conditions of the reaction.



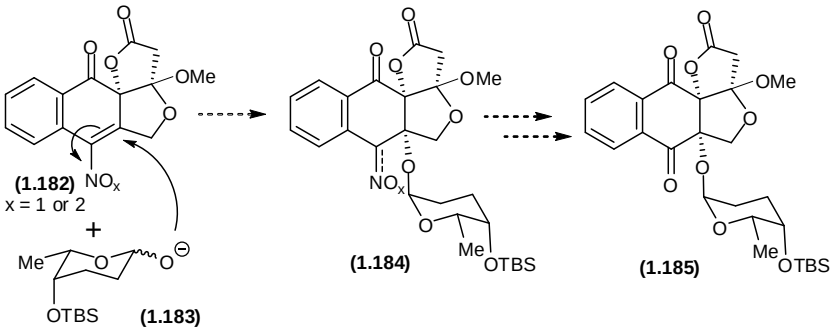
Scheme 1.32 : Reagents and Conditions: (a) PhCHO, pTSA, reflux (30% of **(1.177)** and 60% of **(1.178)**); (b) $LiCH_2COO^tBu$, $TiCl_4$, Et_2O, -40 °C (62%); (c) $LiCH_2COO^tBu$, $TiCl_4$, Et_2O, -40 °C (41%); (d) H_2, Pd/C, MeOH; (e) CSA, MeOH, reflux (63% over 2 steps).

Kelly's efforts constituted the first chiral synthesis of the AB ring system and while the brevity of the route may have suffered somewhat due to the challenges presented by the various protecting groups used, overall it is a significant piece of work. The use of a simple chiral building block such a tartrate ensures not only an elegant synthesis, but should also allow this system to be produced in significant quantity. From all the studies published on the molecule as a whole, the AB system appears to prove the most problematic area of lactonamycin synthesis making this a significant step towards a total chiral synthesis.

1.2.4 Barrett *et al.*

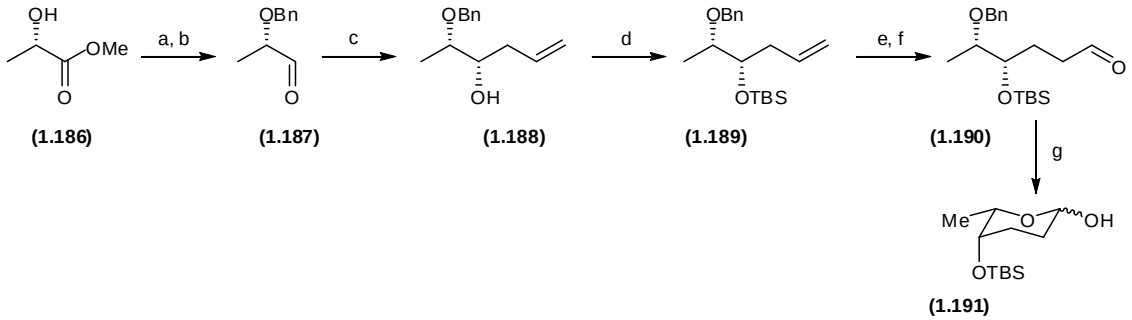
The first publication by the Barrett group concerned the development of new methodologies for tackling the problem of introducing the L-rhodinose residue at the hindered tertiary position of a lactonamycinone type system.[56] It was thought this could

be achieved by the conjugate addition of the alkoxide of the sugar to a highly reactive nitro or nitrosoalkene (scheme 1.33).



Scheme 1.33 : Proposed conjugate addition to a nitro or nitrosoalkene.

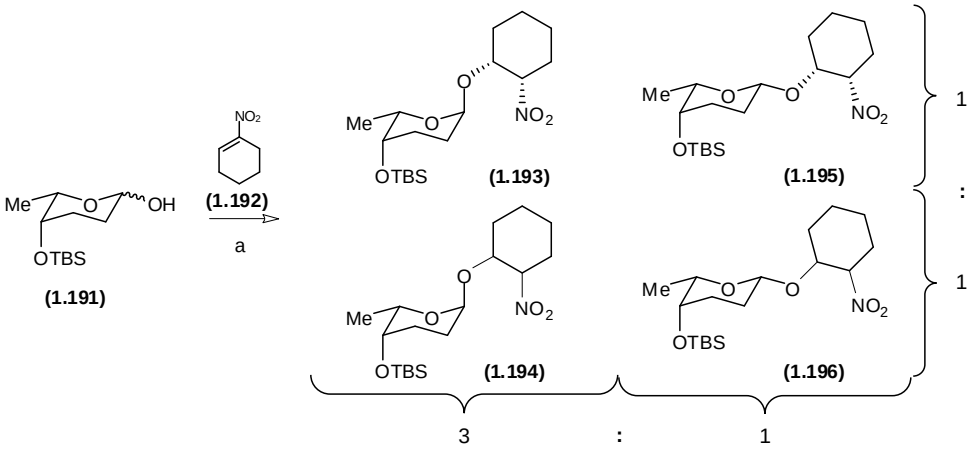
To investigate this hypothesis a series of anomeric alcohols were prepared. Barrett also proposed modifications to the procedure of Schlessinger and Graves for the synthesis of silyl-protected L-rhodinose **(1.191)**[57] that would avoid the use of pharmaceutically undesirable toxic tin and chromium reagents. Starting from methyl L-lactate **(1.186)**, the free alcohol was benzyl protected, allowing for reduction of the ester with DIBAL to give aldehyde **(1.187)**, this in turn was reacted with allylmagnesium bromide, with chelation controlling the stereochemistry of addition, yielding the desired diastereoisomer **(1.188)** in 95% d.e. Hydroboration of the double bond allowed sequential oxidation to the alcohol and then the aldehyde **(1.190)**. Hydrogenolytic debenzylation gave L-rhodinose derivative **(1.191)** after cyclisation.



Scheme 1.34 : Reagents and Conditions: (a) NaH, TBAI, BnBr, THF (85%); (b) DIBAL, CH_2Cl_2, -78 °C; (c) Allylmagnesium bromide, $MgBr_2{\cdot}Et_2O$, CH_2Cl_2, -78 °C; (d) TBSCl, imidazole, DMAP, DMF (89% over 3 steps); (e) Cyclohexene, $BH_3{\cdot}SMe_2$, THF, NaOH, H_2O_2, 50 °C (81%); (f) DMP, CH_2Cl_2 (89%); (g) H_2, Pd/C, EtOH (81%).

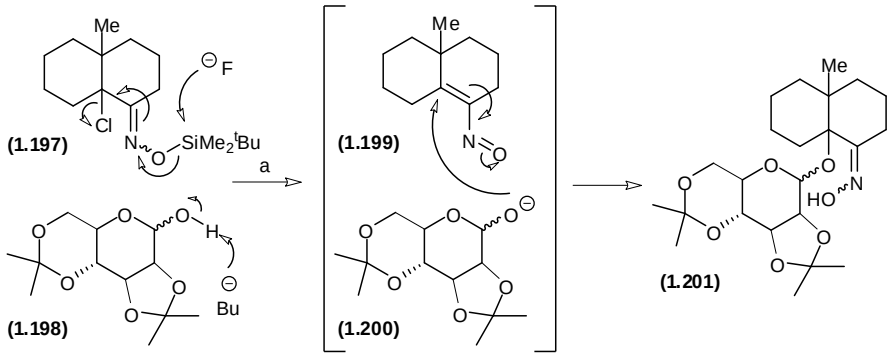
The result obtained for the addition of the rhodinose derivative **(1.191)** to nitrocyclohexene **(1.192)** (scheme 1.35) was broadly representative of the general trends noted. The sugar was first converted to the alkoxide by the addition of *n*-butyllithium, followed by addition of the nitroalkene. Quenching with acetic acid at low temperature

then gave the addition products as the mixture of isomers **(1.193)** to **(1.196)**. Yields were reasonable (44-65%) and where established there was a 3:1 or better selection in favour of the desired α-anomer. The relative stereochemistry was seen to be *cis* however no significant selectivity was noted in the absolute stereochemistry.



Scheme 1.35 : Reagents and Conditions: (a) ^{n}BuLi, THF, **(1.192)**, -10 °C to 25 °C then AcOH, -78 °C (55%).

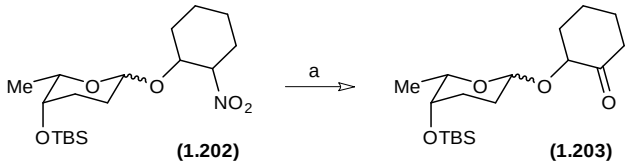
This methodology was extended to the use of nitrosoalkenes, which were generated *in situ* through a fluoride initiated elimination of an *O*-silylated α-chloro-ketoxime (scheme 1.36). This reaction was successful in the case of the analogous nitrosocyclohexene as well as the more hindered tetrasubstituted alkene **(1.199)**. The successful attack of the more hindered system gave hope that this approach may actually be a viable method for the introduction of the required residue in an equivalent lactonamycinone type construct.



Scheme 1.36 : Reagents and Conditions: (a) ^{n}BuLi, THF, -10 °C then TBAF, -78 °C (62%).

The success of these additions was then elaborated upon with the demonstration of how the resultant α-nitro or α-oximino glycosides can be converted to ketones, equivalent to the ketoglycoside unit of lactonamycin **(1.1)**. Taking alkylated rhodinose derivative **(1.202)** as the previously described 3:1 α:β mixture of anomers and exposing it to the

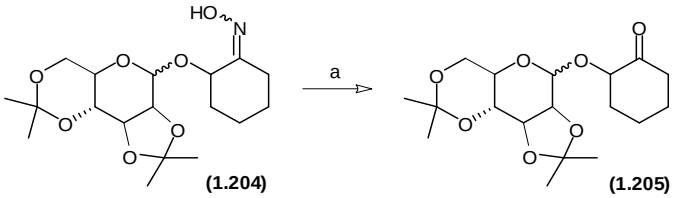
modified Nef reaction[58] conditions of Steliou and Poupart[59] allowed conversion of the nitroalkane to the ketone **(1.203)** with retention of anomeric configuration (scheme 1.37).



(1.202) **(1.203)**

Scheme 1.37 : Reagents and Conditions: (a) $KMnO_4$, KOH, $MgSO_4$, MeOH (50%).

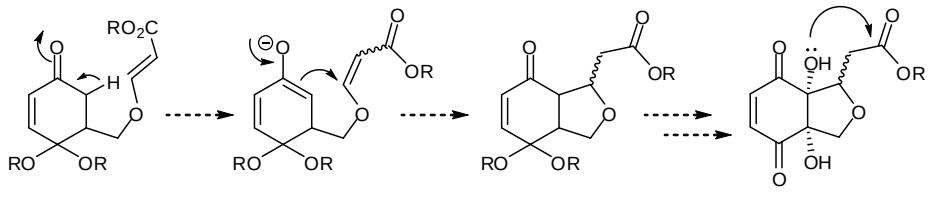
The oxime **(1.204)** resulting from the nitroso addition sequence could be converted into the corresponding ketone **(1.205)** (scheme 1.38) through oxidation with manganese dioxide. This work seemed to provide a much needed route towards forming the necessary tertiary glycosidic linkage required for any lactonamycinone based synthesis to be successful. Indeed Barrett has been able to form the viable silyloxime precursor **(1.224)** as part of his further studies on lactonamycin (*vide infra*, scheme 1.42).



(1.204) **(1.205)**

Scheme 1.38 : Reagents and Conditions: (a) MnO_2, hexane (71%).

Barrett's subsequent publication tackled the ABC ring system.[60] He proposed to form this system through the intramolecular Michael addition of a protected quinone enolate to a pendant α,β-unsaturated ester (scheme 1.39). This paper also included some mention of how to integrate the newly developed glycosidation methodology into a full synthesis.

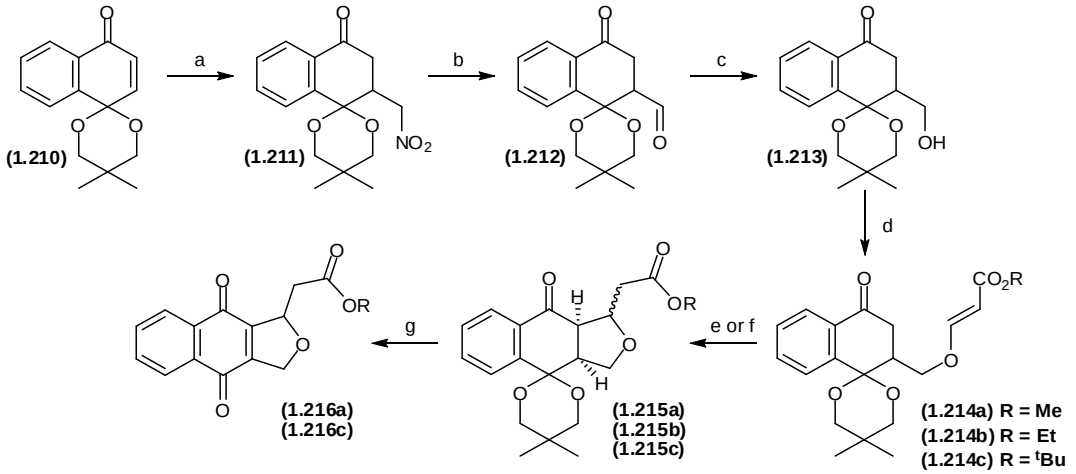


(1.206) **(1.207)** **(1.208)** **(1.209)**

Scheme 1.39 : Proposed conjugate addition sequence for the formation of the B ring.

The synthesis began with the known ketal **(1.210)**[61] which underwent a 1,4-addition with methylene nitronate to give nitroalkane **(1.211)** (scheme 1.40), this was converted to the aldehyde **(1.212)** *via* a Nef reaction and this in turn was reduced to the alcohol

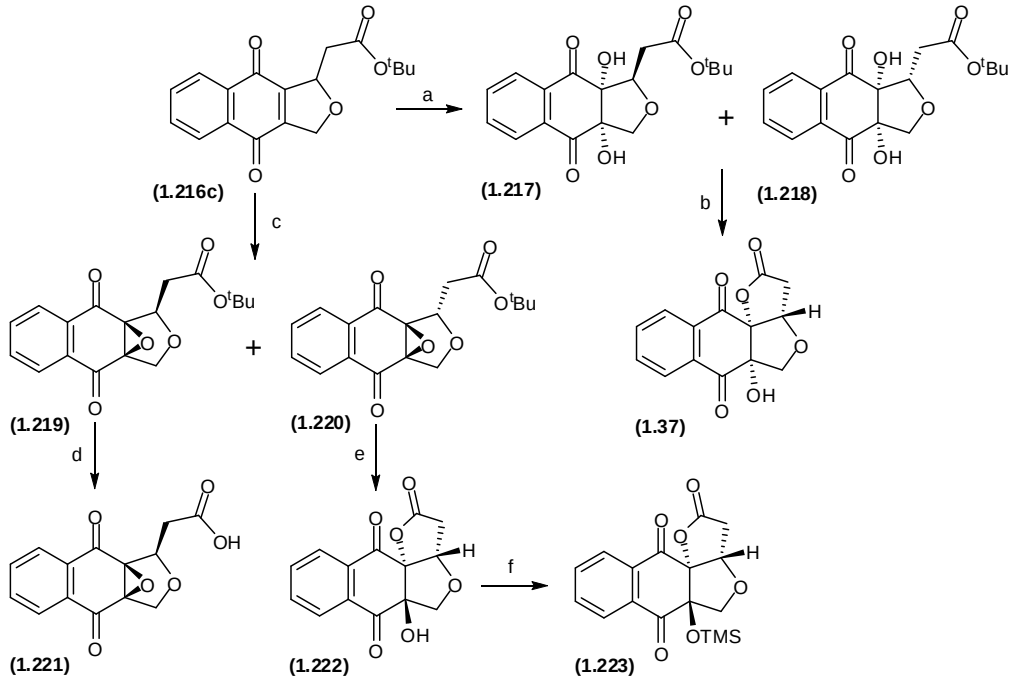
(1.213). Conjugate addition of this alcohol to a variety of propynoate esters (methyl, ethyl, and *tert*-butyl) proceeded smoothly to give enoate esters **(1.214a)**, **(1.214b)** & **(1.214c)** exclusively as their *trans* isomers. The intramolecular Michael addition was initially promoted using LDA and whilst this successfully granted access to the tetrahydrofurans **(1.215a)**, **(1.215b)** & **(1.215c)** the reactions proceeded with poor yields. Attempts to remedy this issue found that the *tert*-butyl ester **(1.214c)** could be converted in excellent yields using Barton's base[62] to provide a 4:6 syn to anti ratio of **(1.215c)**. Heating the ketals in acetic acid under an atmosphere of air allowed for the restoration of the ketone and oxidation to give quinones **(1.216a)** and **(1.216c)**.



Scheme 1.40 : Reagents and Conditions: (a) $MeNO_2$, NEt_3 (83%); (b) $KMnO_4$, KOH, MeOH (55%); (c) $NaBH_4$, MeOH (77%); (d) $HCCO_2R$, *N*-methylmorpholine, Et_2O (a = 88%, b = 74%, c = 68%); (e) LDA, THF, -78 °C to rt (a = 41%, b = 45%, c = 28%); (f) $^tBuNC(NMe_2)_2$, THF (c = 96%); (g) $AcOH/H_2O$ (7:3), 65 °C (a = 70%, c = 57%).

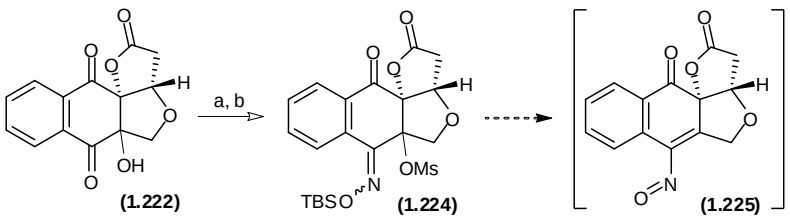
The *tert*-butyl ester **(1.216c)** was then taken forward (scheme 1.41), the first course of action saw this system undergo an Upjohn dihydroxylation to give a mixture (7:3 dr) of the diols **(1.217)** and **(1.218)** respectively. Sadly separation of the diastereomers proved impossible and as such the crude mixture was treated with TFA, the result of which was that only the minor all *cis* diastereomer underwent the necessary cyclisation to give lactone **(1.37)**. Evidence suggested that unfortunately major isomer **(1.217)** was unable to epimerise under the reaction conditions and as such simply underwent degradation to the acid without cyclising. The selectivity of the initial dihydroxylation could not be increased in favour of the desired isomer and as a result it was felt that the exploration of an alternative route might prove more rewarding. When the same *tert*-butyl ester **(1.216c)** was treated with basic hydrogen peroxide to give a mixture of epoxides **(1.219)**

and **(1.220)** (3.7:6.3 dr) these were separable and treatment of each with TFA gave the free acid **(1.221)** and the lactone **(1.222)** respectively.



Scheme 1.41 : Reagents and Conditions: (a) OsO_4, NMO, ^tBuOH (70%); (b) TFA, CH_2Cl_2 (27%); (c) H_2O_2, Na_2CO_3, THF, H_2O (93%); (d) TFA, CH_2Cl_2 (91%); (e) TFA, CH_2Cl_2 (97%); (f) TMSCl, LiHMDS, imidazole, CH_2Cl_2 (95%).

Attempts to convert lactone **(1.222)** to its epimer **(1.37)** under either basic or acid conditions were unsuccessful, however this compound was readily converted to the silyl ether **(1.223)** and these two compounds were used to conduct model studies on the introduction of the ever problematic angular methoxy group. This epimeric form would also prove equally useful if it was decided to introduce the sugar residue *via* the nitrosoalkene methodology established previously (*vide supra*, scheme 1.36). Barrett demonstrated the successful conversion of α-hydroxy ketone **(1.222)** to viable nitroso precursor **(1.224)**, however the yields were somewhat disappointing (scheme 1.42).

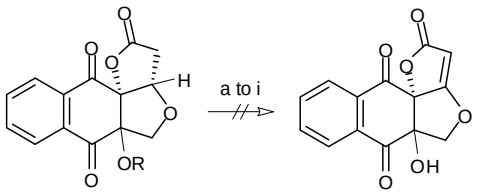


Scheme 1.42 : Reagents and Conditions: (a) 4Å MS, $TBSONH_2$, CH_2Cl_2/MeCN (10:1) 0 °C (18%); (b) MsCl, 2,6-Lutidine, CH_2Cl_2, 0 °C (51%).

Whilst the addition reaction was not attempted using this substrate, it was hoped that it would proceed with inversion of stereochemistry, this would not only be

thermodynamically favourable but hopefully kinetically favourable as the desired product would be derived from attack on the less hindered convex face of nitrosoalkane **(1.225)**.

Barrett felt (as Danishefsky initially had) that given the strain inherent in the γ-lactone ring it should be possible to install the angular methoxy group through a conjugate addition to strained butenolide **(1.226)**. Further work towards forming said butenolide was sadly fruitless. Despite trying a large selection of reagents and conditions Barrett observed only starting material or inseparable, polar mixtures (possibly the same elimination products observed by Danishefsky) (scheme 1.43). Oxidation of ester **(1.216c)** proved equally ill-fated.

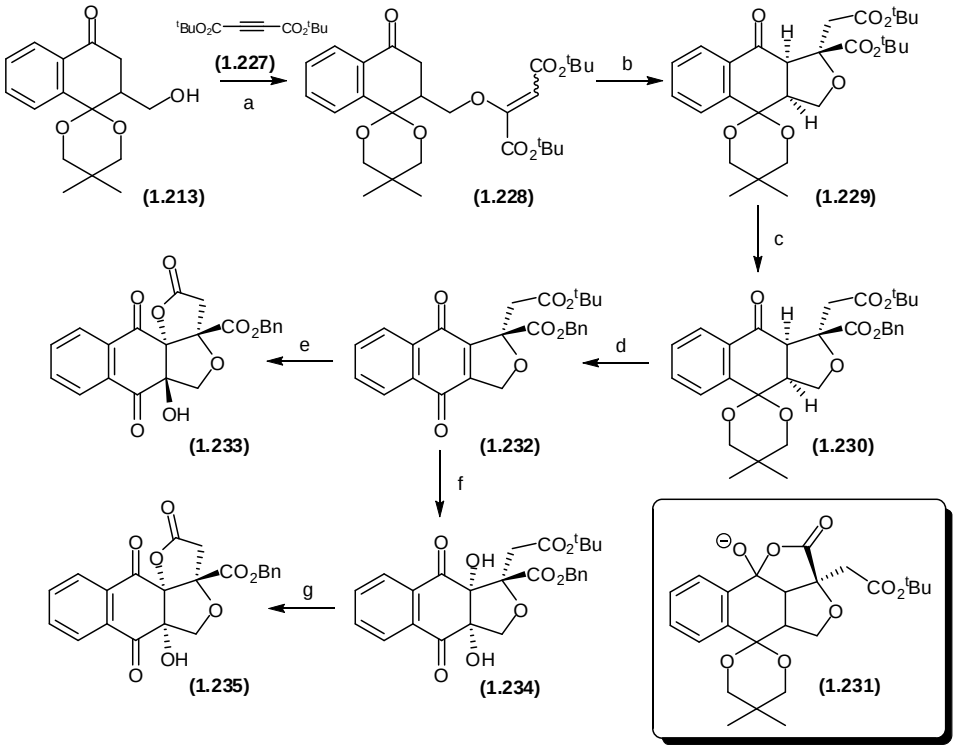


(1.222) R = H
(1.223) R = TMS

(1.226)

Scheme 1.43 : Reagents and Conditions: (a) IBX-NMO, (b) IBX-MPO, (c) Fenton's reagent, (d) $RuCl_3$ and $NaIO_4$, (e) PIDA, (f) $Pb(OAc)_4$ and I_2, (g) CrO_3 and $(Bu_4N)IO_4$, (h) O_3 and SiO_2, (i) DMDO.

Perhaps inevitably the conclusion was drawn that integration of the methoxy group was a far from simple proposition from the unadorned lactone **(1.37)** as Danishefsky found with his protracted endgame sequence (*vide supra*, scheme 1.6). Luckily for Barrett a fairly simple modification to his existing route would allow the methoxy to be incorporated early on in a concealed form. It was proposed that replacement of the alkylpropynoates of the initial route with the acetylene dicarboxylate **(1.227)** (scheme 1.44) would introduce the methoxy group masked as an ester, which could later be converted to the desired functionality through a cleavage and decarboxylation sequence. To this end, existing alcohol **(1.213)** was coupled with the di-*tert*-butyl acetylenedicarboxylate **(1.227)** catalysed by DMAP to give diester **(1.228)**, this underwent a second Michael addition when deprotonated with Barton's base to give the tetrahydrofuran **(1.229)** as the major product, the undesired epimeric product was produced only as a minor by-product.

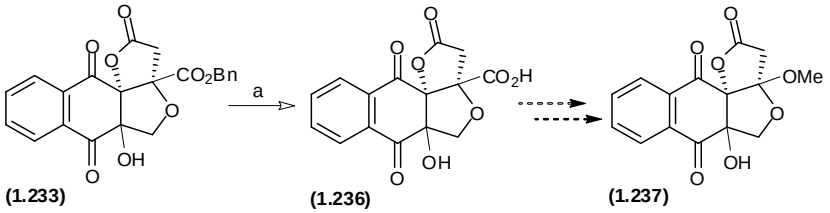


Scheme 1.44 : Reagents and Conditions: (a) **(1.227)**, DMAP (86%); (b) $^{t}BuNC(NMe_2)_2$ (65%); (c) KOH then BnBr (78%); (d) TFA, H_2O, air (70%); (e) K_2CO_3, H_2O_2, THF then TFA, CH_2Cl_2 (42%); (f) $RuCl_3$, $NaIO_4$ (64%); (g) TFA, CH_2Cl_2 (26%).

When exposed to saponification conditions the diester underwent an unforeseen transformation. Instead of the observing cleavage of the less hindered primary ester, the tertiary ester group was cleaved instead and the intermediate anion substituted with benzyl bromide to give the differentiated diester **(1.230)**. Barrett explained this unexpected reactivity as the result of the formation of 5-membered lactone alkoxide intermediate **(1.231)** activating the tertiary carboxyl. Cleavage of the ketal under an atmosphere of air resulted in the formation of quinone **(1.232)**. This quinone could be epoxidised with basic hydrogen peroxide forming a crude 1:1 mixture of epoxides which could then be converted to the *trans* lactone **(1.233)** with TFA, though this reaction proceeded in low yield so presumably only the epoxide that forms *trans* to the butyl ester will undergo cyclisation as seen previously (*vide supra*, scheme 1.41).

The quinone **(1.232)** would not react with osmium tetroxide in either catalytic or stoichiometric amounts, but the substitution of the more reactive ruthenium tetroxide species (formed *in situ* from ruthenium chloride and sodium periodate)[63] gave the desired diol **(1.234)**. In acidic solution this diol would undergo intramolecular transesterification producing the desired *cis*-lactone **(1.235)** albeit in slightly disappointing yield.

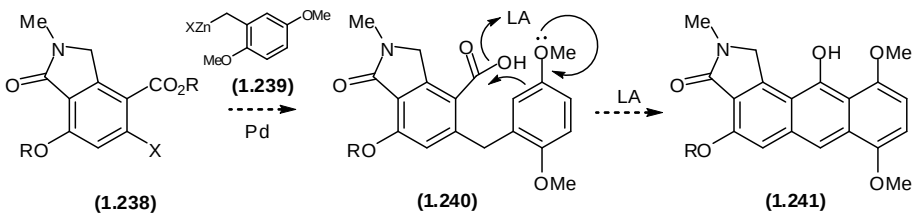
With the benzyl esters **(1.233)** and **(1.235)** in hand Barrett had suitable substrates for both his nitroso-glycosylation methodology, and a more traditional sugar coupling respectively. A brief examination of the literature showed that the *trans*-lactone could be converted to the acid **(1.236)** by transfer hydrogenation (scheme 1.45), the intention was then to use Hunsdiecker[64] or Simonini[65] chemistry to install an alkyl halide at that position followed by a displacement to introduce the methoxy group. This chemistry was not explored, presumably due to a lack of material by this point. Debenzylation of earlier intermediate **(1.230)** was also investigated with no notable success.



Scheme 1.45 : Reagents and Conditions: (a) Pd/C, cyclohexene, EtOH, 80 °C (91%).

This concluded Barrett *et al.*'s very thorough dissection of the ABC system. Synthesis of the unadorned 6,5,5-tricycle **(1.37)** does of course constitute a formal synthesis of Danishefsky's model compound **(1.45)**. The formation of oxime mesylate **(1.224)** was also a valuable indication of the viability of the earlier rhodinosylation methodology, though sadly an actual addition to this system was not demonstrated. Barrett also explored the promising introduction of the methoxy group masked as an ester, sadly this too was not quite taken to its conclusion, confidence in the route however was clearly sufficient for Barrett to proceed toward a total synthesis.

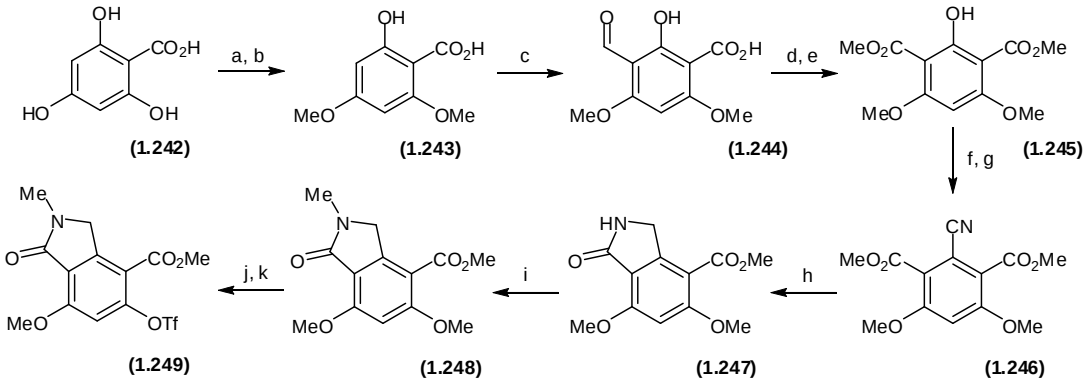
In a subsequent paper Barrett directed attention to the CDEF ring system where he envisaged forming the phenolic D ring through an intramolecular Friedel-Crafts acylation (scheme 1.46).[66] The precursor would in turn be derived from a Negishi coupling.[67]



Scheme 1.46 : Proposed Negishi coupling/Friedel-Crafts acylation route.

Synthesis of the first Negishi precursor began with the commercially available trihydroxybenzoic acid **(1.242)**, this was permethylated before one of the more electron

deficient *ortho*-methoxy groups was deprotected with boron trichloride to give the phenol **(1.243)**. Vilsmeier chemistry was used to formylate at the activated *ortho* position giving benzaldehyde **(1.244)**, which in turn was oxidised to the acid with sodium chlorite. The presence of a chlorine scavenger in the form of methylbutene was required to inhibit chlorination of the aromatic ring. The diacid was then methylated to give the diester **(1.245)** in excellent yield.

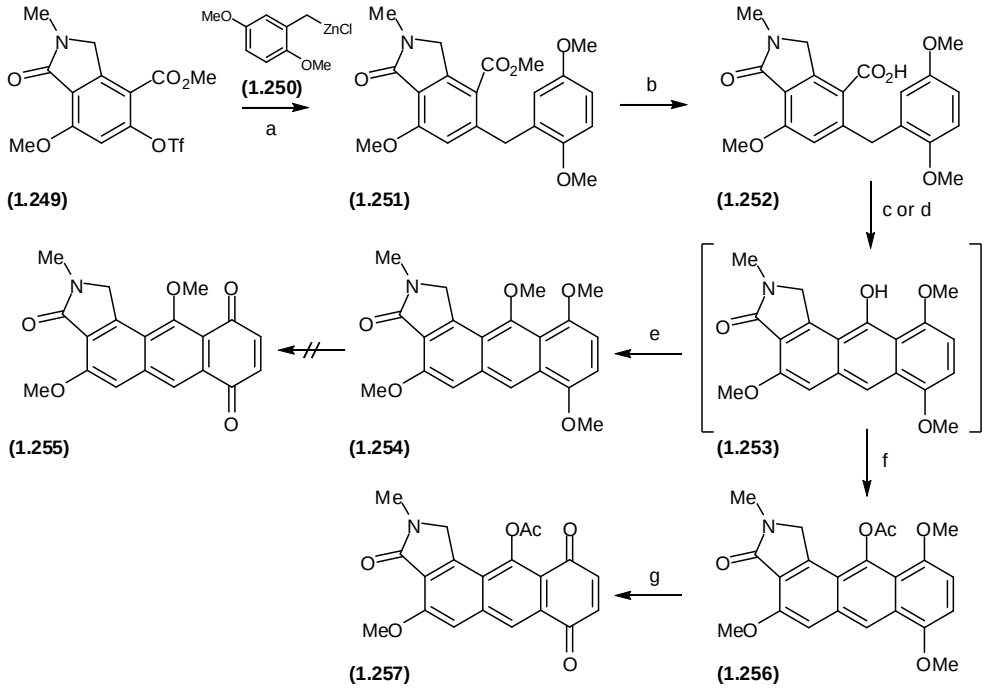


Scheme 1.47 : Reagents and Conditions: (a) Me_2SO_4, K_2CO_3, acetone (84%); (b) BCl_3, CH_2Cl_2, -78 °C (91%); (c) $POCl_3$, DMF, 0 to 25 °C (75%); (d) $NaClO_2$, NH_2SO_3H, 2-methyl-2-butene, THF, H_2O, DMSO; (e) Me_2SO_4, $KHCO_3$, DMF (94% over 2 steps); (f) Tf_2O, pyridine, CH_2Cl_2 (95%); (g) $Zn(CN)_2$, $Pd_2(dba)_3$, dppf, DMF, 60 °C (95%); (h) PtO_2, H_2, THF, AcOH, (94%); (i) NaH, MeI, DMF, 0 °C (91%); (j) BCl_3, CH_2Cl_2, -78 °C (82%); (k) $PhNTf_2$, NEt_3, CH_2Cl_2, reflux (92%).

The free phenol was converted to the triflate which underwent a cross coupling with zinc cyanide to give the benzonitrile **(1.246)**. Following the example of Behar and Deville the nitrile was reduced with cobaltous sodium borohydride (*vide supra*, scheme 1.22), however it was found that on a multigram scale the effectiveness of this method was substantially diminished. Attempts to optimise the reaction with different solvent systems and alternative transition metals all failed to produce the lactam **(1.247)** in sufficiently high yield. Hydrogenation of the nitrile however proved to be quite viable as long as stoichiometric amounts of platinum oxide were used, this method provided excellent yields and the expense was attenuated through very effective recycling of the platinum. Methylation of the lactam was carried out under standard conditions giving ether **(1.248)**. This underwent selective demethylation of the methoxy group adjacent to the ester and the resulting phenol was converted *in situ* to the triflate Negishi precursor **(1.249)**.

With this precursor in hand Barrett was eager to test the route and as such the coupling was carried out with the commercially available alkylzinc species **(1.250)** (scheme 1.48) under standard Negishi conditions giving ester **(1.251)** in excellent yield. The ester was

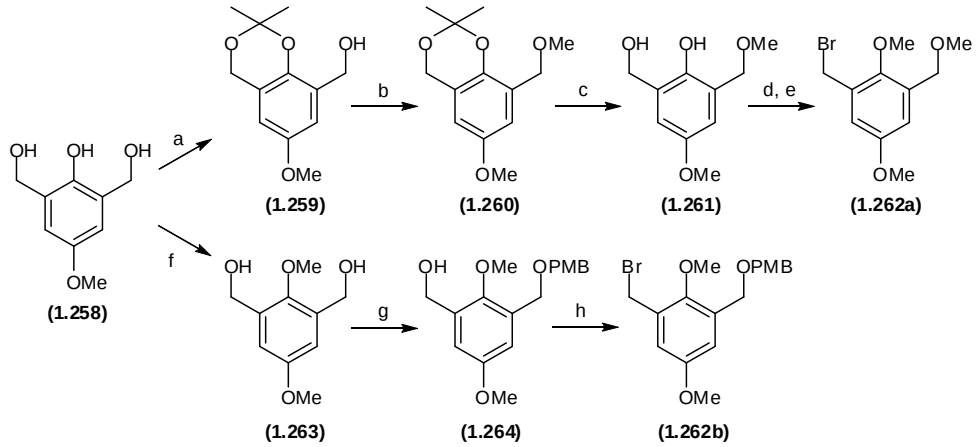
then converted to the corresponding acid **(1.252)** by saponification with lithium hydroxide in what proved to be a somewhat capricious reaction due to both the insolubility of the acid as well as its apparent instability during chromatography. Initial attempts at performing the Friedel-Crafts coupling were unsuccessful, the use of trifluoroacetic anhydride, oxalyl chloride or triflic anhydride failing to catalyse the desired reaction. However the use of polyphosphoric acid gave the required tetracycle **(1.253)**, this phenol was unstable in air however and would readily undergo oxidation to the anthraquinone, this undesired reactivity was first tempered by the *in situ* protection of the phenol as its methyl ether **(1.254).** Attempts to advance this product to the necessary quinone **(1.255)** with PIFA encountered the same difficulty as Behar in his synthesis of TcmA2[68] where the electron donating methoxy group made it favourable for oxidation to occur at the central ring rather than revealing the terminal quinone as hoped. Following Behar's example, the phenol protecting group was switched to the electron-withdrawing acetate **(1.256)**, which as predicted allowed CAN oxidation of the correct ring to give quinone **(1.257)**.



Scheme 1.48 : Reagents and Conditions: (a) **(1.250)**, $Pd(PPh_3)_4$, THF (94%); (b) LiOH, THF/MeOH/H_2O (2:1:1) (37-64%); (c) PPA, 110 °C; (d) $Me_2CC(Cl)NMe_2$, CH_2Cl_2, $ZnCl_2$; (e) Me_2SO_4, K_2CO_3, acetone, 50 °C (<30% over 2 steps); (f) Ac_2O, DMAP, pyridine (80% over 2 steps); (g) CAN, MeCN, H_2O (65%).

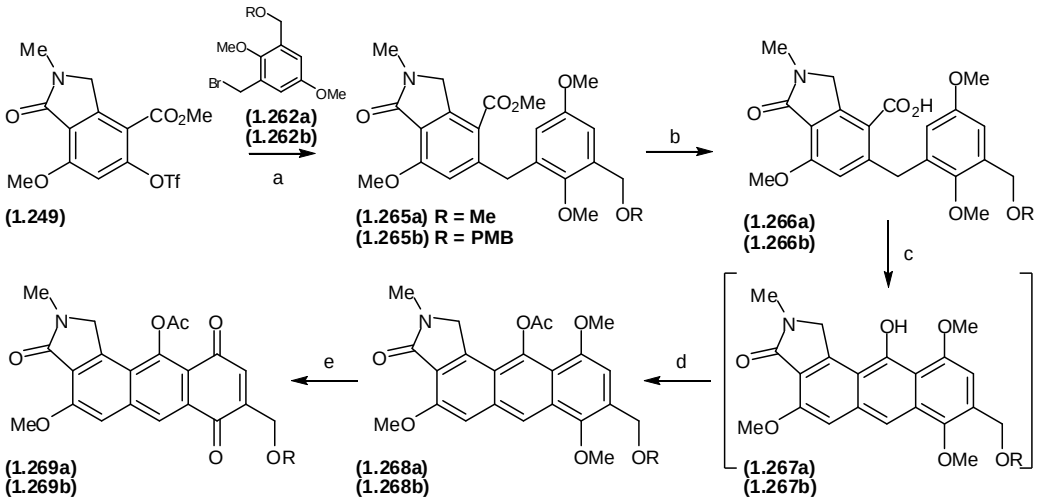
Having concisely completed the model system, Barrett wished to extend the synthesis to include a protected hydroxymethyl group on the quinone, this would then be elaborated to the full lactonamycinone system *via* a series of Michael additions (*vide supra*,

scheme 1.44). This necessitated a new Negishi coupling partner and the decision was made to synthesise two such alternatives, corresponding to different protecting groups in the final tetracyclic construct. Both syntheses began with known triol **(1.258)**[69] (scheme 1.49), towards the first Negishi substrate the triol was protected as the acetonide **(1.259)**, the remaining free alcohol methyl-protected and the acetonide hydrolysed under acidic conditions to give diol **(1.261)**, the phenolic hydroxyl was then methylated under standard conditions before the final hydroxyl group was treated with NBS and triphenylphosphine to give the benzyl bromide **(1.262a)** which would be converted to the required zinc species *in situ* (*vide infra*, scheme 1.50). The second synthesis proceeded from the same triol **(1.258)** *via* methylation of the phenolic hydroxyl. The resulting diol **(1.263)** could then be mono-protected with *para*-methoxybenzyl chloride to give benzyl alcohol **(1.264)** which was in turn converted to the benzyl bromide **(1.262b)** by treatment with carbon tetrabromide and triphenylphosphine.



Scheme 1.49 : Reagents and Conditions: (a) $Me_2C(OMe)_2$, pTSA, acetone (93%); (b) MeI, NaH, THF; (c) pTSA, THF, H_2O (98% over 2 steps); (d) Me_2SO_4, K_2CO_3, acetone; (e) NBS, PPh_3, THF (76% over 2 steps); (f) Me_2SO_4, K_2CO_3, acetone (70%); (g) NaH, PMBCl, TBAI, THF/DMF (5:1) (64% based on recovered SM); (h) PPh_3, CBr_4, THF (73%).

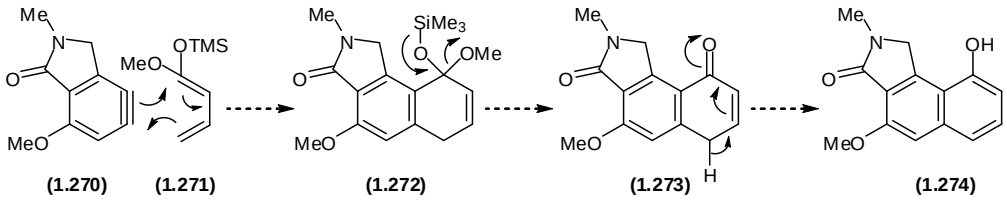
The benzyl bromides **(1.262a)** and **(1.262b)** were converted to the necessary zinc species by stirring with zinc dust with 1,2-dibromoethane acting as an initiator. The zinc species were then used *in situ* for the Negishi coupling with triflate **(1.249)** which proceeded smoothly in both instances. Saponification of both esters **(1.265a)** and **(1.265b)** proceeded in quantitative yield with none of the issues observed previously, possibly due to the side chains conferring greater solubility.



Scheme 1.50 : Reagents and Conditions: (a) **(1.262a)** or **(1.262b)**, Zn, $(BrCH_2)_2$, THF then $Pd(PPh_3)_4$ (a = 85%, b = 92%); (b) LiOH, THF/MeOH/H_2O (2:1:1) (a = quant., b = quant.); (c) $Me_2CC(Cl)NMe_2$, $ZnCl_2$; (d) Ac_2O, DMAP, pyridine (a = 82%, b = 92% both over 2 steps); (e) CAN, MeCN, H_2O (a = 61%, b = 71%).

Unfortunately treatment of acid **(1.266a)** with PPA gave only decomposition products, examination of a range of conditions concluded that using an excess of Ghosez's reagent[70] and zinc chloride as a mild Lewis acid proved most effective. The Ghosez reagent allows for the reaction to be carried out under very mild conditions, resulting in exceptional yields. The phenols **(1.267a)** and **(1.267b)** produced were once again protected *in situ* as the acetates **(1.268a)** and **(1.268b)**. Both compounds underwent CAN oxidation to give the corresponding quinones **(1.269a)** and **(1.269b)**, with only the methyl ether showing signs of anthraquinone formation as a minor (<10%) by-product.

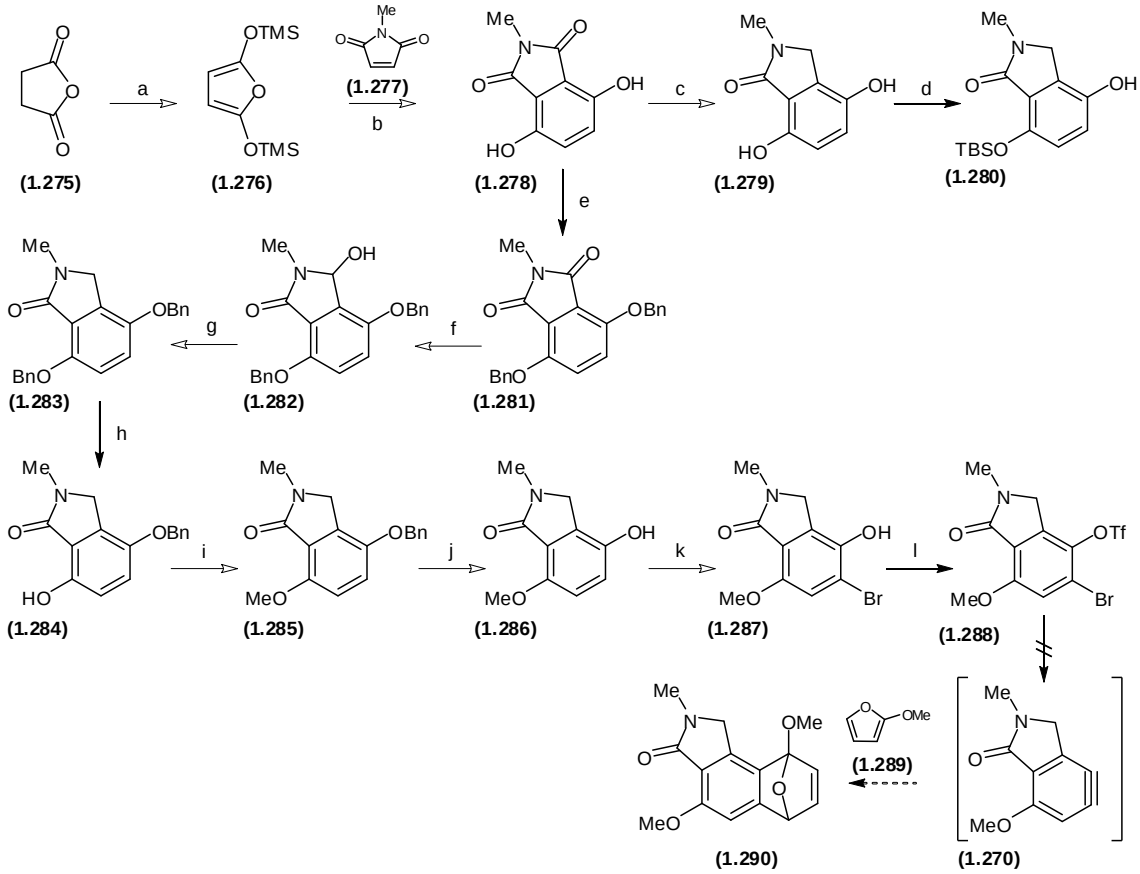
As well as this successful synthesis of the CDEF model, Barrett *et al.*[71] also published some of the alternate approaches they had taken towards these systems which whilst unsuccessful, still proved to be an edifying experience. The first of these routes focused on using benzyne intermediate **(1.270)** to form the D ring (scheme 1.51).



Scheme 1.51 : Proposed benzyne Diels-Alder route to formation of the D ring.

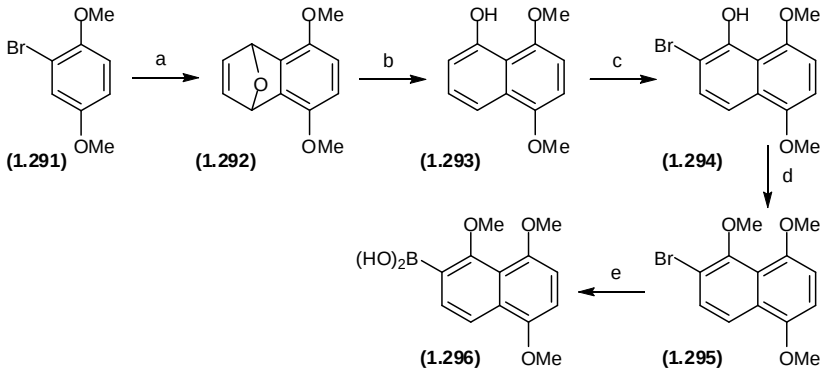
Towards this end work began to develop an appropriate benzyne precursor (scheme 1.52), despite some issues in the reduction of imide **(1.275)** to give an appropriate

lactam the synthesis of precursor **(1.288)** proceeded as planned, however attempts to generate and utilise the benzyne **(1.270)** proved to be entirely unsuccessful.



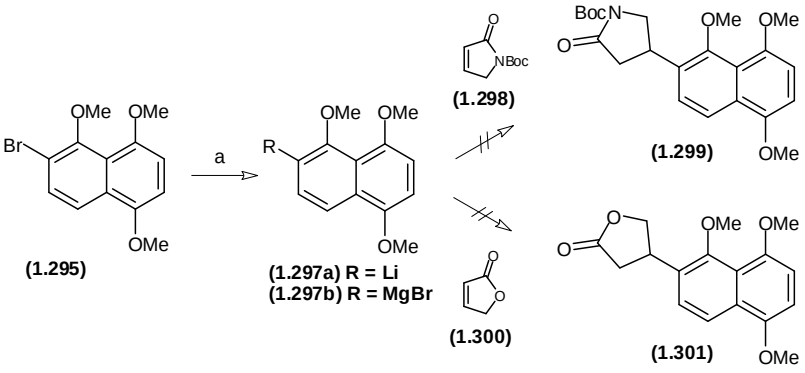
Scheme 1.52 : Reagents and Conditions: (a) NEt_3, $ZnCl_2$, TMSCl (quant.); (b) **(1.277)**, CH_2Cl_2, 40 °C then TFA, 0 °C (92%); (c) Zn/Hg, HCl, AcOH, reflux (30%); (d) ^nBuLi, TBSCl, THF, -78 °C to rt (18%); (e) Cs_2CO_3, BnBr, KI, DMF (92%); (f) $NaBH_4$, MeOH, CH_2Cl_2, 0 °C (quant.); (g) Triethylsilane, TFA, CH_2Cl_2, 0 °C (81%); (h) $MgBr_2.Et_2O$, toluene/Et_2O (6.5:1), reflux (73%); (i) MeI, K_2CO_3, acetone, reflux (91%); (j) Pd/C, H_2, MeOH, EtOAc (quant.); (k) Br_2, $NaOAc.H_2O$, AcOH (52%); (l) Tf_2O, NEt_3, CH_2Cl_2, -78 °C to rt (55%).

A second approach was developed that would mirror their successful approach (*vide supra*, scheme 1.50). This approach would also utilise a palladium mediated cross coupling, followed by a Friedel-Crafts reaction to complete the E ring (scheme 1.53).



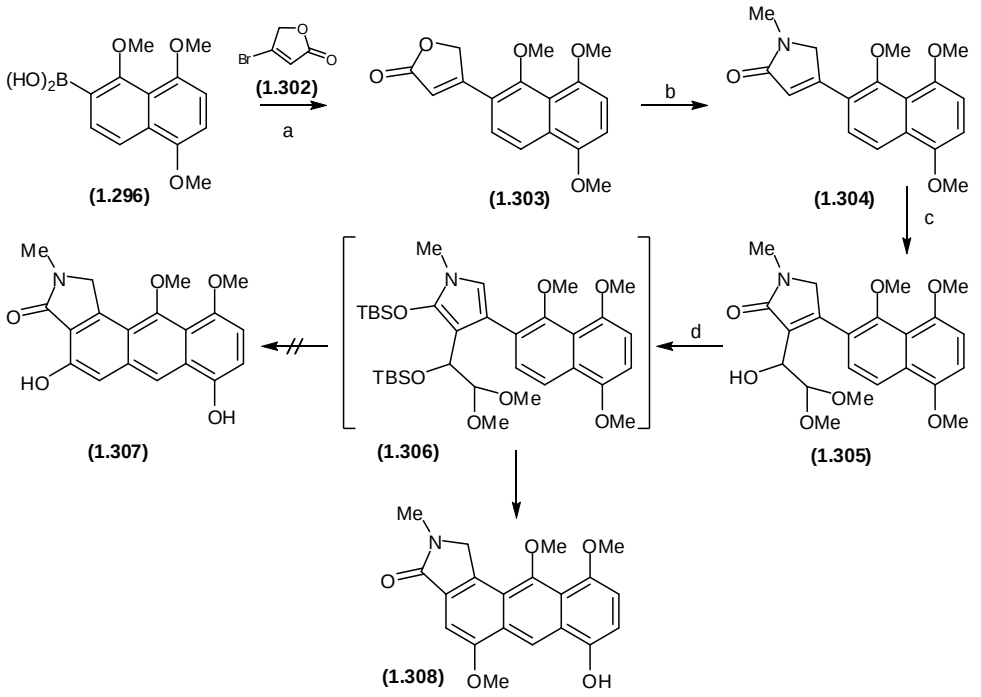
Scheme 1.53 : Reagents and Conditions: (a) $NaNH_2$, furan; (b) HCl, (93%); (c) Br_2, CH_2Cl_2, -78 °C to rt (84%); (d) MeI, Cs_2CO_3, acetone, reflux (94%); (e) ^nBuLi, $B(O^iPr)_3$, THF, -78 °C to rt then HCl (92%).

Synthesis of a suitable Suzuki coupling precursor utilised a successful benzyne cycloaddition as the key step in the generation of boric acid **(1.296)**. The initial strategy had been to convert bromide **(1.295)** into either an aryllithium or the equivalent Grignard reagent and to use this to attack a Michael acceptor such as lactam **(1.298)** or butenolide **(1.300)** (scheme 1.54). Failure of this approach was likely due to the acidity of the methylene protons in the lactam and lactone rings.



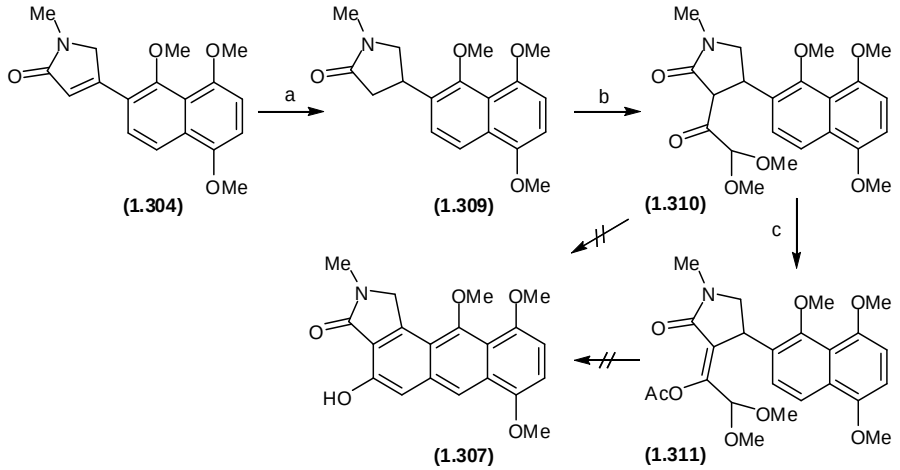
Scheme 1.54 : Reagents and Conditions: (a) Lithiate or Grignard formation.

Adaptation of this strategy to utilise a Suzuki coupling proved both straightforward and successful (scheme 1.55). Progress to dimethoxyacetal **(1.305)** was uninterrupted however attempting to perform the cyclisation on this substrate led to decomposition, concluding that this was due to the inactivating effect of the conjugated pyrrolinone carbonyl the pyrrole **(1.306)** was prepared. When the cyclisation was attempted on this compound only the undesired compound tentatively assigned as **(1.308)** resulted.[72]



Scheme 1.55 : Reagents and Conditions: (a) **(1.302)**, $PdCl_2(PPh_3)_2$, $KF_{(aq)}$, THF, reflux (91%); (b) $MeNH_2$, MeOH, 65 °C then HCl, dioxane, reflux (76%); (c) Bu_2BOTf, CH_2Cl_2, NEt_3, -78 °C then $(MeO)_2CHCHO$ (65%); (d) TMSOTf, DIPEA, CH_2Cl_2, -78 °C to rt then TBSOTf, DIPEA, 0 °C to rt then $ZnBr_2$ (32%).

This route was modified, by the reduction of pyrrolinone **(1.304)** (scheme 1.56) however the modified cyclisation precursors **(1.310)** and **(1.311)** gave only inseparable mixtures of products when exposed to the acidic reaction conditions.



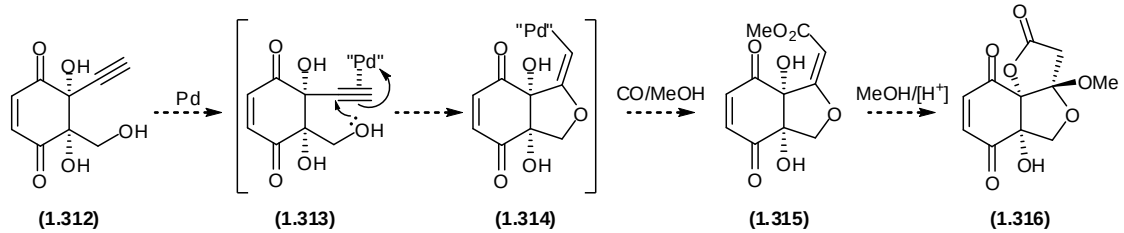
Scheme 1.56 : Reagents and Conditions: (a) Mg, MeOH, 0 °C (93%); (b) LDA, $(MeO)_2CHCO_2Me$, THF, -78 °C (69%); (c) LDA, AcCl, THF, -78 °C to rt (40%).

Whilst these alternative routes were certainly of value in shaping the form of later routes, they were ultimately superceded by the successful strategy detailed previously. Barrett *et al.*'s extensive efforts on this system do grant a particularly detailed insight

into the development of said route and a greater understanding of the chemistry of these ring systems.

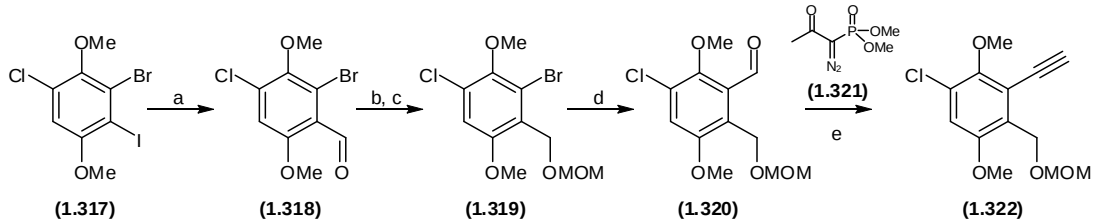
1.2.5 Nakata *et al.*

After a gap of nearly 3 years, Nakata *et al.* published a synthesis of the ABCD ring system.[73] This synthesis featured a particularly elegant construction of the racemic AB ring system (scheme 1.57). This strategy would involve the palladium catalysed intramolecular addition of a benzyl alcohol to an alkyne, which, when performed in methanol under an atmosphere of carbon monoxide would then undergo methoxycarbonylation. The resulting strained α,β-unsaturated ester should then readily undergo addition of methanol which would in turn allow lactone closure.



Scheme 1.57 : Proposed methoxycarbonylation/methanol induced cyclisation route to AB rings.

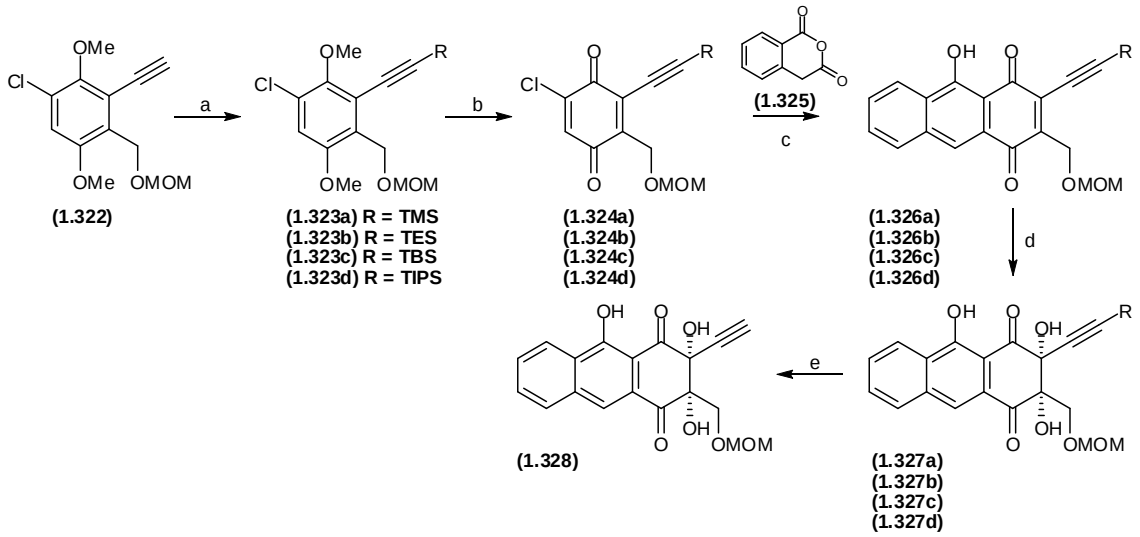
The construction of the precursor for this transformation built on the methods of a number of previous strategies towards lactonamycinone, the synthesis began with the known tri-halogenated benzene derivative **(1.317)**[74] selective lithium halogen exchange was then used to introduce a hydroxymethyl group and subsequently a formyl group to give benzaldehyde **(1.320)**. The carbonyl was then converted to the ethynylbenzene **(1.322)** with the Ohira-Bestmann reagent **(1.321)** which generates a vinyl carbene that then spontaneously rearranges to give the terminal alkyne.[75]



Scheme 1.58 : Reagents and Conditions: (a) ^{n}BuLi, toluene, -78 °C then HCO_2Me (87%); (b) $NaBH_4$, EtOH, 0 °C; (c) MOMCl, DIPEA, CH_2Cl_2 (98%, over two steps); (d) ^{n}BuLi, THF, -78 °C then HCO_2Me (90%); (e) **(1.321)**, K_2CO_3, MeOH (70%).

The alkyne was then converted to silyl alkynes **(1.323a)** to **(1.323d)** through the use of *n*-butyllithium and the corresponding silyl chloride. The silyl acetylenes were converted to the quinones **(1.324a)** to **(1.324d)** by CAN oxidation. The C ring was then appended

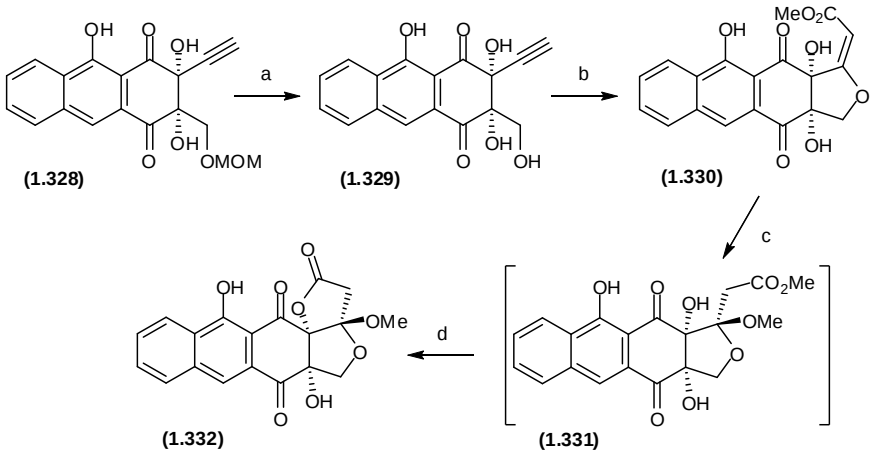
through a Tamura-Diels-Alder reaction[76] with the lithiate of homophthalic anhydride **(1.325)** akin to that used in Danishefsky's total synthesis (*vide supra*, scheme 1.15), selectivity in this case was derived from the directing effect of the chlorine.



Scheme 1.59 : Reagents and Conditions: (a) ^{n}BuLi, THF, -78 °C then TMSCl (a = 96%) or TESCl (b = 89%) or TBSOTf (c = 99%) or TIPSCl (d = 73%); (b) CAN, H_2O, MeCN (a = 92%, b = 92%, c = 85%, d = 54%); (c) **(1.325)**, LDA, THF then **(1.324a)** to **(1.324d)** (a = 51%, b = 52%, c = 58%, d = 22%); (d) $RuCl_3$, $NaIO_4$, MeCN/EtOAc/H_2O (3:3:1), 0 °C (a = 13-18%, b = 11-16%, c = 17-33%, d = 35%); (e) TBAF, THF, 0 °C to rt (from a = 93%, b = 94%, c = 98%, d = 98%).

The resulting addition products **(1.326a)** to **(1.326d)** proved to be almost entirely inert towards osmium tetroxide dihydroxylation providing only traces of the desired product, attempts to increase the rate of this reaction by pyridine coordination resulted in decomposition. Switching to a ruthenium oxide setup instead promoted limited conversion of the TMS and TES alkynes with increased amounts of oxidant resulting in decomposition rather than return of starting material in exchange for very limited increases in yield. The TBS and TIPS alkynes however were converted to the diols **(1.327c)** and **(1.327d)** in more respectable yield. Diols **(1.327a)** to **(1.327d)** were then converted to the terminal alkyne **(1.328)** in excellent yield with TBAF. After methoxymethyl deprotection the palladium (II) chloride/benzoquinone mediated cyclisation/methoxycarbonylation sequence proceeded under the mild conditions of Kato *et al.*[77] (scheme 1.60) to give the cyclised product **(1.330)** as a single stereoisomer, tentatively assigned as the Z-isomer (shown) based on the mechanism of Kato. Acid induced methanolysis of this compound resulted in an equilibrium mixture of the ring closed and ring open products **(1.331)** and **(1.332**) respectively. Redissolving the

resulting crude product in benzene and heating allowed the equilibrium to be driven entirely towards the desired ring closed system.

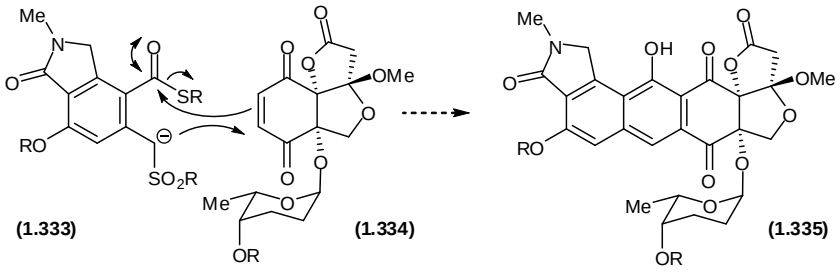


Scheme 1.60 : Reagents and Conditions: (a) TFA, CH_2Cl_2 (98%); (b) $PdCl_2$, 1,4-benzoquinone, CO, MeOH (62%); (c) CSA, MeOH, 80 °C; (d) Benzene, 80 °C (93% over 2 steps).

This synthesis of the ABCD ring system was remarkable for both its brevity and the ease with which the AB system in particular was completed. The uncomplicated introduction of the angular methoxy group which had caused so much trouble for other groups must have been particularly gratifying. One can imagine the expansion of the Tamura cyclisation to include a more developed anhydride coupling partner like that of Danishefsky (*vide supra*, scheme 1.13) which would allow synthesis of a full lactonamycinone system. The one downfall with this route would appear to be a lack of any simple means of converting it to an asymmetric synthesis.

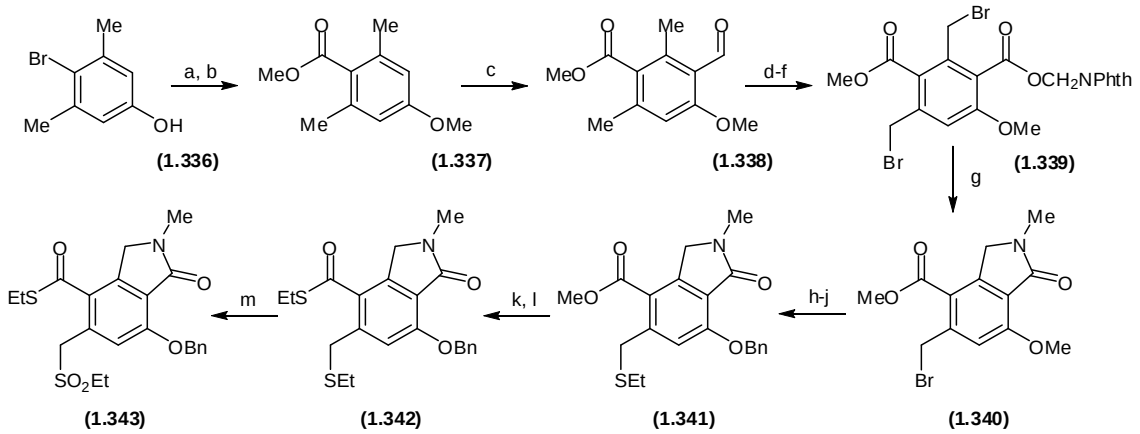
1.2.6 Tatsuta *et al.*

The first and only total synthesis of lactonamycin was described by Tatsuta *et al.* in 2010.[78] The route utilised was highly convergent with the key step a Michael-Dieckmann cyclisation between glycosylated tricycle **(1.334)** and a thioester **(1.333)** (scheme 1.61).



Scheme 1.61 : Proposed convergent Michael-Dieckmann route to the lactonamycin.

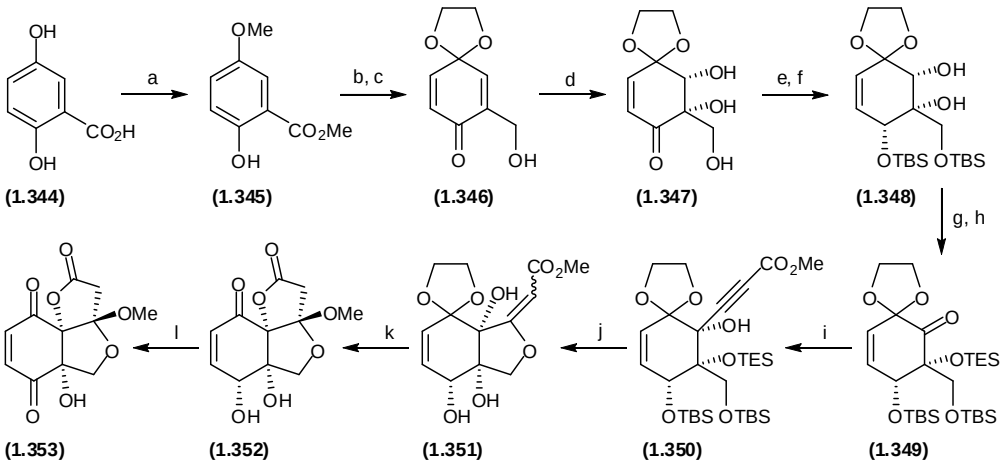
The synthesis of the required thioester **(1.343)** started from bromophenol **(1.336)** (scheme 1.62). The free phenol was initially methyl protected to allow subsequent lithiation of the bromide; addition to methylchloroformate gave methyl ester **(1.337)**. A modification of Danishefsky's formylation procedure[79] allowed conversion to benzaldehyde **(1.338)**. The aldehyde was oxidised to the corresponding acid with sodium chlorite and this acid was treated with phthalimidylmethyl bromide under basic conditions to give the phthalimidylmethyl ester, further treatment with NBS under radical conditions gave the dibromide **(1.339)**. Displacement of bromide with methylamine generated the benzylamine which underwent subsequent lactamisation to give isoindolinone **(1.340)**. The methyl ether was then cleaved with boron trichloride and the free phenol reprotected with benzyl bromide. This protection strategy allowed lactonamycin **(1.1)** to be revealed from protected derivative **(1.360)** (*vide infra*, scheme 1.66) under reductive conditions, leaving the *O*-glycosyl linkage untouched. The benzyl bromide was then converted to sulfide **(1.341)** with ethanethiol. Hydrolysis of the methyl ester was achieved with LiOH solution and the acid generated was coupled with ethanethiol using EDCI as the coupling agent, to give thioester **(1.342)**. Oxidation of the sulfur of the thioether with mCPBA gave key sulfone **(1.343)**.



Scheme 1.62 : Reagents and Conditions: (a) Me_2SO_4, K_2CO_3, acetone, 40 °C (99%); (b) $^{n}BuLi$, $ClCO_2Me$, THF, -78 °C (88%); (c) Cl_2CHOMe, $SnCl_4$, CH_2Cl_2, 0 °C (95%); (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, $H_2O/^{t}BuOH$, rt; (e) $PhthNCH_2Br$, K_2CO_3, acetone, 40 °C; (f) NBS, AIBN, CCl_4, 80 °C (40% over 3 steps); (g) $MeNH_2$, THF, rt (42%); (h) BCl_3, CH_2Cl_2, 0 °C to rt (78%); (i) BnBr, Ag_2O, MeCN, rt (78%); (j) EtSH, DBU, toluene, 60 °C (89%); (k) LiOH, H_2O, THF, 70 °C; (l) EtSH, EDCI, DMAP, CH_2Cl_2, rt (87% over 2 steps); (m) mCPBA, CH_2Cl_2, rt (73%).

The synthesis of the asymmetric portion began with 2,5-dihydroxybenzoic acid **(1.344)** (scheme 1.63). Selective methylation of the acid and the more nucleophilic phenol gave methyl ester **(1.345)**, the ester was then reduced to the alcohol with lithium borohydride before exposure to PIFA allowed ethylene glycol to undergo an oxidative addition to the

aromatic ring, generating acetal **(1.346)**. Oxidation of the more electron rich double bond with osmium tetroxide gave triol **(1.347)**.

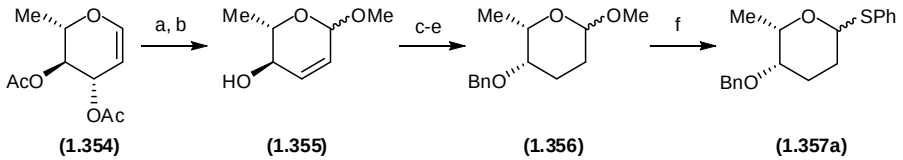


Scheme 1.63 : Reagents and Conditions: (a) Me_2SO_4, K_2CO_3, acetone, 50 °C (94%); (b) $LiBH_4$, THF, 50 °C; (c) $(CH_2OH)_2$, PIFA, CH_2Cl_2, 0 °C, (84% over 2 steps); (d) OsO_4, $NMO.H_2O$, acetone, rt (48%); (e) $NaBH_4$, MeOH, 0 °C; (f) TBSCl, imidazole, DMF, 0 °C to rt (67% over 2 steps); (g) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 °C (71%); (h) TESOTf, pyridine, rt (93%); (i) Methyl propynoate then NaHMDS, THF, -100 °C (93%); (j) TBAF, THF, rt; (k) AcCl, MeOH, 0 °C to rt then addition of toluene and concentration (55% over 2 steps); (l) IBX, CH_2Cl_2, 70 °C (94%).

Stereoselective reduction of the ketone with sodium borohydride (13:1 dr) proceeded *via* the least hindered face to give the tetraol which could then be stereoselectively silyl protected to give diol **(1.348)**. Swern oxidation of the secondary alcohol followed by TES protection of the tertiary alcohol gave ketone **(1.349)**. Addition of the anion of methyl propynoate to the carbonyl in a stereoselective fashion gave the *cis*-alcohol **(1.350)**. Global desilylation of this compound allowed the exposed primary alcohol to cyclise onto the conjugated alkyne in a *5-exo-dig* fashion to give alkene **(1.351)**. Exposure of this compound to methanol under acidic conditions added methanol in a conjugate addition to the double bond, this allowed the ester to undergo a transesterification with the adjacent secondary alcohol. The acetal was also removed under these conditions, giving lactone **(1.352)**. Oxidation of the remaining secondary alcohol with IBX gave tricyclic intermediate **(1.353)**.

The tricylic intermediate was then reacted with the activated rhodinose derivative **(1.357a)**. This derivative was prepared from commercially available 3,4-di-*O*-acetyl-L-rhamnal **(1.354)** which undergoes a Ferrier rearrangement in the presence of methanol and boron trifluoride diethyl etherate to give a methyl ether, deprotection of the remaining acetyl group with sodium methoxide in methanol gave allyl alcohol **(1.355)**. The stereocentre at the alcohol was inverted by the use of a Mitsunobu reaction to

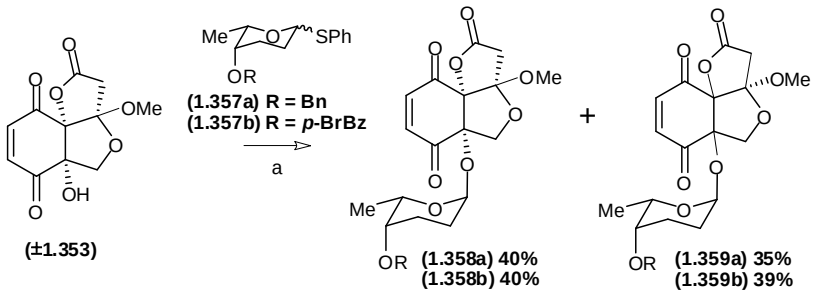
introduce a formyl ester, which was subsequently cleaved by the action of sodium methoxide in methanol, the addition of Amberlite® CG-50 allowed hydrogenation of the alkene in one pot. Protection of the free alcohol with benzyl bromide in the presence of sodium hydride gave benzyl ether **(1.356)**. This was converted to the active thio compound **(1.357a)** by displacement of the methoxy group with thiophenol in the presence of catalytic CSA.



(1.354) **(1.355)** **(1.356)** **(1.357a)**

Scheme 1.64 : Reagents and Conditions: (a) MeOH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, (73%); (b) NaOMe, MeOH, rt (84% over 2 steps); (c) HCO_2H, PPh_3, DEAD, THF, rt; (d) NaOMe, MeOH, rt then CG-50, H_2, Pd/C, MeOH, rt; (e) BnBr, NaH, THF, 60 °C (64% over 3 steps); (f) PhSH, CSA, CH_2Cl_2, rt (93%).

With the activated glycoside in hand it was possible to couple this with racemic alcohol **(±1.353)** using silver triflate as the activating agent, this gave a mixture of the glycosides **(1.358a)** and **(1.359a)** and these were separable by chromatography. *para*-Bromobenzoate derivatives **(1.358b)** and **(1.359b)** were also prepared and from this it was possible to identify the correct diastereoisomer by crystallography. Removal of the glycosyl residues with TFA allowed confirmation that glycoside **(1.358a)** displayed the correct stereochemistry and this compound was carried forwards.

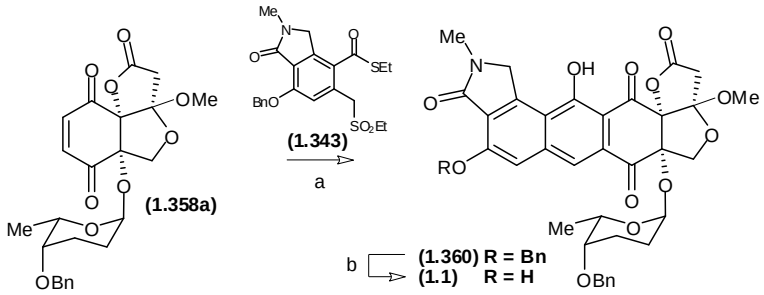


(±1.353)

Scheme 1.65 : Reagents and Conditions: (a) 2-Cyclohexenone, AgOTf, 4Å MS, CH_2Cl_2, -40 °C to rt.

With the chiral glycoside **(1.358a)** and thioester **(1.343)** in hand, Tatsuta completed lactonamycin in just two further steps (scheme 1.66). The thioester was added to a mixture of glycoside **(1.353a)** and KHMDS allowing the predicted Michael-Dieckmann condensation to occur. If criticism were necessary then the selectivity of the final addition would be questionable with very little to distinguish the two ends of the quinone, the low yield and lack of comment to the contrary would seem to support this

notion. The benzyl-protected lactonamycin **(1.355)** that resulted could be deprotected by hydrogenation over palladium black to give lactonamycin **(1.1)**.



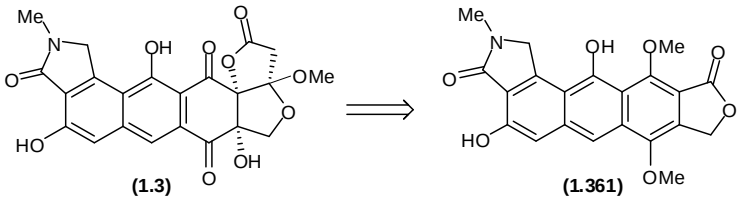
Scheme 1.66 : Reagents and Conditions: (a) **(1.343),** KHMDS then **(1.358a)**, THF, -78 °C to reflux (37%); (b) H_2, Pd/C, THF, rt (40%).

This was a substantial achievement for Tatsuta *et al.*; providing a solution to all three areas of lactonamycin's challenge in such short order was an impressive feat. The methodology for the incorporation of the sugar was also made to look a remarkably uninvolved process given the extensive concern it had generated on the part of other investigators. The resolution of the material evolved from the racemically generated *cis* diol was a particular highlight of the approach. However at 34 discreet steps, the synthesis leaves significant room for improvement and as ever the more useful information to the synthetic chemist is often the details of what didn't work on a given system.

1.3 Previous Work Within the Parsons Group.

1.3.1 Model Studies for the Synthesis of Lactonamycin.

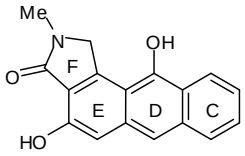
A retrosynthetic analysis of lactonamycin by Parsons *et al*. had led to the conclusion that the chiral AB(C) ring system of lactonamycin **(1.1)** could be derived from the relatively simple pentacyclic system **(1.361)** (scheme 1.67).



Scheme 1.67 : Partial retrosynthesis of lactonamycin, identification of a key intermediate.

It was also thought that the (C)DEF ring system might be prepared relatively simply, as exemplified by the efforts of other groups. Specifically it was thought that the largely planar portion of the molecule might be efficiently constructed through a palladium or radical mediated cascade sequence. With this in mind the tetracyclic construct **(1.362)**

was selected as a model target.



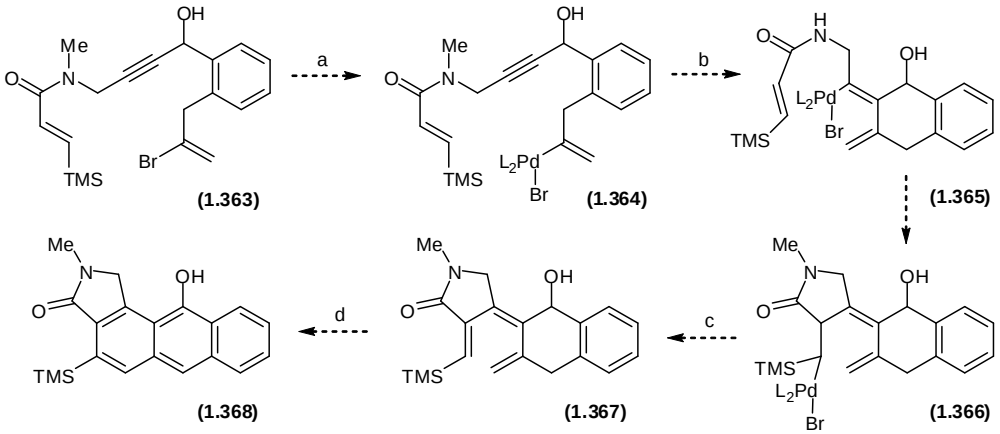
(1.362)

Figure 1.8 : A model (C)DEF ring system.

The bulk of the work on the Lactonamycins was carried out by John Board,[80] with the bulk of the associated mechanistic studies (and some minor total synthesis work) carried out by Alexander J. Waters.[81] Ongoing work is being carried out by Davide Faggiani,[82] Lee Walsh and the author. To date three publications have been presented by Parsons *et al.* on this work.[83]

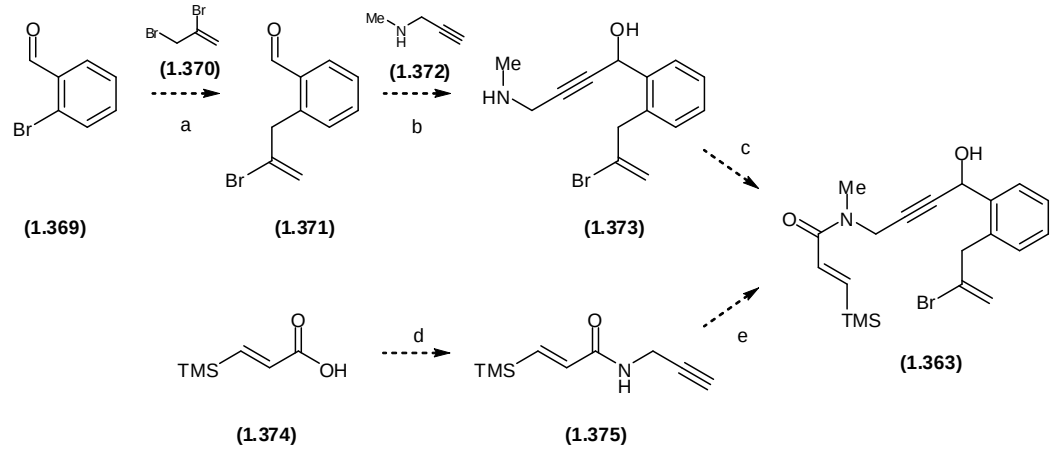
1.3.2 A Palladium Cascade.

It was originally suggested that the amide **(1.363)**, when treated with a palladium (0) catalyst would undergo a series of insertions generating the triene **(1.367)** which would then undergo a Cope rearrangement[84] followed by aromatisation to give the tetracycle **(1.368)** (scheme 1.68).



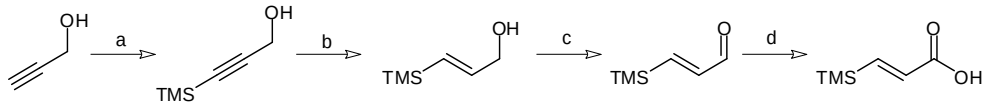
Scheme 1.68 : Proposed palladium mediated cascade mechanism: (a) Oxidative addition, (b) Cyclisation cascade (c) β-elimination, (d) Cope rearrangement and aromatisation.

Two routes to target molecule **(1.363)** were proposed, one a slightly more convergent variant of the other and both were investigated (scheme 1.69).



Scheme 1.69 : Proposed routes to a cascade precursor: (a) *Ortho* metalation then **(1.370)**; (b) **(1.372),** ^{n}BuLi then **(1.371)**; (c) Amide formation with **(1.374)**; (d) Amide formation with **(1.372)**; (e) ^{n}BuLi then **(1.371)**.

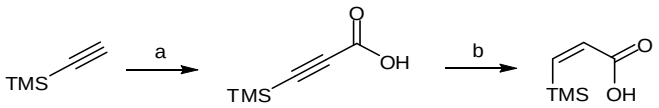
Formation of the *trans*-3-trimethylsilanylacrylic acid **(1.374)** was common to both routes and was investigated first. Despite an abundance of published protocols for the synthesis of the acid,[85] it was felt that improvement was possible, specifically in the avoidance of highly toxic reagents and the development of reproducible yields. After some optimisation an effective and reliable route was developed (scheme 1.70). Propargyl alcohol **(1.368)** could be doubly deprotonated with *n*-butyllithium and this dianion would preferentially undergo silylation on carbon to give the terminal silane **(1.369)**. The *trans* reduction product **(1.378)** was obtained exclusively when the alkyne was reduced with Red-Al®.[86] A two step alcohol oxidation protocol proved most effective with conversion to the aldehyde **(1.379)** achieved using MnO_2 and then a further increase in oxidation level was achieved through the use of sodium chlorite, which worked cleanly in the presence of an alkene acting as a chlorine scavenger. This gave the desired acid **(1.374)**. The key to increasing the efficiency of this synthesis was the ability to go from propargyl alcohol to the target acid with very little workup, as the volatility of the intermediates resulted in a pernicious effect on the yield.



Scheme 1.70 : Reagents and Conditions: (a) ^{n}BuLi, TMSCl, THF, -78 °C (98%); (b) Red-Al, Et_2O; (c) MnO_2, CH_2Cl_2, reflux then partial removal of solvent; (d) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, ^{t}BuOH/H_2O (2:1) (69% over 3 steps).

The *cis* isomer of the acid was also prepared. Following the literature precedent,[85c,87] this was achieved by the partial hydrogenation of the alkynoic acid **(1.381)** using

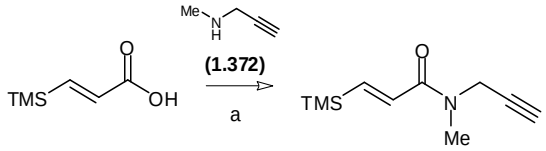
Lindlar's catalyst that was further deactivated by the presence of quinoline, this gave the acid **(1.382)** (scheme 1.71). This reduction however proved to be somewhat capricious with a tendency to produce a mixture of over-reduced product and starting material. As such it was never possible to produce sufficient material for a viable synthesis.



(1.380) **(1.381)** **(1.382)**

Scheme 1.71 : Reagents and Conditions: (a) MeLi, Et_2O then $CO_{2(s)}$ (36%); (b) H_2, Lindlar's catalyst, quinoline, hexane (42%).

Thankfully the *trans*-acid **(1.374)** successfully coupled to *N*-methylpropargylamine to give the amide **(1.375)** and after some optimisation the most successful protocol was found to use isobutyl chloroformate as a coupling agent, delivering the amide in high yield.

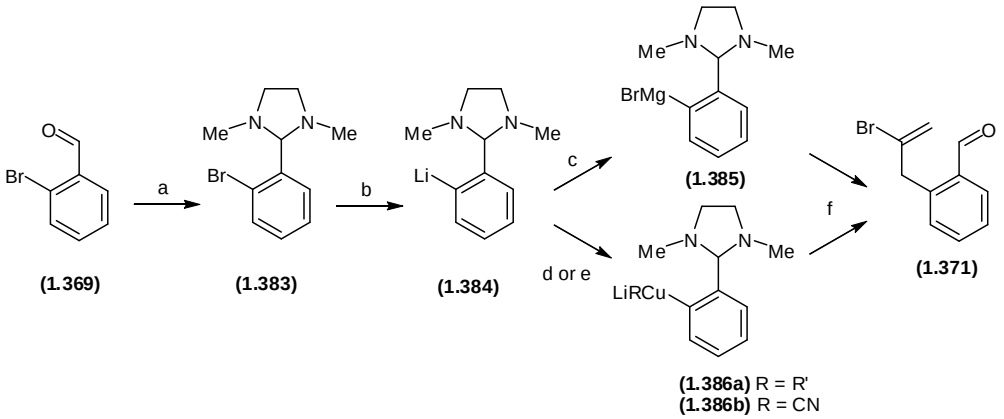


(1.374) **(1.375)**

Scheme 1.72 : Reagents and Conditions: (a) $ClCO_2{}^{i}Bu$, *N*-methylmorpholine, THF, 0 °C to rt then **(1.372)**, 0 °C to rt (74%).

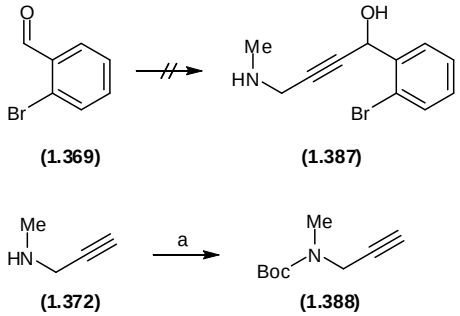
With the amide in hand work on the benzaldehyde **(1.371)** began. Taking the readily available 2-bromobenzaldehyde **(1.369)** it was apparent from the work of Harris *et al.*[88] and Corriu *et al.*[89] that conversion of the aldehyde into an aminal, would allow the formation of the lithiate under relatively mild conditions. Synthesis of the known aminal **(1.383)**[90] proceeded smoothly (scheme 1.73). However it was shown that as predicted by Snieckus *et al.* the lithiate **(1.384)** would not displace the allyl bromide of 2,3-dibromopropene, instead simply abstracting bromine and returning the starting aminal.[91] As such the lithiate was exposed to magnesium bromide etherate, undergoing a transmetalation, to give the Grignard reagent **(1.385)**, upon addition of 2,3-dibromopropene, this species did undergo the required addition and with an acidic workup the labile aminal was removed to give the desired benzaldehyde **(1.371)**. However the early success with this reaction was misleading and subsequent attempts would show it to be entirely unreliable. Frustration with this route led Board to examine alternative transmetalations principally those involving copper salts. Indeed transmetalation with cuprous iodide gave a classic Gilman cuprate **(1.386a)** and

produced the desired product in respectable yield. However the yield restrictions imposed by the formation of the dialkylcopper Gilman system led to the use of the mixed cuprate **(1.386b)** formed by transmetalation with cuprous cyanide. This brought the yield of the reaction to a more practical 73%.



Scheme 1.73 : Reagents and Conditions: (a) *N*,*N*'-Dimethylethylenediamine, EtOH (91%); (b) ^{n}BuLi, THF, -78 °C; (c) $MgBr_2.Et_2O$, -78 °C to rt; (d) CuI, -78 °C; (e) CuCN, -78 °C to -40 °C; (f) 2,3-dibromopropene, -78 °C to rt then HCl, H_2O (79% from **(1.383)** *via* **(1.385)**, 40% *via* **(1.386a)**, 73% *via* **(1.386b)**.

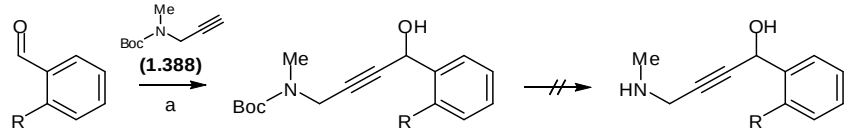
Whilst work toward 2-allylbenzaldehyde **(1.371)** was underway, the integration of the side chain was also being examined, however due to a paucity of the fully functionalised benzaldehyde 2-bromobenzaldehyde **(1.369)** was used for the optimisation of this chemistry. It was initially assumed, quite reasonably, that it may be possible to simply deprotonate the terminal position of *N*-methylpropargylamine **(1.372)** with butyllithium and that this lithiate would undergo 1,2-addition at the carbonyl of benzaldehyde **(1.369)** (scheme 1.74). Attempts at such a reaction yielded only decomposition products and this was attributed to unanticipated competitive deprotonation of the amine proton. In order to counteract this the amine was protected as the carbamate **(1.388)** using di-*tert*-butyl dicarbonate.



Scheme 1.74 : Reagents and Conditions: (a) Boc_2O then *N*,*N*'-dimethylethylenediamine, CH_2Cl_2 (95%).

The now-protected amine was successfully converted to the lithiate with *n*-butyllithium and this underwent the required addition to both bromobenzaldehyde **(1.369)** and

bromoallylbenzaldehyde **(1.371)** (scheme 1.75), giving the corresponding alcohols **(1.389a)** and **(1.389b)** in good yields. Initial attempts revealed the removal of the Boc group to be a more challenging proposition than expected; treatment with a large excess of acid failed to reveal the amine functionality.



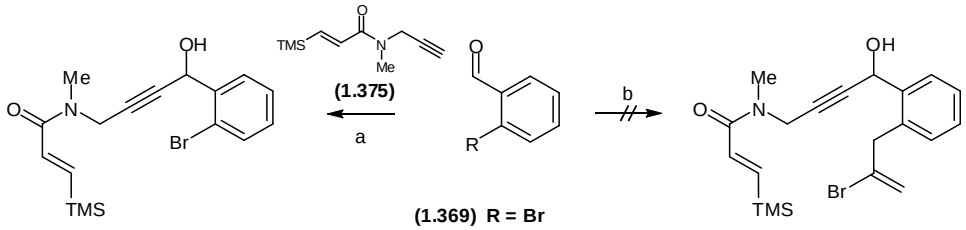
(1.369) R = Br
(1.371) R = CH_2CBrCH_2

(1.389a) R = Br
(1.389b) R = CH_2CBrCH_2

(1.387) R = Br
(1.390) R = CH_2CBrCH_2

Scheme 1.75 : Reagents and Conditions: (a) **(1.388)**, ^{n}BuLi then **(1.369)** or **(1.371)** then ^{t}BuBr, THF, -100 °C (80% from **(1.369)**, 65% from **(1.371)**).

Hampered by this inability to deprotect the Boc group the alternate side chain addition methodology was investigated and the preformed amide **(1.375)** was to be used instead (scheme 1.76). Substitution of this for the Boc-propargylamine **(1.388)** in the existing methodology gave the aryl bromide **(1.391)** in moderate yield. However the use of the allylbenzaldehyde **(1.371)** resulted in no product at all.



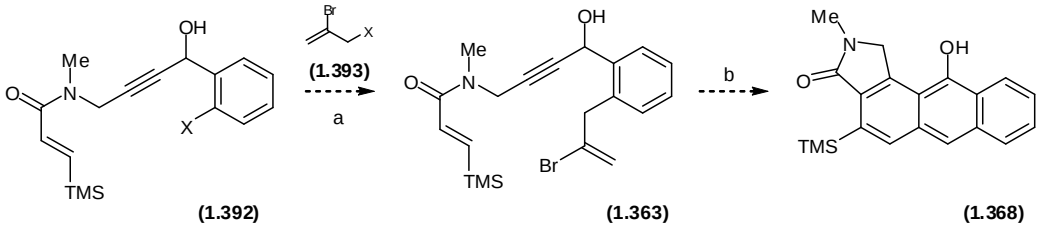
(1.391)

(1.369) R = Br
(1.371) R = CH_2CBrCH_2

(1.363)

Scheme 1.76 : Reagents and Conditions: (a) **(1.375)**, ^{n}BuLi then **(1.369)** then ^{t}BuBr, THF, -100 °C (73% yield based on recovered SM); (b) **(1.375)**, ^{n}BuLi then **(1.371)** then ^{t}BuBr, THF, -100 °C.

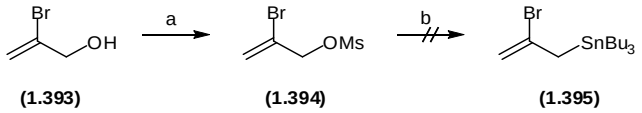
After the trouble encountered in forming allylbenzaldehyde **(1.371)** and also in advancing the Boc-protected intermediate **(1.389b)** the idea of using a Stille coupling[92] was briefly entertained, however it was hoped that not only could it be used to attach the bromopropene unit, but that if the amide side chain was already in place then the palladium based Stille catalyst may also go on to facilitate the palladium cascade (scheme 1.77).



(1.392) **(1.363)** **(1.368)**

Scheme 1.77 : Proposed Stille coupling/palladium mediated cascade sequence: (a) Stille coupling with suitable allyl bromide/stannane, (b) Palladium cascade facilitated by Stille catalyst.

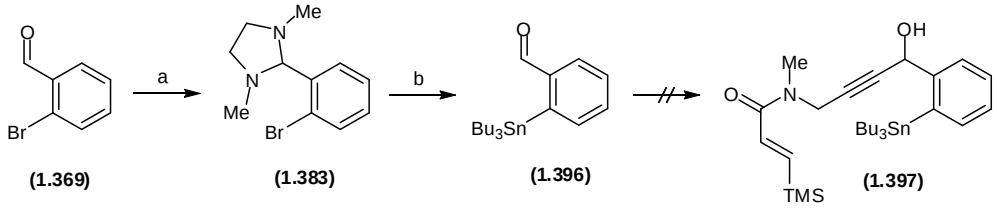
With the aryl bromide **(1.391)** already available and the required tin compound reported in the literature by Corey *et al.*[93] it was thought this route would be relatively simple to follow. However whilst conversion of the allyl alcohol **(1.393)** to the mesylate **(1.394)** was straightforward (scheme 1.78), displacement with tributylstannyllithium[94] failed to deliver the allylstannane **(1.395)**.



(1.393) **(1.394)** **(1.395)**

Scheme 1.78 : Reagents and Conditions: (a) MsCl, NEt_3, CH_2Cl_2, 0 °C (71%); (b) Bu_3SnCl, LDA, THF, -10 °C then CuBr.DMS, -70 °C then **(1.394)**, THF, -78 °C.

Whilst the failure to synthesise the allylstannane was disappointing the reversed Stille coupling was still a possibility (scheme 1.79) and the stannyl benzaldehyde **(1.396)** was also known in the literature.[95]



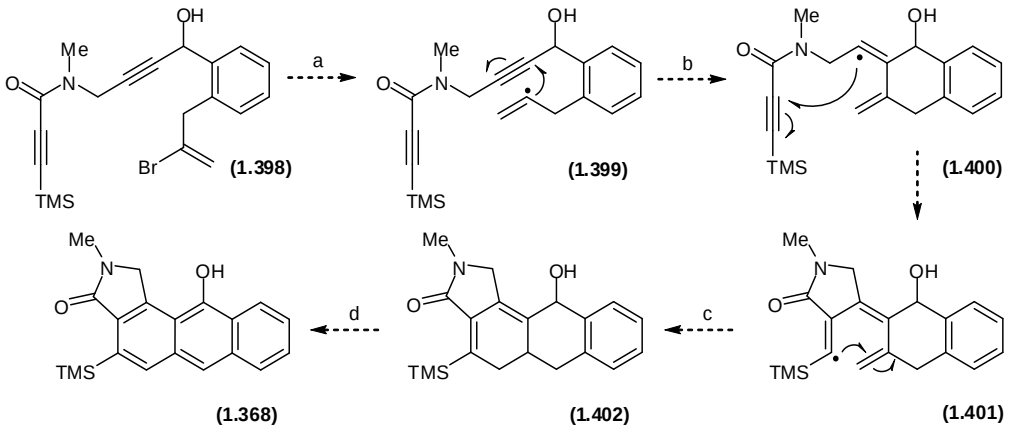
(1.369) **(1.383)** **(1.396)** **(1.397)**

Scheme 1.79 : Reagents and Conditions: (a) *N*,*N*'-dimethylethylenediamine, EtOH (91%); (b) $^{n}BuLi$, Bu_3SnCl, Et_2O then HCl (75%).

This work was easily replicated to derive the arylstannane but introduction of the side chain by the established method was unsuccessful. This led to a hiatus in the development of the palladium cascade routes and subsequent success along alternate lines would ultimately lead to its abandonment.

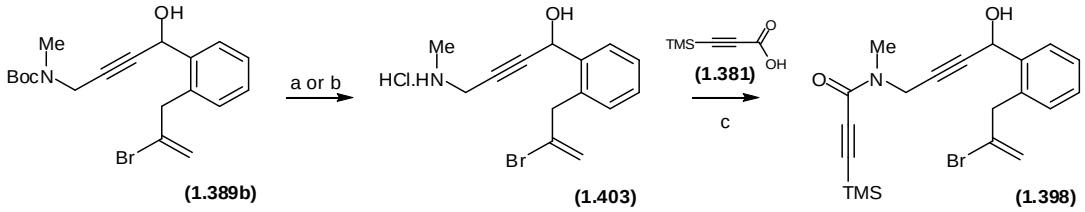
1.3.3 A Radical Cascade.

The continuing difficulties posed by the palladium cascade route led to the development of the second of the originally planned routes, the radical cascade. It was apparent that a lot of the methodology developed for the construction of the palladium cascade precursor **(1.363)** would be directly transferable to the new target. In fact only one subtle change was required, where the palladium route required an alkene adjacent to the silyl residue (to facilitate elimination), a radical sequence could utilise an alkyne (scheme 1.80). This would both shorten and simplify the route by avoiding the use of the unstable acrylates.



Scheme 1.80 : Proposed radical cascade mechanism: (a) Radical initiation; (b) Cyclisation cascade; (c) Radical quenching; (d) Aromatisation.

Further investigation into the deprotection of the carbamate **(1.389b)** eventually resulted in an effective protocol for its removal. Treatment with HCl in dioxane or ether gave the ammonium salt **(1.403)** which readily coupled with the acid chloride of trimethylsilylpropynoic acid **(1.381)** generated *in situ* to give the enediyne **(1.398)** in a succinct sequence.

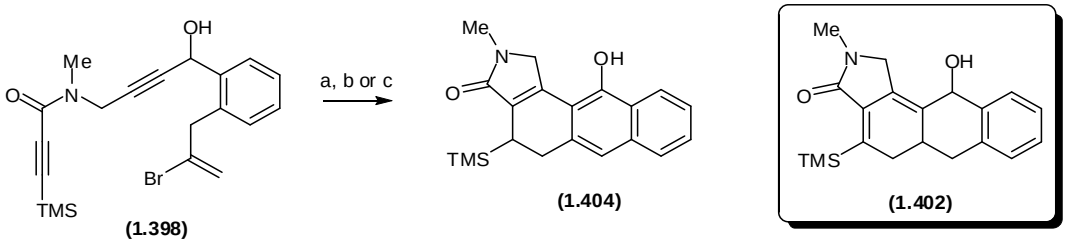


Scheme 1.81 : Reagents and Conditions: (a) HCl, dioxane, CH_2Cl_2 (47%); (b) HCl, Et_2O (77%); (c) **(1.381)**, $(COCl)_2$, DMF then **(1.403)**, NEt_3, CH_2Cl_2 (86%).

1.3.4 A Novel Cyclisation Reaction.

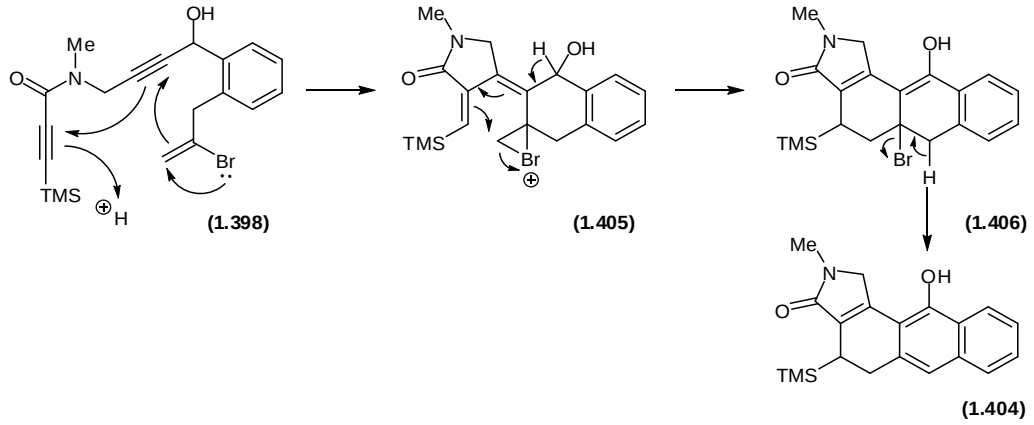
The enediyne was then subjected to radical cyclisation conditions using tributyltin hydride and AIBN as the initiator, the product of this reaction however was quite distinct from the radical cyclisation product **(1.402)** that had been predicted (*vide supra*, scheme 1.80). The compound that in fact resulted was the tetracycle **(1.404)** in poor yield and with an exceptionally messy reaction profile (scheme 1.82). Whilst attempting to improve the yield of this cyclisation a thermal decomposition study was carried out by simply heating the precursor in benzene. It was found that even in the absence of tributyltin hydride the tetracyclic lactam was still produced and in increased yield! As the reaction was clearly not occurring *via* the originally proposed radical mechanism, the reaction was carried out utilising BHT as a radical inhibitor.[96] The success of this reaction appeared to confirm that not only was the desired reaction not radical in nature,

but a further increase in yield suggested that there may be one or more detrimental reaction pathways that were.



Scheme 1.82 : Reagents and Conditions: (a) Bu_3SnH, AIBN, benzene, reflux (14%); (b) Benzene, reflux (26%); (c) Benzene, BHT, reflux (51%).

As a result of this information a mechanism was proposed to explain this unanticipated transformation. As the evidence seemed to suggest a radical pathway was not at work, an acid catalysed mechanism was suggested (scheme 1.83).



Scheme 1.83 : Proposed acid catalysed mechanism.

It was thought a small quantity of HBr could be generated by decomposition of the starting material, or perhaps through interaction with the glassware. The first doubts about this mechanism arose when it was found that when switching from toluene to DMF as the solvent the reaction proceeded in much better yield, 41% compared to 63% respectively. With the knowledge that at reflux DMF undergoes a slow decomposition to give a concentration of dimethylamine, which would act to neutralise any HBr, it seemed possible that once again the agent thought to be driving the reaction was in fact causing decomposition. This led to experimentation with epoxide based acid scavengers, the use of which was inspired by Corey's synthesis of gibberelic acid during which epoxypropane was employed to scavenge HCl.[97] Whilst the low boiling point of epoxypropane resulted in suppression of the maximum reflux temperature, the results were favourable, with a much cleaner reaction returning a good yield of the

tetracycle despite the low reaction temperature. Use of the higher boiling epoxyhexane resolved the temperature issues and led to a significantly boosted yield (76%).

This evidence against an acid-catalysed mechanism, led to further consideration of possible radical pathways as whilst BHT had failed to inhibit the reaction it was not unreasonable to think that the spontaneous generation of a diradical system within the starting material itself would allow a radical reaction to proceed as the relative rates of intra and intermolecular radical quenching would be greatly in favour of the former process. An ongoing examination of the literature showed numerous examples of the spontaneous generation of diradical intermediates in systems containing proximal alkynes or allenes. The work of Bergman,[98] Myers,[99] Saito[100] and Schmittel[101] appeared particularly apposite (figure 1.9).

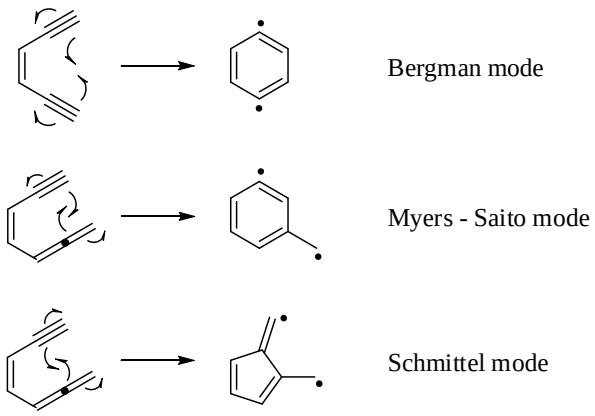
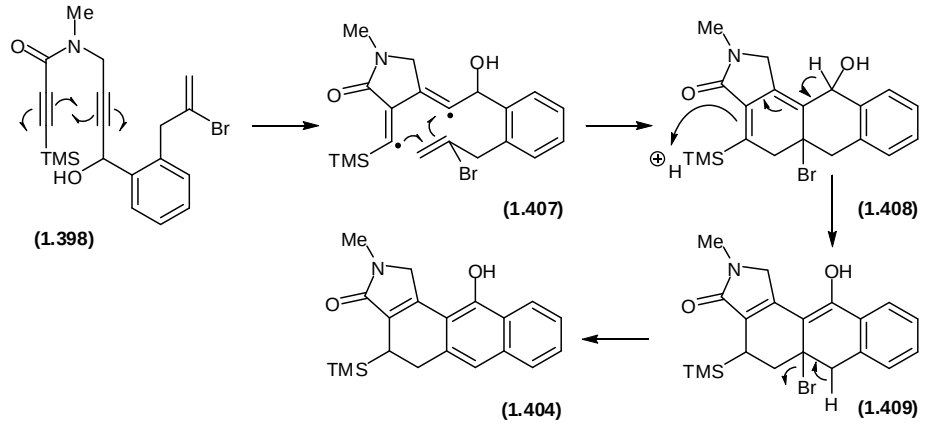


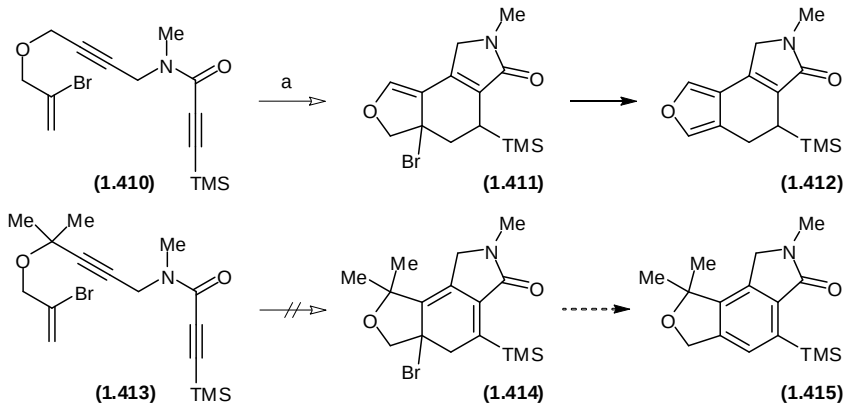
Figure 1.9 : Known modes of diradical formation.

Extensive work by Nicolaou *et al.*[102] had shown that one of the key factors in this type of reaction is the distance between the two reacting bonds and in the classic examples shown above this results from the *cis* geometry of the non-reacting alkene. Computational modelling of cyclisation precursor **(1.398)** suggested that in its iminol tautomer the amide may attain a configuration where the two alkynes are sufficiently close in space that a spontaneous reaction may occur to generate diradical species **(1.407)**. This knowledge led to the proposal of a new radical based mechanism (scheme 1.84).



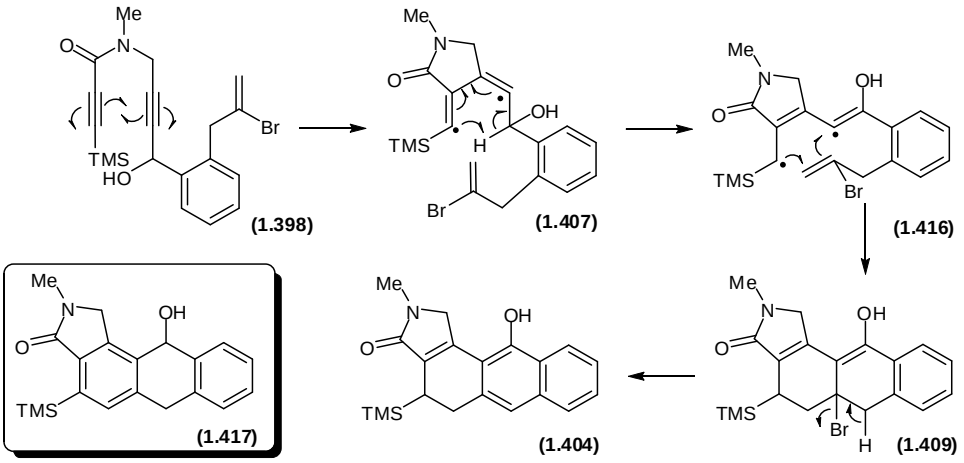
Scheme 1.84 : Initially proposed radical mechanism.

This mechanism was also short-lived as work being undertaken in parallel by A. J. Waters resulted in a further revelation of mechanistic information.[81,83c] During work on a series of analogous enediyne cyclisations towards various heterocyclic targets as well as an alternate route to the Lactonamycins (*vide infra*, scheme 1.97) the cyclisation of the ethers **(1.410)** and **(1.413)** were attempted (scheme 1.85). Whilst the unadorned ether underwent the anticipated cyclisation to give the furan **(1.412)** the *gem*-dimethyl equivalent failed to deliver any product at all even after protracted periods of heating.



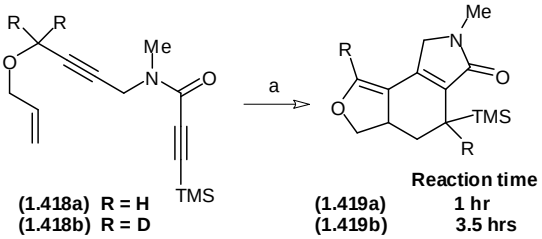
Scheme 1.85 : Reagents and Conditions: (a) Toluene, epoxyhexane, reflux (90%).

Fortunately a straightforward revision of this reaction mechanism (scheme 1.86), involving a well-established 1,6-hydrogen abstraction was all that was required to explain this new experimental data. This also removed the necessity for the slightly awkward double bond rearrangement of the initial radical mechanism and explained away the absence of elimination product **(1.417)** arising from diene **(1.408)** which would have two discreet aromatic rings rather than the observed naphthalene product **(1.398)**.



Scheme 1.86 : Revised radical mechanism including a 1,6-hydrogen abstraction.

The synthesis and cyclisation of the deuterated compound **(1.418b)** appeared to confirm this hypothesis and also suggested that this abstraction may be the rate-limiting step with a clear primary KIE of some three and a half times over the corresponding hydrogen bearing ether **(1.418a)** (scheme 1.87).



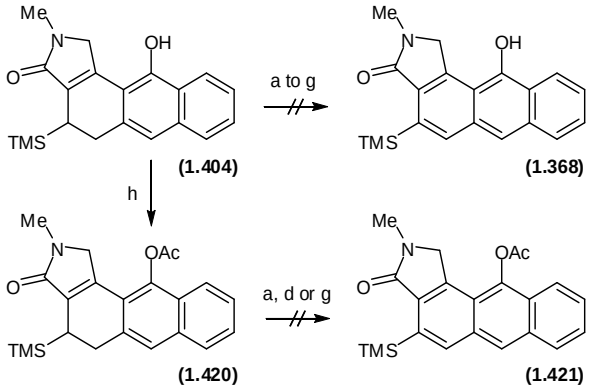
Scheme 1.87. Reagents and Conditions: (a) Toluene, reflux.

The mechanism of this fascinating series of transformations remains a source of interest for the Parsons group and work towards fully elucidating it is ongoing. The work of D. Faggiani should prove particularly insightful when it is published in short order.[82]

1.3.5 Attempted Functionalisation of Cyclisation Products.

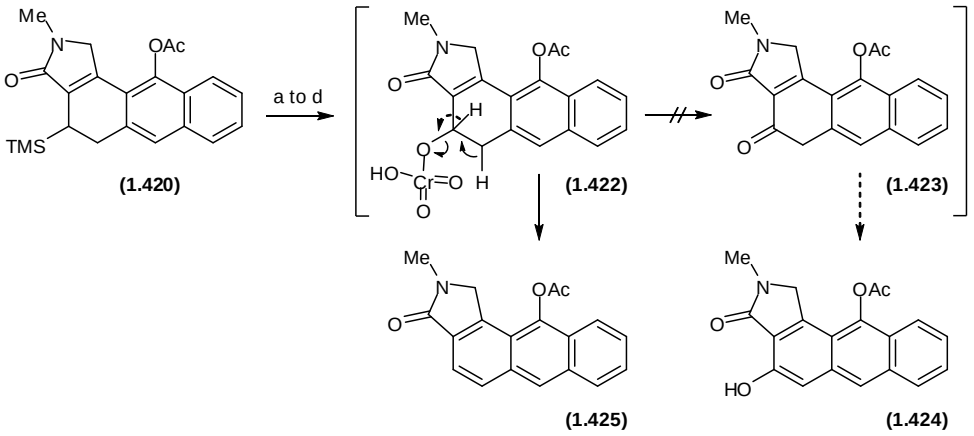
With the cyclisation reaction optimised to deliver the key tetracyclic compound **(1.404)** in good yield it was thought that conversion to the required phenolic state of the E-ring should prove relatively straightforward. This required an aromatisation of the ring and an oxidation of the silane to a hydroxyl group, though not necessarily in that order. The first strategy to this end focused on the dehydrogenation of the ring to acquire the desired aromaticity (scheme 1.88). It was proposed that the resulting aryl silane **(1.368)** could be oxidised to a phenol *via* a Tamao[103]-Fleming[104] oxidation, however this seemed rather optimistic given the known stability of the trimethylsilyl group under

such conditions (*vide infra*, section 2.7.1). A variety of reagents were used with little success with the silane **(1.404)** undergoing decomposition quite readily and failing to give the fully aromatic tetracycle. Fearing that the unprotected phenol of the D-ring may be interfering, either through coordination to reagents, or possibly by promoting oxidation of the D-ring (*vide supra*, scheme 1.48) it was decided that protecting the phenol as the acetate ester **(1.412)** may prevent such reactivity. Sadly the acetylated compound still would not undergo the required dehydrogenation.



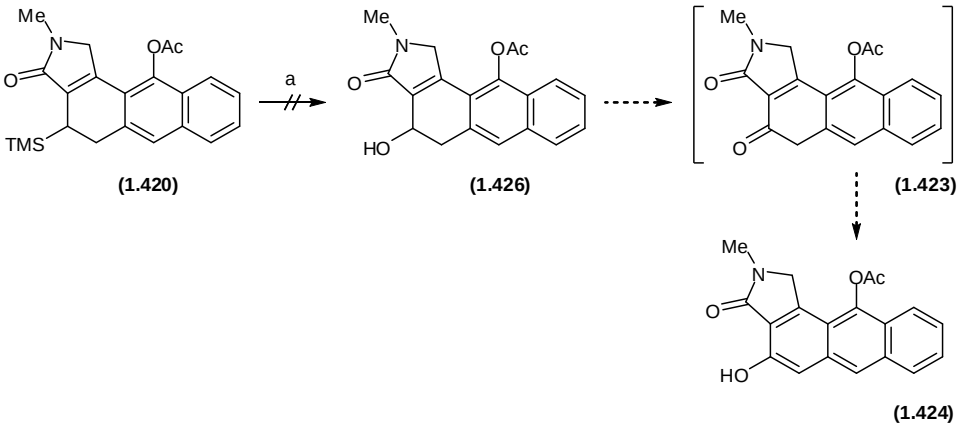
Scheme 1.88 : Reagents and Conditions: (a) Pd/C; (b) DDQ; (c) Sulfur; (d) MnO_2; (e) O_2; (f) BHT; (g) Benzoyl peroxide; (h) AcCl, NEt_3, THF, rt (quant.).

Abandoning the initial aromatisation strategy, the work of Clawson *et al.* led Board to believe that the cyclisation product may be converted directly to the ketone **(1.423)** by the use of sodium dichromate (scheme 1.89).[105] The ketone generated would likely tautomerise rapidly to the desired phenol **(1.424)**. Sadly the use of this and other chromium based oxidants resulted in the fully aromatic, but defunctionalised tetracycle **(1.425)**, it was thought this most likely resulted from the generation of the required chromate ester **(1.422)** which was then undergoing β-elimination, possibly due to the sterically crowded nature of the hydrogen that must undergo abstraction for the oxidation to proceed.



Scheme 1.89 : Reagents and Conditions: (a) $Na_2Cr_2O_7$, AcOH; (b) PDC, TMSCl; (c) PDC; (d) PCC.

Board's final attempt to functionalise the cyclisation product involved attempting to perform a Tamao-Fleming oxidation on the aliphatic silane (scheme 1.90). As mentioned previously the trimethylsilane was a very poor substrate for such an oxidation as both Tamao and Fleming variants of the oxidation require at least one activating group around the silane which would be extremely challenging to generate from the fairly inert TMS group. But it was nonetheless hoped that it would be possible to form the alcohol **(1.426)** which could be oxidised to the ketone **(1.423)** and that this would rapidly tautomerise to the phenol **(1.424)**. Perhaps unsurprisingly attempted oxidation with hydrogen peroxide and a source of fluoride did not yield any of the desired product.

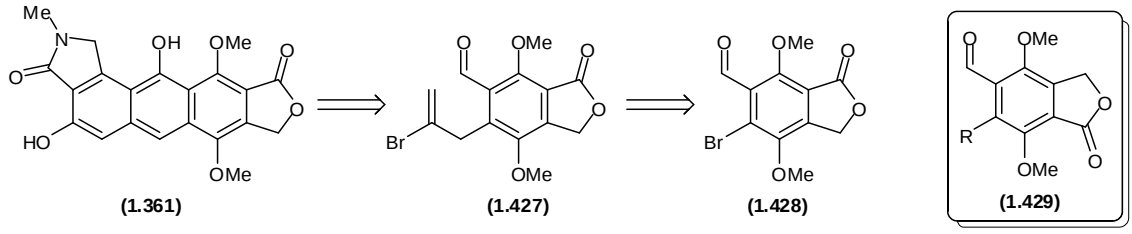


Scheme 1.90 : Reagents and Conditions: (a) H_2O_2, KF, $KHCO_3$, THF/MeOH (1:1), reflux.

The conclusion was drawn that a different, more reactive silyl group would be required at this position in a new system to allow the synthesis to proceed.

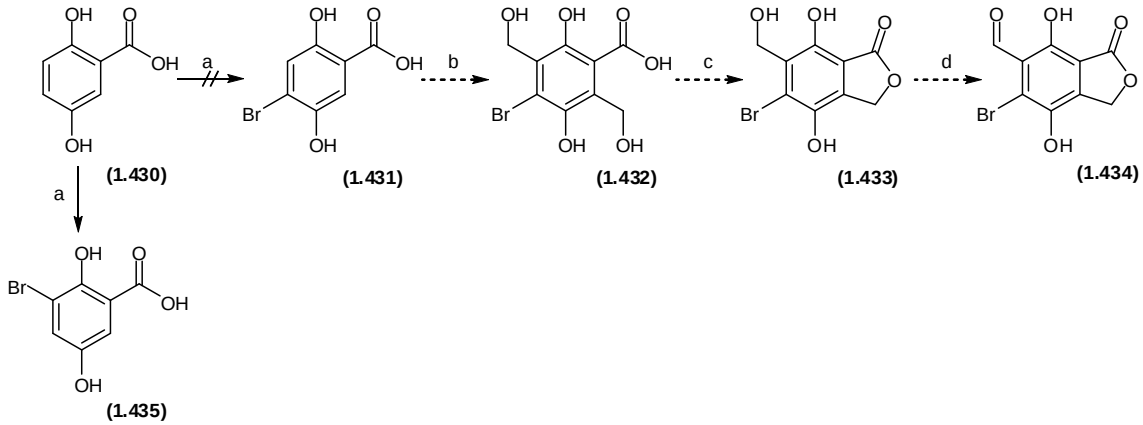
1.3.6 The Beginnings of a Total Synthesis.

Board was eager to apply the lessons learned throughout the model studies toward a full synthesis of lactonamycin. Returning to the initial retrosynthesis the aim became to devise a synthetic route to the pentacyclic lactam **(1.361)** (scheme 1.91), this compound would contain all the functionality to allow a total synthesis of lactonamycin **(1.1)**, the 1,4-dimethoxy moiety constituting a masked quinone and the lactone would be elaborated to the chiral portion of the molecule. This gave the benzaldehydes **(1.427)** and **(1.428)** as suitable targets onto which the necessary side chain might be appended.



Scheme 1.91 : Identification of short term targets.

In his excitement Board also identified the same structures with the lactone inverted as potential targets and whilst it is clear how lactone **(1.427)** might be elaborated to lactonamycin (*vide infra*, scheme 2.5), it is somewhat less so for its inverted equivalent **(1.429)**. However Board proposed routes to both. The first proposed route (scheme 1.92) required the somewhat unlikely bromination of gentisic acid **(1.430)** at the position *para* to the acid, the rest of the route would then utilise standard aromatic chemistry to give benzaldehyde **(1.434)** in a very concise sequence.

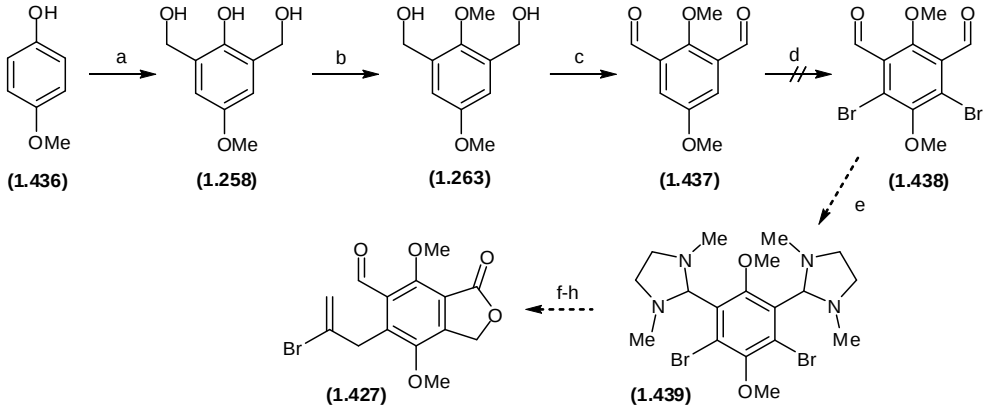


Scheme 1.92 : Proposed lactone formation sequence: (a) Br_2, AcOH (31%); (b) Formylation; (c) Ring closure; (d) Oxidation.

Attempts at the bromination gave exclusively the *meta*-bromide **(1.435)** as one might reasonably expect it to. The literature suggested that access to the *para*-substituted

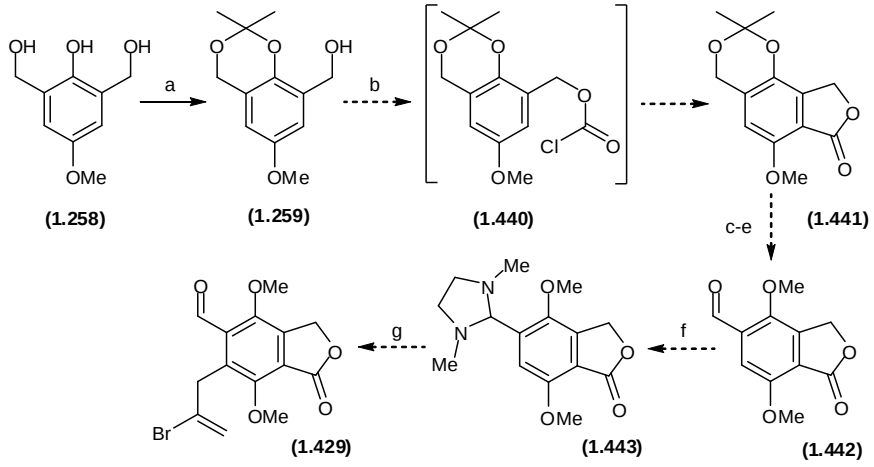
bromide was only possible through the deactivation of the phenol *ortho* to the acid, this was achieved *via* a 4 step sequence by Linderberg *et al.*[106] but it was felt this would make the route unwieldy, with an excess of protection-deprotection steps lengthening the route substantially. As such it was abandoned.

A second proposed route (scheme 1.93) involved another potentially challenging bromination. The dialdehyde **(1.437)** was produced *via* a known route from *para*-methoxyphenol **(1.436)**.[107] Bromination of the dialdehyde was unsuccessful, with undesired reaction of the aldehydes cited as the most likely cause. This route too was swiftly abandoned.



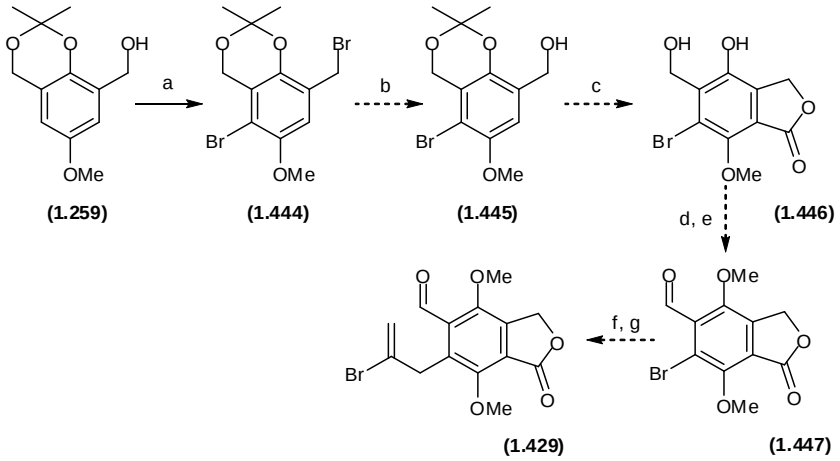
Scheme 1.93 : Reagents and Conditions: (a) Formalin, CaO, H_2O (58%); (b) MeI, K_2CO_3, acetone (82%); (c) PDC, acetone (71%); (d) Bromination; (e) Aminal formation; (f) Lithium halogen exchange then paraformaldehyde; (g) Lithium halogen exchange then transmetalation with CuCN then 2,3-dibromopropene and acidic workup; (h) Oxidation.

A subsequent route, this time towards the inverted lactone mentioned previously, focused on utilising an alternate method of generating the lactone (scheme 1.94).



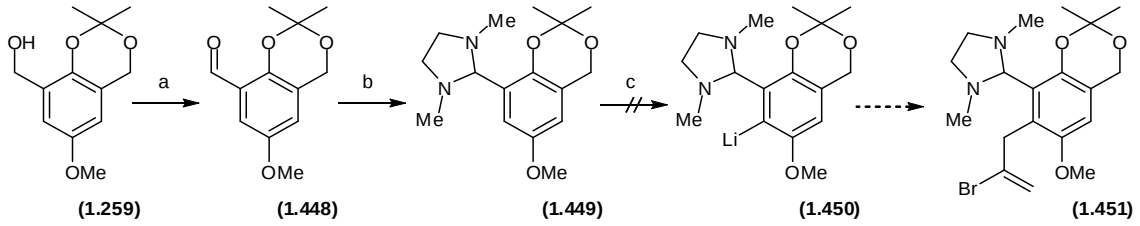
Scheme 1.94 : Reagents and Conditions: (a) 2,2-Dimethoxypropane, acetone, H_2SO_4 (62%); (b) Phosgene; (c) Deprotection; (d) Methylation; (e) Oxidation; (f) Aminal formation; (g) Deprotonation then transmetalation with CuCN then 2,3-dibromopropene and acidic workup.

Taking the previously used triol **(1.258)**, this was protected as the acetonide **(1.259)**. It had been hoped that treating the free benzyl alcohol with phosgene would generate the chloroformate **(1.440)** and that this would undergo a further electrophilic addition to the aromatic ring to furnish the lactone. There was some concern however that deprotonation of the aminal **(1.443)** would prove troublesome as the previously established methodology had only been applied to the *ortho*-lithiation of aryl bromides. Without the bromide in place the deprotonation would require significantly more forcing conditions which may in turn be incompatible with the lactone. It was therefore considered desirable to integrate a ring bromination into the synthesis. Knowing that the benzyl alcohol **(1.259)** could be converted to the dibromide **(1.444)** (scheme 1.95), it seemed not unreasonable to think the aliphatic bromide might be readily hydrolysed to give the alcohol **(1.445)** which would undergo chemistry as per the previous route (*vide supra*, scheme 1.94) and then allow a milder lithium halogen exchange process to install the bromopropene unit.



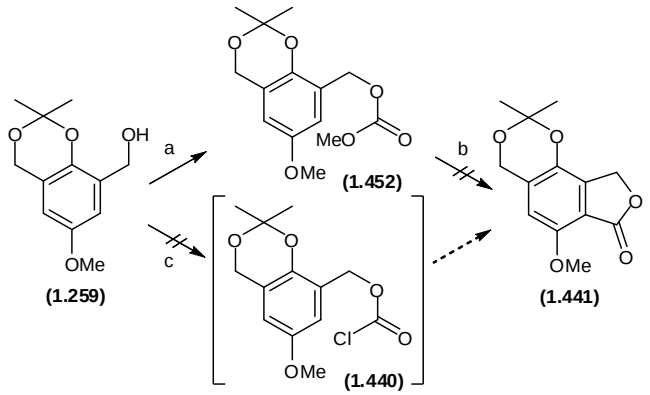
Scheme 1.95 : Reagents and Conditions: (a) Br_2, AcOH (63%); (b) Hydrolysis; (c) Phosgene, acidic workup; (d) MeI, K_2CO_3, acetone; (e) Oxidation; (f) Aminal formation; (g) Lithium halogen exchange then transmetalation with CuCN then 2,3-dibromopropene and acidic workup.

Sadly, due to time constraints, this chemistry was never developed beyond the dibromide **(1.444)**, though whilst this methodology was being explored a couple of alternative aspects of this chemistry were clarified. Firstly the deprotonation of the ring with just the aminal and no bromine in place was attempted (scheme 1.96). As predicted by Board, this approach proved fruitless, with no evidence for the formation of the desired lithiate **(1.450)**, let alone being able to couple it with 2,3-dibromopropene *via* the cuprate. With the failure of this route even without the labile lactone in place further efforts towards the direct deprotonation were not undertaken.



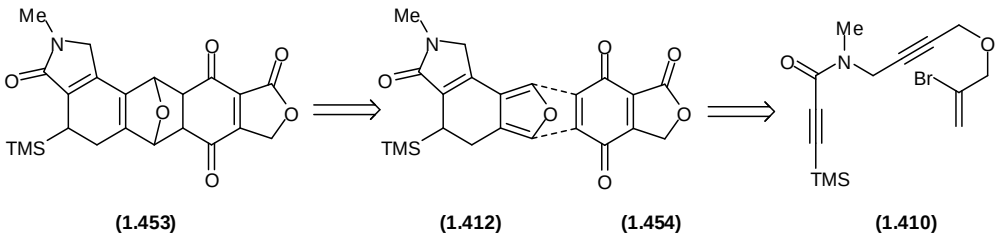
Scheme 1.96 : Reagents and Conditions: (a) MnO_2, CH_2Cl_2, (94%); (b) *N*,*N*'-Dimethylethylenediamine, EtOH (76%); (c) ^{n}BuLi, Et_2O then CuCN, -30 °C to rt then 2,3-dibromopropene.

The lactone formation step was also examined (scheme 1.97), initially this was investigated with the mixed carbonate **(1.445)** which was sufficiently stable to be isolated before attempted cyclisation. Treatment with Lewis acid failed to give the lactone **(1.441)** and as such the more reactive chloroformate was to be formed by the reaction of alcohol **(1.259)** with phosgene. Upon attempting this reaction however none of the anticipated product was formed. This failure cast a significant shadow of doubt upon the proposed syntheses and suggested further work would be required to develop a viable route to fully functionalised benzaldehyde **(1.429)**.



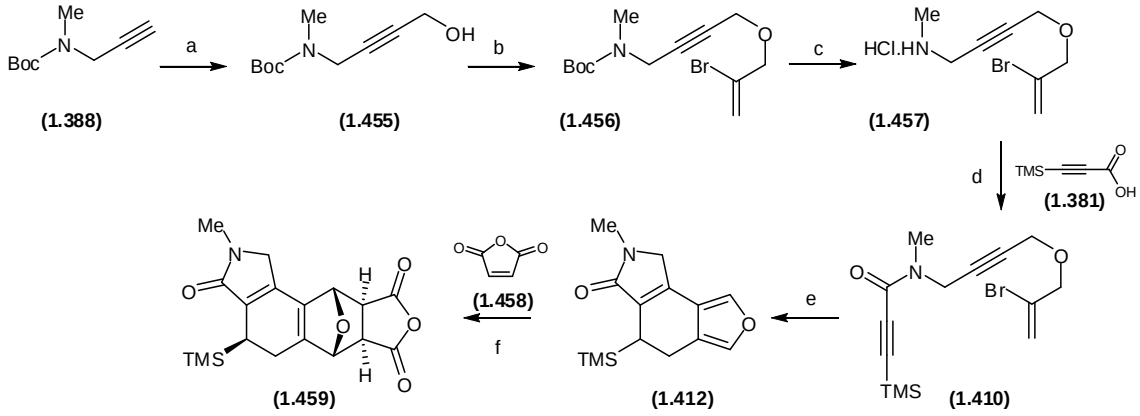
Scheme 1.97 : Reagents and Conditions: (a) MeO_2CCl, *N*-methylmorpholine, THF (50%); (b) $MgBr_2.Et_2O$, toluene, reflux; (c) $(COCl)_2$, CH_2Cl_2, rt.

As mentioned previously, Waters was also working on an alternative strategy for the formation of lactonamycin (scheme 1.98), which would also utilise the novel cyclisation methodology being developed within the Parsons group.



Scheme 1.98 : Retrosynthesis of a Diels-Alder approach to a key pentacycle.

It was proposed that the pentacycle **(1.453)** may be constructed by a Diels-Alder reaction between a quinone and a furan, the furan partner being constructed simply and efficiently by the cyclisation methodology mentioned previously (*vide supra*, scheme 1.85). Synthesis of a model for this approach proved quite straightforward and applied a great deal of the knowledge gained throughout the aforementioned precursor syntheses (scheme 1.99). Starting from the *N*-Boc-*N*-methylpropargylamine **(1.388)** this could be easily hydroxymethylated by treatment with base and then quenching with paraformaldehyde. The newly appended alcohol **(1.455)** underwent Williamson etherification with the familiar 2,3-dibromopropene using sodium hydride to give amine **(1.456)** and then Boc deprotection and coupling with propynoic acid **(1.381)** occurred under what were now standard protocols to give cyclisation precursor **(1.410)**. Once again the cyclisation proved to be highly reliable and heating in toluene in the presence of an acid scavenger gave the furan **(1.412)** in excellent yield. An initial test of a Diels-Alder reaction with the dienophile maleic anhydride **(1.458)** gave hope that such a strategy may indeed prove fruitful with the *exo* Diels-Alder product **(1.459)** formed exclusively.



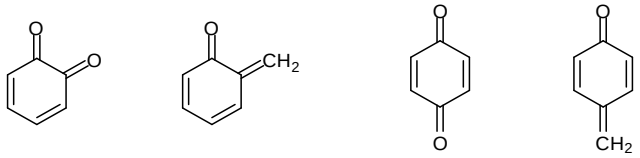
Scheme 1.99 : Reagents and Conditions: (a) ^{n}BuLi, $(CH_2O)_n$, THF, -78 °C (82%); (b) NaH, THF, 2,3-dibromopropene (81%); (c) TFA, CH_2Cl_2; (d) **(1.381)**, CH_2Cl_2, NEt_3 (82% over 2 steps); (e) Toluene, epoxyhexane, reflux (90%); (f) **(1.458)**, Et_2O, rt (50%).

1.4 A Brief Overview of *ortho*-Quinone Methides.

1.4.1 Introduction to Quinone Methides.

The quinone methides (QMs) may be thought of quite simply as quinones in which one of the constituent carbonyls has been replaced with a methylene unit. There are two variants (figure 1.10), corresponding to *ortho*-quinone **(1.460)** and *para*-quinone **(1.462)** and these are simply termed *ortho*-quinone methide (*o*-QM) **(1.461)** and *para*-quinone

methide (*p*-QM) **(1.463)** respectively. This overview will focus on the former.

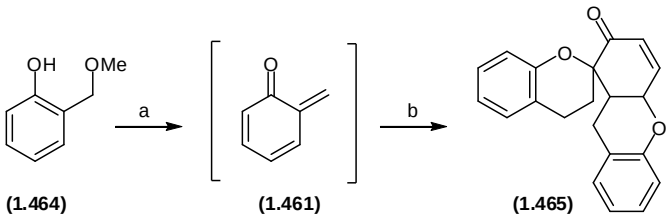


(1.460) **(1.461)** **(1.462)** **(1.463)**

Figure 1.10 : Structural relationship of quinones and quinone methides.

The substantial increase in polarity relative to their quinone equivalents results in a significant increase in the reactivity of such compounds. Indeed most QMs exist only fleetingly, with the ability to form a fully aromatic ring providing a constant, strong driving force for reaction. Where QMs have been isolated as distinct products there is always some significant stabilising influence at work, usually in the form of extended conjugation or the presence of electron donating groups.

The reactivity of these systems meant that for an extended period of time their existence was regarded as mere conjecture. They were first invoked by Fries in 1907 to explain the formation of dimerised products from the reaction he was studying.[108] The structure was frequently cited for a period of some 56 years before the first experimental evidence for its existence was gathered. Gardner *et al.* were able to trap the simple QM **(1.461)** in a liquid N_2 trap after pyrolysing the ether **(1.464)** at high temperature (scheme 1.100).[109] The QM appeared to be stable at temperatures up to -50 °C above which it went on to form the trimer **(1.465)**. This discovery was rapidly followed by reports of the isolation of stabilised QM intermediates.



(1.464) **(1.461)** **(1.465)**

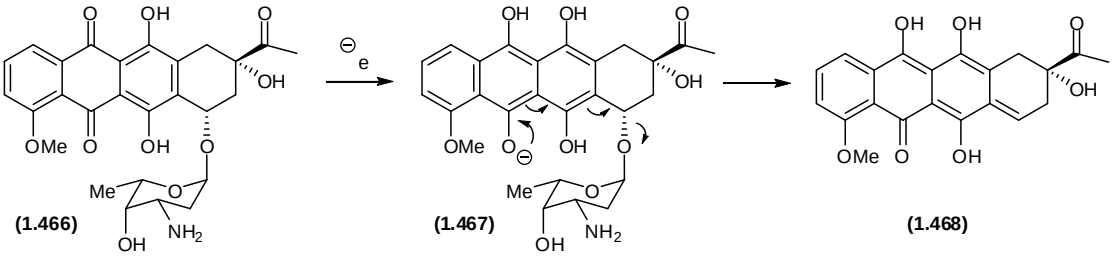
Scheme 1.100 : Reagents and Conditions: (a) 500-650 °C in a stream of N_2 passed through a quartz tube then trapped at -196 °C; (b) -50 °C to rt.

The subject of QMs has generated a significant interest over the years and there has been a much larger body of work published than is included in this brief overview. For a more in depth analysis please see any of the more substantial reviews[110] that have been published as well as a weighty tome on the subject by Rokita.[111]

1.4.2 *ortho*-Quinone Methides in Nature.

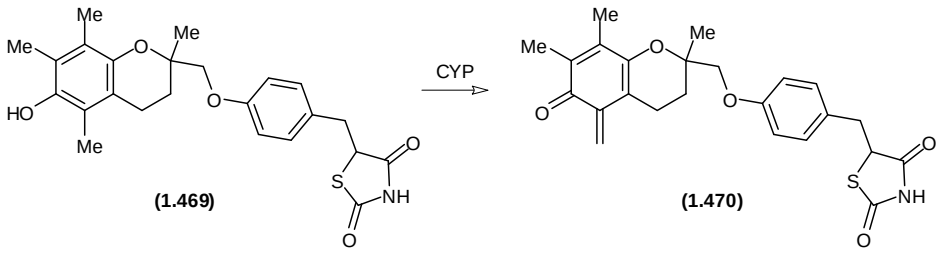
Whilst QMs appear relatively infrequently in synthetic endeavours, where they do they are frequently referred to as forming part of a biomimetic sequence. The QM is frequently posited as a key intermediate in the synthesis of compounds in nature and crucially it is the action of QMs that is proposed to account for the biological activity of a number of drugs and potential drugs. It is frequently proposed that where QMs are generated *in vivo* they act as potent alkylating agents with cytotoxic effect. They may also be utilised by nature when forming certain structural motifs.

This is of particular relevance to the anthraquinone daunomycin **(1.466)**, which belongs to the anthracycline class of antibiotics (though they exhibit significant toxicity in humans and as such are only used in their anti-tumour capacity). Its potent chemotherapeutic activity is explained as the result of the quinone system undergoing bioreduction due to the oxygen starved nature of many tumour cells (scheme 1.101). This results in a localised concentration of the QM system **(1.468)** which then binds to DNA and proteins in the tumour cells.[112] This reactivity is believed to be general to a wide range of anthracyclines.



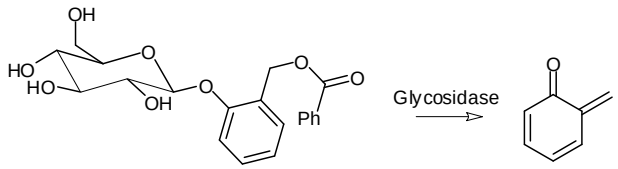
Scheme 1.101: Bioreductive conversion of daunomycin to cytotoxic QM (1.468).

QM formation can however be an unwelcome side reaction in therapeutic drugs. It has been proposed that the hepatotoxicity of the failed anti-diabetic and anti-inflammatory drug troglitazone **(1.469)** is due to its ability to form the cytotoxic QM **(1.470)** (scheme 1.102) after being oxidised by cytochrome P450 in the liver.[113]



Scheme 1.102 : The oxidation of troglitazone by cytochrome P450.

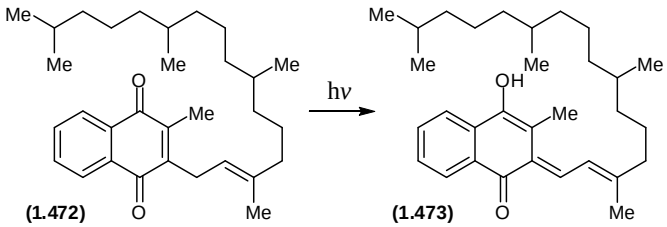
Salicortin **(1.471)**, is one of many phenol glycosides distributed across the plant kingdom, it is a toxic compound thought to play a role in repelling herbivorous insects. It has been suggested that its toxicity arises due to the enzymatic cleavage of the glycosidic bond, this allows for the elimination of the benzoate residue generating the highly reactive QM **(1.461)** at the enzymes active site (scheme 1.103). This results in irreversible alkylation of the enzyme and inactivation.[114]



(1.471) **(1.461)**

Scheme 1.103 : Enzymatic QM formation, the mechanism of salicortin toxicity.

In contrast to the deleterious effects of many QMs *in vivo* the K vitamins including vitamin K_1 **(1.472)** are an important example of the role of QMs in electron transfer chains. It is thought that in plants exposure to sunlight results in excitation and that in the triplet state the molecule undergoes an intramolecular hydrogen abstraction, resulting in tautomerisation to the highly conjugated QM **(1.473)** (scheme 1.104).[115]



(1.472) **(1.473)**

Scheme 1.104 : Tautomerisation of vitamin K_1.

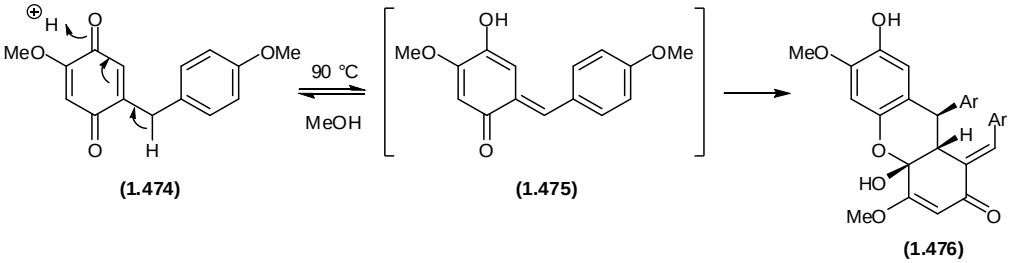
A number of biomimetic syntheses are detailed below (*vide infra*, schemes 1.134 & 1.135) and with QMs appearing in such a diverse range of natural systems, it is no surprise they serve as an inspiration to the synthetic chemist.

1.4.3 Generating *ortho*-Quinone Methides.

Whilst there are a multitude of ways in which QMs may be generated, these conditions are highly varied. When attempting to integrate a QM approach into a more general synthesis it can be challenging to prevent these reactive intermediates from dimerising if their concentration in the reaction mixture becomes too high, it is thus usually desirable to keep the concentration of QM generated as low as possible, whilst reacting it with a great excess of the reaction partner. The method of generation is also of great

significance when considering the stability of other reactants in a given system; frequently it is found that the most convenient method of generation is incompatible with the desired reaction pathway.

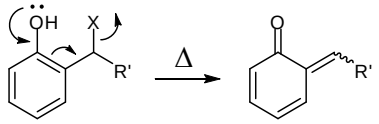
The simplest method of generation is limited to *para*-quinone precursors, which if there are protons present on a carbon beta to the carbonyl then tautomerisation may occur to generate an *o*-QM. This was demonstrated by Jurd and Roitman who showed that the quinone **(1.474)** could be converted to the *o*-QM **(1.475)** simply through heating in methanol (scheme 1.105).[116] This QM was of course further stabilised by conjugation with the electron rich aromatic ring.



(1.474) **(1.475)** **(1.476)**

Scheme 1.105 : Tautomeric generation of a QM.

However the most frequent method by which *o*-QMs are prepared synthetically is through the thermolysis of a suitable precursor. Generally this will involve the presence of a suitable leaving group at the benzylic position of an *ortho*-hydroxybenzyl system **(1.477)** which can undergo elimination assisted by the phenol (scheme 1.106). In the simplest case this may be 2-hydroxybenzyl alcohol. The temperature at which thermolysis occurs are generally high though there is significant reduction where the QM is stabilised by conjugation. The effectiveness of the leaving group under the reaction conditions will also have a significant effect.



(1.477) **(1.478)**

Scheme 1.106 : QM generation by thermolytic elimination.

Among the leaving groups to have been proved effective (figure 1.11) are alcohols **(1.479)**,[117] ethers **(1.480)**,[109a,118] esters **(1.481)**,[119] amines **(1.482)**[120] and their ammonium salts **(1.483)**,[121] sulfides **(1.484)**,[122] and halides **(1.477)**.[117b,123] *ortho*-Vinyl phenols **(1.485)** have been converted through a 1,5-sigmatropic rearrangement.[124] Cyclic systems such as dioxaborinanes **(1.486)**[125] and sulfonates **(1.487)**[126] have also

found use. More exotic precursors include benzoaxazines **(1.488)**,[127] the benzoxetene **(1.489)**,[128] and chromans **(1.490)**.[129]

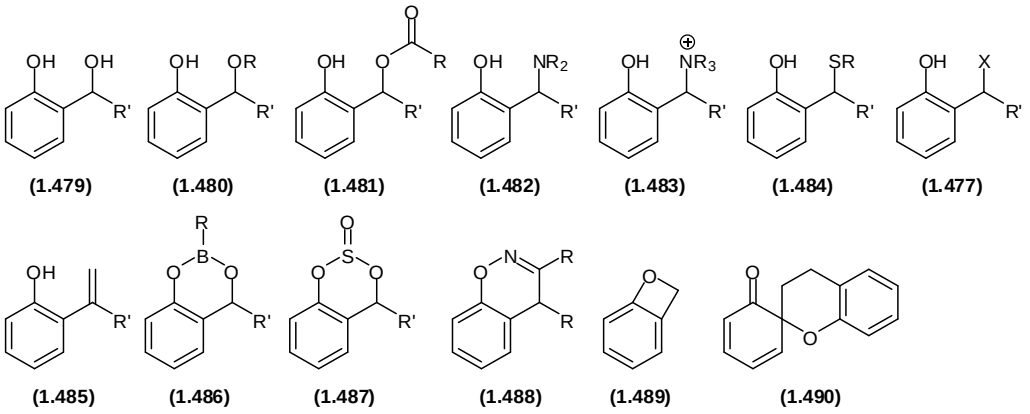
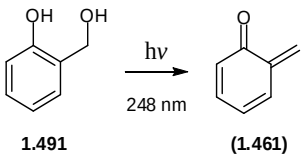


Figure 1.11 : Known thermal precursors to QMs.

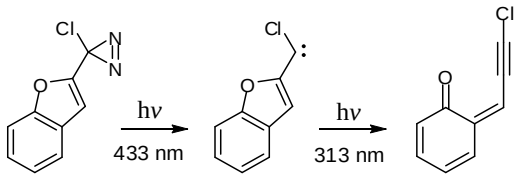
Whilst thermal generation methods are well precedented and reliable, the high temperatures involved obviously preclude the use of any thermally unstable reactants and heating can also promote alternate reaction pathways which may not be readily anticipated. There are a number of methods of lowering the temperature required for the thermal reaction to operate. This can be achieved both chemically, through catalysis with acid or base and physically through irradiation. Whilst these methods can be used to avoid thermal decomposition of both starting material and reagents, they have their own incompatibilities that can limit their use.

Photolysis has been used to achieve the same reaction at much lower temperatures for a number of the thermal precursors listed above. For example, in the case of the simple benzyl alcohol **(1.491)** Kresge *et al.* found that with irradiation at 254 nm the QM **(1.461)** could be generated at room temperature (scheme 1.107).[130] The equivalent reaction initiated purely thermally has been found to require temperatures in excess of 270 °C.[131]



Scheme 1.107 : QM generation by photolysis.

Photochemistry also allows access to alternative precursors such as the diazirine **(1.492)** which upon irradiation decomposes to the carbene **(1.493)** which upon further exposure to UV light undergoes rearrangement to the QM **(1.494)** (scheme 1.108).[132]

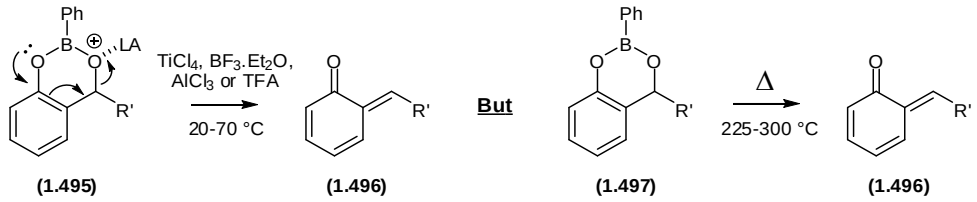


(1.492) **(1.493)** **(1.494)**

Scheme 1.108 : A novel photolabile precursor.

The main disadvantage of photochemical formation is that the amount of energy required to form the QM is high, as such wavelengths of 250-300 nm are common. Such high energy radiation will often activate other functional groups in both the starting material and in any reagents resulting in potentially complex reaction profiles.

Acid or base catalysis by comparison tends to produce rather more predictable results. There are many reports in the literature of catalysis by a wide variety of Lewis acids. As seen with photolytic methods a drastic reduction in reaction temperature can be achieved with acid catalysis. In the case of the dioxaborinanes **(1.495)** examined by Lau and Dufresne temperature reductions of greater than 200 °C were attributed to the presence of an acid catalyst (scheme 1.109).[125b]

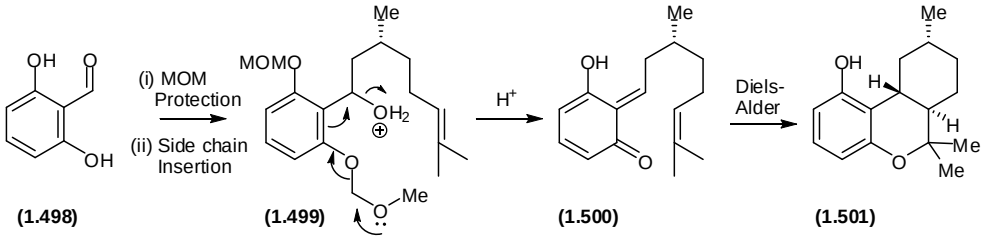


(1.495) **(1.496)** **(1.497)** **(1.496)**

Scheme 1.109 : Effect of acid catalysis on dioxaborin elimination.

Acid catalysis can also be used in conjunction with an acid sensitive protecting group strategy to generate QMs from relatively stable precursors. This is of importance, as due to this same sensitivity to acid and base the thermal precursors mentioned previously can be somewhat unstable, limiting the degree of structural complexity that can be installed before the QM generation step. Inoue *et al.* demonstrated how use of an appropriate protecting group can allow for the development of a more elaborate precursor (scheme 1.110). Taking the benzaldehyde **(1.498)** the two phenols were protected as their methoxymethyl ethers. A nucleophilic addition of the side chain was then possible to give alcohol **(1.499)**. At this point treatment with acid would deprotect both MOM groups leaving the free phenols, the remaining acid catalysing the elimination of the alcohol to give QM intermediate **(1.500)** which would in turn

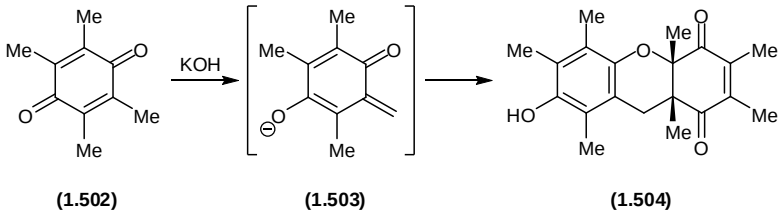
undergo an intramolecular cyclisation with the pendant alkene to give the tricycle **(1.501)**.[133]



Scheme 1.110 : Acid triggered QM generation sequence.

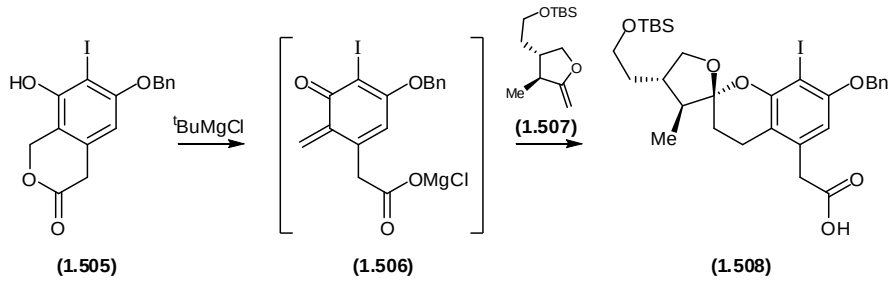
Whilst acid catalysis has its clear advantages over thermal variants, it also comes with certain incompatibilities, a number of nucleophiles by their very nature are intrinsically unsuited to acidic conditions. The presence of acid has an effect on electrocyclic reactions too, making them more ionic in nature and hence limiting diastereoselectivity.[134]

Base catalysis offers similar benefits to acidic methodology, with decreased reaction temperatures and the ability to utilise more complex QM precursors. However base catalysis also offers significantly improved tolerances in terms of nucleophiles. Base can catalyse both tautomeric formation as well as thermolytic eliminations. We see the former in the case of the dimerisation of duroquinone **(1.502)** (scheme 1.111).[135]



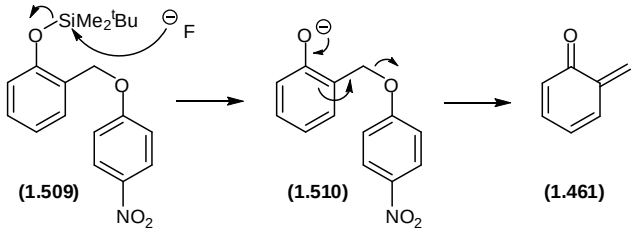
Scheme 1.111 : Base catalysed QM formation through tautomerisation.

Thermal style reactions generally involve the deprotonation of a phenolic precursor, which has the effect of accelerating the elimination of a suitable benzylic leaving group. This approach was utilised in the low temperature generation of the QM **(1.506)** from the novel precursor **(1.505)** in Pettus *et al.*'s synthesis of berkelic acid (scheme 1.112).[136]



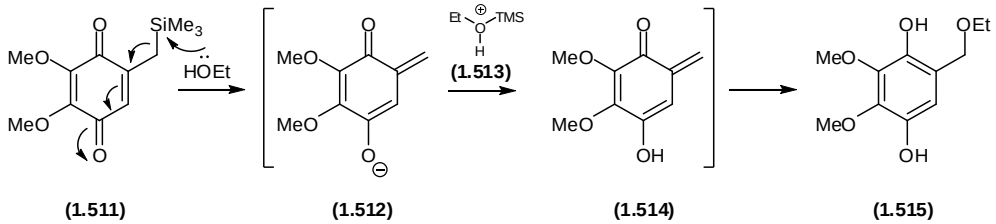
Scheme 1.112 : Quinone methide intermediate in the synthesis of Berkelic acid.

Lewis bases can also be used to trigger the formation of QMs by acting as a nucleophile. This is seen frequently in the work of Rokita *et al.* where they use fluoride to cleave silyl phenol ethers such as TBS ether **(1.509)** under only very mildly basic conditions to generate the phenolate **(1.510)** which rapidly undergoes elimination to give QM **(1.461)** (scheme 1.113).[137]



Scheme 1.113 : Fluoride triggered elimination sequence.

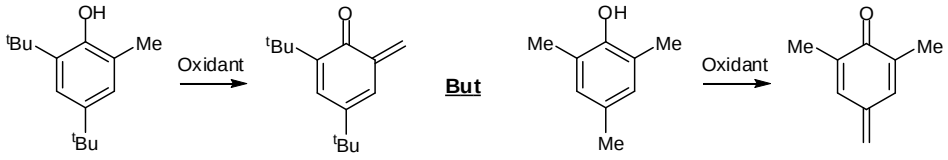
The reverse strategy has also been seen, with the desilylation equivalent of the deprotonation seen for duroquinone **(1.502)** (*vide supra*, scheme 1.111). Moore *et al.* demonstrated this through heating the silane **(1.511)** in ethanol whereupon the silane is removed generating the QM **(1.514)** to which a further molecule of ethanol can add giving the α-ethoxy hydroquinone **(1.515)** (scheme 1.114).[138]



Scheme 1.114 : Atypical desilylation method of forming QM's.

QMs may also be generated through the direct oxidation of a suitable precursor. This precursor is structurally restricted due to the relative stability of *para*-quinone methides meaning such a precursor must be either unsubstituted at the *para* position, or if it is, must contain no protons alpha to the ring. We see this in the comparison of the

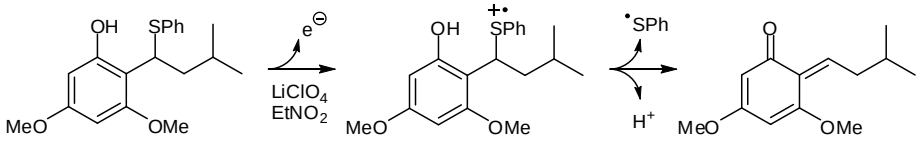
oxidation of butylated phenol **(1.516)**[139] and the methylated equivalent **(1.518)**[140] (scheme 1.115).



(1.516) **(1.517)** **(1.518)** **(1.519)**

Scheme 1.115 : Selectivity of quinone oxidations.

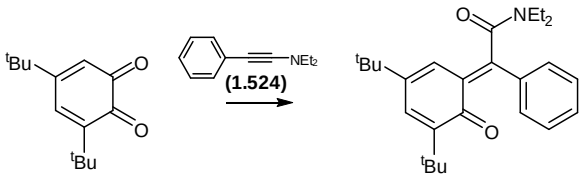
A number of reagents have proved effective in oxidatively forming QMs from appropriately substituted phenols, these include silver (I) oxide,[139,141] potassium ferricyanide,[142] lead (IV) oxide,[142] DDQ,[143] Bromine.[123] Chiba *et al.* were also able to form the QM **(1.522)** through an electrochemical one electron oxidation of benzyl sulfide **(1.520)** resulting in the elimination of a sulfur-based radical (scheme 1.116).[122,144]



(1.520) **(1.521)** **(1.522)**

Scheme 1.116 : Electrochemical QM formation by radical fragment elimination.

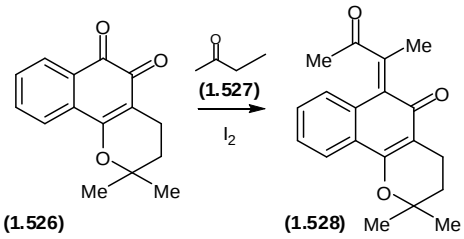
A more minor method of forming QMs is the direct olefination of *ortho*-quinones, this has been achieved in a number of ways, the first attempts at this route utilised Wittig[145] type ylids to install the olefin, however these reactions were not particularly useful given the propensity of the resulting QM to react preferentially with a further equivalent of ylid.[146] Later attempts involving condensation reactions proved more effective, a condensation of the ynamine **(1.524)** with the *ortho*-quinone **(1.523)** produced the stable QM **(1.525)** through a [2+2] cyclisation of the alkyne with the quinone carbonyl followed by an electrocyclic rearrangement (scheme 1.117).[147]



(1.523) **(1.525)**

Scheme 1.117 : Conversion of an *ortho*-quinone to the corresponding *o*-QM.

An aldol condensation between β-lapachone **(1.526)** and a number of different ketones has also been employed by Ferreira *et al.* to isolate QMs such as **(1.528)** (scheme 1.118).[148]

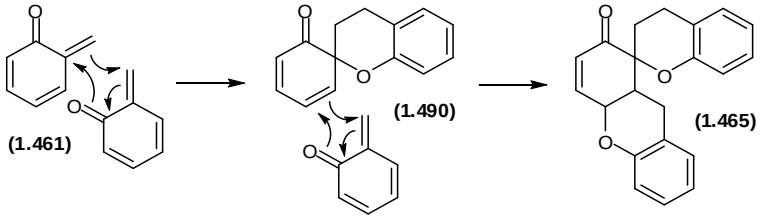


Scheme 1.118 : Aldol route to QM formation.

1.4.4 The Reactions of *ortho*-Quinone Methides.

As mentioned previously QMs are highly reactive, with their polarity making them ready conjugate acceptors and participants in electrocyclic reactions. The restoration of aromaticity is the key driving force in these reactions and as such it is rare to observe a reaction that fails to do so. Importantly for synthetic applications they also exhibit a high degree of fluxionality in the olefin geometry, this being due to a significant degree of zwitterionic character in the QM intermediate.

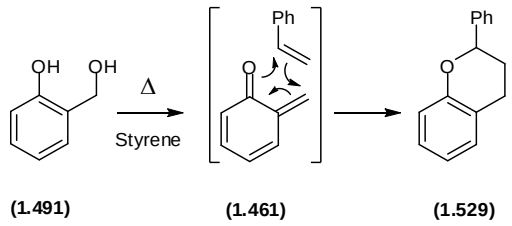
In the absence of external reactants QMs readily undergo dimerisation and trimerisation through [4+2] hetero-Diels-Alder reactions with a second and third equivalent of themselves (scheme 1.119). In the case of the simple unsubstituted QM **(1.461)** the second equivalent of QM is known to react with the more exposed *exo*-alkene to give a spirocyclic chroman such as **(1.490)** and the third equivalent reacts at the less electron deficient of the two remaining double bonds to give the pentacyclic construct **(1.465)**.[149] The dimerisation and trimerisation positions in substituted systems are decided predominantly by sterics, with the process frequently stopping at the dimer stage if the remaining alkenes are sufficiently hindered. Such reactions are the only examples of a QM acting as the two-membered component of such a cyclisation.



Scheme 1.119 : Trimerisation mechanism for unsubstituted QM (1.461).

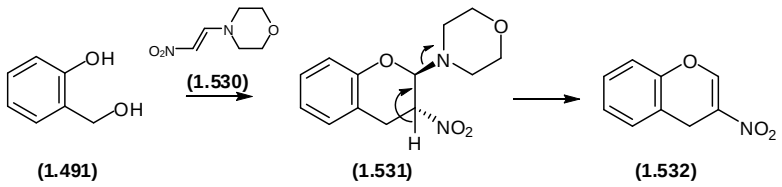
The logical extension of this behaviour is the [4+2] cycloadditions with other substrates.

Such reactions are seen frequently and both inter and intramolecular variants have been observed. The core principal of these reactions is demonstrated by the early work of Hultzsch, who demonstrated the reaction of the simple QM **(1.461)** with styrene to generate the chroman **(1.529)** (scheme 1.120).[117a]



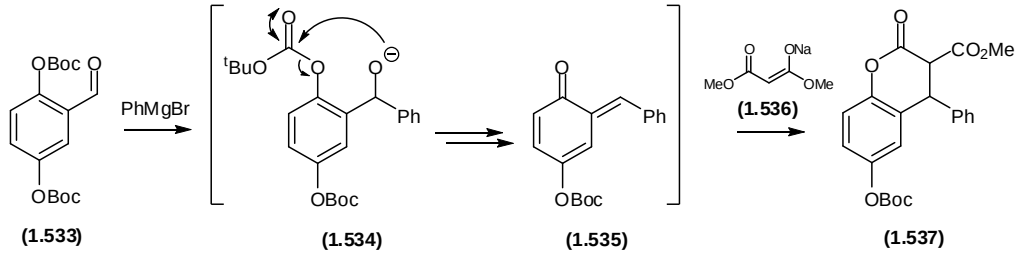
Scheme 1.120 : [4+2] Cycloaddition of a QM with styrene.

This concept has been extended to a wide variety of alkenes allowing for the production of an equally broad range of chromans. A suitable substituent at the β-position of the alkene can also allow access to the chromenes through a hetero-Diels-Alder/elimination sequence (scheme 1.121).[150]



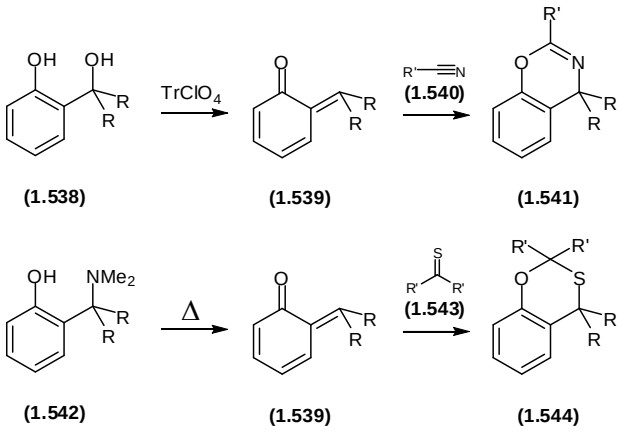
Scheme 1.121 : Cycloaddition/elimination sequence to give chromenes.

Similarly Pettus *et al.* demonstrated that an appropriately substituted alkene such as the enolate **(1.536)** could be used to generate a δ-lactone after cyclisation and workup (scheme 1.122).[151]



Scheme 1.122 : δ-Lactone formation through [4+2]-cycloaddition.

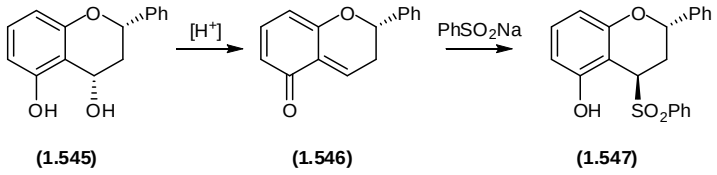
[4+2] Cycloadditions have also been extended to include nitrogen and sulfur based multiple bonds (scheme 1.123) generating oxazines **(1.541)** through a reaction with nitriles **(1.540)**[152] and oxathianes **(1.544)** with thiocarbonyl compounds **(1.543)**.[153]



Scheme 1.123 : Nitrogen and sulfur containing heterocycle formation.

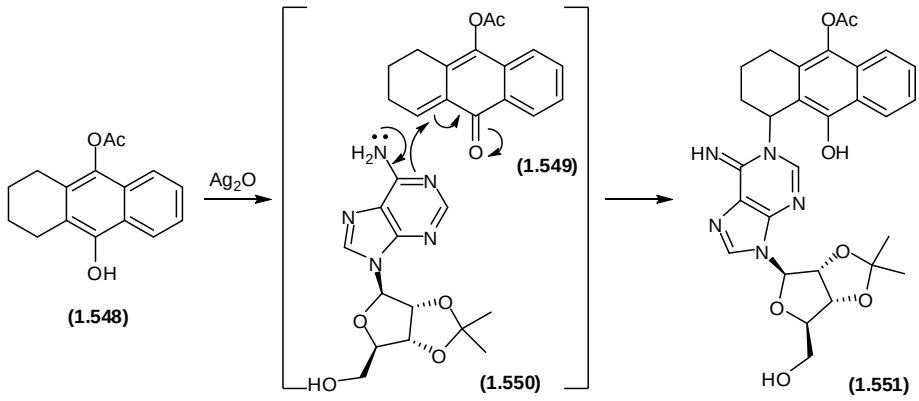
There is also a wealth of examples of QMs acting as conjugate acceptors. In this capacity they behave simply as an enone of enhanced reactivity. The primary issue that prevents the use of QMs in such a fashion is the side reaction to form dimers, as such it is necessary to prevent this either by generating a QM intermediate that is sufficiently stable with respect to cyclisation that the desired nucleophile has sufficient time to react or alternately a reactive QM may be utilised provided it is only ever present in low concentration and the nucleophile concentration is high.

Brown *et al.* formed the sulfone **(1.547)** by treating the starting diol **(1.545)** with acid and by doing so at low concentration they were able to identify the intermediate QM **(1.546)** spectroscopically before using a large excess of sodium benzenesulfinate to both quench the acid and undergo a nucleophilic addition to the QM (scheme 1.124).[154]



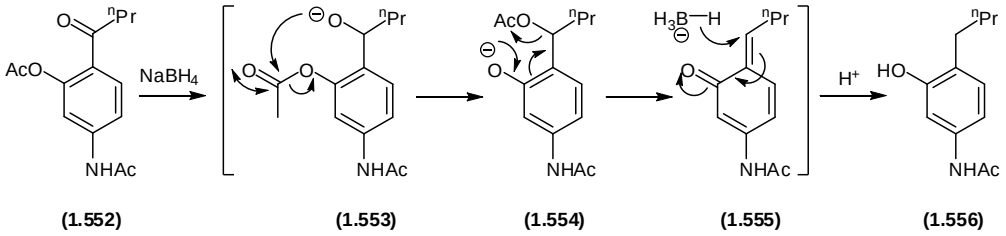
Scheme 1.124 : Nucleophilic addition to a QM.

An interesting piece of work by Angle and Yang demonstrated the nucleophilic addition of the nucleoside adenosine **(1.550)** to the stable oxidatively formed QM **(1.549)** which is a proposed model of the manner in which the anthracyclines (*vide supra*, scheme 1.101) act to cross-link DNA strands (scheme 1.125).[155]



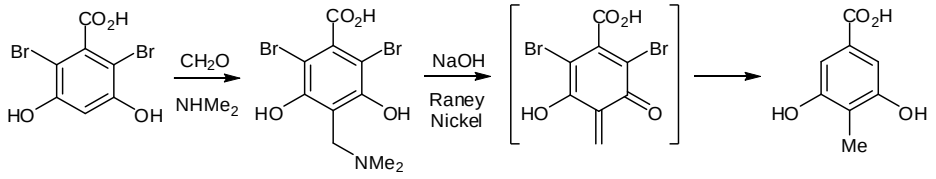
Scheme 1.125 : A QM DNA alkylation model.

As with an enone it is also possible to simply reduce a QM if it is formed in the presence of an appropriate reducing agent, however this has been observed to occur exclusively as an effective 1,4-addition of hydride to the conjugated ketone as opposed to the predominantly 1,2-addition one would expect from a typical enone, the result being that it is the benzylic position rather than the carbonyl that is reduced. Frequently this is carried out with aluminium or boron hydrides. In the case of the ketone **(1.552)** (scheme 1.126) the carbonyl is first reduced in the standard manner, the resulting alkoxide is then able to facilitate a transfer of the adjacent acetyl group to give the activated QM precursor **(1.554)**, this rapidly eliminates to generate the QM **(1.555)** and this species is further reduced by a second equivalent of borohydride.[156]



Scheme 1.126 : Borohydride mediated QM formation and subsequent reduction.

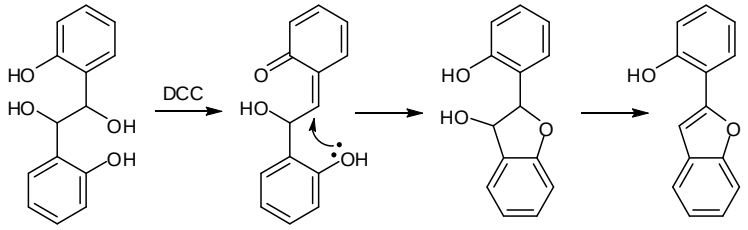
Reduction *via* single electron transfer has also been recorded. Borchardt and Sinhababu demonstrated such a reduction, which they integrated into a novel method of methylating aromatics (scheme 1.127). The benzoic acid **(1.557)** was first converted to benzylamine **(1.558)** by a Mannich reaction. This compound then underwent base catalysed QM formation, which when carried out on the presence of Raney nickel is reduced to give the *ortho*-methyl phenol **(1.560)**.[157]



(1.557) **(1.558)** **(1.559)** **(1.560)**

Scheme 1.127 : Raney nickel reduction of a QM.

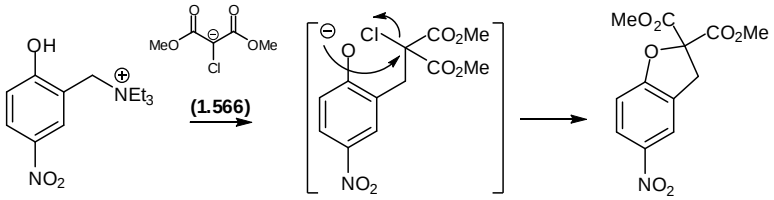
Another interesting if minor application of QM methodology has been in the synthesis of furans. For example, the DCC facilitated elimination of the tetraol **(1.561)** allowed for the intramolecular addition of the remaining phenol to the QM intermediate **(1.562)** giving the dihydrobenzofuran **(1.563)** DCC activation of the aliphatic hydroxyl promoted its elimination to furnish benzofuran **(1.564)** (scheme 1.128).[158]



(1.561) **(1.562)** **(1.563)** **(1.564)**

Scheme 1.128 : Benzofuran synthesis *via* a QM intermediate.

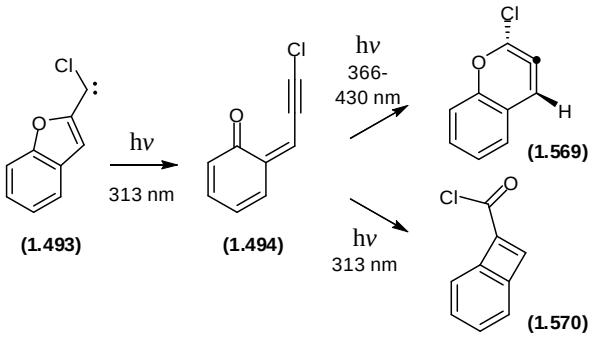
A further example shows the formation of the furan after the addition of the nucleophile (scheme 1.129). In this case the enolate **(1.566)** acts as both the triggering base as well as the nucleophile, upon addition the resulting anion **(1.567)** is able to displace the benzyl chloride to form the dihydroisobenzofuran **(1.568)**.[159]



(1.565) **(1.567)** **(1.568)**

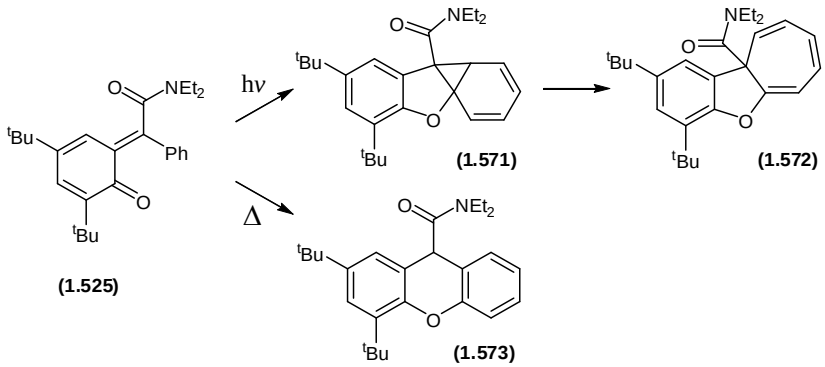
Scheme 1.129 : Benzohydrofuran synthesis *via* a QM intermediate.

As well as being formed by photochemistry the reactivity of QMs may also be affected by exposure to light. Earlier we saw how the QM **(1.494)** could be generated from the carbene **(1.493)** by exposure to UV light at 313nm (*vide supra*, scheme 1.108). Continued exposure at 313 nm resulted in a further transformation to the fused cyclobutene **(1.570)** whilst a shift to less energetic wavelengths (430 nm) resulted in the strained cyclic allene **(1.569)** (scheme 1.130).



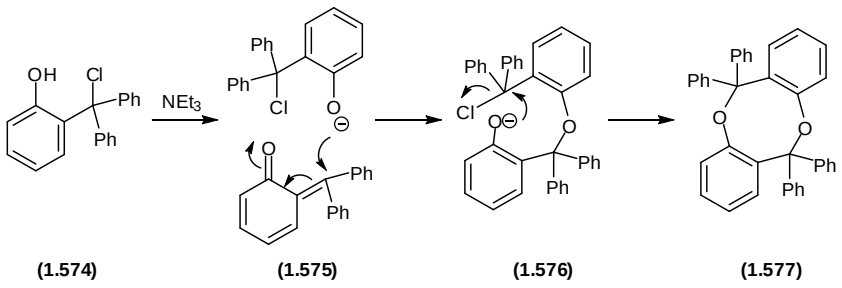
Scheme 1.130 : Applications of photolabile QM precursor (1.489).

An investigation into the photochemistry of phenyl substituted QM **(1.525)** (scheme 1.131) further exemplifies the alternate modes of reactivity accessible through photoexcitation. Exposure of the QM to light resulted in the formation of the 5,7-ring system **(1.572)** where as allowing the same QM to react under thermal conditions resulted in the 6,6-ring system **(1.573)**.[147,160]



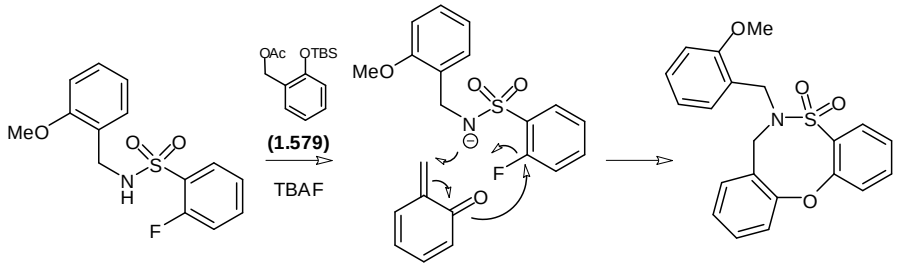
Scheme 1.131 : The differing reactivity of QM (1.525) under photochemical and thermal conditions.

Finally, in a few rare cases QMs have been observed to undergo formal [4+4] cyclisations. The atypical dimerisation of the benzyl chloride **(1.574)** was noted by Soucek *et al.* in which the macrocyclic dioxin **(1.577)** was formed rather than the usual [4+2] addition product (scheme 1.132), presumably due to the significant steric bulk around the QM due to the two aromatic rings.[161]



Scheme 1.132 : The atypical dimerisation of a sterically hindered QM.

An example of another [4+4] reaction was discovered only recently, with the observation of Hanson *et al.* that the sulfonamide **(1.578)** when exposed to the simple QM **(1.461)** underwent cyclisation to give the sultam **(1.580)** (scheme 1.133).[162] Both of these examples are thought to operate *via* stepwise rather than concerted mechanisms.

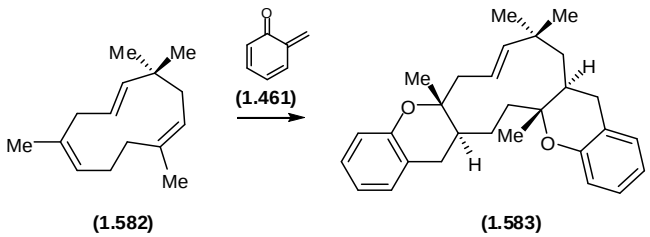


Scheme 1.133 : A rare example of a hetero [4+4] cyclisation.

1.4.5 *ortho*-Quinone Methides in Synthesis.

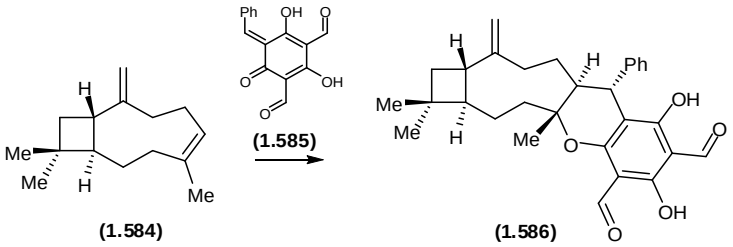
Despite the extensive examination of both their formation and reactivity very few examples of QMs being used in synthesis are found in the literature and where they are they almost exclusively focus on [4+2] cycloadditions to form chroman ring systems, with intermolecular reactions being again the most common form of such reactions. A number of interesting examples are described below.

In Baldwin *et al.*'s synthesis of the sesquiterpene natural product lucidene **(1.583)** we see the use of the simple QM **(1.461)** undergoing a double [4+2] cycloaddition with naturally derived α-humulene **(1.582)** to furnish the more complex natural product (scheme 1.134), this was believed to be a biomimetic route. The QM in this case was generated by thermolysis of 2-hydroxybenzyl alcohol.[163]



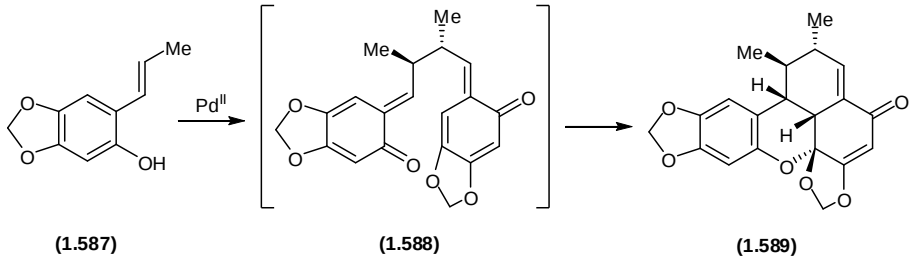
Scheme 1.134 : The biomimetic synthesis of lucidene (1.576).

In a further biomimetic approach toward the natural product guajadial **(1.586)** (scheme 1.135) Lee *et al.*[164] utilised a rather more complex QM system **(1.585)** in a cycloaddition reaction with macrocyclic alkene **(1.584)**.



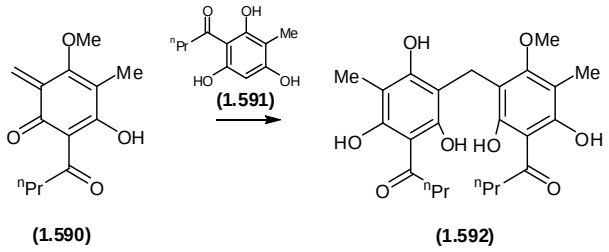
Scheme 1.135 : Utilising a highly developed QM in the synthesis of guajadial.

In a particularly elegant synthesis of carpanone **(1.589)** by Chapman *et al.* the alkene **(1.587)** underwent an oxidative coupling with a second molecule generating the bis-QM intermediate **(1.588)**, this underwent an intramolecular hetero-Diels-Alder reaction to generate the 5 contiguous stereocentres of the hexacyclic product in a single synthetic operation (scheme 1.136).[165]



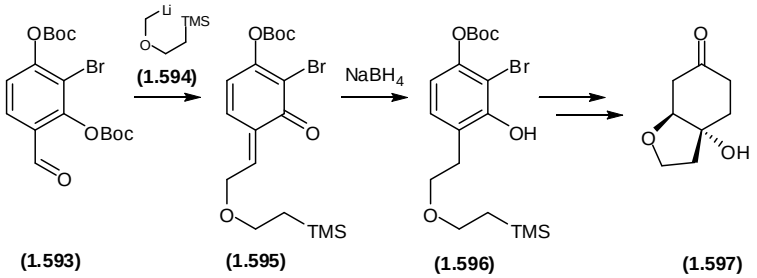
Scheme 1.136 : The efficient synthesis of carpanone.

Work by Penttila *et al.* demonstrated a rare example of a nucleophile trapping reaction, the QM **(1.590)** was found to undergo an electrophilic addition to the electron rich ring of the trisphenol **(1.591)** to give the natural product margaspidin **(1.592**) (scheme 1.137).[166]



Scheme 1.137 : Electrophilic addition to a QM in the synthesis of margaspidin.

Finally, Pettus *et al.* utilised a nucleophilic addition to the benzaldehyde **(1.593)** to generate the QM **(1.595)** *via* a transfer of a Boc group to the intermediate alkoxide and subsequent elimination of the carbonate. Reduction of the QM with sodium borohydride then gave an early intermediate **(1.596)** in the synthesis of a number of the cleroindicins, including cleroindicin C **(1.597)** (scheme 1.138).[167]



Scheme 1.138 : A general scheme for the cleroindicins including an early QM reduction.

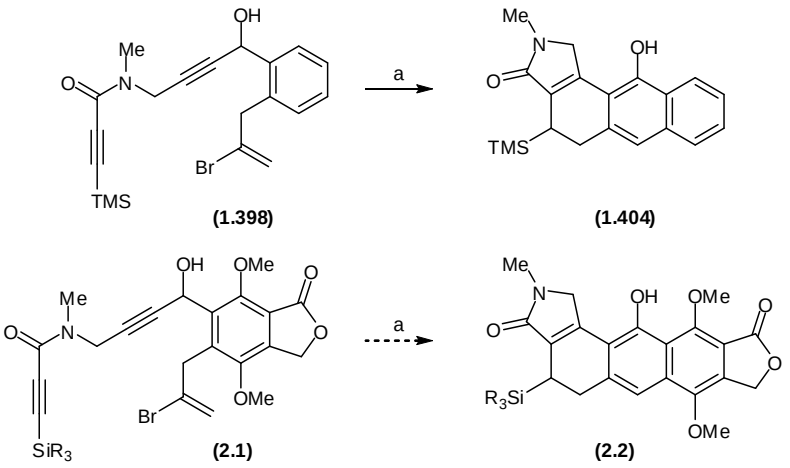
Whilst a handful of other syntheses have integrated a QM approach into their grander schemes, it is clear that the vast majority of research in this area has been focused on the theory and methodology of these sometimes ephemeral intermediates. The broad range of reactivities these intermediates display in nature is surely an indication of their huge synthetic potential in the synthesis of chromans and *ortho*-substituted phenols. However the reluctant use of this particular tool is understandable given the sometimes complex nature of both its generation and utilisation, but this only emphasises the need for further research on the subject, with a focus on developing practical synthetic methods.

2. Results and Discussion

"There's hardly a thing a man can name
Of beauty or use in life's small game,
But you can extract in alembro or jar,
From the physical basis of black coal tar:
Oil and ointment, and wax and wine,
And the lovely colours called aniline:
You can make anything, from salve to star
(If only you know how), from black coal tar." [168]

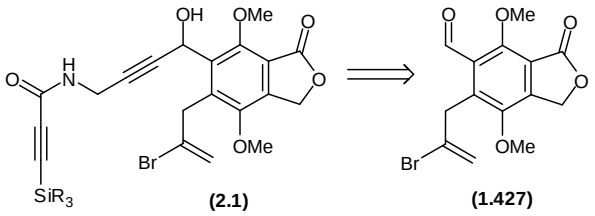
2.1 Retrosynthetic Approach.

The combined work of Parsons, Board and Waters constituted significant progress towards the synthesis of lactonamycin and as such our retrosynthetic analysis aimed to incorporate the key cyclisation they had developed as its key step (scheme 2.1). This would allow us to form key pentacycle **(2.2)** in a very short sequence from commercially available starting materials.



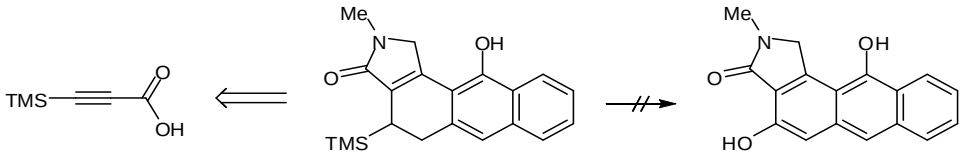
Scheme 2.1 : Reagents and Conditions: (a) Epoxyhexane, toluene, sealed tube, 150 °C, 6 hrs.

To form the precursor, it was decided to continue working toward the lactone **(1.427)** identified as a target by Board, though in our case we would focus on forming the lactone in the orientation shown (scheme 2.2) as we were confident this would enable us to proceed onward to lactonamycin. Board's unsuccessful attempts at forming this key intermediate also made it clear that an entirely new approach would be necessary.



Scheme 2.2 : Key intermediates and short term targets.

It was equally clear that we would need to develop an alternative propynoic acid to replace the TMS propynoic acid **(1.381)** as Board had established that the trimethylsilane moiety of tetracycle **(1.404)** could not be converted to the necessary phenol **(1.362)** (scheme 2.3).

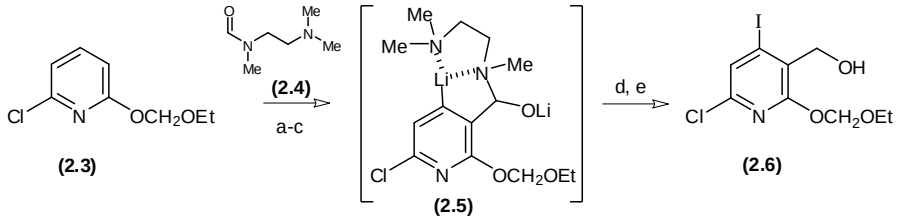


(1.381) **(1.404)** **(1.362)**

Scheme 2.3 : The need for an alternate propynoic acid.

With these three broad aims in mind, we devised a new retrosynthesis of lactonamycin (scheme 2.5) (overleaf). We envisioned the formation of cyclisation precursor **(2.1)** from benzaldehyde **(1.427)** by the well established side chain insertion methodology developed by Board, though with the inclusion of a new silyl propynoic acid derivative to circumvent the issues Board had with subsequent oxidation of the trimethylsilanes.

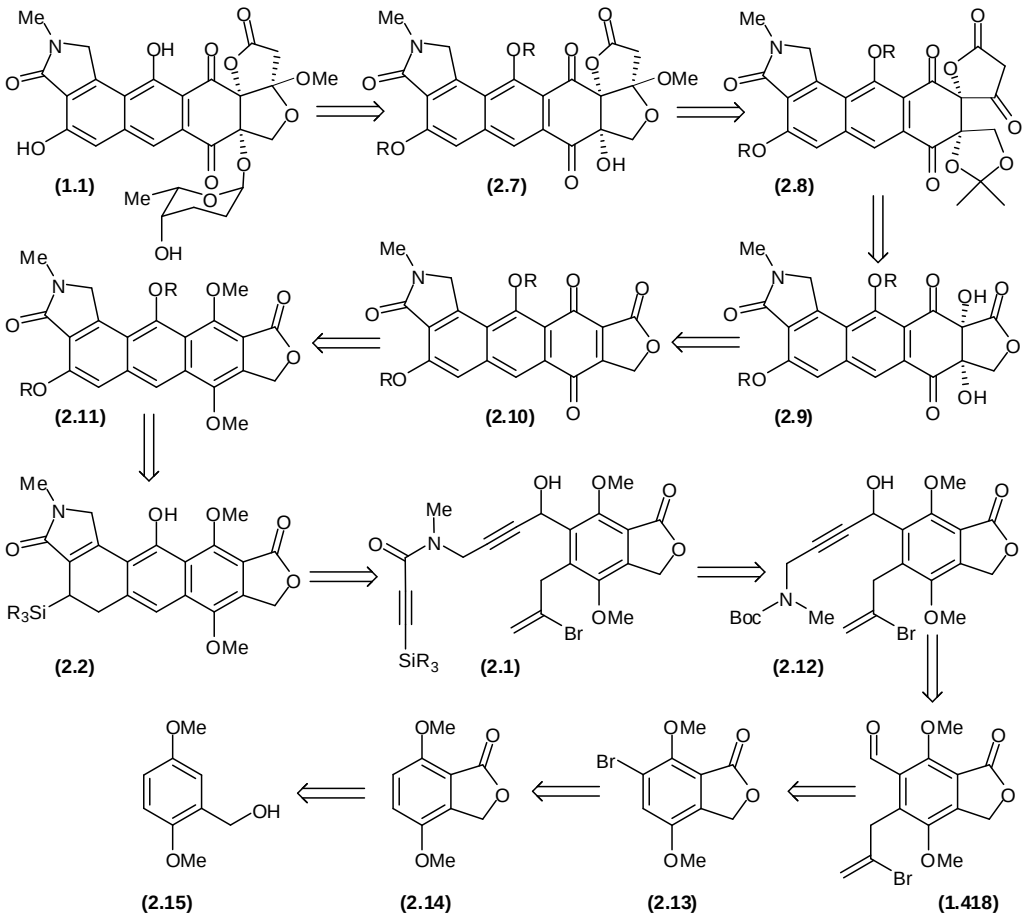
The benzaldehyde would itself be formed from bromophthalide **(2.13)** in one pot, utilising a metal-halogen exchange to form the lithiate then *in situ* formylation with the formamide **(2.4)**. The transient addition product would direct a second metalation to the *ortho* position allowing for ring alkylation to take place before acid workup give the benzaldehyde. This approach was demonstrated by Comins *et al.* during the synthesis of pyridine derivative **(2.6)** (scheme 2.4).[169]



(2.3) **(2.5)** **(2.6)**

Scheme 2.4 : Reagents and Conditions: (a) ^{n}BuLi, THF, -10 °C, 10 min; (b) **(2.4)**, -23 °C, 30 min; (c) ^{n}BuLi, -23 °C, 4 hrs; (d) I_2; (e) $NaBH_4$ (41% yield over 5 steps).

Brominated phthalide **(2.13)** (scheme 2.5) should be accessible by a simple aromatic substitution on the more electron rich position of the known phthalide **(2.14)**. The pentacycle **(2.2)** resulting from the cyclisation of ene-diyne **(2.1)** would contain all the necessary functionality to allow elaboration to the natural product **(1.1)**, the proposed route is described in greater detail below (*vide infra*, section 2.9.3).

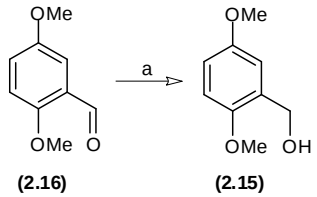


Scheme 2.5 : Retrosynthesis of lactonamycin.

2.2 Synthetic Approach.

2.2.1 Synthesis of Dimethoxyphthalide (2.14).

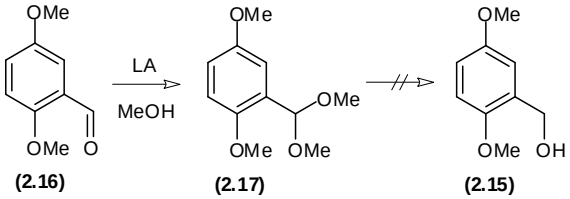
Work began with commercially available 2,5-dimethoxybenzaldehyde **(2.16)**, which was efficiently converted to the corresponding 2,5-dimethoxybenzyl alcohol with sodium borohydride in methanol according to the method of Kumar *et al.*[170] (scheme 2.6).



Scheme 2.6 : Reagents and Conditions: (a) $NaBH_4$ (1 eq.), MeOH, -20 °C to rt, 3 hrs (97%).

Whilst benzyl alcohol **(2.15)** was commercially available, the benzaldehyde was available on a kilogram scale and the yield of the conversion was such that this was the most economical method of obtaining large quantities of the benzyl alcohol for scale up. Whilst generally reliable, it was on a number of occasions necessary to further purify

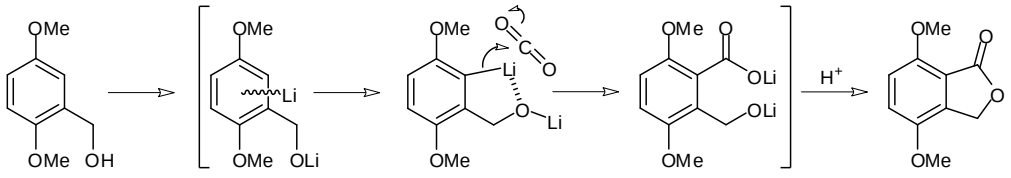
the commercially provided material, due to an unidentified inorganic impurity, that appeared to act as a Lewis acid catalysing the formation of the dimethyl acetal **(2.17)** causing the reaction to stall and lowering yields to between 50-70% (scheme 2.7). Filtration through silica gel resulted in starting material that did not undergo this undesired side reaction.



(2.16) **(2.17)** **(2.15)**

Scheme 2.7 : Proposed reason for the stalling of the reduction.

Magnus *et al.* had already described a method of forming the desired phthalide **(2.14)** as part of his partial synthesis of Dynemicin A.[171] This involved a deprotonation of benzyl alcohol **(2.15)** with two equivalents of *n*-butyllithium (scheme 2.8). The first equivalent deprotonating the alcohol and the second removing one of the aromatic protons. The dianion **(2.18)** was then allowed to undergo equilibration, resulting in the negative charge residing *ortho* to the hydroxymethyl group, this position being stabilised by coordination of the negative charge on the oxygen to lithium. Attack of the carbanion **(2.19)** on carbon dioxide at low temperature installed a carboxylate residue at that same position and subsequent acidification during workup resulted in rapid cyclisation to furnish the lactone.

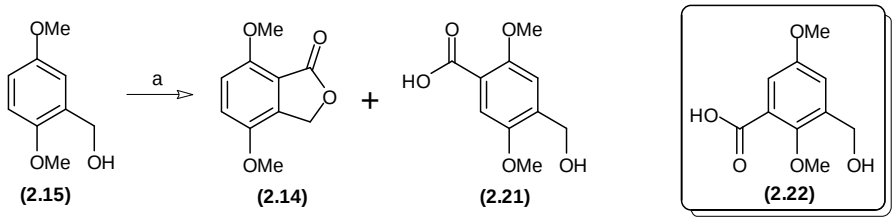


(2.15) **(2.18)** **(2.19)** **(2.20)** **(2.14)**

Scheme 2.8 : Mechanism of lactone formation.

Our methodology differed from Magnus' due to the fact we added carbon dioxide to the reaction mixture as a solid. This allowed for very rapid quenching, with comparable yields. We also established that it was essential to allow the reaction mixture to equilibrate for sufficient time and also that it was crucial to cool the reaction mixture to at least -20 °C before quenching (scheme 2.9). This was necessary to avoid the production of undesired by-product **(2.21)**. This compound was isolated in low (10-20%) yield if the aforementioned requirements were not adhered to. The formation can be explained by the attack of the kinetically generated carbanion (situated *para* to the

hydroxymethyl group) on carbon dioxide before it had a chance to equilibrate to the thermodynamically favoured *ortho* lithiate **(2.19)**. Interestingly none of the corresponding *meta*-substituted product **(2.22)** was identified under any conditions even though one might imagine this to be comparably stable to the *para* product, perhaps marginally more so.



Scheme 2.9 : Reagents: (a) 2.5M ^{n}BuLi in hexanes (2.2 eq.), THF. **Conditions:** *See table below.*

Conditions	Yield (2.14) (%)[a]	Yield (2.21) (%)[a]
-78 to 70 °C, 3.0 hrs then $CO_{2(s)}$, -20 °C, 1 hr.	65%	--
-78 to 70 °C, 1.5 hrs then $CO_{2(s)}$, -20 °C, 1 hr.	48%	20%
-78 to 70 °C, 3.0 hrs then $CO_{2(s)}$, rt, 1 hr.	55%	14%

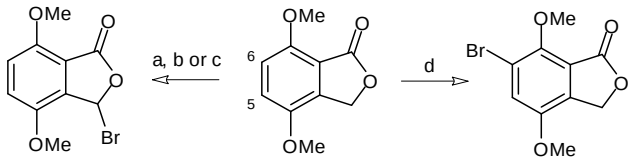
[a] Isolated yield.

2.2.2 Aromatic Bromination.

It seemed logical that an electrophilic bromination of phthalide **(2.14)** would occur at the required position. The two aromatic positions were distinguished only by their *para* substituents and as such the 6 position should prove slightly activated by the inductively electron donating *para*-methylene, while the 5 position should be deactivated by the *para*-carbonyl. *N*-bromosuccinimide has frequently been used to perform aromatic brominations,[172] with Kelly using it on a similar phthalide system in his model synthesis of the CDEF ring system (*vide supra*, scheme 1.25). However upon exposure to NBS in carbon tetrachloride, the phthalide was instead converted in high yield to the γ-bromolactone **(2.23)** (scheme 2.10).

It seemed that the reaction may be proceeding *via* a resonance-stabilised benzyl radical; under the right conditions NBS is known to undergo homolytic cleavage of the nitrogen bromine bond generating bromine radicals and this could result in the observed non-aromatic substitution. It was hoped that a change of solvent to dichloromethane, the addition of catalytic conc. sulfuric acid and performing the reaction shielded from light may close down this radical pathway in favour of the desired ionic one. However the same result was obtained, albeit in reduced yield. The ring system simply did not seem

to be sufficiently electron rich to undergo reaction with NBS, which was somewhat surprising given the electron-donating effect of the two methoxy groups. It was hoped the use of more ionic reaction conditions would allow us access to the desired product. Bromine became our preferred brominating agent and treatment of the phthalide with bromine and iron powder was intended to generate a quantity of ferric bromide *in situ*, which would act as a Lewis acid, sadly this too gave only the undesired product. Addition of a more powerful Lewis acid however proved to be the key and the addition of aluminium chloride combined with a move to acetic acid as the solvent produced the desired 6-bromophthalide **(2.13)**. Whilst a yield of 69% was good, there appeared to be some degradation of material which was attributed to the instability of the lactone ring under the strongly acidic reaction conditions.



(2.23) **(2.14)** **(2.13)**

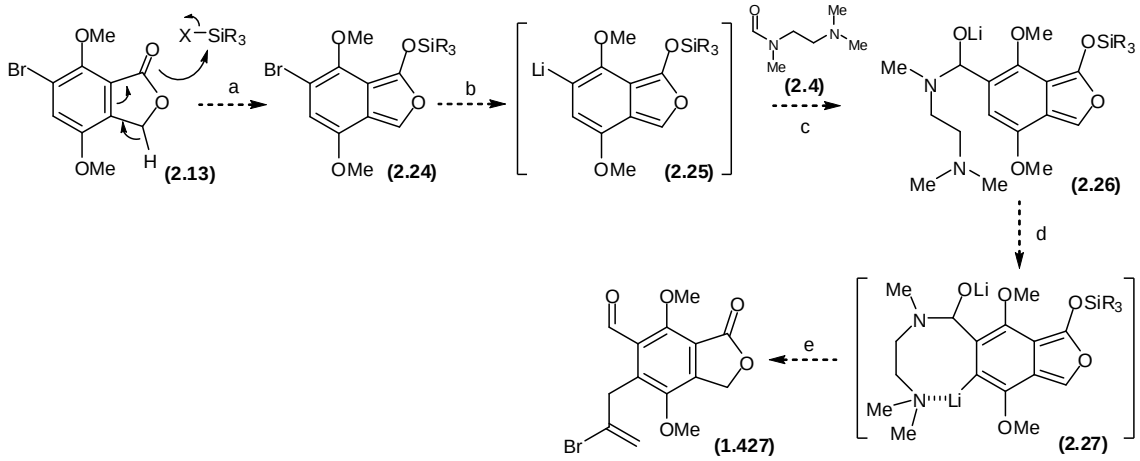
Scheme 2.10 : Reagents and Conditions: *See table below.*

	Reagent	Conditions	Product	Yield (%)[a]
(a)	NBS (1.0 eq.)	CCl_4, rt, 24 hrs.	**(2.23)**	91
(b)	NBS (1.0 eq.)	H_2SO_4 (cat.), CH_2Cl_2, rt, 12 hrs.	**(2.23)**	78
(c)	Br_2 (1.2 eq.)	$Fe_{(s)}$ (0.2 eq.), CCl_4, 2 hrs, 70 °C	**(2.23)**	45
(d)	Br_2 (1.0 eq.)	$AlCl_3$ (0.2 eq.), AcOH, 70 °C, 6 hrs.	**(2.13)**	69

[a] Isolated yield.

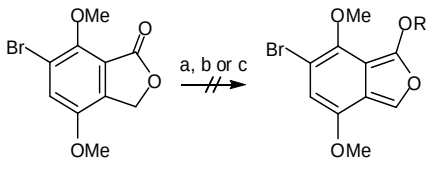
2.2.3 Attempted Functionalisation of Bromophthalide (2.13).

With the bromine in place it was hoped this would act as a synthetic handle allowing further functionalisation of the ring. As we intended to functionalise the bromide through a lithium-halogen exchange process it was anticipated that the acidic protons of the lactone may give rise to complications. The phthalide ring system would therefore need to be masked. We had hoped to achieve this by treating the benzolactone **(2.13)** with base and trapping the resulting enolate as the silyl ether **(2.24)** (scheme 2.11). The resulting furan should then be stable under lithium-halogen exchange conditions allowing the functionalisation of both ring positions in a single pot, as per the example of Comins *et al.* (*vide supra*, scheme 2.4).[169]



Scheme 2.11 : Reagents and Conditions: (a) Silylation; (b) Lithiation; (c) Addition of amide **(2.4)**; (d) Amine stabilised deprotonation; (e) Addition of 2,3-dibromopropene followed by acidic workup.

It was clear from the literature that the protection of the phthalide may not be entirely straightforward. Bloomer and Lankin had found that attempts to silyl protect a similar phthalide system with TMS or TES chlorides had invariably resulted in silylation at the benzylic carbon rather than the desired oxygen.[173] Kelly *et al.* had also struggled with a similar protection in their own work on lactonamycin (*vide supra*, scheme 1.26), they too had found that the use of TMS chloride resulted in preferential *C*-silylation. Only by switching to the bulkier TBS chloride did they manage to direct addition to the oxygen. This seems to suggest that the anion is principally localised on the carbon and that the degree of *O*-silylation is determined purely by the steric bulk of the incoming silyl group. As it was thought we may need to isolate the intermediate silyl enol ether we opted for the bulkier TIPS group, we also elected to utilise the triflate rather than the chloride as this would hopefully prove more oxophilic.[174] Deprotonation of the phthalide **(2.13)** with LDA appeared to produce the brightly coloured anion in solution as expected, but quenching with the TIPS triflate did not produce any of the desired product **(2.24a)** (scheme 2.12).

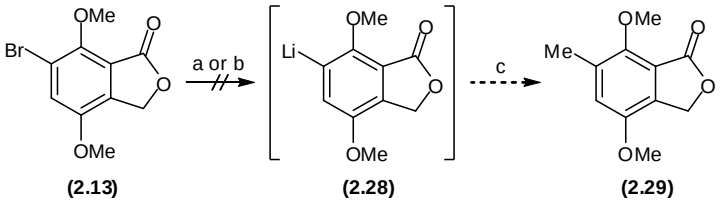


Scheme 2.12 : Reagents and Conditions: (a) LDA -78 °C to -20 °C, Et_2O then TIPSOTf -20 °C to rt; (b) MeLi -95 °C to -70 °C, Et_2O then TIPSOTf -70 °C to rt; (c) LDA -78 °C to -20 °C, Et_2O then TBSCl -20 °C to rt.

Concerned that the LDA may be reacting in an undesired manner we also attempted the

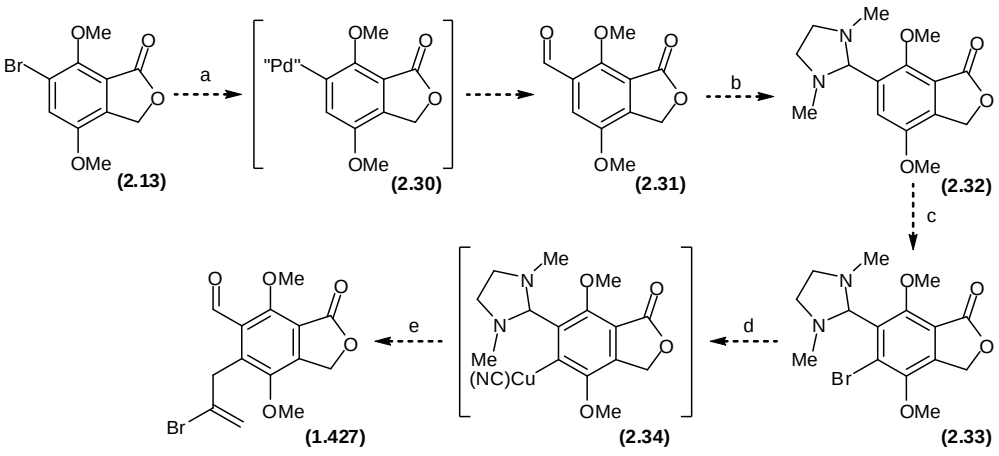
reaction, using methyllithium as a base, unfortunately this resulted in polymerisation of the material. With these setbacks we resorted to using TBS chloride as per Kelly *et al.*'s example reasoning that the TIPS group had simply been too bulky, however the reaction with TBS chloride also failed to deliver any of the silylenol ether **(2.24b)**.

The unexpected failure of these silyl protections forced us to consider functionalising the bromide by alternate means. To rule out the possibility of direct lithium-halogen exchange, this area was briefly investigated (scheme 2.13). Treatment of the bromide **(2.13)** with either ^{t}BuLi or ^{n}BuLi and then attempting to simply quench the lithiate **(2.28)** with methyl iodide resulted in extremely messy reactions and an intractable mixture of products.



Scheme 2.13. Reagents and Conditions: (a) ^{t}BuLi (2 eq.), -78 °C to -10 °C, Et_2O then MeI (excess); (b) ^{n}BuLi, -78 °C to -10 °C, Et_2O then MeI (excess).

With the bromine in place we were keen to persist with attempts to functionalise it. It was hoped that the aryl bromide would serve as a suitable substrate for palladium chemistry and that this may allow for the introduction of a formyl group *via* a reductive carbonylation (scheme 2.14).

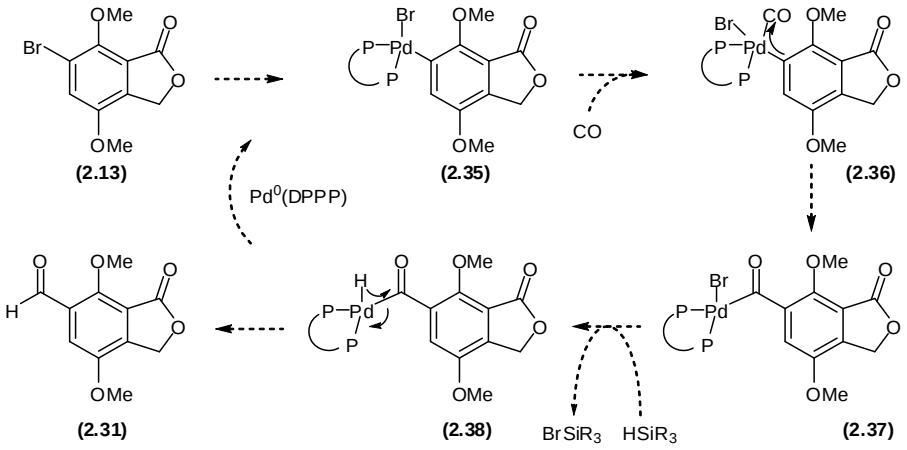


Scheme 2.14 : Reagents and Conditions: (a) Reductive carbonylation; (b) Aminal formation; (c) Bromination; (d) Lithium halogen exchange then transmetallation wih CuCN; (e) 2,3-Dibromopropene then acid workup.

The resulting benzaldehyde **(2.31)** would be converted into the aminal **(2.32)** as favoured by Board. The formation of this aminal would invert the electron demand of the remaining unsubstituted ring position allowing a further aromatic bromination to

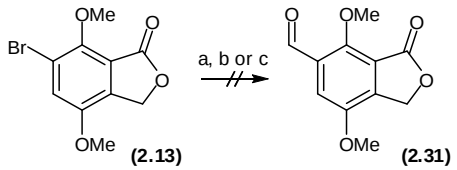
proceed giving bromide **(2.33)**. With the bromide in position and the stabilising aminal at the *ortho* position lithium halogen exchange would allow us to access the lithiate cleanly, even in the presence of the lactone. Transmetalation to the cuprate **(2.34)** would in turn allow a coupling with 2,3-dibromopropene to furnish key intermediate **(1.427)** after hydrolysis of the aminal.

Reductive carbonylation of aryl halides has traditionally been carried out using a gaseous mixture of carbon monoxide and hydrogen (synthesis gas) over a palladium catalyst, however this reaction required extremely high pressures, in excess of 80 atms.[175] Without suitable equipment available it was necessary to seek an alternative procedure; the use of an alternate source of hydride was found to lower the pressures required substantially. Stille *et al.* presented the use of alkyltin hydrides, where reactions proceeded under an atmospheric pressure of CO.[176] The appeal of those procedures was lessened by the subsequent revelation that silanes may prove equally effective at reasonable temperatures and pressures.[177] It was the work of Kotsuki *et al.* on aryl triflates that we hoped to extend to our system (scheme 2.15).[178]



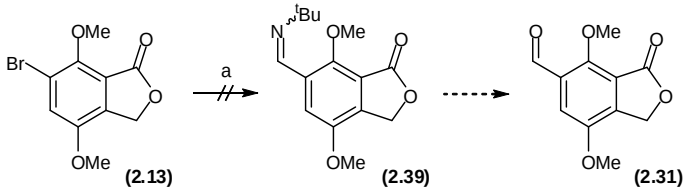
Scheme 2.15 : Mechanism of palladium mediated reductive carbonylation.

As such the aryl bromide **(2.13)** was treated with the palladium (II) acetate DPPP catalyst system under an atmospheric pressure of CO (scheme 2.16). For reasons of cost and availability we opted to use triisopropylsilane as our hydride source as opposed to the tri-*n*-octylsilane used by Kotsuki. However despite extended heating time only starting material was returned. Repeating the reaction under higher overpressures of CO failed to give any improvement, though this was not entirely surprising as the primitive pressure apparatus we had available was unable to heat the reaction mixture whilst it was under pressure.



Scheme 2.16 : Reagents and Conditions: (a) $Pd(OAc)_2$(dppp) (4 mol%), CO (1 atm), DMF then NEt_3, triisopropylsilane, 48 hrs, 70 °C; (b) $Pd(OAc)_2$(dppp) (4 mol%), CO (2 atm), DMF, NEt_3, triisopropylsilane, 48 hrs, rt; (c) $Pd(OAc)_2$(dppp) (4 mol%), CO (5 atm), DMF, NEt_3, triisopropylsilane, 24 hrs, rt.

Unable to gain access to the combined temperatures and pressures required this line of enquiry was also abandoned. Reading around this area it was shown that similar chemistry could be performed using the isoelectronic isonitriles to effect analogous imidoylations (scheme 2.17).[179] Whilst no reductive variant had been reported, the surrounding chemistry was so similar that a brief examination of a reductive variant seemed prudent. The isocyanide could be added into the reaction mixture as a liquid, simplifying our previous procedure substantially. Sadly repeating the earlier procedure with *tert*-butylisonitrile in place of gaseous CO returned only starting material.



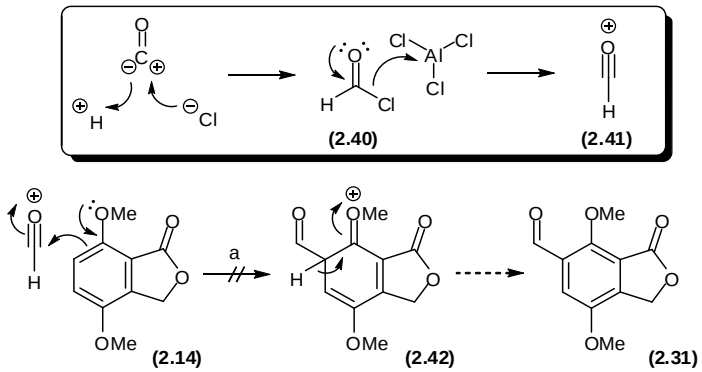
Scheme 2.17 : Reagents and Conditions: (a) $Pd(OAc)_2$(dppp) (4 mol%), ^tBuNC (excess), DMF, NEt_3, triisopropylsilane, 24 hrs, 70 °C.

Whilst it was decided to abandon palladium chemistry at this point a later publication gave some insight into a likely reason for the failure of this work. Ashfield and Barnard had also attempted to extend the method of Kotsuki to aryl bromides, with great success and whilst they found that the general conditions used in our attempts were near optimal, the choice of silane was more critical than we had anticipated.[178] They established that whilst the overall mass of the alkyl groups of the silane was unimportant, it was crucial that these groups were straight chains to prevent excessive hinderance of the silicon-hydrogen bond. Thus triethyl, tri-*n*-butyl and tri-*n*-octyl silanes were all highly effective, but the use of triisopropyl silane along with other branched silanes was found to result in low yields where it was effective at all.

2.2.4 Alternate Electrophilic Substitutions of Parent Phthalide (2.14).

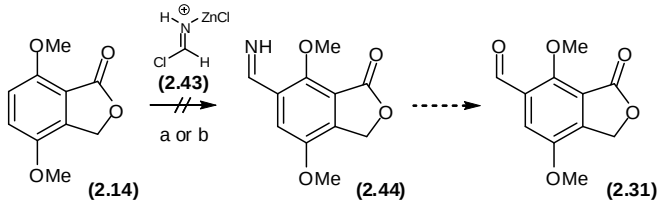
After encountering so many difficulties in our attempts to advance the synthesis from bromophthalide **(2.13)** we decided to attempt the formylation of parent phthalide **(2.14)**

directly. A review of the literature suggested a number of protocols for the direct formylation of aromatic rings.[180] The preceding work with carbon monoxide naturally drew attention to work of Gattermann and Koch where CO is used in conjunction with HCl to form the unstable formyl chloride **(2.40)** *in situ* (scheme 2.18).[181] A strong Lewis acid is then used to form the acylium ion **(2.41)** which should react readily with the aromatic ring. Exposure of the phthalide to these conditions returned only starting material.



Scheme 2.18 : Reagents and Conditions: (a) CO (5 atm), $AlCl_3$ (1 eq.), CuCl (15 mol%), 4M HCl (excess), dioxane, rt, 12 hrs.

A more reactive variant of this reaction, developed by Gattermann alone, utilises an iminium species as the active reagent formed by the addition of HCl across the triple bond of hydrocyanic acid.[182] The resulting imine **(2.44)** would then be hydrolysed to give the benzaldehyde. The preferred protocol for this reaction involves the use of zinc cyanide as this allows the generation of the volatile HCN *in situ* and generates the Lewis acid $ZnCl_2$ as a by-product. However these conditions also failed to deliver any of the desired benzaldehyde **(2.31)** or the intermediate imine (scheme 2.19).

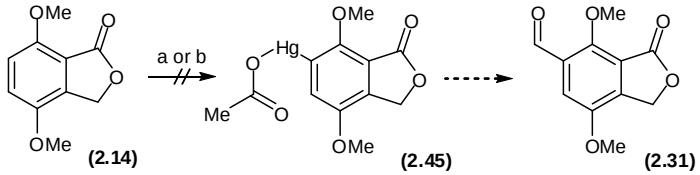


Scheme 2.19 : Reagents and Conditions: (a) $Zn(CN)_2$, $HCl_{(g)}$, Et_2O, rt, 2 hrs; (b) $Zn(CN)_2$, HCl, dioxane, Et_2O, rt, 2 hrs.

Of the remaining standard formylation protocols the Vilsmeier-Haack[183] reaction was deemed too similar in nature and reactivity to the Gattermann reaction and the behaviour of our substrate suggested it was insufficiently electron rich for the Duff protocol to be effective.[184] As such our attention was turned to the formation of a suitable precursor for a carbonylation reaction and it had come to our attention that

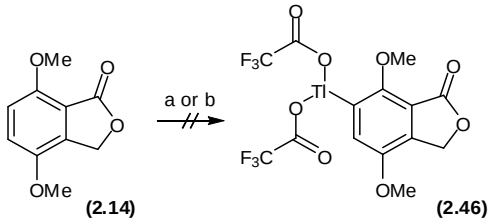
heavy metals such as mercury and thallium could be introduced to the aromatic ring by an electrophilic substitution, transmetalation with palladium then allowed both organomercury[185] and organothallium[186] compounds to act as viable carbonylation precursors.

It was suggested that organomercuration could be achieved relatively simply by stirring the aromatic compound with mercuric acetate.[187] Heating the phthalide **(2.14)** in MeCN with $Hg(OAc)_2$ did not produce the desired organomercury compound **(2.45)** and returned only starting material (scheme 2.20). It was noted that these metalations were often accelerated when carried out in acidic solvents and as such the reaction was repeated whilst exchanging the solvent for acetic acid with no change in the result observed.



Scheme 2.20 : Reagents and Conditions: (a) $Hg(OAc)_2$, MeCN, 80 °C, 12 hrs; (b) $Hg(OAc)_2$, AcOH, 85 °C, 12 hrs.

Similarly it was hoped that the organothallium species **(2.46)** would be prepared by stirring the phthalide with thallium (III) trifluoroacetate.[188] Once again only starting material was returned when heated in MeCN (scheme 2.21). This was not improved by the use of TFA as the solvent which resulted in decomposition of the starting material.



Scheme 2.21 : Reagents and Conditions: (a) $Tl(O_2CCF_3)_3$, MeCN, dark, 80 °C, 12 hrs; (b) $Tl(O_2CCF_3)_3$, TFA, dark, 70 °C, 12 hrs.

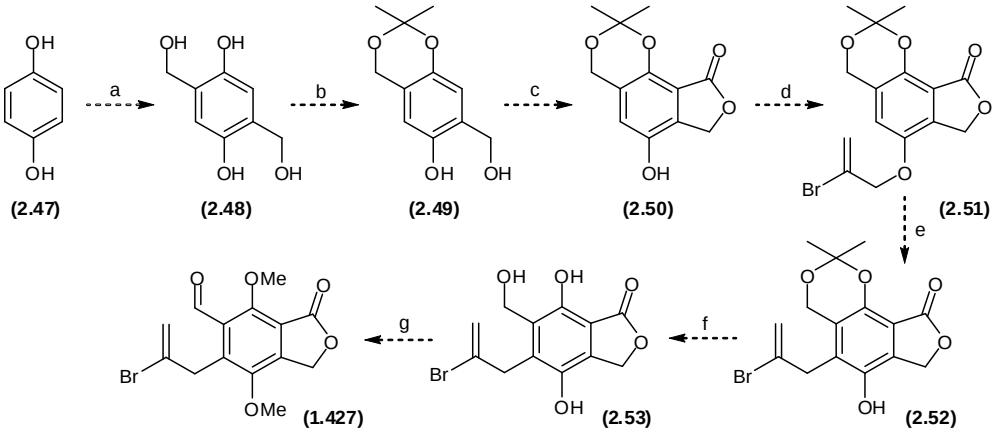
2.3 A Revised Synthetic Approach.

2.3.1 Alternate Route to Key Intermediate (1.427).

With both phthalide systems appearing to be surprisingly inert towards further functionalisation it was apparent that a more radical change in direction may be required. As phthalide system **(2.14)** had proved to be less electron rich than

anticipated, substitution had been challenging and as such we were keen to try and introduce all the necessary functionality before installing the electron withdrawing carbonyl of the lactone. It was also clear that installing the 2-bromo-allyl unit through anion chemistry would prove challenging with the base-sensitive lactone in place.

A new route was proposed which would hopefully circumvent these issues (scheme 2.22). It was known that the tetraol **(2.48)** could be derived from commercially available hydroquinone **(2.47)** through simple hydroxymethylation. It was then hoped that mono-protecting one of the 1,3-diols to give the acetonide **(2.49)** would allow the formation of the lactone **(2.50)** as previously demonstrated either *via* the trianion or through the use of a temporary phenol protection. The ether **(2.51)** would be derived from the alkylation of the free phenol with base and 2,3-dibromopropene and when heated this allyl-phenyl ether would undergo a Claisen rearrangement to give the phenol **(2.52)**. Acid hydrolysis of the acetal would restore the diol **(2.53)**. Methylation of the phenols under standard conditions and the oxidation of the benzylic alcohol would yield the fully functionalised key intermediate **(1.427)**.

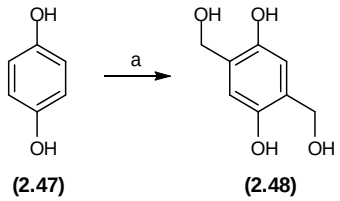


Scheme 2.22 : Reagents and Conditions: (a) Hydroxymethylation; (b) Mono-acetal protection; (c) Lactone formation; (d) Alkylation with 2,3-dibromopropene; (e) Claisen rearrangement; (f) Acetal deprotection; (g) Oxidation and methylation.

2.3.2 Hydroxymethylation of Hydroquinone (2.47).

It had been demonstrated by von Euler *et al.* that the hydroxymethylation of hydroquinone **(2.47)** to the tetraol **(2.48)** could be achieved by exposure to formaldehyde solution in the presence of base (scheme 2.23).[189] Indeed, when exposed to the literature conditions conversion to the desired product was successful, though the reaction proceeded very slowly and in very poor yield (10%). This reaction mixture was very prone to polymerisation and all attempts to increase the yield through standard

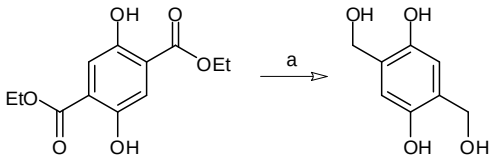
methods: increasing concentration, employing extra equivalents of formaldehyde or raising the reaction temperature resulted in this end. Exposure to light would also initiate polymerisation necessitating the use of completely opaque glassware. After optimisation a disappointing maximum yield of 15% was obtained. Though woefully inefficient this was not deemed excessively problematic as hydroquinone **(2.47)** was readily available in kilogram quantities.



(2.47) **(2.48)**

Scheme 2.23 : Reagents and Conditions: (a) Formalin (37% wt. formaldehyde) (2 eq.), NaOH, H_2O, dark, rt, 7 days (15%).

Alternatively the tetraol could also be prepared by the reduction of diester **(2.54)** with lithium aluminium hydride according to the method of Wegner *et al*. (scheme 2.24).[190] Whilst this route had numerous advantages including more reasonable reaction times and superior yields the prohibitively high price of the starting material meant it was still more economical to persist with the low yielding route.

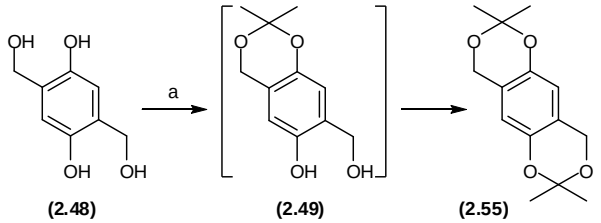


(2.54) **(2.48)**

Scheme 2.24 : Reagents and Conditions: (a) $LiAlH_4$ (4 eq.), THF, reflux, 1 hr (68%).

2.3.3 Protection of Tetraol (2.48).

With the tetraol **(2.48)** in hand, we envisaged that treatment with stoichiometric amounts of acetonide protecting agents would deliver the diol **(2.49)** required (scheme 2.25). Acetonide formation was therefore attempted with 2,2-dimethoxypropane,[191] 2-methoxypropene[191a,192] and acetone[193] under a variety of conditions.



(2.48) **(2.49)** **(2.55)**

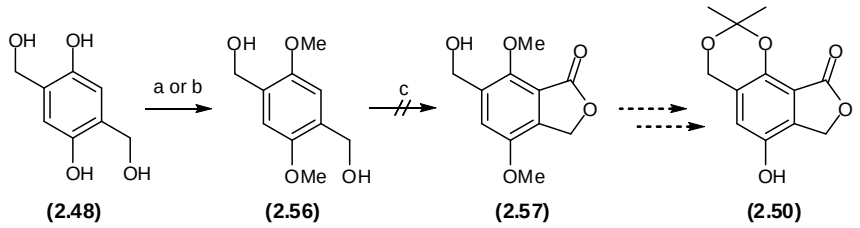
Scheme 2.25 : Reagents and Conditions: (a) *See table below.*

Reagent	Equivalents	Conditions	Result
2,2-Dimethoxypropane	1	pTSA (cat.), DMF, rt to 80 °C.	SM.
2,2-Dimethoxypropane	2	pTSA (cat.), DMF, rt to 80 °C.	SM.
2,2-Dimethoxypropane	5	pTSA (cat.), DMF, rt to 80 °C.	SM.
2-Methoxypropene	1	PPTS (cat.), DMF, rt to 80 °C.	SM.
2-Methoxypropene	2	PPTS (cat.), DMF, rt to 80 °C.	SM.
2-Methoxypropene	5	PPTS (cat.), DMF, rt to 80 °C.	SM.
Acetone	excess	pTSA (cat.), rt to reflux.	SM.
Acetone	excess	H_2SO_4 (cat.), rt.	**(2.55)**[a]
2-Methoxypropene	5	H_2SO_4 (cat.), MeCN, rt to reflux.	SM.
2,2-Dimethoxypropane	5	H_2SO_4 (cat.), MeCN, rt to reflux.	SM.

[a] 35% isolated yield

Sadly the reactions with restricted quantities of protecting agents failed to deliver the desired product, despite extended periods of time both with and without heating only starting material was returned. Attempting to use a large excess of protecting agent in the hope of stopping the reaction before it progressed past the mono-acetonide **(2.49)** also proved impossible due to the formation of bisacetonide **(2.55)**. All these reactions were hindered by the limited solubility of the tetraol in even very polar solvents. This meant that where the monoacetonide formed it was significantly more soluble than the starting material, leading to preferential formation of a second acetonide.

With attempts at acetal protecting one of the diol units having failed it was hoped we may instead be able to protect the two phenolic hydroxyl groups of tetraol **(2.48)** as the corresponding methyl ethers (scheme 2.26). The resulting diol **(2.56)** should then undergo the required lactonisation with 3 equivalents of *n*-butyllithium and the resulting lactone could be converted to the phenol **(2.50)** through sequential demethylation and acetal formation. Methylation of the tetraol proved more challenging than anticipated, but some limited success was had, the limited solubility of the starting material once again proving problematic. The desired diol **(2.56)** was obtained, albeit in very low yields when the tetraol was treated with either methyl iodide or dimethyl sulfate in the presence of base. This material was sufficient to test the lactonisation, though disappointingly a modification of the earlier procedure (*vide supra*, scheme 2.9) gave only decomposition products. This resulted in the abandonment of this route prior to optimisation of the methylation.

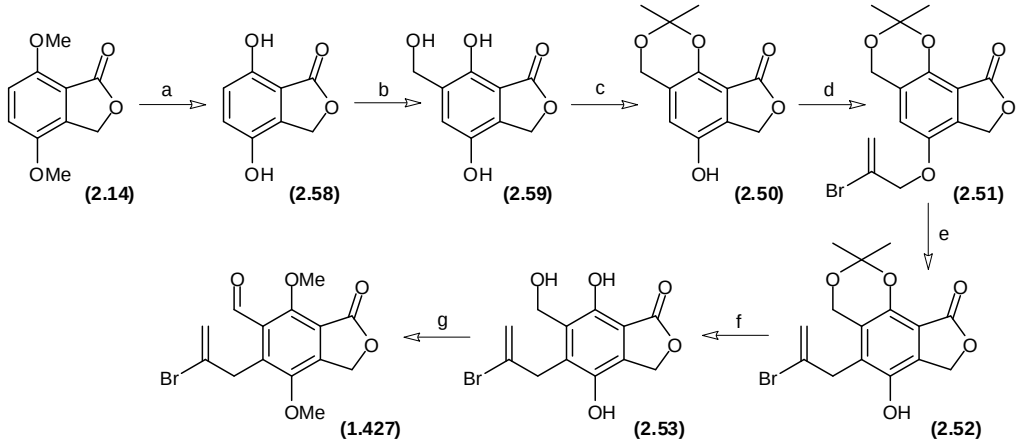


Scheme 2.26 : Reagents and Conditions: (a) MeI (excess), K_2CO_3, MeCN, 8 hrs, 60 °C (18%); (b) Me_2SO_4 (2.5 eq.), K_2CO_3, Acetone, 12 hrs, reflux (14%); (c) ^{n}BuLi (3 eq.), -78 °C to 70 °C, 3 hrs then $CO_{2\,(s)}$.

2.4 Finalised Synthetic Approach.

2.4.1 Alternate Route to Lactone (2.50).

It was at this point that a route was devised that would allow us access to the lactone intermediate **(2.50)** without needing to proceed through troublesome tetraol **(2.48)** (scheme 2.27). It was proposed that by demethylating our existing dimethoxyphthalide **(2.14)** to give the hydroquinone **(2.58)** we would activate the aromatic ring, allowing an electrophilic hydroxymethylation to occur, generating the benzyl alcohol **(2.59)**. This would allow us to selectively protect the alcohols of the 1,3-diol unit as the acetonide **(2.50)** which would be converted to the hexasubstituted key intermediate **(1.427)** by the previously described chemistry (*vide supra*, scheme 2.22).

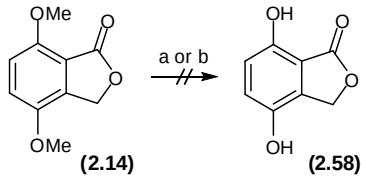


Scheme 2.27 Reagents and Conditions: (a) Demethylation; (b) Hydroxymethylation; (c) Acetonide protection; (d) Alkylation with 2,3-dibromopropene; (e) Claisen rearrangement; (f) Acetonide deprotection; (g) Oxidation and methylation.

2.4.2 Demethylation of Dimethoxyphthalide (2.14).

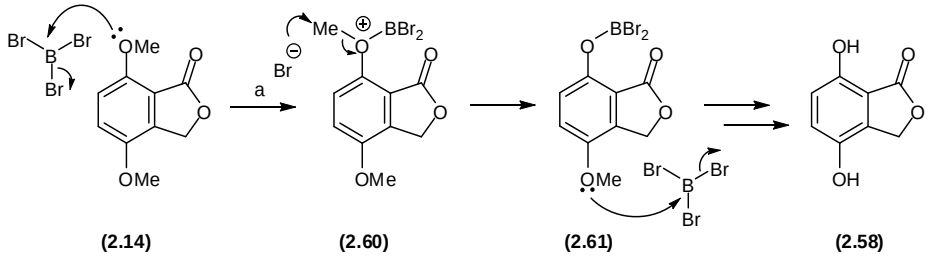
The dihydroxyphthalide **(2.58)** had been prepared previously by Myers *et al.* by a rather ponderous route that eventually revealed the target lactone by a silyl deprotection of the two phenols.[194] This resulted in some initial concern that the strongly Lewis-acidic reagents typically used to perform the demethylation could lead to degradation of the lactone ring. However Duan *et al.* had shown that iodocyclohexane could be used as a

very mild reagent for carrying out this transformation on a similar methoxy-substituted phthalide through the generation of small quantities of hydrogen iodide *in situ*.[195] Heating dimethoxyphthalide **(2.14)** with cyclohexyl iodide at 80 °C in DMF returned only starting material (scheme 2.28). It occurred that it may in fact be the thermal decomposition of DMF generating small quantities of dimethylamine at reflux that catalyses the elimination of iodide from iodocyclohexane and that 80 °C may not have been a sufficient temperature to allow this to occur; repeating this reaction at higher temperature produced the same result.



Scheme 2.28 : Reagents and Conditions: (a) CyI (10 eq.), DMF, 80 °C; (b) CyI (10 eq.), DMF, reflux.

With this failure in mind an attempt was then made to obtain the dihydroxyphthalide **(2.58)** *via* a more traditional Lewis acid mediated route. Staunton and Evans used boron tribromide to reveal a similar methoxyphthalide system in their work on citromycetin and whilst their yields were only moderate,[196] we had accepted that some degree of decomposition would be associated with such forcing conditions. When we exposed dimethoxyphthalide to BBr_3 initial yields of 60-70% of the deprotected phthalide were recorded (scheme 2.29). This was deemed high enough to carry through and we were pleased to note that upon scale-up using a freshly prepared solution of boron tribromide yields were increased significantly to 94%, suggesting fears about the stability of the lactone moiety may have been excessive.

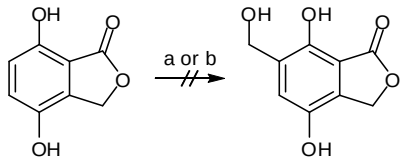


Scheme 2.29 : Reagents and Conditions: (a) BBr_3 (2 eq.), CH_2Cl_2, -78 °C to rt, 4 hrs (94%).

2.4.3 Hydroxymethylation of Dihydroxyphthalide (2.58).

Given the unfavourable results experienced in the hydroxymethylation of hydroquinone **(2.58)** (*vide supra*, scheme 2.23) we were keen to avoid the use of the same conditions. Casiraghi *et al.* had demonstrated the efficient hydroxymethylation of electron rich

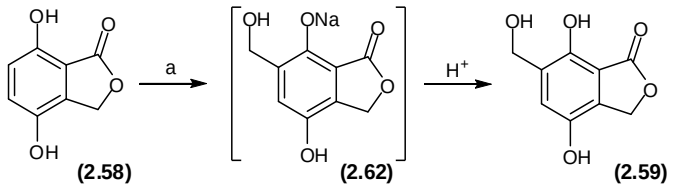
aromatics utilising a microwave based method.[197] Heating a large excess of paraformaldehyde in a sealed tube should lead to thermal depolymerisation, generating a significant pressure of formaldehyde gas, in the presence of the phenolic phthalide **(2.58)** this should undergo a rapid hydroxymethylation. However in our hands this method never produced any of the desired product **(2.59)** (scheme 2.30).



(2.58) **(2.59)**

Scheme 2.30 : Reagents and Conditions: $(CH_2O)_n$ (10 eq.), DME, *p*-xylene, 135 °C, MW, 12 hrs; (b) Formalin (37% wt. Formaldehyde), CaO, H_2O, dark, rt.

A formalin based approach using calcium oxide as the base was also attempted, with no success.[198] However a test reaction using the earlier conditions was surprisingly successful with hydroxymethylation actually proceeding in good yield (scheme 2.31). The reaction was still painfully slow and prone to polymerisation but the desired triol **(2.59)** was delivered in 65-80% yield depending on the degree of polymerisation observed. We were pleased to observe complete selectivity for the desired substitution position as anticipated.



(2.58) **(2.62)** **(2.59)**

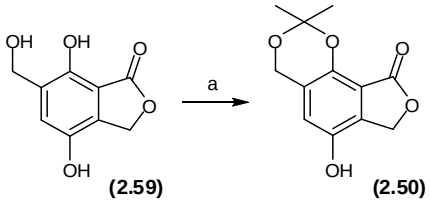
Scheme 2.31 : Reagents and Conditions: (a) Formalin (37% wt. Formaldehyde), NaOH, H_2O, dark, rt, 6 days (65-80%).

We were also able to isolate the intermediate tentatively assigned as sodium alkoxide salt **(2.62)** where the reaction mixture was not sufficiently acidified during workup, emphasising the notable difference in pK_a between the two phenolic protons.

2.4.4 Selective Alkylation of Triol (2.59).

The acetal protection of the 1,3-diol unit of the triol **(2.59)** proceeded smoothly. Treatment with 2,2-dimethoxypropane led to ready transacetalisation in the presence of catalytic acid to cleanly afford the desired acetonide **(2.50)** in good yield (scheme 2.32). This reaction was slowed due to the poor solubility of the triol in organic solvents, however the reaction proceeded cleanly under heterogeneous conditions in acetone and

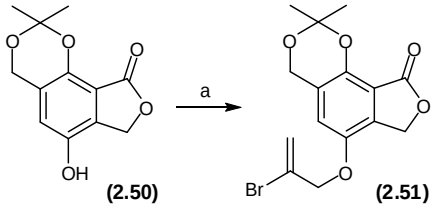
it proved a lot easier to separate our product from this reaction mixture than when more polar solvents such as DMF or DMSO were used. This reaction could occasionally become sluggish for no obvious reason, but this could be remedied by the addition of a few drops of sulfuric acid, though this tended to produce a minor amount of decomposition.



(2.59) **(2.50)**

Scheme 2.32 : Reagents and Conditions: (a) 2,2-Dimethoxypropane (5 eq.), acetone, pTSA (cat.), 60 °C, 3 hrs (87%).

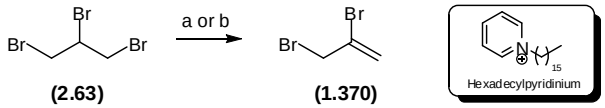
With the 1,3-diol protected as the benzodioxin **(2.50)** attachment of the 2-bromoallyl chain to the remaining exposed phenol was to be achieved using the Williamson ether synthesis. This was achieved simply, using KOH to form the alkoxide, which was able to displace the primary bromide of 2,3-dibromopropene giving the ether **(2.51)** (scheme 2.33). Prolonged heating seemed to result in some decomposition, as such it was usually preferable to halt the reaction early and harvest the product and remaining starting material.



(2.50) **(2.51)**

Scheme 2.33 : Reagents and Conditions: (a) 2,3-Dibromopropene, KOH, EtOH, 80 °C, 2.5 hrs (61% isolated yield, 81% based on recovered SM).

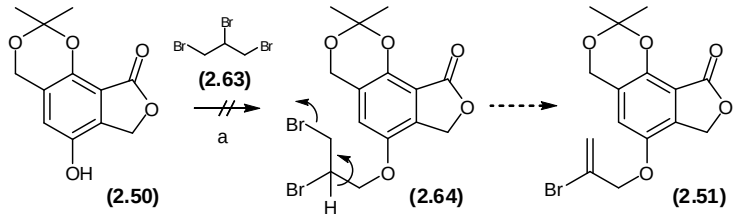
There was initially significant variation in the yield of this reaction, this was attributed to the variable quality of commercially available 2,3-dibromopropene **(1.370)** which is prone to decomposition with the generation of HBr. Freshly prepared material produced superior alkylation yields and was readily synthesised from 1,2,3-tribromopropane **(2.63)** according to a literature procedure which utilised hexadecylpyridinium bromide to allow the elimination to occur with aqueous potassium hydroxide under emulsion conditions (scheme 2.34).[199] It was also found that hexadecylpyridinium chloride could be substituted as the phase transfer agent with no ill effect and comparable yields.



(2.63) **(1.370)**

Scheme 2.34 : Reagents and Conditions: (a) Hexadecylpyridinium bromide, KOH, H_2O, reflux, 2 hrs (70%); (b) Hexadecylpyridinium chloride, KOH, H_2O, reflux, 2 hrs (66%).

The literature also noted examples of the formation of 2-bromoallyl ethers from 1,2,3-tribromopropane directly through an *in situ* elimination of an intermediate alkyl bromide **(2.64)** (scheme 2.35).[200] This alkylation route proved unsuccessful when applied to the phenol **(2.50)** with the reaction returning starting material and decomposition products.



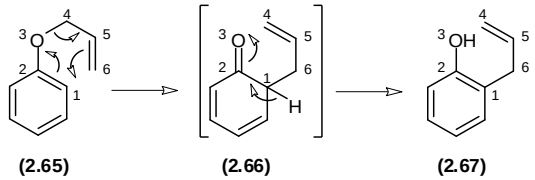
(2.50) **(2.64)** **(2.51)**

Scheme 2.35 : Reagents and Conditions: (a) **(2.63)**, NaOH (2 eq.), EtOH, reflux.

2.5 Effecting the Claisen Rearrangement.

2.5.1 The Claisen Rearrangement of β-Bromoallyl Phenyl Ethers.

The Claisen rearrangement was the first of a series of [3,3]-sigmatropic rearrangements to be discovered in the early 20th century and it continues to this day to provide a powerful method of forming carbon-carbon bonds; converting an allyl vinyl ether into a continuous carbon chain terminated with a carbonyl. In the case of the aromatic rearrangement the ketone generated undergoes rapid tautomerisation to generate an *ortho*-allyl phenol (scheme 2.36).

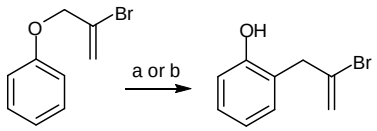


(2.65) **(2.66)** **(2.67)**

Scheme 2.36 : Mechanism of the aromatic Claisen rearrangement.

The structural constraints of our system precluded any of the regioselectivity concerns that can sometimes accompany the rearrangement with the *para* position already substituted and only one of the two *ortho* positions available. In addition, the α,γ-unsubstituted allyl group would mean that the abnormal rearrangement was not of concern. There was also adequate precedent for the rearrangement of the 2-bromoallyl

phenyl ether **(2.68)**, with both Baldwin *et al.*[201] and Sarpong *et al.*[202] providing examples (scheme 2.37). As such we felt confident that the presence of bromine on the β-carbon would not prove deleterious.



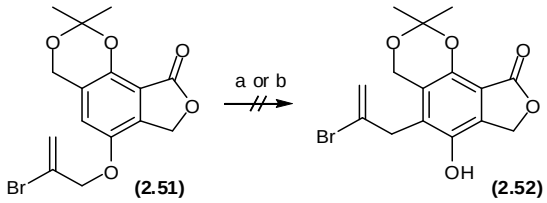
(2.68) **(2.69)**

Scheme 2.37 : Reagents and Conditions: (a) *N*,*N*-Diethylaniline, sealed tube, 200 °C (76%); (b) Et_2AlCl, hexanes, 0 °C to rt, 15 hrs (75%).

2.5.2 The Claisen Rearrangement in Practice.

Microwave heating methods have a number of advantages when trying to perform organic reactions and the Claisen rearrangement is no exception.[203] The use of sealed reaction vessels allowed us to perform reactions at temperatures significantly higher than the boiling points of the solvents (at atmospheric pressure) in use. It has also been demonstrated that due to the negative ΔV of activation associated with the Claisen rearrangement increased pressure will increase the rate of reaction.[204] There are also suggestions that there may be specific advantageous microwave effects that arise entirely separately from the thermal effects of microwave irradiation.[205] As such we endeavoured to use microwave heating where it was practical to do so.

Our first attempt at effecting the rearrangement of the ether **(2.51)** saw it undergo microwave heating in toluene at 150 °C (scheme 2.38). This returned only starting material though we were aware that the temperature of this reaction was at the low end of the range of effective temperatures for aromatic Claisen rearrangements.[206] One disadvantage to microwave methodology was that non-polar solvents such as toluene are very poor microwave absorbers, this gave toluene (and similarly apolar solvents) an effective maximum temperature of 150 °C with the equipment available.



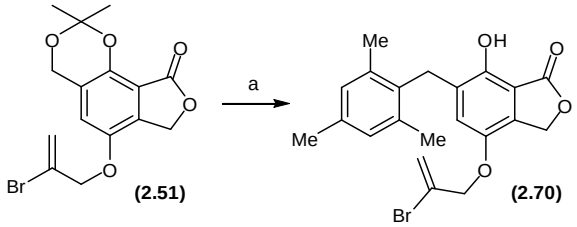
(2.51) **(2.52)**

Scheme 2.38 : Reagents and Conditions: (a) Toluene, 150 °C, MW, 6 hrs; (b) DMSO, 210 °C, MW.

Wishing to persist with microwave heating our next approach was to use a higher boiling, polar solvent which would be a better microwave absorber. DMSO seemed to

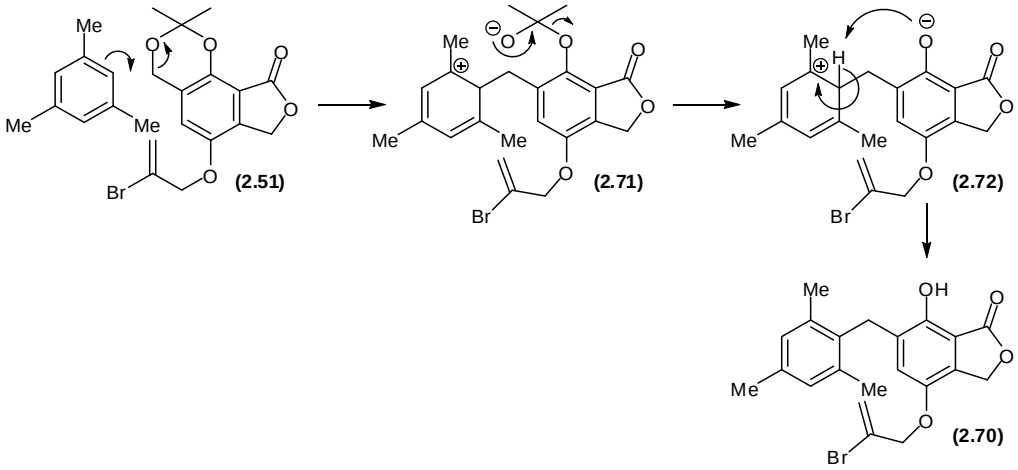
meet these requirements, however heating this mixture at 210 °C was found to result in explosive decomposition and as such DMSO was quickly abandoned as a solvent.

With our generic conditions proving ineffectual, a further examination of the literature was carried out; Khan *et al.* recorded the transformation of a similarly substituted 2-bromoallyl ether by heating the substrate in refluxing mesitylene.[207] When the acetonide **(2.51)** was heated under similar conditions (scheme 2.39) we were delighted to see a promising new spot by TLC, the product isolated however was not the product of a Claisen rearrangement but the unforeseen mesityl adduct **(2.70)**.



Scheme 2.39 : Reagents and Conditions: (a) Mesitylene, reflux, 24 hrs (78%).

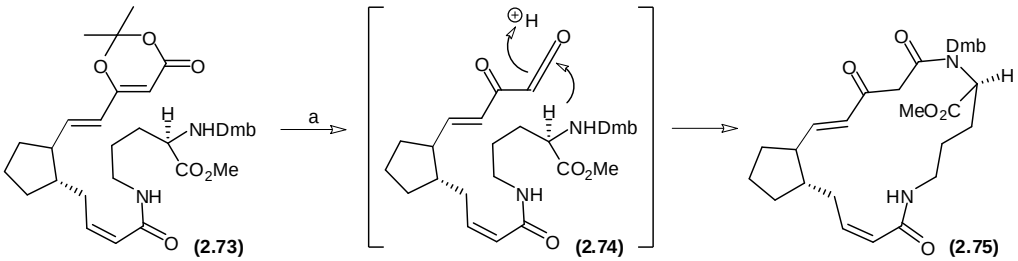
There was some initial uncertainty about the mechanism of this transformation; though the product appeared to be the result of a nucleophilic displacement at the benzyl position of the acetonide (scheme 2.40) there was little evidence of mesitylene acting as a nucleophile in the absence of a Lewis acid-activated electrophile and nor did the sterics seem particularly favourable.



Scheme 2.40 : Proposed mechanism for the addition of mesitylene to acetonide (2.51).

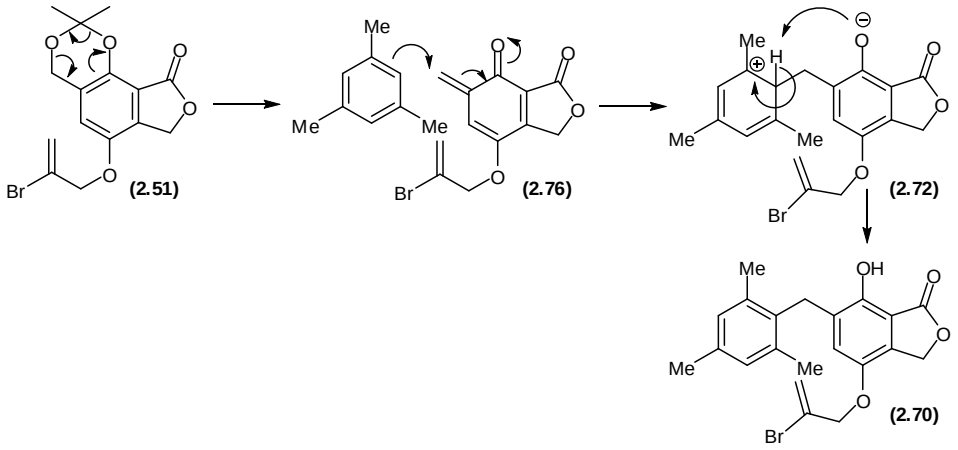
We were reminded of the work of Boeckman and Perni who through the course of their work on the synthesis of ikarugamycin (scheme 2.41) developed a novel macrolactamisation method that worked through the thermally induced extrusion of acetone from the acetonide **(2.73)**.[208] The resulting β-ketoketene **(2.74)** is rapidly

attacked in an intramolecular addition of the hindered secondary amine to give the macrocycle **(2.75)**.



Scheme 2.41 : Reagents and Conditions: (a) Toluene, 110 °C, 5 hrs (80%).

This led us to consider whether a similar extrusion of acetone was occurring in the case of acetonide **(2.51)** to generate an analogous enone intermediate. A review of the literature revealed a wealth of examples of such enones, and while no such quinone methide had been generated from a benzodioxin precursor without acid catalysis there was sufficient evidence to suggest it would be entirely reasonable. As such the formation of mesitylene adduct **(2.70)** was explained by the acetonide **(2.51)** undergoing a thermal retro-hetero-Diels-Alder reaction releasing acetone and generating the quinone methide intermediate **(2.76)** *in situ* (scheme 2.42). This highly reactive intermediate would be sufficiently electrophilic to add to the aromatic ring of a solvent molecule, rearomatisation of the intermediate adduct **(2.72)** would give the observed product.

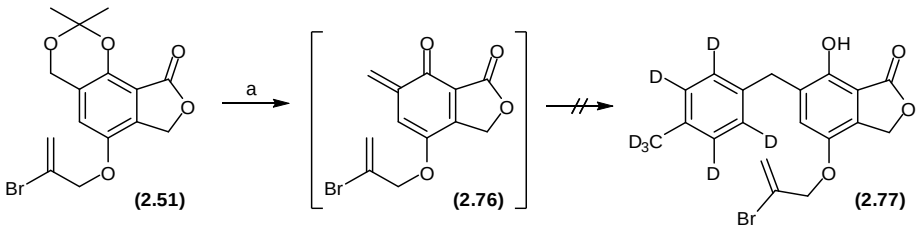


Scheme 2.42 : Revised mechanism for the addition of mesitylene to acetonide (2.51).

To further explore this mechanism and hopefully confirm our suspicions an NMR study was conducted. A sample of the precursor **(2.51)** was dissolved in toluene-d_8 inside a sealed NMR tube, it was hoped that by heating this solution and periodically recording

its NMR spectrum we might track the progress of the reaction and observe the formation and consumption of the enone intermediate. The use of conventional heating allowed us to heat the solution to the higher temperatures required for reaction.

Sadly no intermediates could be identified in the spectra with the starting material appearing to steadily decompose upon heating (figure 2.1). However we did observe the gradual disappearance of the methyl protons of the acetonide at 1.39 ppm and this was coupled with a corresponding increase in intensity of a peak at 1.58 ppm congruent with the methyl protons of acetone in toluene-d_8. From this information it was also possible to gain a qualitative grasp of the rate of reaction at different temperatures, with acetone extrusion occurring only relatively slowly below 170 °C. These data were also consistent with a scenario in which the retro-Diels-Alder was occurring as proposed, generating acetone. However the reactive enone generated was then unable to react with the solvent, the ring of toluene being less electron rich than in trimethylbenzene, the very low concentration also precluded dimerisation resulting in thermal degradation of the reactive intermediate preventing it being observed in the NMR spectra (scheme 2.43). This supports the proposal that the extrusion of acetone is a spontaneous pericyclic reaction, rather than one initiated by a nucleophilic attack by the solvent.



Scheme 2.43 : Reagents and Conditions: (a) *See figure 2.1.*

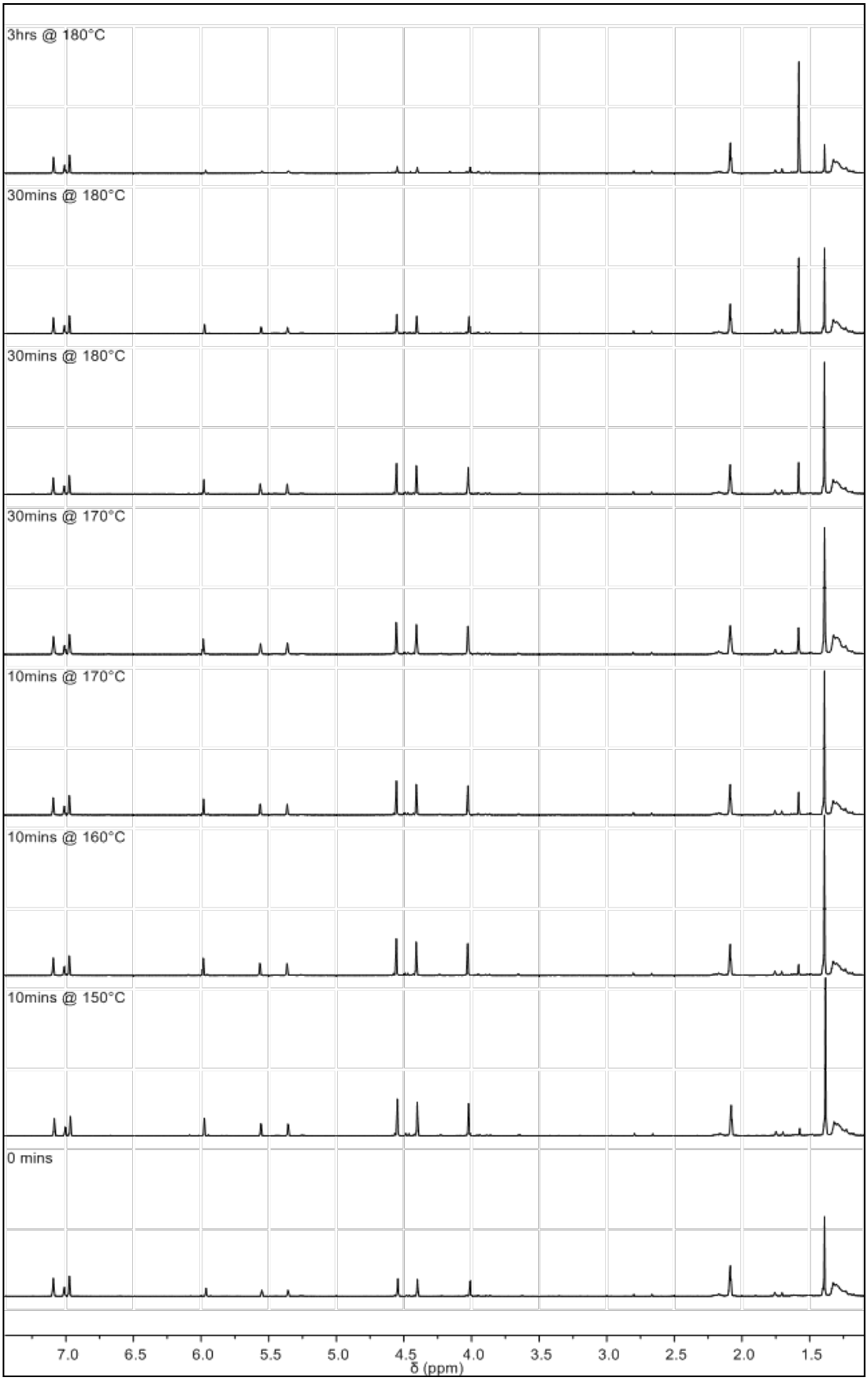
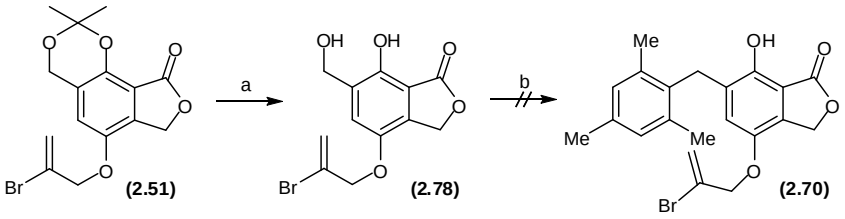


Figure 2.1 : Sealed tube NMR studies heating (2.51) in toluene-d_8.
(All heating durations are sequential.)

2.5.3 Catalysis of the Claisen Rearrangement and Avoiding QM Formation.

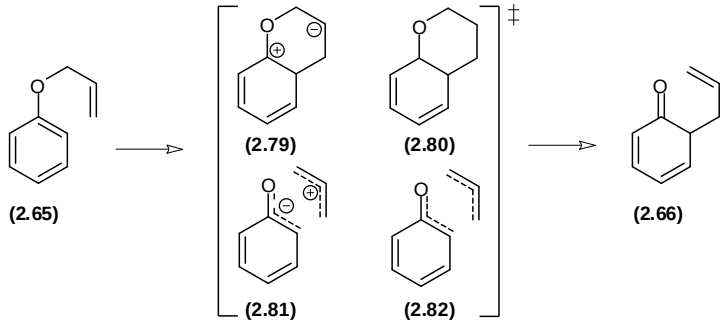
Before we could effect a synthetically useful Claisen rearrangement it would be necessary to identify conditions which would achieve the rearrangement in isolation. The literature suggested that QM formation from benzyl alcohol precursors tended to require higher temperatures than those we were using to effect the rearrangement. Thus it was hoped that deprotecting acetal **(2.51)** to reveal the 1,3-diol would help to prevent the thermolytic elimination and inhibit the undesired mode of reactivity. The deprotection was achieved by heating the acetonide at reflux in a 50% aqueous AcOH solution to give the corresponding *ortho*-hydroxybenzyl alcohol **(2.78)** in quantitative yield (scheme 2.44). It was rewarding to note that when heated in mesitylene this deprotected substrate did not form the mesityl adduct. The reaction was also attempted in decalin[209] but that too only resulted in decomposition.



Scheme 2.44 : Reagents and Conditions: (a) AcOH/H_2O (1:1), 60 °C, 2.5 h (quant.); (b) Mesitylene, reflux, 24 hrs.

With our experiments so far failing to deliver any material which had undergone the desired Claisen rearrangement irrespective of the troublesome side reactions, we were led to consider why the material had proved so reluctant to rearrange when equivalent reactions had been carried out successfully by numerous preceding authors.

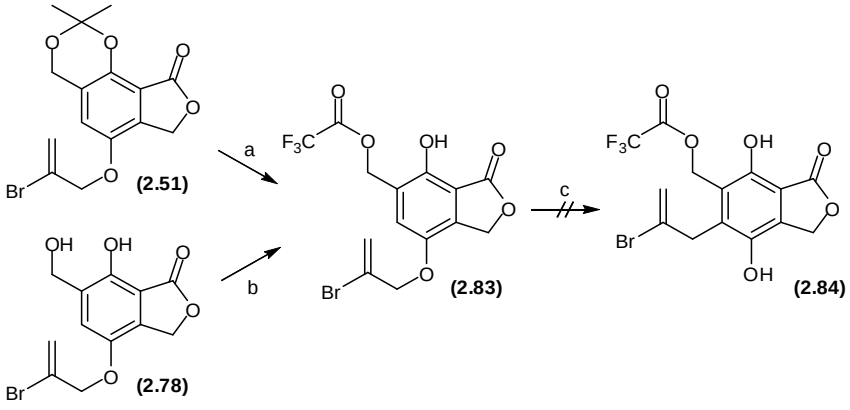
The Claisen rearrangement, whilst being relatively simple on paper, presents a far more complicated proposition when trying to understand its true mechanism and hence the means by which it can be accelerated. The consensus of many years of research seems to suggest that the transition state of the rearrangement displays the mixed characteristics of a number of different forms (scheme 2.45).[210] These are defined by whether they are ionic or radical in nature and whether the compound experiences early bond making, or early bond breaking. The specific substituent pattern in the precursor and the solvent and catalysis conditions in which the reaction is carried out heavily affect the dominant form of the transition state and as ever it is the ability of the aforementioned to stabilise that transition state that affects the rate of rearrangement.



Scheme 2.45 : The complex nature of the Claisen transition state.

Whilst there is surprisingly little discussion in the literature about substituent effects in the aromatic Claisen there was evidence to suggest that the *para*-alkoxy residue would be mildly activating with respect to the Claisen and that the remaining substituents should exhibit very little influence.[211] With no apparent reason why our substrate should be intrinsically less reactive than the literature examples, we were resolved to press on with this course and with a great deal of research dedicated to the catalysis of the rearrangement we were confident that an appropriate set of conditions would be revealed.[212]

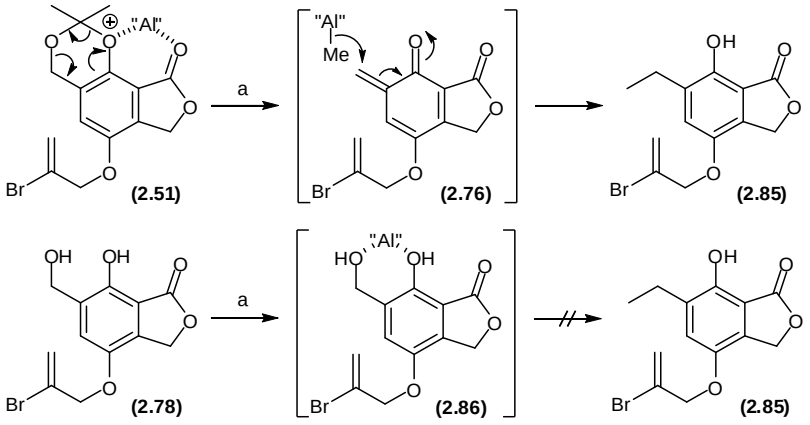
It was noted that the Claisen rearrangement may be catalysed by Brønsted acids, with protonation of the etheric oxygen acting to alter the transition state further towards the ion pair structure **(2.81)** which is stabilised by the acid. Remarkable rate increases have been demonstrated by Svanholm *et al.* using TFA as both solvent and acid catalyst.[213] It was appreciated that the use of such conditions would risk forming the trifluoroacetate ester **(2.84)**, but this ester could be easily removed should the compound undergo the much sought after Claisen reaction simultaneously. When acetonide **(2.51)** or the diol **(2.78)** were stirred in TFA at room temperature only the esterified product **(2.83)** was isolated (scheme 2.46).



Scheme 2.46 : Reagents and Conditions: (a) TFA, rt, 3 hrs (97%); (b) TFA, rt, 2 hrs (96%); (c) TFA, 60 °C, 12 hrs.

It is unclear whether this compound resulted from a QM based mechanism, which may also be catalysed by the strongly acidic conditions.[214] Alternatively a simple esterification may have been responsible, the prior deprotection of the acetonide precursor being attributable to the 0.5% water present in commercially supplied TFA.[215] Further exposure of the ester **(2.83)** to TFA at elevated temperature still failed to deliver the rearranged product **(2.84)**.

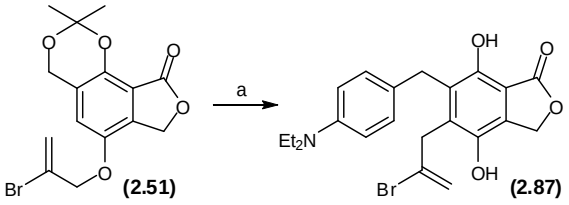
Lewis acids accelerate the rate of the Claisen rearrangement through a similar polarisation of the transition state. Wipf and Ribe found that a methylaluminoxane based catalyst generated *in situ* from trimethylaluminium and water was highly effective at catalysing the Claisen at low temperature.[214] It was hoped that this would avoid the generation of the QM intermediate allowing the Claisen reaction to occur exclusively. Exposure of the acetonide **(2.51)** to the aluminoxane catalyst resulted in a further example of a benzyl substituted product (scheme 2.47). The acid catalyst was able to generate the enone **(2.76)** and then a source of methyl anion from either the mixed polymeric aluminoxane or residual $AlMe_3$ was able to add to this system generating the ethylphthalide derivative **(2.85)**. The unprotected diol **(2.78)** displayed no reactivity under the same conditions, presumably due to chelation of the catalytic species by the 1,3-diol.



Scheme 2.47 : Reagents and Conditions: (a) $AlMe_3$ (4.5 eq.), H_2O (1 eq.), CH_2Cl_2, -30 °C, 10 mins then **(2.51)** or **(2.78)** -30 °C to rt overnight (64% from **(2.51)**).

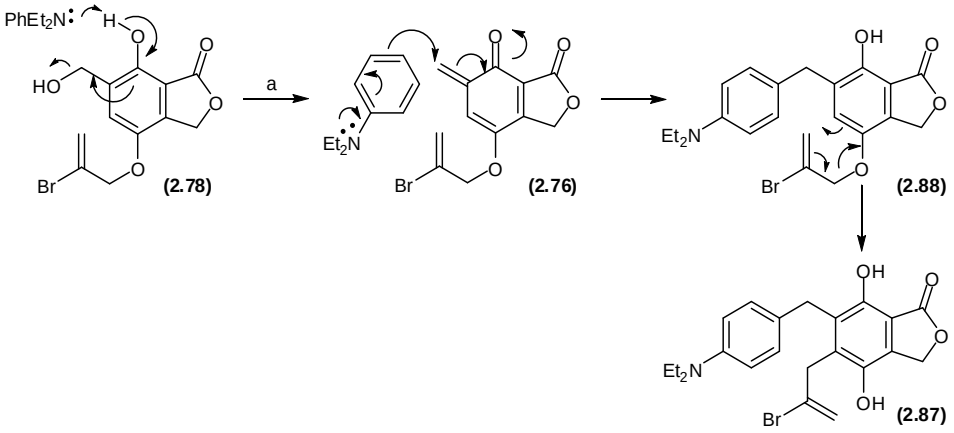
Solvent effects have been shown to have a significant effect on the rate of the Claisen rearrangement, with the rate of reaction becoming more rapid with an increase in the polarity of the reaction solvent due to improved solvation of the polarised transition state.[211b,215] It was therefore desirable to identify a solvent that was not only polar but also sufficiently high boiling to enable access to workable reaction temperatures.

N-methylpyrrolidinone was utilised as a Claisen rearrangement solvent by Robertson *et al.* in their synthesis of the $5HT_3$ antagonist zatosetron.[216] Initial results with acetonide **(2.51)** proved promising, with the development of promising peaks in the crude NMR spectrum. The reaction profile was very messy though and the mixture proved utterly intractable. *N*,*N*-diethylaniline shared a number of the same solvent properties and it was hoped that its slightly more greasy nature would make separation of products easier. It had also been successfully utilised by Baldwin *et al.* (*vide supra*, scheme 2.37).[201] When the acetonide was heated at 220 °C for 30 minutes only decomposition products were observed (scheme 2.48), however reducing the temperature to 200 °C produced a single product in which we observed a sadly familiar addition to the benzylic position through the *para* carbon of the aniline, however the resulting phenol **(2.87)** also exhibited the first example of a successful Claisen rearrangement!



Scheme 2.48 : Reagents and Conditions: (a) *N*-Methylpyrrolidone, 220 °C, MW, 1 hr (no yield); (b) *N*,*N*-Diethylaniline, 220 °C, MW, 30 mins (no yield); (c) *N*,*N*-Diethylaniline, 200 °C, MW, 30 mins (44%).

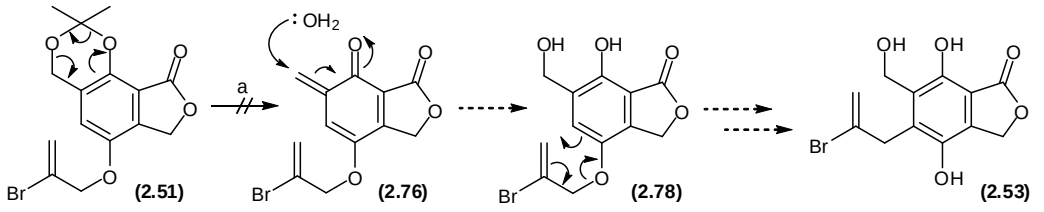
Optimistic that we could avoid the addition of the aniline we subjected the deprotected Claisen precursor **(2.78)** to the same reaction conditions with the hope that the diol would prove more resistant to enone formation. To our dismay the same product aniline **(2.87)** resulted. This may reasonably be explained as the result of base catalysis, with the aniline able to catalyse the extrusion of hydroxide anion under the basic reaction conditions (scheme 2.49).



Scheme 2.49 : Reagents and Conditions: (a) *N*,*N*-Diethylaniline, 200 °C, MW, 30 mins (50%).

The decision to show the Claisen rearrangement occurring after formation of the QM is arbitrary, with no evidence gathered from the crude NMR to suggest which process occurs first.

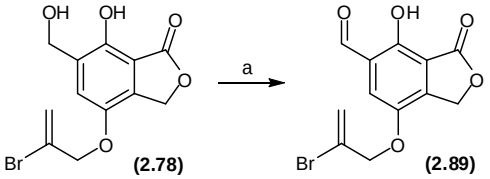
More polar solvents appeared to be the key to success. Extensive research has been conducted on the use of water as a medium for organic reactions.[203b,217] Most recently this has been driven by a desire to develop more environmentally friendly chemistry; water is non-toxic, abundant, cheap and safe to dispose of and reaction products are often readily separated from it. It is a particularly useful solvent in combination with microwave technology as not only is it an exceptional microwave absorber, but at temperatures above its atmospheric boiling point its solvent properties become more compatible with organic substrates. As temperature increases the angle of the H-O-H bonds increases, this results in a decrease in the dipole moment. The result of this is that at 150 °C the dielectric constant of water is roughly equal to that of MeCN at room temperature.[203c] Most importantly water has been shown to offer some of the greatest solvent derived rate increases for the Claisen rearrangement, this is derived through a combination of hydrophobic effects and as a result of preferential transition state solvation.[218] Also significant is the fact that if the rearrangement were accompanied by a concomitant formation of the QM, the water adduct would simply restore the diol functionality nullifying the effect of that side reaction (scheme 2.50). Heating ether **(2.51)** in water at 140 °C returned only a black insoluble tar, lowering the temperature produced the same results down to 80 °C below which only starting material was returned.



Scheme 2.50 : Reagents and Conditions: (a) H_2O, 80-140 °C, MW, 10 min.

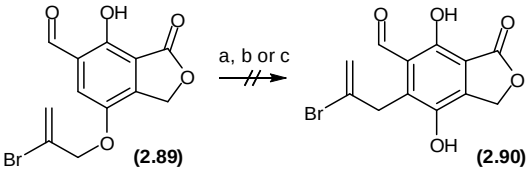
With the 1,3-diol **(2.78)** also able to form the undesired QM intermediate we were still unable to isolate the rearranged product without simultaneously introducing some undesired substituent at the benzyl position. However by oxidising the benzyl alcohol **(2.78)** to the benzaldehyde **(2.89)** it was hoped we may finally be able to prevent such side reactions. Exposure of the alcohol to a large excess of activated manganese dioxide

in acetone on a small scale gave the desired aldehyde in respectable yield (72%) (scheme 2.51). This aldehyde had a high affinity for the manganese dioxide and a large amount of solvent was required to rinse the product off the solid residue of the reaction. Trouble encountered later in the synthesis (*vide infra*, scheme 2.57 & 2.58) required that the product be extensively purified and this had a detrimental effect on yields.



Scheme 2.51 : Reagents and Conditions: (a) MnO_2 (10 eq.), acetone, rt, 3 hrs (54-72%).

The benzaldehyde **(2.89)** was first exposed to a Lewis acid based protocol.[219] We had hoped to compensate for the coordinating effect of the oxygen functionality by utilising a large excess of Lewis acid, however treatment with 20 equivalents of boron trichloride at room temperature returned only starting material (scheme 2.52). The diol and acetonide also failed to rearrange under these conditions with the diol proving completely inert and the acetonide being deprotected.

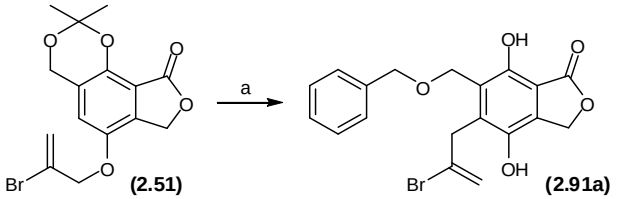


Scheme 2.52 : Reagents and Conditions: (a) BCl_3, 1M in CH_2Cl_2 (20 eq.), rt, 12 hrs; (b) *N*,*N*-Diethylaniline, 200 °C, MW, 30 mins; (c) *N*,*N*-Diethylaniline, 180 °C, MW, 30 mins.

Heating the benzaldehyde in *N*,*N*-diethylaniline as per the previously successful Claisen conditions resulted in a complex and inseparable mixture of products and significant decomposition at 200 °C. Decreasing the reaction temperature to 180 °C would produce the same result, this may be a result of Cannizzaro type chemistry affecting the benzaldehyde (given the basicity of the aniline) or may simply have been related to the inherent thermal instability of phenolic aldehydes at elevated temperatures.[220]

With heating in high-boiling, polar solvents so far the only conditions shown to be effective as far as enacting the rearrangement was concerned we selected a number of other suitable solvents. The first of these to be tried was benzyl alcohol, which would also be non-basic, enhancing compatibility with the benzaldehyde. To preserve material the method was first examined by using the acetonide **(2.51)**. Heating at 180 °C gave

the anticipated benzyl adduct, but the product also exhibited a successful rearrangement giving the hydroquinone **(2.91a)** (scheme 2.53).



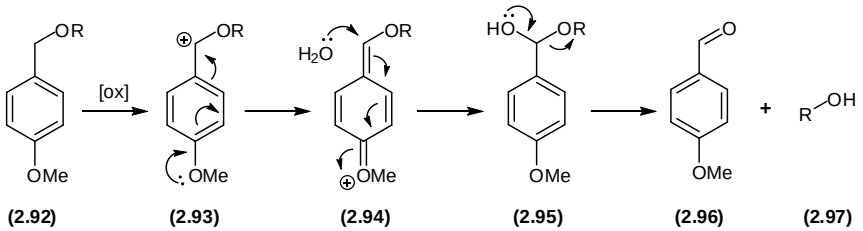
Scheme 2.53 : Reagents and Conditions: (a) BnOH, 180 °C, MW, 15 mins (64%).

As well as providing a second example of a successful rearrangement this product offered significantly more potential than we had anticipated. With the oxygen functionality at the benzyl position having been retained (albeit concealed as the benzyl ether), removal of the benzyl group would restore the alcohol allowing the synthesis to proceed much as previously intended (*vide supra*, scheme 2.27).

The deprotection would not be trivial however, given the wide range of other functionality present in ether **(2.91a)** and the fact that the system as a whole is more accurately viewed as a hetero benzyl ether, meaning any deprotection would be in danger of cleaving the wrong side of the ether bond to reveal the simple benzyl alcohol, degrading our desired substrate in the process.

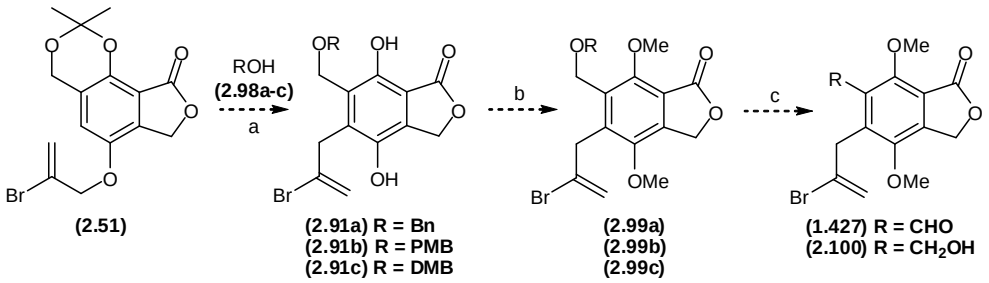
Benzyl deprotection is commonly carried out by hydrogenolysis but this course would likely prove incompatible with the presence of the alkene.[191a] An acid mediated deprotection may also prove incompatible with the allyl moiety and achieving selectivity in cleaving the correct side of the ether may prove challenging. Especially considering the potential for direction by coordination from the adjacent oxygen functionality in the more developed ring.

The most promising approach would appear to be to cleave the ether oxidatively. Whilst this approach would also involve a competitive oxidation of the two benzyl groups, the relative rates are significantly altered by the electronic configuration of the aromatic rings. The oxidative removal of benzyl ethers with DDQ has been studied in some depth by Yonemitsu *et al.*[221] and specifically the relative rates of oxidation of different methoxy substituted benzyl groups.[222] The mechanism of the oxidation (scheme 2.54) involves the formation of the benzyl cation **(2.93)** and it is primarily the ability of the ring substituents to stabilise this charge that determines the rate of reaction.



Scheme 2.54 : Mechanism of oxidative benzyl ether cleavage.

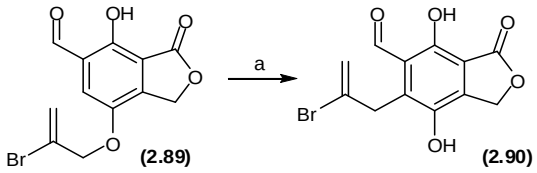
Therefore, if we were to consider the phthalide side of ether **(2.91a)** as a simple 2,5-dimethoxybenzyl moiety (the phenols would need to be protected as their methyl ethers to inhibit oxidation of the ring to the quinone) then it would seem likely that oxidative cleavage would favour the generation of the benzaldehyde **(1.427)** (scheme 2.55). This would conveniently deliver the key intermediate with a decreased step count relative to the original scheme. Should the real system prove less labile than the simplified system, possibly due to the electron withdrawing carbonyl *ortho* to the methoxy group, or if the *para*-dimethoxy system were still prone to ring oxidation adjustments could be made to invert the selectivity of the oxidation, by using an alternate, electron rich benzyl alcohol such as 4-methoxybenzyl alcohol **(2.98b)**[221a] or 3,4-dimethoxybenzyl alcohol **(2.98c)**[221b] as the Claisen solvent, the appropriately substituted ethers **(2.99b)** & **(2.99c)** could be produced. Both of these ethers would undergo oxidation much more rapidly than either the unsubstituted benzyl moiety, or the highly substituted benzyl group, the benzyl alcohol **(2.100)** would result in both cases. This inverted oxidation would require a separate oxidation step to deliver the benzaldehyde **(1.427)** though this should be relatively straightforward.



Scheme 2.55 : Reagents and Conditions: (a) Tandem Claisen, QM formation/addition sequence with **(2.98a)** R = Bn, **(2.98b)** R = PMB or **(2.98c)** R = PMB; (b) Methylation; (c) Selective oxidative cleavage of the benzyl ether with DDQ.

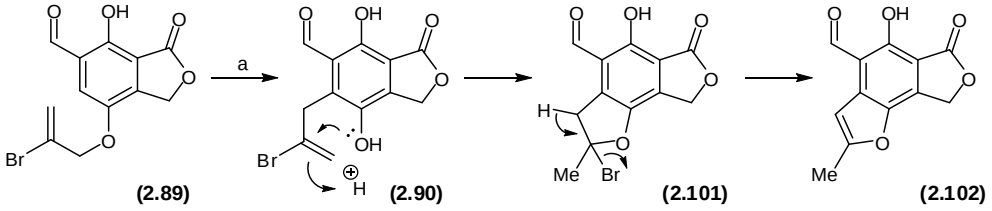
This direction appeared promising, but whilst its merits were still being evaluated we decided to attempt one further experiment with the goal of effecting a Claisen rearrangement without side reactions. With the rearrangement in benzyl alcohol successful we were confident that it would be repeated with the benzaldehyde precursor

(2.89) given that the neutral alcohol should not display the incompatibility associated with the basic aniline. Heating the benzaldehyde in benzyl alcohol (scheme 2.56) finally delivered the rearranged product **(2.90)** with all the other functionality intact. This result was a great relief after so much time had been invested in delivering this key intermediate. This initial reaction was also relatively high-yielding.



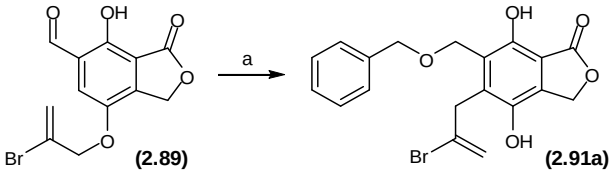
Scheme 2.56 : Reagents and Conditions: (a) BnOH, 180 °C, MW, 15 mins (0-72%).

This result led to the abandonment of the work proposed in scheme 2.55, with the planned chemistry seeming a safer prospect. Unfortunately this success was achieved with the last of a batch of the precursor and such positive results would not be observed when attempting to repeat this reaction. Subsequent batches of the benzaldehyde **(2.89)** resulted in extremely capricious results when the rearrangement was attempted. Results included rapid and complete decomposition, extremely slow reactions giving <5% conversion after extended periods of heating and abnormal reaction products. These abnormal products included the benzofuran **(2.102)**, arising as the result of a cyclisation of the rearranged product **(2.90)** (scheme 2.57). This is a known side reaction of the Claisen rearrangement[223] though it had not been produced at any detectable level in the original attempt at this reaction.



Scheme 2.57 : Mechanism for the formation of tricyclic by-product (2.102).

A further abnormal result came in the form of the benzyl ether **(2.91a)** the product of an apparent reductive etherification (scheme 2.58).



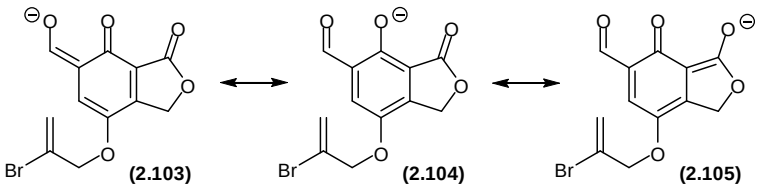
Scheme 2.58 : Reagents and Conditions: (a) BnOH, 180 °C, MW, 30 mins (12%).

Initially there was evidence to suggest that these effects may have occurred as the result of contamination with manganese residues from the preceding oxidation step, with apparent paramagnetic line broadening present in the NMR spectrum. This broadening had not been observed when the material was prepared on a smaller scale and purified by recrystallisation. The presence of acidic metal ions may be consistent with the acid catalysed formation of tricycle **(2.102)**. There is also some precedent for transition metal catalysed reductive etherifications, though they have all required an external hydride source, commonly a silane.[224] However the formation of tricycle **(2.102)** may also be base catalysed[219] and a base catalysed Cannizzaro reaction could produce diol **(2.78)** which might reasonably produce the benzyl ether **(2.91a)** through a QM addition sequence.

Column chromatography of the SM removed the line broadening but failed to remedy the inconsistent reactivity of the material. To further purify the material it was stirred with activated charcoal under acidic conditions, with the intention of removing any trace impurities and to ensure the phenol was present in its protonated form. This protocol reversed the trend in reactivity (though neither charcoal nor acid was effective separately) and allowed the consistent formation of the Claisen product **(2.90).** The reaction was never restored to its original high yield however and all subsequent attempts produced yields of 20-25%.

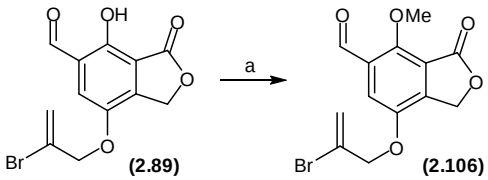
Working on the hypothesis that the difficulties experienced and the continuing low yields were the result of manganese residues retained due to chelation through the extensive oxygen functionality in benzaldehyde **(2.89)** and/or due to acid catalysed processes resulting from the acidity of the highly conjugated phenol, it was thought that a minor adjustment to the substrate would remedy the problem. Protection of the free phenol would remove the acidic proton and prevent the oxygen chelating as the phenolate. This would also have the added benefit of removing the thermally unstable *ortho*-formyl phenol unit.

We hoped to perform a straightforward methylation of the phenol, however due to the extensive delocalisation possible in the corresponding alkoxide **(2.104)** (scheme 2.59) this would prove challenging.



Scheme 2.59 : Canonical forms of the alkoxide (2.104).

Standard phenol methylation conditions utilising methyl iodide as the methylating agent resulted in gradual decomposition of material with none of the desired methyl ether produced (scheme 2.60).[225] Moving to the more reactive dimethyl sulfate failed to deliver any improvement. The anion **(2.104)** appeared to be insufficiently nucleophilic to attack the methylating agent before decomposing due to the presence of the base. Switching to the more reactive trimethyloxonium tetrafluoroborate combined with Hünig's base gave a very limited yield of the desired methyl ether **(2.106)** amongst the decomposition products.[226] The apparent key to this reaction was to treat the highly acidic phenol as if it were a carboxylic acid, accordingly a methylation protocol using trimethylsilyldiazomethane in a mixed solvent system of methanol and toluene proved very effective.[227] On a small scale the reaction with phenol **(2.89)** was near quantitative, however upon scale up the reaction was found to stall at around 50-60% conversion, though the starting material was easily recovered. Slowing the rate of addition produced no discernible benefit and increasing the number of equivalents of $TMSCHN_2$ resulted in some decomposition of residual starting material.



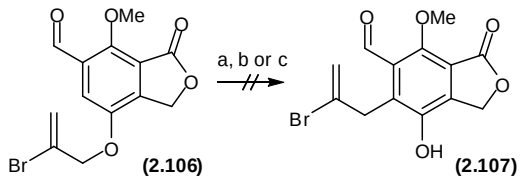
Scheme 2.60 : Reagents and Conditions: (a) *See table below.*

Reagent	Equivalents	Conditions	Result
MeI	10	K_2CO_3, Acetone, Reflux, 8 hr.	decomp
Me_2SO_4	10	K_2CO_3, Acetone, Reflux, 12 hr.	decomp
$[Me_3O]^+[BF_4]^-$	1.1	DIPEA, CH_2Cl_2, rt, 12 hr.	12%
$TMSCN_2$	1.2	Toluene/MeOH (3:2), rt, 10 mins.	97%[a,b]
$TMSCN_2$	1.2	Toluene/MeOH (3:2), rt, 30 mins.	96%[a,c]
$TMSCN_2$	1.5	Toluene/MeOH (3:2), rt, 10 mins.	81%[a]

[a] Figure based on recovered starting material; [b] 55% isolated yield of **(2.106)**; [c] 52% isolated yield of **(2.106)**.

When heated in diethylaniline the methyl ether **(2.106)** was entirely decomposed (scheme 2.61) giving credence to the aforementioned hypothesis that decomposition was occurring *via* a Cannizzaro type reaction at the aldehyde. Heating in benzyl alcohol instead also gave no evidence of the Claisen reaction, with the starting material instead being slowly converted to an unidentified by-product.

Finally, methyl ether **(2.106)** was heated in a mixed solvent system of TFE and water with the hope that this more polar solvent system may accelerate the rate of the Claisen rearrangement relative to the rate of the by-product formation.[228] Sadly whilst some of the crude NMR data for this experiment looked promising, the low-boiling point of the solvent system meant the highest attainable temperature was between 164-166 °C in the microwave before the pressure limit was reached extending the reaction time significantly and resulting in substantial decomposition of the material.



Scheme 2.61 : Reagents and Conditions: (a) BnOH, 180 °C, MW, 2 hrs; (b) *N*,*N*-Diethylaniline, 200 °C, MW, 15 mins; (c) TFE/H_2O (4:1), 165 °C, MW.

2.5.4 Conclusions Regarding Capricious Claisen Rearrangements.

Effecting this deceptively simple Claisen rearrangement was far more challenging than anticipated, proving to be something of a case study on the unpredictability of high temperature chemistry. Whilst a number of the side-reactions proved to be of some academic interest, the ongoing synthesis of lactonamycin became mired in this unproductive chemistry for much longer than we would have wished resulting in a real dearth of material for the ongoing synthesis. All the precursors we employed proved to be less thermally stable than anticipated due to the broad range of functionality present. This resulted in a situation where there was a need to strike a fine balance between a temperature that was sufficient to effect the rearrangement whilst at the same time not being so high as to lead to decomposition and/or side reactions. Frequently this was simply not possible.

The acetonide precursor **(2.51)** was highly prone to thermolysis of the benzodioxin moiety resulting in QM formation and the clean introduction of benzyl substituents with all but the most non-nucleophilic solvents where it was observed to slowly degrade.

Exposure of the phenol through this side reaction also appeared to have a catalytic effect on the Claisen rearrangement and with an appropriate polar solvent this system would also undergo the desired rearrangement in good yield. The rate of QM formation always appeared to be higher than that of the Claisen and all catalysts of the Claisen also catalysed the QM formation preventing us from performing the Claisen rearrangement alone. The chemistry of the diol **(2.78)** was similar, though QM formation was less facile requiring acid or base catalysis to occur.

The chemistry of the aldehyde **(2.89)** proved to be dominated by the reactivity of the highly conjugated phenol. It provided a notable catalytic effect allowing for rapid and occasionally efficient rearrangement in benzyl alcohol. However whilst the phenolic aldehyde prevented the formation of the QM intermediates that plagued the preceding precursors, it rendered the molecule liable to decomposition, being readily decomposed thermally and even more readily in the presence of base. Furthermore it exhibited capricious reactivity when trying to effect the Claisen rearrangement with a number of possible explanations. The low yield and reliability of the rearrangement poses a real challenge in the ongoing synthesis.

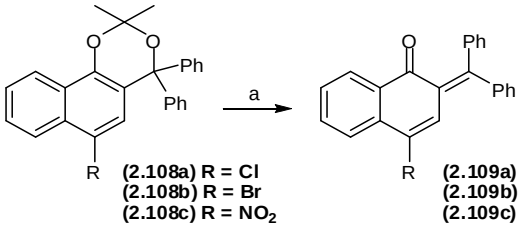
That the methylated precursor **(2.106)** should rearrange less readily than the phenolic precursor is unsurprising without the acidic phenol acting as an internal catalyst. The methylated precursor exhibited increased stability over its predecessor, though the aldehyde was still base sensitive. Reactivity in the absence of the acidic phenol was attenuated accordingly and this attenuation was such that the rate of decomposition was always higher than the rate of rearrangement, preventing this compound being of any great synthetic use.

2.6 Quinone Methide Methodology.

2.6.1 Benzodioxins as Quinone Methide Precursors.

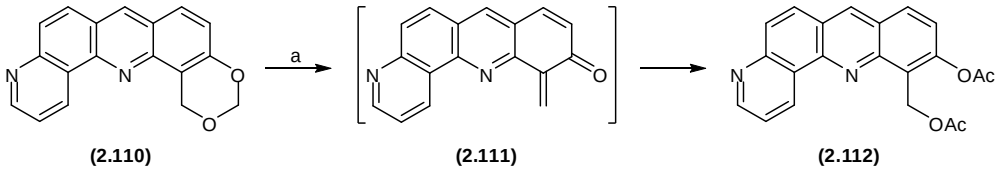
While the generation of quinone methide intermediates was an unfortunate and unwelcome side reaction in many of our attempts to effect the Claisen rearrangement, it was not lost on us that there is a great deal of potential in developing new methods for the utilisation of those same reactive intermediates. Whilst there are a handful of examples of benzodioxin QM precursors noted in the literature, none of these have been utilised in as straightforward a manner as we had serendipitously achieved.

Chumachenko *et al.* demonstrated an acid catalysed means of generating the highly stabilised and isolable quinone methides **(2.109a)-(2.109c)** from the acetonides **(2.108a)-(2.108c)** using HCl in AcOH at elevated temperature (scheme 2.62).[229]



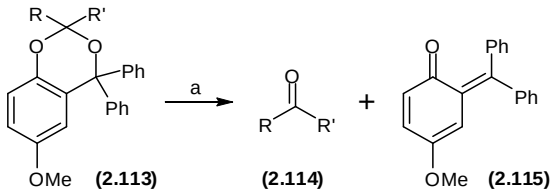
Scheme 2.62 : Reagents and Conditions: (a) HCl, AcOH, 110 °C, 20 mins (a = 88%, b = 86%, c = 66%).

Lhomme *et al.*[230] used even harsher acidic conditions to generate the unstabilised QM **(2.111)** from the methylene acetal **(2.110)** which underwent nucleophilic attack by AcOH and subsequent *in situ* acylation of the resulting phenol (scheme 2.63).



Scheme 2.63 : Reagents and Conditions: (a) Ac_2O, AcOH, MsOH, 70 °C, 9 hrs (75%).

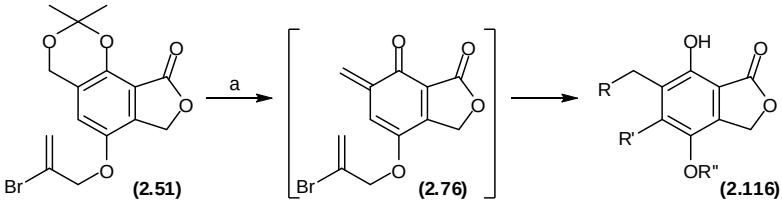
Wang *et al.* demonstrated the use of acetals as photolabile protecting groups, photolysis of the general benzodioxin **(2.113)** was used to reveal the corresponding ketone **(2.114)** generating the QM **(2.115)** as a by-product (scheme 2.64).[231] Extending this work to precursors where the phenyl groups at the benzyl position are absent the reaction proceeded more slowly and in the absence of the methoxy group on the ring the reaction failed entirely.[232]



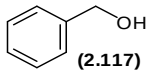
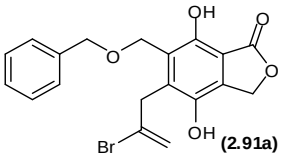
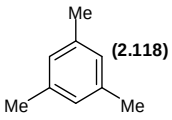
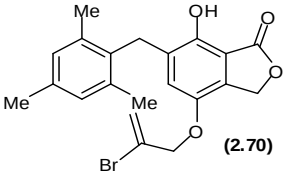
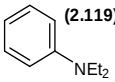
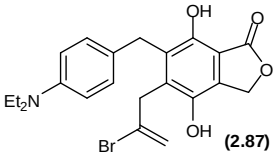
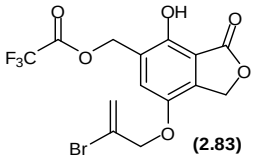
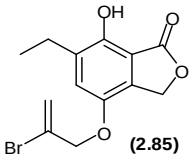
Scheme 2.64 : Reagents and Conditions: (a) h*ν*, MeCN, 40-80 mins (74-90% of **(2.114)**).

The reactions we had observed thus far fell into two broad categories (scheme 2.65), those that were acid catalysed and occurred at relatively low temperature, such as the reactions with TFA and MAO and those that were initiated by a purely thermal process, without the need for further catalysis as observed with the additions of benzyl alcohol, mesitylene and *N*,*N*-diethylaniline. It was this latter class of reactions that were of particular interest, as no previous examples of the uncatalysed reaction have been noted

in the literature. The method of carrying these reactions out was straightforward and with the broad range of nucleophile compatibility associated with a thermal approach there was potential for the development of a synthetically useful method.



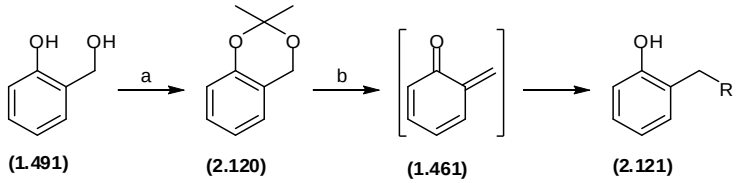
Scheme 2.65 : Reagents and Conditions: *See table below.*

Reagent	Conditions	Result	Yield (%)
 (2.117)	180 °C, MW, 15 mins.	 (2.91a)	64
 (2.118)	Reflux, 24 hrs.	 (2.70)	78
 (2.119)	200 °C, MW 30 mins.	 (2.87)	44
TFA	TFA, rt, 3 hrs.	 (2.83)	97
MAO	CH_2Cl_2, -30 °C to rt, overnight.	 (2.85)	64

2.6.2 Model Quinone Methide Addition Reactions.

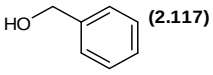
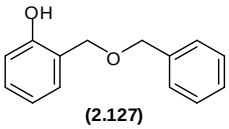
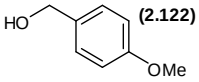
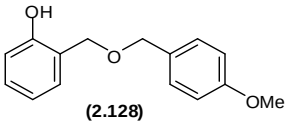
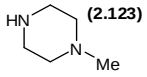
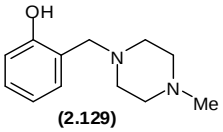
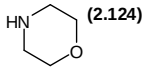
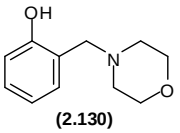
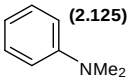
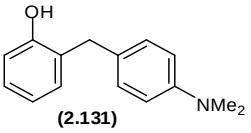
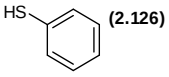
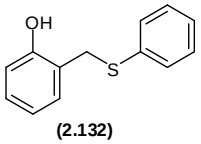
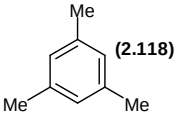
The simple model benzodioxin **(2.120)** was prepared from salicyl alcohol **(1.491)** by stirring with 2,2-dimethoxypropane in acetone with catalytic acid (scheme 2.66). This model would allow us to repeat the QM formations in isolation and expand upon the examples already discussed. It would also serve as a model for the introduction of a methoxy-substituted benzyl ether should that prove desirable in the synthesis of

lactonamycin (*vide supra*, scheme 2.55). This model was heated with an excess of various high-boiling, nucleophilic reactants, with that reactant also serving as the reaction solvent (0.65 mL of solvent was used per mmol of benzodioxin **(2.120)** as standard). Reactions were followed by crude NMR and considered complete when all the starting material has been consumed.



(1.491) **(2.120)** **(1.461)** **(2.121)**

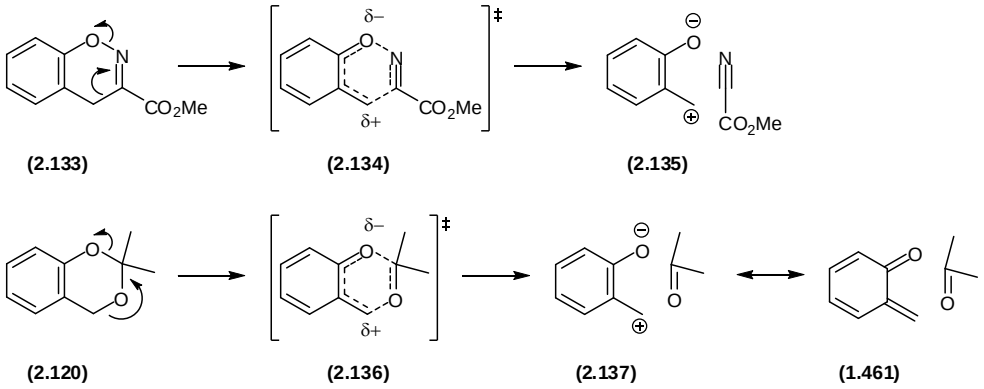
Scheme 2.66 : Reagents and Conditions: (a) 2,2-Dimethoxypropane (5 eq.), pTSA (cat.), acetone, rt, 2 days (83%); (b) *See table below.*

Reagent/Solvent	Conditions	Result	Yield (%)
 **(2.117)**	180 °C, MW, 30 mins.	 **(2.127)**	87
 **(2.122)**	180 °C, MW, 30 mins.	 **(2.128)**	85
 **(2.123)**	180 °C, MW, 10 hrs.	 **(2.129)**	76
 **(2.124)**	180 °C, MW 12 hrs.	 **(2.130)**	79
 **(2.125)**	180 °C, MW 2 hrs.	 **(2.131)**	68
 **(2.126)**	170 °C, 12 hrs.	 **(2.132)**	85
 **(2.118)**	Reflux, 12 hrs.	SM	---

The results were very satisfying, with the analogous benzyl alcohol and aniline additions successfully repeated and a number of new nucleophilic adducts formed in good yield. Only the mesitylene reaction failed to provide the anticipated product.

Importantly the substituted benzyl alcohol **(2.122)** displayed the same reactivity as the unadorned version. The reactions were high yielding, though in the case of the nitrogenous solvents there was a small amount of decomposition noted (presumably base induced), which led to somewhat lower yields in those instances.

There were noticeable variations in the rates of reactions between the different solvents. The reaction times would seem to suggest that addition of the nucleophile to the QM was not the rate determining step, if it were we would expect to see shorter reaction times associated with the more nucleophilic solvents such as methylpiperazine and morpholine especially compared to weak nucleophiles such as dimethylaniline. These results were consistent with the observations of Ohwada *et al.* who studied the formation of QM's from benzoaxazines which also occurs *via* a retro-Diels-Alder mechanism (scheme 2.67).[233] They noted that it was always the formation of the QM that was rate determining and that the primary factors in deciding this rate were the substitution pattern of the QM precursor and the polarity of the solvent. Both of these effects are explained if the formation of the QM goes through the highly polarised transition state **(2.134)**, with more effective solvation of the transition state lowering the activation energy. We can envision a similar structure for the acetonide transition state **(2.136)**.



Scheme 2.67 : A highly polarised transition state in the formation of QMs.

When the reaction times of our reactions were compared with the polarity of the corresponding solvents (measured as the molecular dipole moment) in the case of additions to benzodioxin **(2.120)** (figure 2.2) the same trend was readily apparent, with the faster reaction times correlating with increased polarity. The main exception to this trend was thiophenol which exhibited a significantly faster rate than its polarity would suggest, however Ohwada's results included only aprotic solvents therefore given the

acidity of the thiol proton of thiophenol (pK_a = 6.51)[234] we attributed this acceleration to acid catalysis of the QM formation step.

Solvent	Reaction time (mins)	Dipole moment (D)
Benzyl Alcohol	30	1.67[c, [235]]
N,*N*-Dimethylaniline	240	1.59[d, [236]]
Morpholine	720	1.48[d, [237]]
Thiophenol	*360* [a]	1.33[c, [238]]
N-Methylpiperazine	600	1.14[c, [239]]
Mesitylene	--- [b]	0.10[c, [240]]

[a] Extrapolated to 180 °C for comparison; [b] No conversion detected by crude NMR after 12 hrs at reflux; [c] Measured at 25 °C in benzene; [d] Measured at 20 °C in benzene.

Figure 2.2 : Comparison of reaction time and solvent polarity in QM addition reactions.

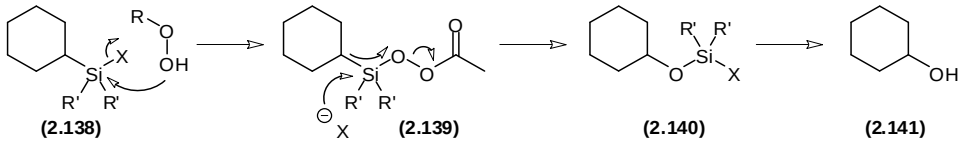
Substituent effects are also a pertinent point to consider in trying to explain the failure to repeat the formation of a mesityl adduct in the model system when the solvent system and temperature remained constant. Where the substituents in a system are such that they are able to stabilise the developing positive charge at the benzyl position in the transition state, as well as being able to stabilise the same positive charge in the zwitterionic resonance form of the QM **(2.137)** formation of the QM will be more rapid.

The model system contains no substituents, but the Claisen precursor has three, the allyloxy residue which is strongly electron donating, the methylene of the lactone which is weakly electron donating and the carbonyl of the lactone which is strongly electron withdrawing. Rokita *et al.* have demonstrated that the presence of a methoxy substituent *meta* to the benzyl position can lead to a 10-fold increase in the rate of QM formation relative to the hydrogen bearing equivalent, the suppressive effect of a similarly positioned ester was much less substantial.[241] The reactivity of the more complex benzodioxin **(2.51)** is therefore likely to be dominated by the alkyloxy residue resulting in a more reactive substrate than model **(2.120)**. The mesitylene reaction was carried out at the lowest temperature due to the low boiling point of the solvent (165 °C) and its poor microwave absorption and as such represented a borderline case as far as temperature was concerned.

2.7 Development of Side-Chain Insertion Methodology.

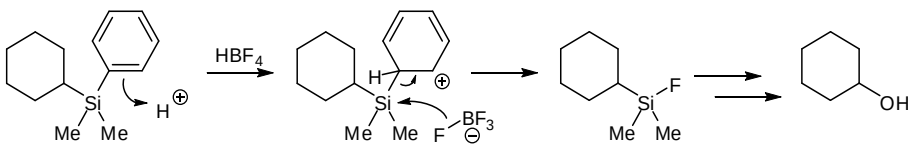
2.7.1 The Need for a New Propynoic Acid.

In all previous cyclisations Board had utilised the trimethylsilylpropynoate residue to produce a cyclised product bearing a trimethylsilyl group, his unsuccessful attempts at trying to oxidise this silyl residue made it clear that this particular silane was unsuitable for a full synthesis of lactonamycin *via* the planned Fleming-Tamao chemistry (*vide supra*, scheme 1.90). The mechanism of both Fleming and Tamao oxidations requires the nucleophilic attack of a peroxide on silicon (scheme 2.68), for this to occur it is therefore necessary for there to be one or more suitable leaving groups on silicon. Tamao *et al.* utilised silyl chlorides, fluorides and hydrides as well as siloxy, alkoxy and silanamine derivatives to this end.[103d] Whilst all these activated silanes allowed for efficient and high-yielding conversion of the silyl residue to the corresponding alcohol they are more challenging to produce and more reactive than the corresponding all carbon silanes limiting their appeal as masked hydroxyl groups.



Scheme 2.68 : Mechanism of the Tamao oxidation.

Fleming developed an alternate protocol (in parallel), utilising an aryl silane.[104a] The all carbon dimethylphenylsilane employed benefited from much decreased lability relative to the silanes employed by Tamao *et al.*, increasing the utility of this group in more elaborate syntheses. Conversion of the silane to the alcohol could still be achieved by protodesilylation of the aromatic ring. When Fleming performed this transformation with fluoroboric acid, benzene and a silyl fluoride **(2.144)** resulted (scheme 2.69). This fluoride would then undergo oxidation with a peracid to give the alcohol **(2.141)**. This concept was subsequently extended to include a number of one-pot procedures, where the activated silane is formed *in situ*.[104e,242] A wide range of alternative all carbon silanes have subsequently been developed.[103e,243]

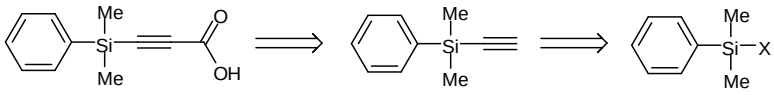


Scheme 2.69 : Fleming *et al.*'s conversion of DMPS to a reactive silyl fluoride.

As well as acting as a masked hydroxyl group, the silyl residue has been shown to play an important role in stabilising the intermediate radical formed at the α-carbon during Parsons, Board, Waters type cyclisations.[83b] This made it crucial that not only should it be possible to efficiently reveal the alcohol, but also that the silane should be electronically similar to the trimethylsilane that had already been proven efficacious. The substitution of trimethylsilane with dimethylphenylsilane was therefore proposed.

2.7.2 Synthesis of Dimethylphenylpropynoic Acid (2.145).

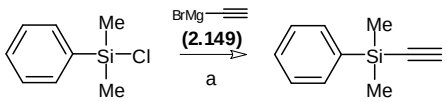
We had intended to synthesise the required DMPS propynoic acid **(2.143)** in a fashion analogous to Board's synthesis of the TMS equivalent (*vide supra*, scheme 1.71). The acid would be prepared from the silane **(2.146)** by deprotonation followed by quenching with carbon dioxide (scheme 2.70). Unlike trimethylsilylacetylene the dimethylphenylsilane was not commercially available however so this would first need to be prepared. Fortunately both the intermediate silane and the acid were reported in the literature, but the procedure for formation of the silane was poorly described. As such work was carried out to establish the optimum conditions for its formation.



(2.145) **(2.146)** **(2.147)**

Scheme 2.70 : Retrosynthesis of the modified propynoic acid.

The silane was invariably prepared from silyl chloride **(2.148)** and methods were published by a number of authors.[244] The majority of authors opted to form the lithiate or the Grignard of acetylene *in situ*, necessitating the careful measuring and handling of acetylene gas but Hasegawa *et al.*[244a] demonstrated the use of commercially available ethynylmagnesium bromide solution with some success. This approach was adopted for its convenience. Unfortunately Hasegawa *et al.* failed to report the number of equivalents of silyl chloride employed in their method. Investigation however revealed that 1.0 equivalent provided the optimum yield from this reaction (scheme 2.71).



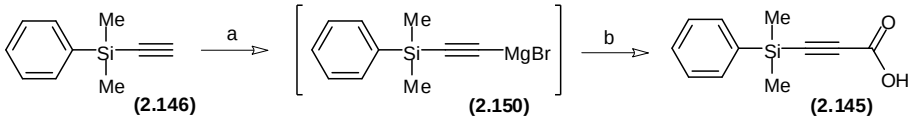
(2.148) **(2.146)**

Scheme 2.71 : Reagents and Conditions: (a) *See table below.*

Equivalents (2.146)	Conditions[a]	Yield (2.144) (%)[b]
0.9	0.5 M **(2.149)** in THF, THF, 0 °C to rt, 24 hrs.	71
1.0	0.5 M **(2.149)** in THF, THF, 0 °C to rt, 24 hrs.	81
1.1	0.5 M **(2.149)** in THF, THF, 0 °C to rt, 24 hrs.	75
5.0	0.5 M **(2.149)** in THF, THF, 0 °C to rt, 24 hrs.	76

[a] All aliquots of Grignard reagent were from the same bottle, the concentration was verified by titration with phenanthroline and ^{s}BuOH [245]; [b] Isolated Yield.

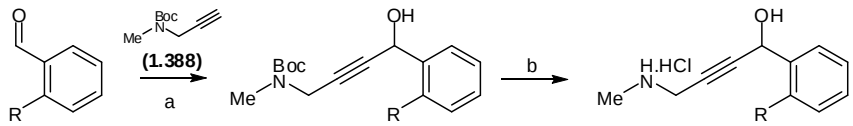
Fleming *et al.*[246] reported that the propynoic acid **(2.143)** was prepared by the formation of the alkynyl Grignard reagent with methylmagnesium chloride solution in THF followed by the addition of gaseous carbon dioxide. Following this procedure but using commercially available methylmagnesium bromide solution to form Grignard reagent **(2.148)** and then quenching the mixture over solid carbon dioxide provided the desired product in comparable yield (scheme 2.72).



Scheme 2.72 : Reagents and Conditions: (a) 3M MeMgBr in THF, 0 °C to rt, 2 hrs; (b) $CO_{2(s)}$, rt, 1 hr (79%).

2.7.3 Synthesis of Triisopropyl-*N*-methyl-*N*-(prop-2-ynyl)silanamine (2.154).

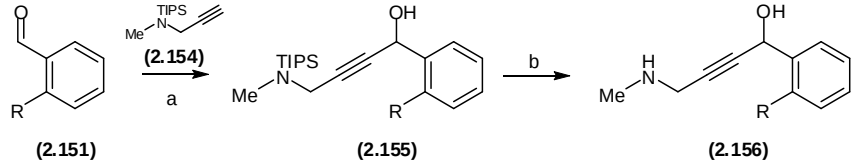
Throughout his studies Board had used the Boc-protected *N*-methylpropargylamine **(1.388)** prepared according to the method of Jacobson *et al.* (*vide supra*, scheme 1.74).[247] The lithiate of this amine would then be added to the chosen benzaldehyde and the resulting Boc-protected adduct would require deprotection with HCl before the amine could be coupled with the propynoic acid residue (scheme 2.73).



Scheme 2.73 : Reagents and Conditions: (a) **(1.388)**, ^{n}BuLi then **(2.151)** then ^{t}BuBr, THF, -100 °C; (b) HCl, Et_2O.

There was some suggestion in Board's work that this deprotection could be problematic, leading at one point to an abandonment of such a route. Those difficulties were later resolved however and the Boc protection/deprotection sequence became the standard

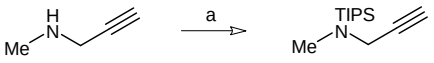
method of introducing the amine side chain section. Upon expanding this method to a wider range of substrates however Faggiani found that the results of this sequence were rather unreliable, with the deprotection proving to be a recurring problem. The search for a more labile protecting group led to the preparation of the silyl protected amine **(2.154)**. The TIPS-protected amine underwent addition to various benzaldehydes **(2.151)** in comparable yields to the Boc-protected variant (scheme 2.74), the relatively weak N-Si bond in the resulting alcohols **(2.155)** could then be reliably cleaved with aqueous hydrogen fluoride to give the free amine after treatment with basic resin during workup.[82]



(2.151) **(2.155)** **(2.156)**

Scheme 2.74 : Reagents and Conditions: a) **(2.154)**, 2.5M ^{n}BuLi in hexanes, THF, -78 °C to -20 °C, 30 min then **(2.151)**, THF, -78 °C to rt, 30 min; (b) HF (40% wt. in H_2O), MeCN, rt, 10min.

Given the apparent efficacy of this modified methodology the Boc-protected amine was abandoned in favour of the silylamine. Accordingly we prepared the *N*-methyl-*N*-triisopropylpropargylamine **(2.154)** by the same method as Faggiani using the silyl triflate with triethylamine to give the protected amine in excellent yield (scheme 2.75).



(1.372) **(2.154)**

Scheme 2.75 : Reagents and Conditions: (a) TIPSOTf (1.05 eq.), NEt_3 (1.5 eq.), CH_2Cl_2, 0 °C to rt, 16 hrs (88%).

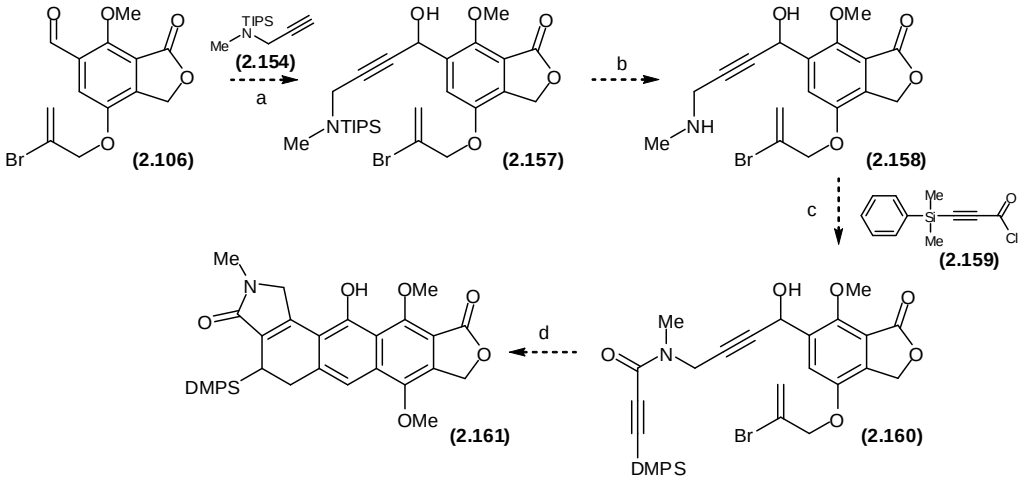
2.8 Post-Claisen Chemistry.

2.8.1 A Postponement of the Claisen Rearrangement.

Given the lack of a reliable supply of material from the Claisen rearrangement we were still very much open to alternate routes. Along this line we elected to pursue a somewhat more outlandish sequence, alongside that we had planned. This route would utilise what material remained of the methylated precursor **(2.106)** and would further delay work on the Claisen until a later point in the synthesis.

It was proposed that we would form the Parsons, Board, Waters cyclisation precursor **(2.160)** in which the Claisen had yet to be carried out (scheme 2.76). Heating the enediyne at 180 °C would then hopefully effect both the Claisen rearrangement and

Parsons, Board, Waters cyclisations in sequence to give pentacyclic lactone **(2.161)**, however any identified product from this reaction would be of interest in terms of the mechanism of the PBW reaction.



Scheme 2.76 : Reagents and Conditions: (a) Addition of lithiate of **(2.154)**; (b) Silyl deprotection with HF; (c) Amide formation with acid chloride **(2.159)**; (d) Tandem Claisen rearrangement / Parsons, Board, Waters cyclisation.

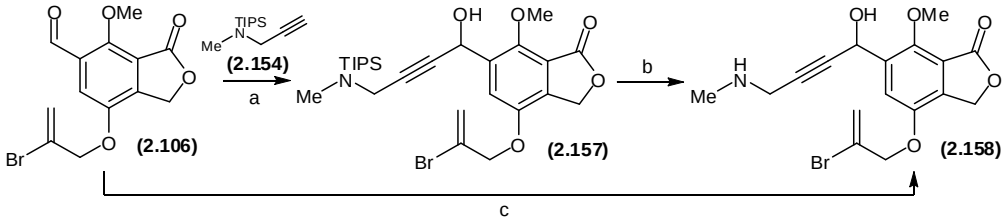
This chemistry would also be a valuable opportunity to test side chain incorporation methodology developed by Faggiani. Due to the presence of the lactone there was some concern about the issue of selectivity of the nucleophilic lithiate insertion and it would be beneficial to establish whether this would necessitate a more cautious addition procedure. Upon following the method outlined below these fears proved to be needless, with the lactone surviving intact.

It would still prove necessary to modify the original procedure (*vide supra*, scheme 2.74) however. That protocol utilised an excess of the benzaldehyde to ensure all the amine was consumed. The residual aldehyde was then separated from the product by formation of the sodium bisulfite adduct. This way the silyl-protected addition product, which was not stable on silica, could be purified without the need for chromatography. A small scale test revealed that formation of the bisulfite adduct was particularly sluggish in the case of our more complex benzaldehyde **(2.106)** leaving us doubtful this procedure would prove effective.

When the benzaldehyde was treated with the lithiate of amine **(2.154)** the reaction was found not to go to completion, leaving an excess of silylamine after workup (scheme 2.77). Fortunately it proved possible to purify the adduct **(2.157)** from the unreacted starting materials by careful recrystallisation from diethyl ether/hexane though the

isolated yield of material was disappointing. The silyl protected adduct was then successfully desilylated by stirring in MeCN with an excess of hydrofluoric acid, with the deprotection proceeding in good yield to give amine **(2.158)**. The free base was obtained exclusively by passing a solution of the crude product over the tertiary amine resin Amberlyst® A21.

However it would prove significantly more efficient to resist the temptation to isolate the intermediate alcohol. Instead simply exposing the crude addition mixture to HF would result in global desilylation, allowing the resulting *N*-methylpropargyl amine **(1.372)** to be removed under reduced pressure, the product amine could then be purified effectively by chromatography. This gave a yield for comparison of some 47% against 31% for the two step procedure.



Scheme 2.77 : Reagents and Conditions: (a) **(2.154)** (1 eq.), 2.5M ^{n}BuLi in hexanes (1 eq.), THF, -78 °C to -20 °C, 30 min, then **(2.106)** (1.05 eq.), THF, -78 °C to rt, 30 mins (45%); (b) HF (40% wt. in H_2O) (excess), MeCN, rt, 10 mins (68%); (c) **(2.154)** (1 eq.), 2.5M ^{n}BuLi in hexanes (1 eq.), THF, -78 °C to -20 °C, 30 min then **(2.106)** (1.05 eq.), THF, -78 °C to rt, 30 mins, solvent removed then HF (40% wt. in H_2O) (excess), MeCN, rt, 10 mins (47%).

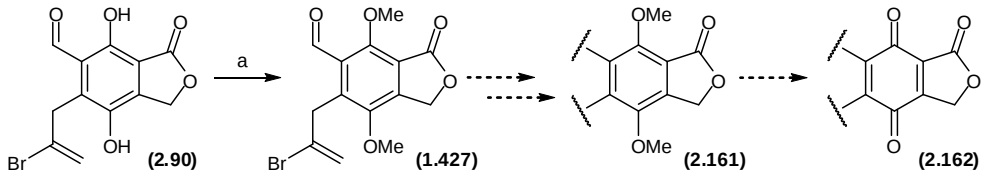
The speculative nature of this chemistry meant it was never a top priority and it would be found that a lack of material prevented us from carrying this sequence on any further.

2.8.2 Protection of Claisen Product (2.90).

Proceeding with the original synthesis necessitated a protection of the two phenols in Claisen product **(2.90)** (scheme 2.78), this was necessary both to allow the use of organolithium reagents in the introduction of the side chain and because acid had been shown to have a detrimental effect on the results of the cyclisation. Methylation was the preferred means of protection as the methyl ether would be completely inert under the conditions required to furnish the pentacyclic lactone **(2.161)**, there is also an abundance of examples of the oxidation of the *para*-dimethoxy unit to the desired quinone **(2.162)**.

The methylation of hydroquinone **(2.90)** would prove trying. This compound appeared to be even more unstable than the preceding benzaldehyde **(2.89)**. As such efforts to

derive the dimethylated lactone **(1.427)** under fairly standard conditions were extremely poor yielding, with what little material resulted being challenging to separate from the detritus of decomposition.

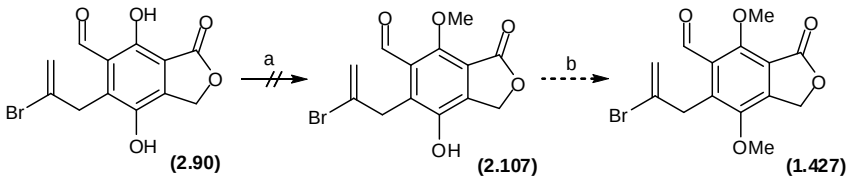


Scheme 2.78 : Reagents and Conditions: (a) *See table below.*

Reagent	Equivalents	Conditions	Yield (%)[a]
MeI	10	K_2CO_3, acetone, 50 °C, 5 hrs	11%
MeI	4	Cs_2CO_3, DMF, 80 °C, 4 hrs	6%
Me_2SO_4	10	K_2CO_3, acetone, 50 °C, 2 hrs	decomp.

[a] Isolated Yield.

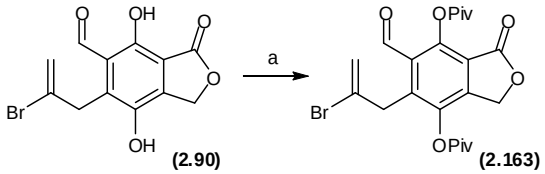
Having attributed the decomposition to the same lack of base stability observed in the case of the phenolic benzaldehyde **(2.89)** (*vide supra*, scheme 2.60), the prospect of a two-step methylation in which the reagents could be tailored to the two different phenolic environments seemed reasonable. TMS diazomethane would be used to methylate the more acidic phenol under neutral conditions and the resulting methyl ester **(2.107)** should then prove more resilient when the remaining phenol is protected under standard basic methylation conditions allowing for the formation of key intermediate **(1.427)** (scheme 2.79). Unfortunately the addition of a single equivalent of $TMSCHN_2$ to the hydroquinone still resulted in rapid decomposition of the starting material.



Scheme 2.79 : Reagents and Conditions: (a) $TMSCN_2$ (1 eq.), toluene/MeOH (3:2), rt, 10 mins; (b) MeI, K_2CO_3, Acetone.

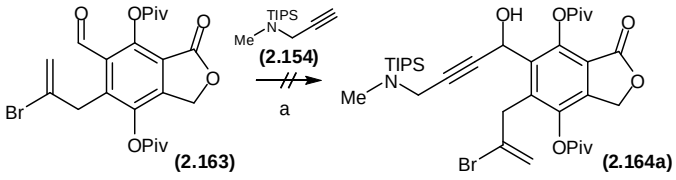
With work toward the methylated compound faltering a different approach was devised, the phenols would instead be protected as their pivaloyl esters (scheme 2.80). The reaction with pivaloyl chloride would prove more facile than the alkylation and the steric bulk of the ester should make the ester robust enough to survive a careful addition of the lithiate to the aldehyde, this view was further reinforced by the fact the lactone

had survived that same addition as noted earlier. When benzaldehyde **(2.90)** was treated with pivaloyl chloride in pyridine at room temperature the reaction was both rapid and clean; the diester **(2.160)** was produced in good yield.[248]



Scheme 2.80 : Reagents and Conditions: (a) PivCl (excess), pyridine, rt, 3 hrs (79%).

We had sufficient remaining material to make a singular attempt at introducing the first side chain segment. Following the procedure for the methylated benzaldehyde **(2.106)** (*vide supra*, scheme 2.77) the pivaloyl ester **(2.163)** was dissolved in THF and added to a pre-prepared solution of the lithiate of amine **(2.154)** (scheme 2.81). This resulted in a complex multi-spot mixture by TLC presumably due to competitive nucleophilic attack on the Pivaloyl esters, none of the products were identifiable. This was an accepted consequence of this method given the presence of the more labile phenolic esters and a clear indication that greater care is required in its execution. This failure was therefore not unduly discouraging.



Scheme 2.81 : Reagents and Conditions: (a) **(2.154)** (0.95 eq.), 2.5M ^{n}BuLi in hexanes (0.95 eq.), THF, -78 °C to -20 °C, 30 min, then **(2.163)**, THF, -78 °C to rt, 30 mins.

2.9 Future Work.

2.9.2 Proposed Route Modifications.

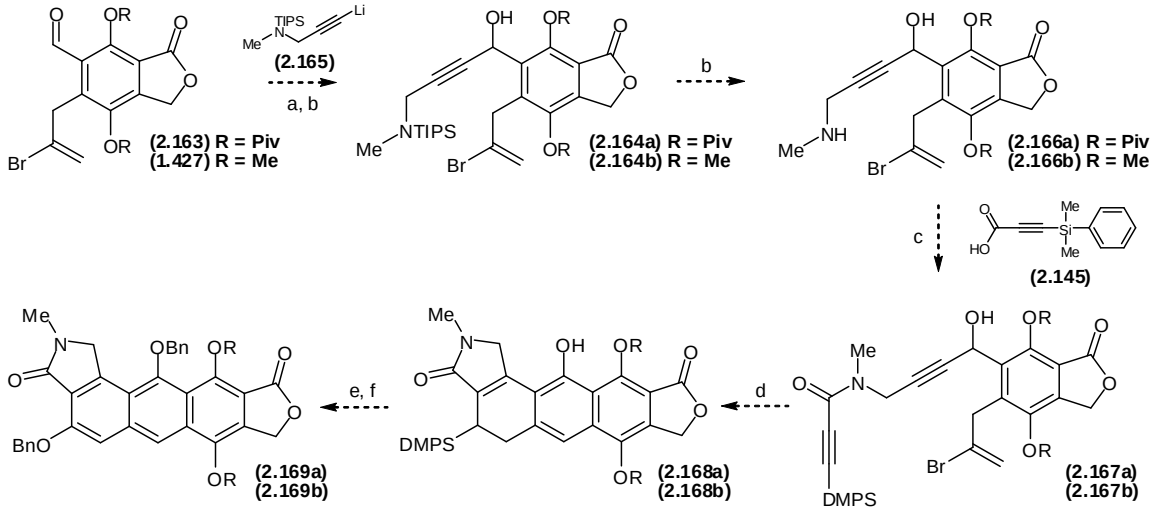
Whilst the route described above is generally reliable with respectable yields, up to the synthesis of the diol Claisen precursor **(2.78)**, the author would strongly encourage anyone charged with the continuation of this work to invest a small amount of time investigating the oxidation of the hetero benzyl ethers **(2.91a)-(2.91c)** (*vide supra*, scheme 2.55). This would allow the circumvention of the most problematic chemistry of the route and the poor yield of the Claisen rearrangement. The rearrangement generating benzyl ether **(2.91a)** exhibited far superior yields and reliability and there is every

reason to believe a DDQ oxidation of this system would be successful. In addition the protection of the resulting hydroquinone system is likely to proceed with fewer complications in the absence of the electron withdrawing aldehyde, this should allow for a straightforward methylation allowing the use of the pivalate ester and its attendant complications to be avoided.

2.9.2 Toward the Completion of the Achiral CDEF Ring System.

With the hard fought battle to derive a fully substituted benzaldehyde now complete, progress towards lactonamycin should prove to be somewhat more rapid. The forward route (scheme 2.82) can be adapted to either the diester **(2.163)** resulting from the established work, or the methylated equivalent **(1.427)** that would result from the modification in route proposed above.

The diester **(2.163)** should be apt to deliver the alcohol **(2.164a)** with a more careful approach involving a slow addition of the lithiate to the benzaldehyde. The diether **(1.427)** should prove less sensitive giving the equivalent alcohol **(2.164b)** by the previously established method. The immediate addition products will be desilylated using HF, either by the stepwise sequence preferred by Faggiani or a one-pot procedure from the benzaldehyde as demonstrated. Free amine **(2.166a)** or **(2.166b)** will be coupled with the dimethylsilylpropynoyl chloride, generated *in situ* from the corresponding carboxylic acid **(2.145)** with oxalyl chloride and catalytic DMF.



Scheme 2.82 : Reagents and Conditions: (a) **(2.165)**; (b) HF; (c) **(2.145)**, $(COCl)_2$, DMF then **(2.166a)** or **(2.166b)**; (d) Toluene, epoxyhexane, reflux; (e) Br_2, AcOOH, AcOH; (f) BnBr, K_2CO_3.

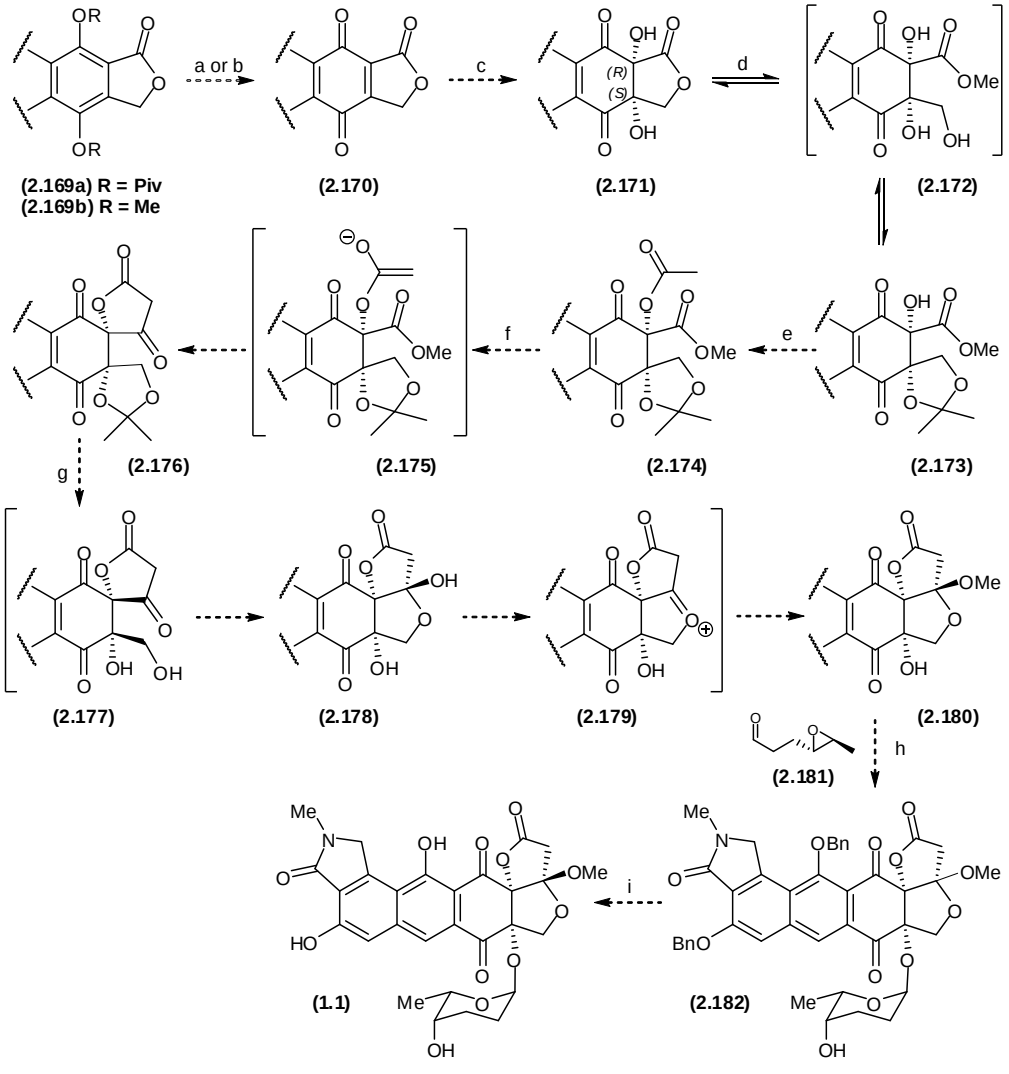
With the second alkyne in place, both precursors **(2.167a)** and **(2.167b)** should undergo the well precedented radical cyclisation when heated in toluene with epoxyhexane acting as an acid trap. This would deliver either pentacyclic compound **(2.168a)** or **(2.168b)** respectively. The DMPS residue will allow for a Fleming oxidation of either silane by a one-pot procedure using bromine to effect a halodesilylation which in the presence of peracetic acid would result in the corresponding alcohol. This should be rapidly oxidised in air to the bisphenol. Protection of both phenols as their benzyl ethers would be achieved under standard conditions with benzyl bromide to give either lactone **(2.169a)** or **(2.169b)**.

2.9.3 Finishing the Chiral AB Ring System.

Both of the protected hydroquinones will then be oxidised to the quinone **(2.170)** (scheme 2.83). In the case of the methylated substrate **(2.169b)** the 1,4-dimethoxy moiety will be readily oxidised to the quinone with argentic oxide[249] or CAN.[250] The pivalate **(2.169a)** may prove somewhat more resistant to oxidation but this too should be oxidised to the quinone with CAN as is observed with similar 1,4-diacetoxy systems.[251] Should that fail saponification of the pivaloyl esters would reveal the hydroquinone which should be readily oxidised by heating in air.[252] Any accompanying cleavage of the lactone should be easily reversed upon acidification.

The formation of quinone **(2.170)** exposes a single non-aromatic double bond, dihydroxylation of this bond will install the *cis*-diol around which the AB ring system will be constructed. For an achiral synthesis a simple dihydroxylation with OsO_4 or $RuCl_3$ would suffice, delivering the racemic diol. However to incorporate the correct (7aS, 10aR) stereochemistry in diol **(2.171)** a more considered approach is required. The Sharpless asymmetric dihydroxylation is the method of choice for such transformations.[253] Whilst the tetra-substituted alkene may prove a less than ideal substrate it is hoped that with increased catalyst loadings and the addition of the accelerating methanesulfonamide the desired enantiomer will be acquired in a viable e.e. using AD mix β.[254] Should this fail an approach utilising stoichiometric quantities of OsO_4 may be applied, though this is undesirable due to the expense and high toxicity of the reagent. With the diol introduced either in enantiomerically enriched form or as the racemate, heating the lactone **(2.171)** in methanol under acid conditions should transesterify the lactone to give the methyl ester **(2.172)** in equilibrium, with a large

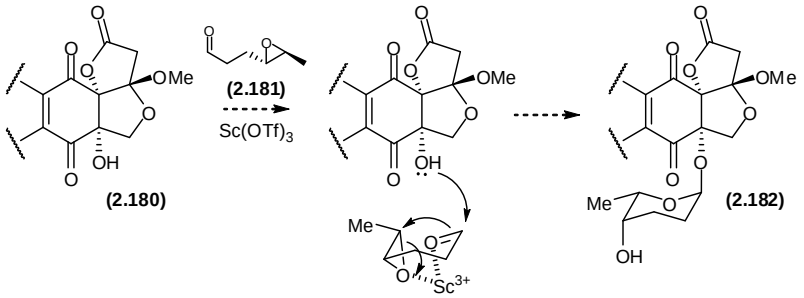
excess of 2-methoxypropene the exposed 1,2-diol will be trapped as the dioxolane **(2.173)**. The remaining free alcohol will be acetylated with acetic anhydride to give ester **(2.174)**. Treatment of this ester with LDA will form enolate **(2.175)** which will spontaneously cyclise onto the methyl ester to give β-ketolactone **(2.176)**. Exposure of the dioxolane to methanol under acidic conditions will result in deprotection, the revealed primary alcohol will then cyclise onto the adjacent ketone resulting in hemi-acetal **(2.178)** which under the reaction conditions will be readily displaced by methanol to give the methyl ester **(2.180)**, thus furnishing the main body of lactonamycinone in protected form.



Scheme 2.83 : Reagents and Conditions: (a) $Ag_2O.Ag_2O_3$, HNO_3; (b) CAN, H_2O, MeCN; (c) AD Mix β; (d) 2-Methoxypropene, MeOH, CSA; (e) Ac_2O, DMAP; (f) LDA; (g) MeOH, pTSA; (h) **(2.181)**, $Sc(OTf)_3$; (i) H_2, Pd/C.

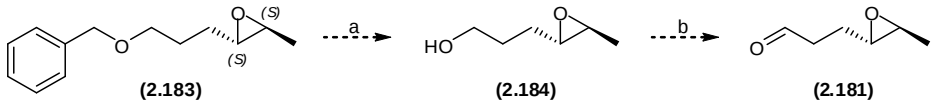
We propose to add the required sugar residue *via* a Lewis acid mediated addition/ring opening cascade sequence (scheme 2.84). Exposure of the tertiary alcohol **(2.180)** to the

chiral epoxy aldehyde **(2.181)** in the presence of scandium (III) triflate will lead to nucleophilic attack on the aldehyde, the resulting alkoxide will then open the proximal epoxide, the configuration of this ring opening being controlled by coordination of both oxygen atoms to the Lewis acid.[255]



Scheme 2.84 : Proposed glycosylation procedure.

The aldehyde **(2.181)** will be prepared by the careful hydrogenolytic debenzylation of known chiral epoxide **(2.183)**,[256] followed by oxidation of the resulting alcohol **(2.184)** (scheme 2.85).



Scheme 2.85 : Reagents and Conditions: (a) Hydrogenolysis; (b) Oxidation.

Should this novel approach prove to be unsuccessful, it is possible that the α-rhodinose sugar might be added by the methodology of Tatsuta *et al.* by coupling the activated thiosaccharide **(1.357a)** with the exposed tertiary alcohol **(2.180)** (*vide supra*, scheme 1.65). In the event that chirality was not introduced successfully at the osmylation stage, a resolution of the resulting diastereomeric glycosides should be possible by chromatography. Standard hydrogenolysis of the benzyl ethers will yield lactonamycin **(1.1)** as demonstrated on the analogous benzyl-protected lactonamycin **(1.360)** (*vide supra*, scheme 1.66).

Modelling the chemistry detailed in schemes 2.82 & 2.83 is highly advised, fortunately Danishefky has already described the synthesis of two appropriate models for this work (figure 2.3) (*vide supra*, scheme 1.4). The tricyclic lactone **(1.28)** should serve as an apt model for methylated pentacycle **(2.169b)** whilst the demethylated precursor **(1.27)** should be readily Piv protected to serve as a model for the corresponding pentacycle **(2.169a).**

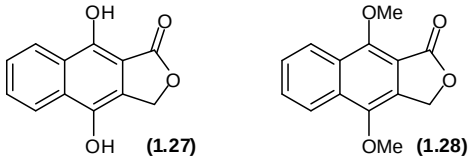
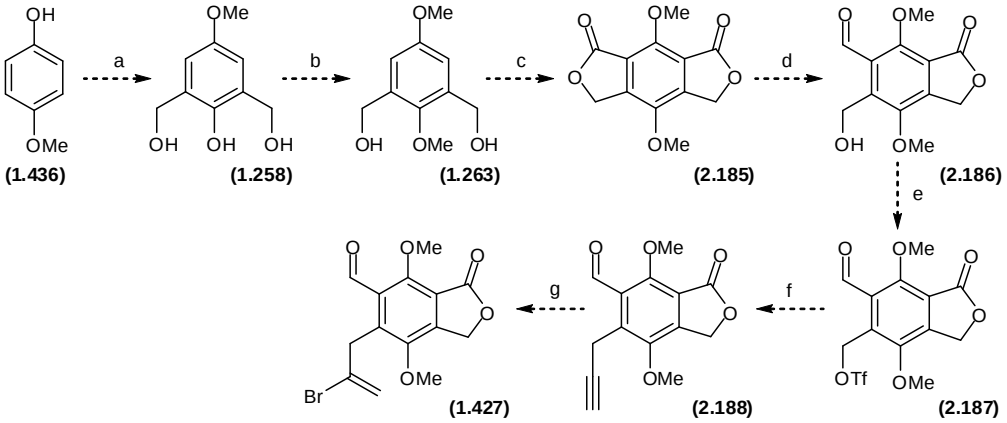


Figure 2.3 : Models for developing the synthesis of the ABC ring system.

2.9.4 An Additional Route to Key Intermediate (1.427).

One further route to the hexacyclic intermediate was envisioned but never expanded upon (scheme 2.86). Starting from the known triol **(1.258)**[69] this species would be selectively methylated on the phenolic oxygen with dimethylsulfate to give the diol **(1.263)**.[107] This diol would serve as the substrate for the formation of the symmetrical bislactone **(2.185)**, which may be formed by an extension of the lithiate method employed previously (*vide supra*, scheme 2.9) or should the formation of the required tetra-lithiated species prove impossible an alternate lactone synthesis has been demonstrated by Larock and Fellows, an electrophilic thalliation/carbonylation sequence should be successful on the activated ring.[257] A single equivalent of DIBAL would reduce one of the lactone rings to give the aldehyde **(2.186)**. Conversion of the benzylic alcohol to an appropriate leaving group such as triflate **(2.187)** would allow the formation of the alkyne **(2.188)**, introduced by a displacement with ethynylmagnesium bromide. Finally addition of the sterically hindered *B*-bromo-9-BBN across the acetylene would give the vinyl bromide **(1.427)** whilst avoiding the deprotection of the more hindered methyl ethers.[258]



Scheme 2.86 : Reagents and Conditions: (a) Hydroxymethylation, (b) Methylation with Me_2SO_4, (c) Lactone formation, (d) DIBAL reduction, (e) Leaving group formation with Tf_2O, (f) Addition of ethynylmagnesium bromide, (g) *B*-bromo-9-BBN then acid workup.

3. Experimental

"Now if by chance we are missing a flask
We go to our neighbour, and timidly ask,
"Can you give us the low down - who stole our glass?"
With innocent surprise or utter dismay
He tells us he has not seen it today
So we give up our search, but the suspicion is strong
That our chemical neighbour has done us the wrong." [259]

3.1 General Procedure

All reactions were carried out under an atmosphere of nitrogen unless otherwise stated, using oven dried glassware. Commercially available chemicals and reagents were used as supplied unless otherwise stated.

Tetrahydrofuran and diethyl ether were distilled from sodium using benzophenone as an indicator. Dichloromethane and acetonitrile were distilled from calcium hydride. Dry alcohol solvents were distilled from magnesium turnings and stored over 4 Å molecular sieves. Nitrogenous solvents were distilled from calcium hydride and stored over potassium hydroxide. All solvents for high temperature reactions (>100 °C) were deoxygenated by sparging for at least 1 hour with nitrogen or argon gas.

Microwave reactions were carried out using a CEM Discover-S 300W microwave system with a pressure tolerance of up to 18bar.

Reactions were monitored either by crude NMR of the RM or by tlc using Merck glass backed tlc plates coated with a 0.25 mm layer of 60 F_{254} silica gel. Visualisation was achieved using 254 nm UV radiation (where applicable) and potassium permanganate, phosphomolybdic acid or vanillin stains as deemed appropriate. Column chromatography was carried out using Merck Kieselgel 60.

NMR spectroscopy was performed using either Varian NMR System-600 MHz (600 MHz for ^{1}H and 151 MHz for ^{13}C), or Varian NMR System-500 MHz (500 MHz for ^{1}H and 126 MHz for ^{13}C). The solvent used for NMR samples was either perdeuterated chloroform or perdeuterated dimethylsulfoxide. Chemical shifts were measured on the ppm scale and internally referenced to the shift of residual unlabelled chloroform (7.260 ppm for ^{1}H, 77.160 ppm for ^{13}C) and dimethylsulfoxide (2.500 ppm for ^{1}H, 39.520 ppm for ^{13}C).[260] All ^{13}C NMR was performed with proton decoupling.

Heteronuclear Single Quantum Coherence (HSQC), Heteronuclear Multiple Bond Coherence (HMBC), Correlation Spectroscopy (COSY) and Hydrogen-Deuterium exchange (H-D) experiments were also run where necessary to allow for the full elucidation of structures.

Mass spectrometry was performed using a Fissons Instrument VG Autospec and a Bruker Daltonics Apex III.

Infrared spectra were recorded on a Perkin-Elmer 1710 Fourier transform instrument with ATR attachment.

Melting points were recorded using a Gallenkamp melting point apparatus and are uncorrected.

Whilst all compounds are named in accordance with IUPAC guidelines, atoms in the following section were numbered solely to aid in the assignment of NMR data and should be interpreted as such.

3.2 Index of Compounds

(1) (2,5-Dimethoxy-phenyl)-methanol
(2) 4,7-Dimethoxy-2-benzofuran-1(3H)-one
(3) 6-Bromo-4,7-dimethoxy-2-benzofuran-1(3H)-one
(4) 2,5-Bis-(hydroxymethyl)-benzene-1,4-diol
(5) 2,2,7,7-Tetramethyl-4,9-dihydro[1,3]dioxino[4,5-g][1,3] benzodioxine
(6) (4-Hydroxymethyl-2,5-dimethoxy-phenyl)-methanol
(7) 4,7-Dihydroxy-2-benzofuran-1(3H)-one
(8) 4,7-Dihydroxy-6-(hydroxymethyl)-2-benzofuran-1(3H)-one
(9) 4-Hydroxymethyl-2,5-dimethoxy-benzoic acid
(10) 6-Hydroxy-2,2-dimethyl-4,7-dihydro-9H-furo[3,4-h][1,3] benzodioxin-9-one
(11) 6-[(2-Bromo-2-propenyl)oxy]-2,2-dimethyl-4,7-dihydro-9H-furo[3,4-h] [1,3]benzodioxin-9-one
(12) 4-[(2-Bromo-2-propenyl)oxy]-7-hydroxy-6-(mesitylmethyl)-2-benzofuran-1(3H)-one
(13) 4-[(2-Bromo-2-propenyl)oxy]-7-hydroxy-6-(hydroxymethyl)-2-benzofuran-1(3H)-one
(14) 4-[(2-Bromo-2-propenyl)oxy]-6-ethyl-7-hydroxy-2-benzofuran-1(3H)-one
(15) {7-[(2-Bromo-2-propenyl)oxy]-4-hydroxy-3-oxo-1,3-dihydro-2-benzofuran-5-yl}methyl trifluoroacetate
(16) 5-(2-Bromo-2-propenyl)-6-[4-(diethylamino)benzyl]-4,7-dihydroxy-2-benzofuran-1(3H)-one
(17) 7-[(2-Bromo-2-propenyl)oxy]-4-hydroxy-3-oxo-1,3-dihydro-2-benzofuran-5-carbaldehyde
(18) 6-(2-Bromo-2-propenyl)-4,7-dihydroxy-3-oxo-1,3-dihydro-2-benzofuran-5-

carbaldehyde

(19) 6-[(Benzyloxy)methyl]-5-(2-bromo-2-propenyl)-4,7-dihydroxy-2-benzofuran-1(3H)-one

(20) 5-Hydroxy-2-methyl-6-oxo-6,8-dihydrofuro[2,3-e][2]benzofu-ran-4-carbaldehyde

(21) 7-[(2-Bromo-2-propenyl)oxy]-4-methoxy-3-oxo-1,3-dihydro-2-benzofuran-5-carbaldehyde

(22) 4-[(2-Bromo-2-propenyl)oxy]-6-{1-hydroxy-4-[methyl(triisopropylsilyl)amino]-2-butynyl}-7-methoxy-2-benzofuran-1(3H)-one

(23) 4-[(2-Bromo-2-propenyl)oxy]-6-[1-hydroxy-4-(methylamino)-2-butynyl]-7-methoxy-2-benzofuran-1(3H)-one

(24) 6-(2-Bromo-2-propenyl)-4,7-dimethoxy-3-oxo-1,3-dihydro-2-benzofuran-5-carbaldehyde

(25) 5-(2-Bromo-2-propenyl)-7-[(2,2-dimethylpropanoyl)oxy]-6-formyl-1-oxo-1,3-dihydro-2-benzofuran-4-yl pivalate

(26) Ethynyl(dimethyl)phenylsilane

(27) 3-[Dimethyl(phenyl)silyl]-2-propynoic acid

(28) 2,2-Dimethyl-4H-1,3-benzodioxine

(29) 2-[(Benzyloxy)methyl]phenol

(30) 2-{[(4-Methoxybenzyl)oxy]methyl}phenol

(31) 2-[(4-Methyl-1-piperazinyl)methyl]phenol

(32) 2-(4-Morpholinylmethyl)phenol

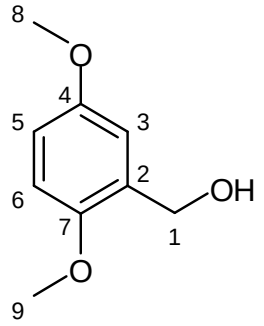
(33) 2-[(Phenylsulfanyl)methyl]phenol

(34) 2-[4-(Dimethylamino)benzyl]phenol

(35) 1,1,1-Triisopropyl-*N*-methyl-*N*-(prop-2-ynyl)silanamine

(36) 2,3-Dibromopropene

(2.15) (2,5-Dimethoxyphenyl)methanol



Prepared by a modification of the method of Kumar et al.[170]

2,5-Dimethoxybenzaldehyde **(2.18)** (25.00 g, 150 mmol) was dissolved in methanol (500 mL) and the solution cooled to -10 °C. Sodium borohydride (6.85 g, 165 mmol) was then added portionwise over 10 minutes. The RM was left to stir for three hours at rt after which the reaction was carefully quenched with water (500 mL) resulting in the evolution of a large quantity of hydrogen gas. The methanol was removed under reduced pressure to leave a white aqueous emulsion. This emulsion was extracted with diethyl ether (3 x 500 mL). The combined organic extracts were washed with water (500 mL) and aqueous sodium chloride solution (sat., 500 mL) before being dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting yellow oil was washed with hexane and then dried under vacuum to give the title compound as a yellow oil (24.44g, 97%). Spectra were consistent with those previously reported.[170]

LRMS: (EI) *m/z* 168 (M^+, 100%), 153 (23), 125 (62), 65 (41).

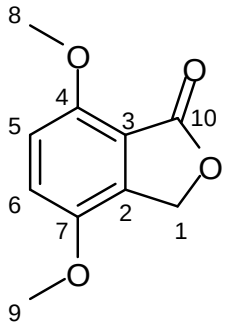
IR: (neat, ν cm^{-1}) 3401 (v. br), 2944, 2835, 1592.

δ_H: (500 MHz, $CDCl_3$): 6.90 (1H, d, *J* = 2.6 Hz, 3-H), 6.80 (2H, m, 5-H & 6-H), 4.66 (2H, s, 1-H), 3.82 (3H, s, 8-H), 3.77 (3H, s, 9-H).

δ_C: (126 MHz, $CDCl_3$): 153.5 (C4), 151.0 (C7), 130.5 (C2), 114.0 (CH, C6), 112.6 (CH, C5), 111.1 (CH, C3), 60.2 (CH_2, C1), 55.5 (CH_3, C8 & C9).

R_f: (5% MeOH in CH_2Cl_2) = 0.31

(2.14) 4,7-Dimethoxy-2-benzofuran-1(3H)-one



Prepared by a modification of the method of Magnus et al.[171]

(2,5-Dimethoxyphenyl)methanol **(2.15)** (3.00 g, 17.8 mmol) was dissolved in dry tetrahydrofuran (50 mL), this solution was cooled to -78 °C and a solution of *n*-butyllithium in hexanes (1.9M, 18.7 mL, 35.6 mmol) was added dropwise. The mixture was slowly warmed to 70 °C and allowed to stir for 2 hours. The RM was then cooled to -20 °C and solid carbon dioxide (large excess) added over 30 minutes. The reaction was quenched by the addition of aqueous hydrochloric acid (2M, 100 mL) resulting in the formation of a white precipitate. The precipitate was isolated by filtration, washed with hexanes and dried under vacuum to yield a white crystalline solid (0.98 g, 28%). The filtrate was extracted with chloroform (3 x 100 mL) and the combined organic extracts dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the resulting crude yellow solid was recrystallised from hot methanol to yield a further batch of white solid (0.85 g, 24%) giving an overall yield of 52%. Spectra were consistent with those previously reported. [171]

LRMS: (EI) *m/z* 194 (M^+, 100%), 165 (81), 148 (76), 135 (29), 107 (23).

HRMS: (ESI+) Calculated for $C_{10}H_{10}O_4Na$, *m/z* 217.0471 found 217.0471

IR: (neat, ν cm^{-1}) 2843, 1756 (s), 1608, 1504, 1270.

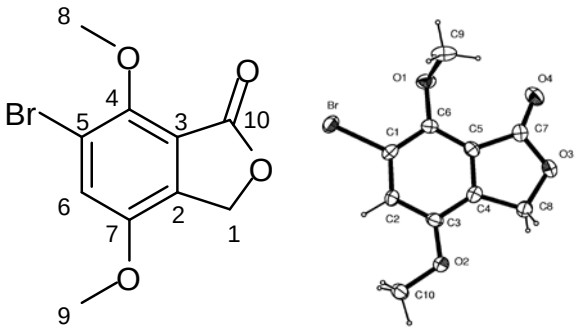
δ_H: (500 MHz, $CDCl_3$): 7.05 (1H, d, *J* = 8.8 Hz, 6-H), 6.85 (1H, d, *J* = 8.7 Hz, 5-H), 5.19 (2H, s, 1-H), 3.95 (3H, s, 8-H), 3.86 (3H, s, 9-H).

δ_C: (126 MHz, $CDCl_3$): 169.0 (C10), 152.2 (C4), 147.5 (C7), 136.9 (C2), 116.7 (CH, C6), 114.5 (C3), 111.6 (CH, C5), 67.1 (CH_2, C1), 56.2 (CH_3, C8), 55.8 (CH_3, C9).

R_f: (50% EtOAc in Hexane) = 0.30

m.p.: 167-169 °C (Lit: 167-168 °C)[261]

(2.13) 6-Bromo-4,7-dimethoxy-2-benzofuran-1(3H)-one



4,7-Dimethoxy-2-benzofuran-1(3H)-one **(2.14)** (1.00 g, 5.15 mmol) and aluminium chloride (137 mg, 1.03 mmol) were dissolved in acetic acid (50 mL) and this solution was cooled in an ice bath while a solution of bromine (0.26 mL, 5.15 mmol) in acetic acid (25 mL) was carefully added over the course of 5 minutes. The RM was heated to 70 °C and left to stir for 6 hours before being cooled to rt and left to stir overnight. The reaction was diluted with water (400 mL) resulting in the formation of a white precipitate which was separated by filtration and dried under vacuum to give a crude yellow solid. This solid was further purified by column chromatography eluting with a hexane: ethyl acetate gradient (1% to 20%). This produced the title compound as an off-white crystalline solid (0.98 g, 69%).

HRMS: (ESI+) Calculated for $C_{10}H_9O_4{}^{81}BrNa$, *m/z* 296.9561 found 296.9552

IR: (neat, ν cm^{-1}) 2920, 1758, 1611, 1485, 1254.

δ_H: (500 MHz, DMSO-d_6): 7.53 (1H, s, 6-H), 5.22 (2H, s, 1-H), 3.85 (3H, s, 8-H), 3.84 (3H, s, 9-H).

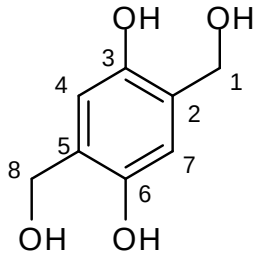
δ_C: (126 MHz, $CDCl_3$): 167.6 (C10), 149.8 (C7), 149.3 (C4), 136.0 (C2), 120.1 (CH, C6), 119.6 (C3), 117.7 (C5), 67.2 (CH_2, C1), 62.6 (CH_3, C8), 56.1 (CH_3, C9).

R_f: (30% Hexane in EtOAc) = 0.59

m.p.: 177-180 °C

Crystal Structure also determined. (Appendix A)

(2.48) 2,5-Bis(hydroxymethyl)-1,4-benzenediol



Hydroquinone **(2.47)** (5.0 g, 45.4 mmol)) and sodium hydroxide (3.81 g, 95.3 mmol) were dissolved in water (35 mL) to give a clear brown solution and to this was added formalin solution (6.88 g, 37% wt. formaldehyde, 90.8 mmol). The RM was stirred in the dark for 5 days at rt. The reaction was quenched with acetic acid (5 mL) to give a solution of approximately pH 1, this solution was stirred for 10 minutes with decolourising charcoal before being filtered. The filtrate was cooled in the fridge overnight developing off-white needle crystals. These crystals were further purified by recrystallisation from dimethylformamide by the addition of diethyl ether, this gave the title compound as an off-white crystalline solid (784 mg, 10%). Spectra were consistent with those previously reported.[190]

HRMS: (ESI+) Calculated for $C_8H_{10}O_4Na$, *m/z* 193.0471 found 193.0473

IR: (neat, ν cm^{-1}) 3395, 3138, 2949, 2901, 1413, 1197, 1003.

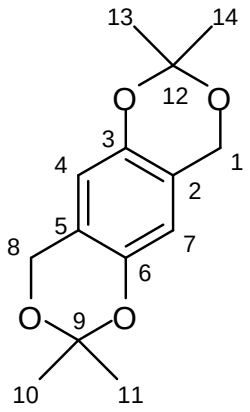
δ_H: (500 MHz, DMSO-d_6): 8.46 (2H, br s, 3-O*H* & 6-O*H*), 6.73 (2H, s, 4-H & 7-H), 4.82 (2H, br s, 8-O*H* & 1-O*H*), 4.40 (4H, s, 1-H & 8-H).

δ_C: (126 MHz, DMSO-d_6): 146.3 (C3 & C6), 127.0 (C2 & C5), 113.7 (CH, C4 & C7), 58.2 (CH_2, C1 & C8).

R_f: (10% MeOH in CH_2Cl_2) = 0.18

m.p.: Decomposed above ~185 °C (Lit: Decomposed)[190]

(2.55) 2,2,7,7-Tetramethyl-4,9-dihydro[1,3]dioxino[4,5-g][1,3] benzodioxine



2,5-Bis-(hydroxymethyl)-1,4-benzenediol **(2.48)** (500 mg, 2.94 mmol) was dissolved in acetone (50 mL, excess) acidified with sulfuric acid (conc., 3 drops) to give a light brown solution that was stirred at rt for 48 hours. The RM was diluted with water (100 mL) and then extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with water (100 mL) and aqueous sodium chloride solution (sat., 100 mL), before being dried over anhydrous magnesium sulfate. The solvent removed under reduced pressure, to give a crude brown solid. This solid was then further purified by recrystallisation from the minimum volume of boiling acetone. Cooling overnight produced the title compound as an off-white crystalline solid (258 mg, 35%).

LRMS: (EI) *m/z* 250 (M^+, 10%), 192 (100), 150 (34), 134 (51), 78 (96).

HRMS: (ESI+) Calculated for $C_{14}H_{18}O_4Na$, *m/z* 273.1097 found 273.1098

IR: (neat, ν cm^{-1}) 2989, 2938, 1742, 1508, 1441, 1129.

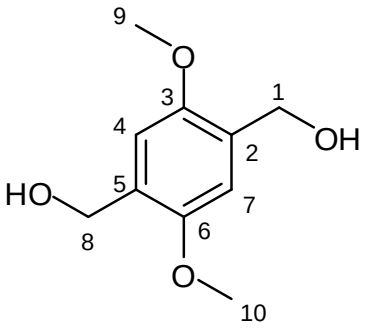
δ_H: (500 MHz, $CDCl_3$): 6.44 (2H, s, 4-H & 7-H), 4.79 (4H, s, 1-H & 8-H), 1.52 (12H, s, 10-H, 11-H, 13-H & 14-H).

δ_C: (126 MHz, $CDCl_3$): 144.8 (C3 & C6), 119.4 (C2 & C5), 112.3 (CH, C4 & C7), 99.2 (C9 & C12), 60.8 (CH_2, C1 & C8), 24.7 (CH_3, C10, C11, C13 & C14).

R_f: (10% EtOAc in Hexane) = 0.35

m.p.: 197-199 °C

(2.56) (4-Hydroxymethyl-2,5-dimethoxy-phenyl)-methanol



2,5-Bis-(hydroxymethyl)-benzene-1,4-diol **(2.48)** (200 mg, 1.18 mmol) and potassium carbonate (359 mg, 2.60 mmol) were dissolved in acetonitrile (5 mL) this mixture was warmed to 60 °C and methyl iodide (0.2 mL, 3.21 mmol) was added, the mixture was then heated at reflux for 8 hours with hourly additions of methyl iodide (0.2 mL, 3.21 mmol). The RM was diluted with water (25 mL) before being extracted with dichloromethane (3 x 25 mL). The combined organics were dried over anhydrous magnesium sulfate before the solvent was removed under reduced pressure to give an off-white solid. This solid was further purified by recrystallisation from the minimum volume of hot ethyl acetate by the addition of hexane. Cooling overnight gave the title compound as a white solid (42 mg, 18%). Spectra were consistent with those previously reported.[262]

HRMS: (ESI+) Calculated for $C_{10}H_{14}O_4Na$, *m/z* 221.0784 found 221.0794

IR: (neat, ν cm^{-1}) 3267 (v br), 3006, 1504, 1403, 1203.

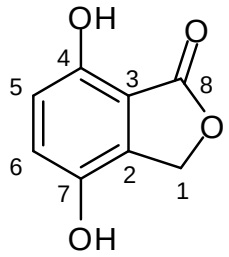
δ_H: (500 MHz, $CDCl_3$): 6.89 (2H, s, 4-H & 7-H), 4.68 (4H, d, *J* = 6.2 Hz, 1-H & 8-H), 3.85 (6H, s, 9-H & 10-H), 2.23 (2H, t, *J* = 6.3 Hz, 8-O*H* & 1-O*H*).

δ_C: (126 MHz, $CDCl_3$): 151.2 (C3 & C6), 128.9 (C2 & C5), 111.4 (CH, C4 & C7), 61.9 (CH_2, C1 & C8), 55.9 (CH_3, C9 & C10).

R_f: (2% MeOH in CH_2Cl_2) = 0.18

m.p.: 157-158 °C (Lit: 162-164 °C)[262]

(2.58) 4,7-Dihydroxy-2-benzofuran-1(3H)-one



4,7-Dimethoxy-2-benzofuran-1(3H)-one **(2.14)** (2.91 g, 15 mmol) was dissolved in dichloromethane (15 mL) to give a yellow solution. This solution was cooled to -78 °C. A solution of boron tribromide in dichloromethane (33 mL, 1M, 33 mmol) was added drop-wise over 10 minutes. The RM was stirred at -78 °C for 4 hours before being allowed to warm slowly to rt overnight. The RM was cooled in an ice bath and quenched by the careful addition of water (50 mL) and then this mixture was extracted with ethyl acetate (5 x 100 mL). The combined organic extracts were washed with water (100 mL) and aqueous sodium chloride solution (sat., 100 mL) before being dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, to give a crude brown solid, this was further purified by column chromatography eluting with 5% methanol in dichloromethane to give the title compound as a tan solid (2.34 g, 94%). Spectra were consistent with those previously reported.[194]

LRMS: (EI) *m/z* 166 (M^+, 90%), 137 (100), 109 (21), 81 (25).

HRMS: (ESI+) Calculated for $C_8H_6O_4Na$, *m/z* 189.0158 found 189.0159

IR: (neat, ν cm^{-1}) 3310 (br), 3072 (br), 2855, 1717, 1502, 1403, 1288.

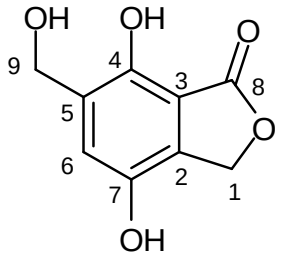
δ_H: (500 MHz, DMSO-d_6): 9.80 (1H, s, 4-O*H*), 9.48 (1H, s, 7-O*H*), 6.94 (1H, d, *J* = 8.6 Hz, 6-H), 6.73 (1H, d, *J* = 8.6 Hz, 5-H), 5.14 (2H, s, 1-H).

δ_C: (126 MHz, DMSO-d_6): 169.4 (C8), 149.9 (C4), 144.1 (C7), 133.8 (C2), 122.9 (CH, C6), 117.0 (CH, C5), 111.9 (C3), 67.4 (CH_2, C1).

R_f: (10% MeOH in CH_2Cl_2) = 0.52

m.p.: Decomposed ~225 °C

(2.59) 4,7-Dihydroxy-6-(hydroxymethyl)-2-benzofuran-1(3H)-one



4,7-Dihydroxy-2-benzofuran-1(3H)-one **(2.58)** (5.0 g, 30 mmol) and NaOH (2.4 g, 60 mmol) were dissolved in water (30 mL) to give a dark brown solution and to this solution was added a formalin solution (3.24 g, 37% wt. formaldehyde, 36 mmol), the RM was stirred in the dark at rt for 6 days. Acetic acid (15 mL) was added, resulting in the formation of a white precipitate which was isolated by filtration. The filtrate was then extracted with *n*-butanol (3 x 100 mL), the combined organic extracts were then washed with water (350 mL) and aqueous sodium chloride solution (sat., 350 mL) before being dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give an off-white solid. Residual solvent was removed by azeotroping with toluene. The solids were then combined and further purified by recrystallisation from boiling ethyl acetate. This gave the title compound as a white solid (4.07 g, 69%).

LRMS: (EI) *m/z* 196 (M^+, 39%), 178 (100), 149 (30), 121 (18).

HRMS: (ESI+) Ion not found.

IR: (neat, ν cm^{-1}) 3367 (br), 3048 (v br), 1717, 1443, 1098.

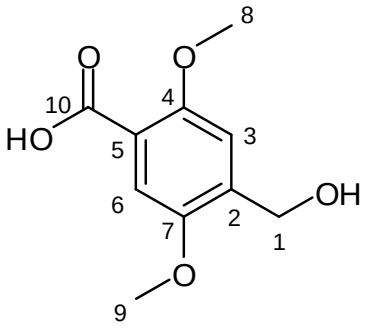
δ_H: (500 MHz, DMSO-d_6): 9.50 (1H, s, 4-O*H*), 8.81 (1H, s, 7-O*H*), 7.13 (1H, s, 6-H) 5.22 (1H, t, *J* = 5.5 Hz, 9-O*H*), 5.16 (2H, s, 1-H), 4.48 (2H, d, *J* = 5.3 Hz, 9-H).

δ_C: (126 MHz, DMSO-d_6): 170.4 (C8), 145.7 (C4), 144.4 (C7), 131.9 (C2), 130.9 (C5), 121.4 (CH, C6), 112.3 (C3), 67.7 (CH_2, C1), 58.1 (CH_2, C9).

R_f: (10% MeOH in CH_2Cl_2) = 0.22

m.p.: 200-203 °C

(2.21) 4-Hydroxymethyl-2,5-dimethoxy-benzoic acid



(2,5-Dimethoxyphenyl)methanol **(2.15)** (32.3 g, 192 mmol) was dissolved in tetrahydrofuran (200 mL) this solution was cooled to -78 °C and a solution of *n*-butyllithium in hexane (240 mL, 1.6M, 384 mmol) was slowly added. The mixture was slowly warmed to 70 °C and allowed to stir for 3 hours. The RM was then allowed to cool to rt and solid carbon dioxide added continuously over 60 minutes. Aqueous hydrochloric acid (700 mL, 2M) was added, developing a white precipitate of **(2.58)** (10.2 g), this was isolated by filtration. The filtrate was then extracted with chloroform (3 x 500 mL) and the combined organic extracts washed with water (1000 mL) and aqueous sodium chloride solution (sat., 1000 mL) before being dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give an off-white solid which was further purified by recrystallisation from boiling ethyl acetate giving the title compound as a crystalline white solid (5.81 g, 14%).

LRMS: (EI) *m/z* 212 (M^+, 100%), 194 (81), 165 (62), 148 (44).

HRMS: (ESI+) Calculated for $C_{10}H_{12}O_5Na$, *m/z* 235.0577 found 235.0576

IR: (neat, ν cm^{-1}) 3451, 3195, 2928, 1703, 1406, 1205.

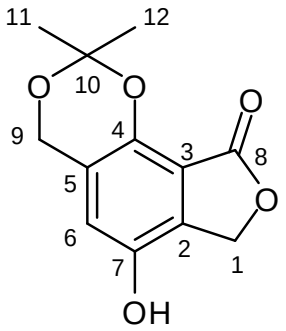
δ_H: (500 MHz, DMSO-d_6): 12.44 (1H, s, 10-O*H*), 7.19 (1H, s, 6-H), 7.17 (1H, s, 3-H), 5.19 (1H, t, *J* = 4.8 Hz, 1-O*H*), 4.50 (2H, d, *J* = 4.2 Hz, 1-H), 3.77 (3H, s, 9-H), 3.74 (3H, s, 8-H).

δ_C: (126 MHz, DMSO-d_6): 167.4 (C10), 153.2 (C7), 149.5 (C4), 136.6 (C2), 119.2 (C5), 112.6 (CH, C6), 112.3 (CH, C3), 58.2 (CH_2, C1), 56.9 (CH_3, C9), 56.1 (CH_3, C8).

R_f: (10% MeOH in CH_2Cl_2) = 0.45

m.p.: 158-159 °C

(2.50) 6-Hydroxy-2,2-dimethyl-4,7-dihydro-9H-furo[3,4-h][1,3] benzodioxin-9-one



4,7-Dihydroxy-6-(hydroxymethyl)-2-benzofuran-1(3H)-one **(2.59)** (23.0 g, 117 mmol) was suspended in acetone (490 mL), to this suspension was added 2,2-dimethoxypropane (72 mL, 579 mmol). A crystal of *para*-toluenesulfonic acid was added and the RM was then heated to 60 °C and stirred for 3 hours after which the solid had dissolved to give an orange solution. This solution was diluted with water (2000 mL) and then extracted with ethyl acetate (3 x 1000 mL), the combined organics were washed with water (1500 mL) and aqueous sodium chloride solution (sat., 1500 mL) before being dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, to give a solid. This solid was further purified by column chromatography eluting with 5% methanol in dichloromethane to give the title compound as an off-white solid (24.1 g, 87%).

HRMS: (ESI+) Calculated for $C_{12}H_{12}O_5Na$, *m/z* 259.0577 found 259.0577

IR: (neat, ν cm^{-1}) 3375, 3090, 1717, 1443, 1094.

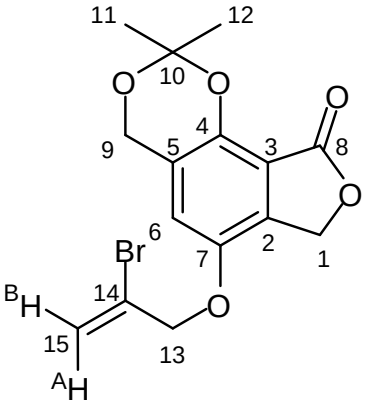
δ_H: (500 MHz, DMSO-d_6): 9.78 (1H, s, 7-O*H*), 6.83 (1H, s, 6-H), 5.19 (2H, s, 1-H), 4.84 (2H, s, 9-H), 1.50 (6H, s, 11-H & 12-H).

δ_C: (126 MHz, DMSO-d_6): 168.3 (C8), 144.7 (C4), 142.7 (C7), 134.1 (C2), 121.2 (CH, C6), 117.8 (C5), 113.3 (C3), 100.3 (C10), 67.4 (CH_2, C1), 60.5 (CH_2, C9), 25.0 (CH_3, C11 & C12).

R_f: (10% MeOH in CH_2Cl_2) = 0.41

m.p.: 200-203 °C

(2.51) 6-[(2-Bromo-2-propenyl)oxy]-2,2-dimethyl-4,7-dihydro-9H-furo[3,4-h][1,3]benzodioxin-9-one



6-Hydroxy-2,2-dimethyl-4,7-dihydro-9H-furo[3,4-h][1,3]benzodioxin-9-one **(2.50)** (15.3 g, 64.8 mmol) and potassium hydroxide (3.64 g, 64.8 mmol) were dissolved in ethanol (225 mL) and heated to 80 °C giving a dark brown solution. 2,3-dibromopropene **(1.370)** (7.3 mL, 15.5 g, 77.8 mmol) was added and the RM stirred at 80 °C for 2.5 hours. The reaction was quenched with water (1500 mL) resulting in the formation of an off-white precipitate, this precipitate was isolated by filtration before being redissolved in dichloromethane. This solution was washed with aqueous sodium hydroxide solution (0.2M, 1000 mL), water (1000 mL) and aqueous sodium chloride solution (sat., 1000 mL) the solvent was removed under reduced pressure to give a crude solid which was further purified by column chromatography eluting with 2% methanol in dichloromethane. This gave the title compound as an off-white solid (14.0 g, 61%). Unreacted starting material was recovered by neutralisation of the basic extract with an equal volume of aqueous hydrochloric acid (0.2M, 1000 mL) followed by extraction with ethyl acetate (3 x 500 mL). Removal of the solvent under reduced pressure gave a crude red oil, this was recrystallised from dichloromethane by the addition of hexane to produce 6-hydroxy-2,2-dimethyl-4,7-dihydro-9H-furo[3,4-h][1,3]benzodioxin-9-one as an off white solid (3.1 g, 20%) giving a combined yield of 81%.

HRMS: (ESI+) Calculated for $C_{15}H_{15}O_5{}^{79}BrNa$, *m/z* 376.9995 found 376.9990

IR: (neat, ν cm^{-1}) 2991, 1760 (s), 1499, 1301, 1012.

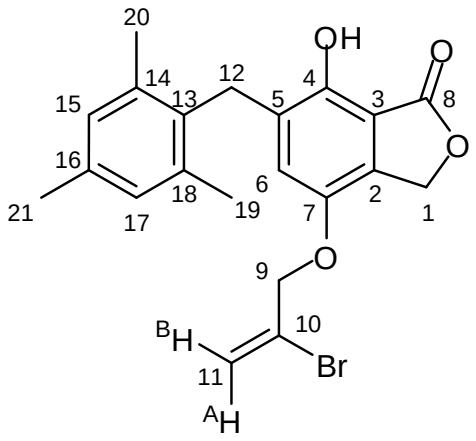
δ_H: (500 MHz, DMSO-d_6): 7.19 (1H, s, 6-H), 6.15 (1H, d, *J* = 2.1 Hz, 15-H^A), 5.76 (1H, d, *J* = 2.2 Hz, 15-H^B), 5.27 (2H, s, 1-H), 4.86 (2H, s, 9-H), 4.80 (2H, s, 13-H), 1.51 (6H, s, 11-H & 12-H).

δ_C: (126 MHz, DMSO-d_6): 167.4 (C8), 144.3 (C7), 143.7 (C4), 136.1 (C2), 127.0 (C14), 120.6 (C5), 120.4 (CH_2, C15), 116.1 (CH, C6), 113.2 (C3), 100.3 (C10), 72.0 (CH_2, C13), 66.7 (CH_2, C1), 60.1 (CH_2, C9), 24.5 (CH_3, C11 & C12).

R_f: (25% Ethyl Acetate in Hexane) = 0.20

m.p.: 129-132 °C

(2.70) 4-[(2-Bromo-2-propenyl)oxy]-7-hydroxy-6-(mesitylmethyl) -2-benzofuran-1(3H)-one



6-[(2-Bromo-2-propenyl)oxy]-2,2-dimethyl-4,7-dihydro-9H-furo[3,4-h][1,3]benzodiox-in-9-one **(2.51)** (100 mg, 0.28 mmol) was dissolved in mesitylene (6 mL), this solution was then heated to reflux for 24 hours. The solvent was then removed under reduced pressure and the residue was further purified by column chromatography eluting with dichloromethane to give the title compound as a white solid (92 mg, 78%).

HRMS: (ESI+) Calculated for $C_{21}H_{21}O_4{}^{79}BrNa$, *m/z* 439.0515 found 439.0497

IR: (neat, ν cm^{-1}) 3448, 2918, 1746, 1429, 1312.

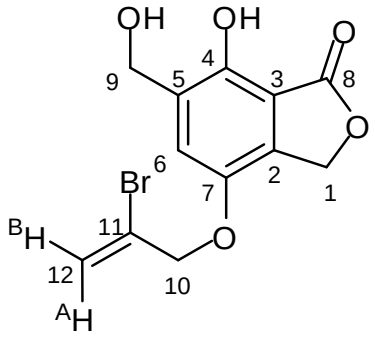
δ_H: (500 MHz, $CDCl_3$): 7.66 (1H, s, 4-OH), 6.91 (2H, s, 15-H & 17-H), 6.31 (1H, s, 6-H), 5.59 (1H, d, *J* = 1.8 Hz, 11-H^B), 5.53 (d, *J* = 2.3 Hz, 11-H^A), 5.28 (2H, s, 1-H), 4.38 (2H, s, 9-H), 3.97 (2H, s, 12-H)), 2.30 (3H, s, 21-H), 2.16 (6H, s, 19-H & 20-H).

δ_C: (126 MHz, $CDCl_3$): 172.8 (C8), 148.8 (C4), 144.7 (C7), 137.1 (C14 & C18), 136.3 (C16), 132.4 (C13), 131.5 (C2), 129.2 (CH, C15 & C17), 128.8 (C5), 127.3 (C10), 120.3 (CH, C6), 119.7 (CH_2, C11), 111.6 (C3), 72.9 (CH_2,C9), 69.1 (CH_2, C1), 27.6 (CH_2 ,C12), 21.1 (CH_3, C21), 20.0 (CH_3, C19 & C20).

R_f: (CH_2Cl_2) = 0.57

m.p.: 157-159 °C

(2.78) 4-[(2-Bromo-2-propenyl)oxy]-7-hydroxy-6-(hydroxy methyl)-2-benzofuran-1(3H)-one



6-[(2-Bromo-2-propenyl)oxy]-2,2-dimethyl-4,7-dihydro-9H-furo[3,4-h][1,3]benzodiox-in-9-one **(2.51)** (40 mg, 0.11 mmol) was suspended in a solution of acetic acid in water (50% v/v, 10 mL), and heated to 60 °C for 2.5 hours. The solvent was then removed under reduced pressure and residual acetic acid removed by azeotroping with toluene to give the title compound as a white solid (35 mg, quant.).

LRMS: (EI) *m/z* 316 (M^+(^{81}Br), 26%), 314 (M^+(^{79}Br), 27%), 217 (68), 195 (98), 149 (90).

HRMS: (ESI+) Ion not found.

IR: (neat, ν cm^{-1}) 3415, 3287 (br), 3006, 1748, 1630.

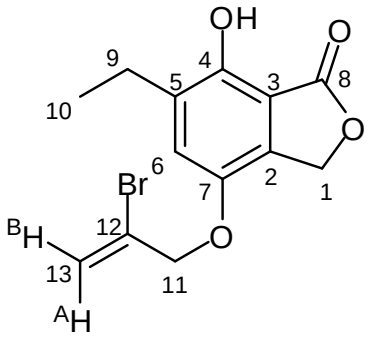
δ_H: (500 MHz, $CDCl_3$): 7.58 (1H, s, 4-O*H*), 7.17 (1H, s, 6-H), 5.96 (1H, d, *J* = 1.0 Hz, 12-H^A), 5.71 (1H, d, *J* = 1.1 Hz, 12-H^B), 5.33 (2H, s, 1-H), 4.78 (2H, s, 9-H), 4.69 (2H, s, 10-H).

δ_C: (126 MHz, $CDCl_3$): 172.1 (C8), 148.0 (C4), 145.0 (C7), 133.2 (C2), 129.1 (C11), 126.7 (C5), 120.0 (CH, C6), 119.0 (CH_2, C12), 112.1 (C3), 73.0 (CH_2, C10), 68.9 (CH_2, C1), 59.9 (CH_2, C9).

R_f: (5% MeOH in CH_2Cl_2) = 0.43

m.p.: 125-126 °C

(2.85) 4-[(2-Bromo-2-propenyl)oxy]-6-ethyl-7-hydroxy-2-benzofuran-1(3*H*)-one



Trimethylaluminium (0.24 mL, 2.52 mmol) was dissolved in dry dichloromethane (3 mL) and cooled to -30 °C and to this mixture was added water (9 μL, 0.56 mmol). The colourless RM was then stirred for 10 minutes before a solution of 6-[(2-bromo-2-propenyl)oxy]-2,2-dimethyl-4,7-dihydro-9H-furo[3,4-h][1,3]benzodioxin-9-one **(2.51)** (200 mg, 0.56 mmol) in dichloromethane (2 mL) was added. This mixture was stirred at -30 °C for 1 hour. The RM was then allowed to warm slowly to rt overnight. The reaction was quenched by bubbling oxygen gas through the RM until all volatiles had been evaporated to give a gummy orange solid. This solid was redissolved in dichloromethane (10 mL) which was then extracted with aqueous sodium hydroxide solution (2M, 3 x 10 mL) the combined aqueous extracts were combined and neutralised with an equal volume of aqueous hydrochloric acid (2M, 30 mL). The neutralised aqueous extract was then extracted with dichloromethane (3 x 10 mL), the combined organics were then dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to give the title compound as a white solid (113 mg, 64%).

HRMS: (ESI+) Calculated for $C_{13}H_{13}O_4{}^{79}BrNa$, *m/z* 334.9889 found 334.9896

IR: (neat, ν cm^{-1}) 3425, 2975, 2944, 1751, 1630, 1319, 1007.

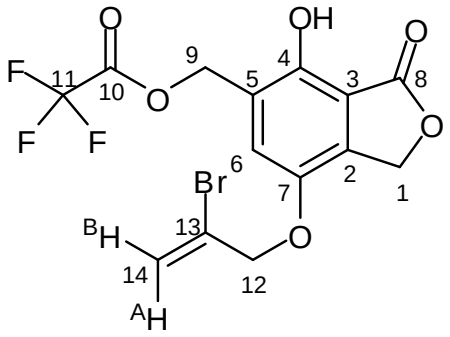
δ_H: (500 MHz, $CDCl_3$): 7.52 (1H, s, 4-O*H*), 6.93 (1H, s, 6-H), 5.96 (1H, d, *J* = 1.8 Hz, 13-H^A), 5.71 (1H, d, *J* = 2.0 Hz, 13-H^B), 5.30 (2H, s, 1-H), 4.66 (2H, s, 11-H), 2.70 (2H, q, *J* = 7.3 Hz, 9-H), 1.23 (3H, t, *J* = 7.6 Hz, 10-H).

δ_C: (126 MHz, $CDCl_3$): 172.6 (C8), 148.6 (C4), 144.7 (C7), 132.6 (C5), 131.2 (C2), 126.9 (C12), 121.4 (CH_2, C13), 118.7 (CH, C6), 111.5 (C3), 73.1 (CH_2, C11), 68.8 (CH_2, C1), 22.4 (CH_2, C9), 14.1 (CH_3, C10).

R_f: (CH_2Cl_2) = 0.54

m.p.: 108-110 °C

(2.83) (7-[(2-Bromo-2-propenyl)oxy]-4-hydroxy-3-oxo-1,3-dihydro-2-benzofuran-5-yl)methyl trifluoroacetate



*From **(2.78)***

4-[(2-Bromo-2-propenyl)oxy]-7-hydroxy-6-(hydroxymethyl)-2-benzofuran-1(3H)-one **(2.78)** (100 mg, 0.63 mmol) was dissolved in trifluoroacetic acid (5 mL), this solution was stirred at rt for 2 hours. The solvent was removed under reduced pressure to give the title compound as a white solid. (126 mg, 96%).

*From **(2.51)***

6-[(2-Bromo-2-propenyl)oxy]-2,2-dimethyl-4,7-dihydro-9H-furo[3,4-h][1,3]benzodiox-in-9-one **(2.51)** (100 mg, 0.28 mmol) was dissolved in trifluoroacetic acid (2 mL), this solution was stirred at rt for 3 hours. The solvent was removed under reduced pressure to give the title compound as a white solid. (111 mg, 97%).

LRMS: (EI) *m/z* 412 (M^+(^{81}Br), 5.2%), 410 (M^+(^{79}Br), 5.4%), 316 (^{81}Br, 8), 314 (^{79}Br, 8), 291 (18), 217 (69).

HRMS: (ESI+) Ion not found.

IR: (neat, ν cm^{-1}) 3421, 1774, 1747, 1433, 1138.

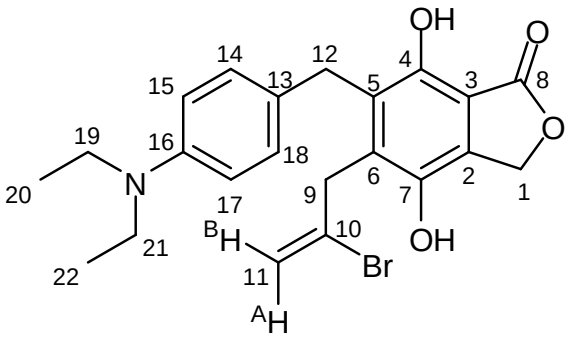
δ_H: (500 MHz, $CDCl_3$): 7.65 (1H, s, 4-O*H*), 7.12 (1H, s, 6-H), 5.96 (1H, d, *J* = 2.1 Hz, 14- H^A), 5.74 (1H, d, *J* = 2.2 Hz, 14- H^B), 5.45 (2H, s, 9-H), 5.36 (2H, s, 1-H), 4.69 (3H, s, 12-H).

δ_C: (126 MHz, $CDCl_3$): 171.9 (C8), 157.5 (q, *J* = 42.6 Hz, C10), 149.2 (C4), 145.2 (C7), 136.0 (C2), 126.6 (C13), 121.7 (CH, C6), 121.4 (C5), 119.7 (CH_2, C14), 114.6 (CF_3, q, *J* = 285.7 Hz, C11), 112.9 (C3), 73.23 (CH_2, C12), 69.1 (CH_2, C1), 63.3 (CH_2, C9).

R_f: (CH_2Cl_2) = 0.20

m.p.: 112-114 °C

(2.87) 5-(2-Bromo-2-propenyl)-6-[4-(diethylamino)benzyl]-4,7-dihydroxy-2-benzofuran-1(3H)-one



4-[(2-Bromo-2-propenyl)oxy]-7-hydroxy-6-(hydroxymethyl)-2-benzofuran-1(3H)-one **(2.51)** (100 mg, 0.32 mmol) was suspended in *N*,*N*-diethylaniline (2 mL), this red solution was heated in the microwave at 200 °C for 30 minutes. The resulting brown solution was subjected to column chromatography eluting with a 10% ethyl acetate in hexanes. This gave the title compound as a red oil (72 mg, 50%).

HRMS: (ESI+) Calculated for $C_{22}H_{25}O_4{}^{81}BrNH$, *m/z* 448.0947 found 448.0944

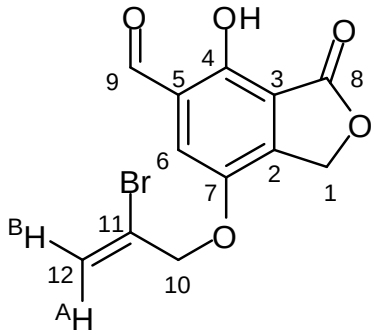
IR: (neat, ν cm^{-1}) 3435 (v br), 2968, 2927, 1728, 1517.

δ_H: (500 MHz, $CDCl_3$): 7.58 (1H, br s, O*H*), 6.98 (2H, d, *J* = 8.2 Hz, 14-H & 18-H), 6.59 (2H, d, *J* = 8.4 Hz, 15-H & 17-H), 5.52 (1H, d, *J* = 1.9 Hz, 11-H^B), 5.43 (1H, d, *J* = 1.9 Hz, 11-H^A), 5.32 (2H, s, 1-H), 4.00 (2H, s, 12-H), 3.86 (2H, s, 9-H), 3.30 (4H, q, *J* = 7.0 Hz, 19-H & 21-H), 1.13 (6H, t, *J* = 7.0 Hz, 20-H & 22-H).

δ_C: (126 MHz, $CDCl_3$): 172.9 (C8), 149.1 (C4), 146.5 (C16), 141.7 (C7), 133.0 (C5), 130.8 (C2), 129.6 (C10), 129.4 (C6), 129.1 (CH, C14 & C18), 125.9 (C13), 118.3 (CH_2, C11), 112.5 (CH, C15 & C17), 110.6 (C3), 69.1 (CH_2, C1), 44.6 (CH_2, C19 & C21), 39.0 (CH_2, C9), 30.1 (CH_2, C12), 12.7 (CH_3, C20 & C22).

R_f: (2% MeOH in CH_2Cl_2) = 0.22

(2.89) 7-[(2-Bromo-2-propenyl)oxy]-4-hydroxy-3-oxo-1,3-dihydro-2-benzofuran-5-carbaldehyde



4-[(2-Bromo-2-propenyl)oxy]-7-hydroxy-6-(hydroxymethyl)-2-benzofuran-1(3H)-one **(2.78)** (200 mg, 0.64 mmol) was dissolved in acetone (5 mL) to give a yellow solution, to which was added manganese dioxide (556 mg, 6.4 mmol), this mixture was stirred under nitrogen for 3 hours at rt. The mixture was then filtered through celite, and the solid residue rinsed with further acetone. The solvent was removed under reduced pressure before the residue was redissolved in a solution of formic acid in dichloromethane (1% v/v, 20 mL) activated carbon powder was added and the mixture stirred for 10 minutes. This solution was filtered through celite, which was flushed with further dichloromethane. The combined organics were dried over anhydrous magnesium sulfate and then the solvent removed under reduced pressure. This gave a pale yellow solid that was further purified by column chromatography eluting with 40% ethyl acetate in hexane. This gave the title compound as a white solid (107 mg, 54%).

HRMS: (ESI+) Calculated for $C_{12}H_9O_5{}^{81}BrNa$, *m/z* 336.9511 found 336.9498

IR: (neat, ν cm^{-1}) 3449, 2917, 1748, 1311, 997.

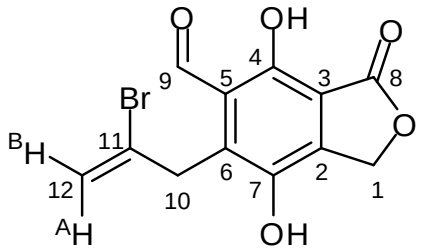
δ_H: (500 MHz, $CDCl_3$): 10.66 (1H, s, 4-O*H*), 10.08 (1H, s, 9-H), 7.32 (1H, s,6-H), 6.00 (1H, d, *J* = 1.7 Hz, 12-H^A), 5.77 (1H, d, *J* = 2.1 Hz, 12-H^B), 5.34 (2H, s, 1-H), 4.75 (2H, s, 10-H).

δ_C: (126 MHz, $CDCl_3$): 193.3 (CH, C9), 168.2 (C8), 155.1 (C4), 145.1 (C2), 144.9 (C7), 126.1 (C11), 121.9 (C5), 120.1 (CH, C6), 119.7 (CH_2, C12), 115.3 (C3), 73.0 (CH_2, C10), 67.9 (CH_2, C1).

R_f: (2% MeOH in CH_2Cl_2) = 0.25

m.p.: 152-154 °C

(2.90) 6-(2-Bromo-2-propenyl)-4,7-dihydroxy-3-oxo-1,3-dihydro-2-benzofuran-5-carbaldehyde



7-[(2-Bromo-2-propenyl)oxy]-4-hydroxy-3-oxo-1,3-dihydro-2-benzofuran-5-carbaldehyde **(2.89)** (110 mg, 0.35 mmol) was in benzyl alcohol (6 mL) and stirred under nitrogen for 15 minutes. The RM was heated in the microwave at 180 °C for 2 hours. When complete the RM was diluted with methanol (20 mL) to this was added Amberlyst® A21 resin (10 g). The mixture was stirred for 10 minutes at rt before the resin was isolated by filtration. The resin was washed with methanol (3 x 100 mL) before being added to a solution of formic acid in methanol (5% v/v, 50 mL), this was stirred for 10 minutes before the resin was filtered off. This was repeated twice more before the filtrates were combined and the solvent removed under reduced pressure. The resulting solid was further purified by column chromatography, eluting with 0.5% methanol in dichloromethane. This gave the title compound as a yellow solid (23 mg, 21%).

HRMS: (ESI+) Calculated for $C_{12}H_9O_5{}^{79}BrNa$, *m/z* 334.9526 found 334.9533

IR: (neat, ν cm^{-1}) 3176 (v br), 1728, 1646, 1630, 1253.

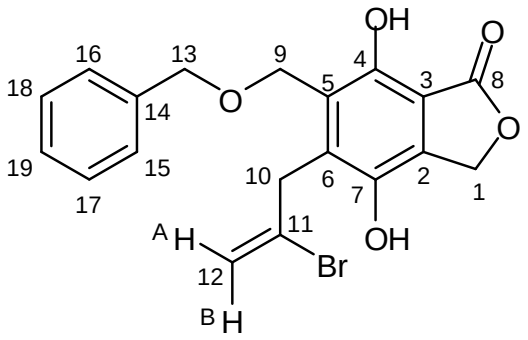
δ_H: (500 MHz, DMSO-d_6): 11.92 (1H, s, 4-OH), 10.28 (1H, s, 9-H), 9.76 (1H, s, 7-OH), 5.52 (1H, d, *J* = 2.1 Hz, 12-H^A), 5.50 (1H, d, *J* = 2.1 Hz, 12-H^B), 5.32 (2H, s, 1-H), 4.26 (2H, s, 10-H).

δ_C: (126 MHz, DMSO-d_6): 195.8 (CH, C9), 167.4 (C8), 154.2 (C4), 143.8 (C2), 141.8 (C7), 133.3 (C6), 130.6 (C11), 119.4 (C5), 118.4 (CH_2, C12), 112.3 (C3), 67.7 (CH_2, C1), 35.4 (CH_2, C10).

R_f: (5% MeOH in CH_2Cl_2) = 0.31

m.p.: Decomposed ~140 °C

(2.91a) 6-[(Benzyloxy)methyl]-5-(2-bromo-2-propenyl)-4,7-dihydroxy-2-benzofuran-1(3H)-one



6-[(2-Bromo-2-propenyl)oxy]-2,2-dimethyl-4,7-dihydro-9H-furo[3,4-h][1,3]benzodiox-in-9-one **(2.51)** (100 mg, 0.28 mmol) was dissolved in benzyl alcohol (6 mL) and stirred under nitrogen for 15 minutes. The RM was heated in the microwave at 180 °C for 15 minutes. The solvent was removed under reduced pressure to give a yellow oil. The addition of hexanes produced an off-white precipitate and this solid was further purified by column chromatography eluting with 20% ethyl acetate in hexane, to give the title compound as a white solid (73 mg, 64%).

HRMS: (ESI+) Calculated for $C_{19}H_{17}O_5{}^{81}BrNa$, *m/z* 429.0137 found 429.0142

IR: (neat, ν cm^{-1}) 3248 (v br), 1732, 1637, 1107.

δ_H: (500 MHz, $CDCl_3$ 7.66 (1H, s, 4-O*H*), 7.38 (4H, app d, *J* = 4.7 Hz, 15-H, 16-H, 17-H & 18-H), 7.35 - 7.30 (1H, m, 19-H), 5.49 (1H, d, *J* = 1.9 Hz, 12-H^A), 5.35 (1H, d, *J* = 1.8 Hz, 12-H^B), 5.24 (2H, s, 1-H), 5.20 (1H, br s, 7-O*H*), 4.65 (2H, s, 9-H), 4.62 (2H, s, 13-H), 3.95 (2H, s, 10-H).

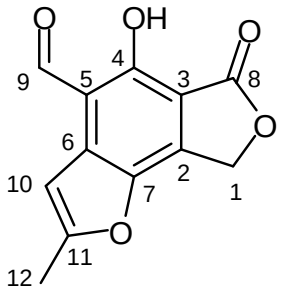
δ_C: (126 MHz, $CDCl_3$): 172.2 (C8), 149.5 (C4), 141.7 (C7), 137.6 (C14), 134.2 (C6), 133.8 (C2), 129.7 (C11), 128.7 (CH, C17 & C18), 128.4 (CH, C15 & C16), 128.2 (CH, C19), 124.6 (C5), 118.6 (CH_2, C12), 110.9 (C3), 73.3 (CH_2, C13), 68.9 (CH_2, C1), 62.2 (CH_2, C9), 38.6 (CH_2, C10).

R_f: (2% MeOH in CH_2Cl_2) = 0.44

m.p.: 165-166 °C

NMR Data appended (Appendix B).

(2.102) 5-Hydroxy-2-methyl-6-oxo-6,8-dihydrofuro[2,3-e][2] benzofuran-4-carbaldehyde



*This compound was isolated during the preparation of **(2.90)**.*

The title compound was isolated as an orange solid in variable yield (0-20%)

HRMS: (ESI+) Calculated for $C_{12}H_8O_5Na$, *m/z* 255.0264 found 255.0260

IR: (neat, ν cm^{-1}) 3145, 1750, 1637, 1276, 1272, 1051.

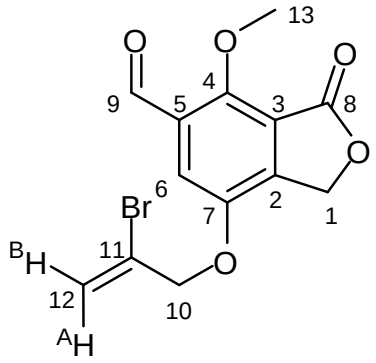
δ_H: (500 MHz, $CDCl_3$): 10.51 (1H, br s, 4-OH), 10.45 (1H, s, 9-H), 7.08 (1H, s, 10-H), 5.49 (2H, s, 1-H), 2.56 (3H, s, 12-H).

δ_C: (126 MHz, $CDCl_3$): 190.5 (CH, C9), 169.7 (C8), 164.0 (C11), 157.8 (C4), 141.4 (C7), 136.9 (C6), 136.1 (C2), 112.1 (C5), 108.1 (C3), 103.2 (CH, C10), 67.0 (CH_2, C1), 14.7 (CH_3, C12).

R_f: (5% MeOH in CH_2Cl_2) = 0.55

m.p.: Decomposed above 265 °C

(2.106) 7-[(2-Bromo-2-propenyl)oxy]-4-methoxy-3-oxo-1,3-dihydro-2-benzofuran-5-carbaldehyde



7-[(2-Bromo-2-propenyl)oxy]-4-hydroxy-3-oxo-1,3-dihydro-2-benzofuran-5-carbaldehyde **(2.89)** (500 mg, 1.6 mmol) was suspended in a mixture of methanol (6.4 mL) and toluene (9.6 mL). To which was added a solution of trimethylsilyldiazomethane in hexane (2M, 0.85 mL, 1.9 mmol) dropwise. The RM was allowed to stir for 10 minutes at rt. The RM was then quenched with acetic acid (3 drops) before the solvent was removed under reduced pressure. This material was then purified by column chromatography eluting with 0.5% methanol in dichloromethane. This gave the title compound as a white solid (289 mg, 55%) and recovered starting material (210 mg, 42%) to give a combined yield of 97%.

HRMS: (ESI+) Calculated for $C_{13}H_{11}O_5{}^{79}BrNa$, *m/z* 348.9682 found 348.9691

IR: (neat, ν cm^{-1}) 2875, 1764, 1686, 1013.

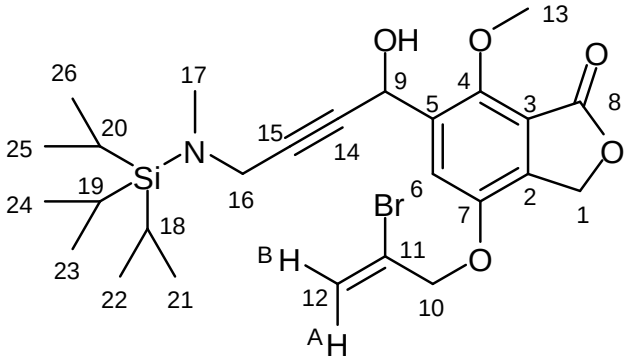
δ_H: (500 MHz, $CDCl_3$): 10.44 (1H, s, 9-H), 7.53 (1H, s, 6-H), 6.00 (1H, d, *J* = 2.0 Hz, 12-H^A), 5.75 (1H, d, *J* = 2.2 Hz, 12-H^B), 5.32 (2H, s, 1-H), 4.76 (2H, s, 10-H), 4.24 (3H, s, 13-H).

δ_C: (126 MHz, $CDCl_3$): 188.2 (CH, C9), 167.4 (C8), 156.7 (C4), 147.8 (C7), 144.4 (C2), 130.3 (C5), 126.0 (C11), 120.0 (C3), 119.9 (CH_2, C12), 115.2 (CH, C6), 72.6 (CH_2, C10), 67.7 (CH_2, C1), 64.6 (CH_3, C13).

R_f: (2% MeOH in CH_2Cl_2) = 0.51

m.p.: 174-175 °C

(2.157) 4-[(2-Bromo-2-propenyl)oxy]-6-{1-hydroxy-4-[methyl(triisopropylsilyl)amino]-2-butynyl}-7-methoxy-2-benzofuran-1(3H)-one



1,1,1-Triisopropyl-*N*-methyl-*N*-(prop-2-ynyl)silanamine **(2.154)** (131 mg, 0.58 mmol) was dissolved in tetrahydrofuran (2 mL) and cooled to -78 °C, to this mixture was added a solution of *n*-butyllithium in hexane (2.5M, 0.24 mL, 0.58 mmol). The RM was stirred at -78 °C for 10 minutes before being allowed to warm to -20 °C, after stirring for 15 minutes the mixture was cooled to -78 °C and stirred for a further 30 minutes. 7-[(2-Bromo-2-propenyl)oxy]-4-methoxy-3-oxo-1,3-dihydro-2-benzofuran-5-carbaldehyde **(2.106)** (200 mg, 0.61 mmol) was dissolved in tetrahydrofuran (4 mL) and then the resulting solution transferred into the cold lithiate solution in one portion. This resulted in an immediate colour change from pale yellow to bright orange. The mixture was stirred at -78 °C for 30 minutes before being allowed to warm to rt. The reaction was quenched by the addition of aqueous ammonium chloride solution (sat., 2 mL) and water (10 mL). Ethyl acetate (20 mL) was added and the layers separated. The organic layer was washed with water (20 mL) and aqueous sodium chloride solution (sat., 20 mL) before being dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give an oily residue comprised of the desired product and 1,1,1-triisopropyl-*N*-methyl-*N*-(prop-2-ynyl)silanamine. This residue could be recrystallised from diethyl ether and hexane by cooling overnight to give the title compound as a white solid (151 mg, 45%).

HRMS: (ESI+) Calculated for $C_{26}H_{38}O_5N^{81}BrSiH$, *m/z* 554.1760 found 554.1778

IR: (neat, ν cm^{-1}) 3349 (v br), 2941, 2864 1741, 1494, 1007.

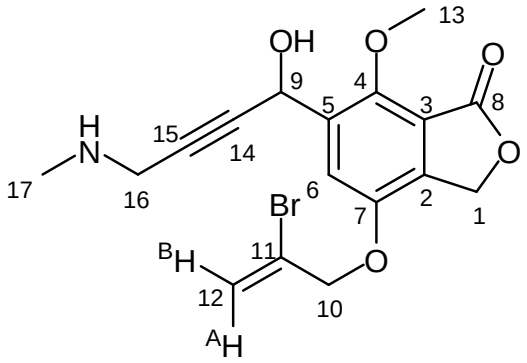
δ_H: (500 MHz, $CDCl_3$): 7.37 (1H, s, 6-H), 5.97 (1H, d, *J* = 1.7 Hz, 12-H^A), 5.81 (1H, s, 9-H), 5.72 (1H, d, *J* = 2.0 Hz, 12-H^B), 5.24 (2H, s, 1-H), 4.71 (2H, s, 10-H), 4.10 (3H, s, 13-H), 3.63 (2H, s, 16-H), 2.82 (1H, br s, 9-O*H*), 2.58 (3H, s, 17-H), 1.16 - 1.08 (3H, m, 18-H, 19-H & 20-H), 1.02 (18H, d, *J* = 7.2 Hz, 21-H, 22-H, 23-H, 24-H, 25-H & 26-H).

δ_C: (126 MHz, $CDCl_3$): 168.3 (C8), 150.3 (C4), 147.7 (C7), 137.1 (C2), 136.5 (C5), 126.4 (C11), 119.2 (CH_2, C12), 118.9 (C3), 117.1 (CH, C6), 86.6 (C14), 81.7 (C15), 72.6 (CH_2, C10), 67.4 (CH_2, C1), 63.5 (CH_3, C13), 59.9 (CH, C9), 41.1 (CH_2, C16), 36.6 (CH_3, C17), 18.5 (CH_3, C21, C22, C23, C24, C25 & C26), 12.2 (CH, C18, C19 & C20).

R_f: Decomposes on silica.

m.p.: 130-132 °C

(2.158) 4-[(2-Bromo-2-propenyl)oxy]-6-[1-hydroxy-4-(methylamino)-2-butynyl]-7-methoxy-2-benzofuran-1(3H)-one



4-[(2-Bromo-2-propenyl)oxy]-6-{1-hydroxy-4-[methyl(triisopropylsilyl)amino]-2-butynyl}-7-methoxy-2-benzofuran-1(3H)-one **(2.157)** (80 mg, 0.14 mmol) was dissolved in acetonitrile (5 mL) and to this was added hydrofluoric acid (40% wt. in water, 1 mL) in one portion, the RM was allowed to stir for 10 minutes at rt. The reaction was then quenched by pouring the RM into stirred aqueous potassium carbonate solution (10% w/w, 20 mL). The aqueous phase was saturated with sodium chloride and subsequently extracted with ethyl acetate (3 x 10 mL). The combined organic fractions were dried over anhydrous sodium sulfate and the solvent removed under reduced pressure. The residue was redissolved in dichloromethane (100 ml) and Amberlyst® A21 resin (2 g) added, this mixture was stirred for 10 minutes before being filtered. Evaporation of the solvent under reduced pressure gave an oily residue which was further purified by column chromatography eluting with 2% methanol in dichloromethane. This gave the title compound as a viscous yellow oil (39 mg, 68%).

HRMS: (ESI+) Calculated for $C_{17}H_{18}O_5N^{79}BrNaH$, *m/z* 396.0441 found 396.0446

IR: (neat, ν cm^{-1}) 3500-2800 (v br), 2939, 1756, 1489, 1015.

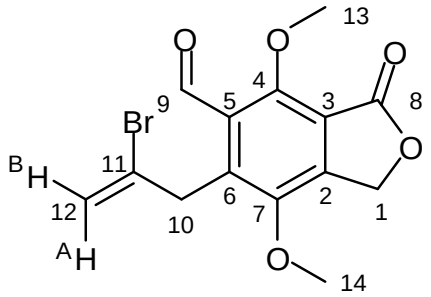
δ_H: (500 MHz, $CDCl_3$): 7.39 (1H, s, 6-H), 5.99 (1H, d, *J* = 2.2 Hz, 12-H^A), 5.81 (1H, t, *J* = 1.8 Hz, 9-H), 5.74 (1H, d, *J* = 2.2 Hz, 12-H^B), 5.27 (2H, s, 1-H), 4.75 (2H, s, 10-H), 4.14 (3H, s, 13-H), 3.50 (2H, d, *J* = 1.7 Hz, 16-H), 2.50 (3H, s, 17-H), 2.46 (2H, v.br s, 9-OH & 16/17-NH).

δ_C: (126 MHz, $CDCl_3$): 168.2 (C8), 150.4 (C4), 147.7 (C7), 137.2 (C2), 136.1 (C5), 126.4 (C11), 119.2 (CH_2, C12), 119.0 (C3), 117.1 (CH, C6), 84.4 (C15), 83.5 (C14), 72.6 (CH_2, C10), 67.5 (CH_2, C1), 63.5 (CH_3, C13), 59.9 (CH, C9), 40.4 (CH_2, C16), 35.5 (CH_3, C17).

R_f: (5% MeOH in CH_2Cl_2) = 0.16

NMR Data appended (Appendix B).

(1.427) 6-(2-Bromo-2-propenyl)-4,7-dimethoxy-3-oxo-1,3-dihydro-2-benzofuran-5-carbaldehyde



6-(2-Bromo-2-propenyl)-4,7-dihydroxy-3-oxo-1,3-dihydro-2-benzofuran-5-carbaldehyde **(2.90)** (50 mg, 0.16 mmol) was dissolved in acetone (5 mL) and to this was added potassium carbonate (221 mg, 1.6 mmol) to give a yellow solution. The RM was allowed to stir at rt for 10 minutes before being heated to 50 °C, methyl iodide (0.2 mL, 3.2 mmol) was added and the RM stirred at 50 °C for 5 hours. The RM was then allowed to cool and was subsequently filtered before the solvent was removed under reduced pressure to give a yellow solid. This solid was further purified by column chromatography eluting with 10% ethyl acetate in hexane to give the title compound as a white solid (6 mg, 11%).

HRMS: (ESI+) Calculated for $C_{14}H_{13}O_5{}^{79}BrNa$, *m/z* 362.9839 found 362.9853

IR: (neat, ν cm^{-1}) 2940, 1767, 1686, 1601, 1392, 1021.

δ_H: (500 MHz, $CDCl_3$): 10.52 (1H, s, 9-H), 5.44 (1H, d, *J* = 1.7 Hz, 12-H^A), 5.40 (2H, s, 1-H), 5.26 (1H, d, *J* = 1.8 Hz, 12-H^B), 4.28 (2H, s, 10-H), 4.21 (3H, s, 13-H), 3.88 (3H, s, 14-H).

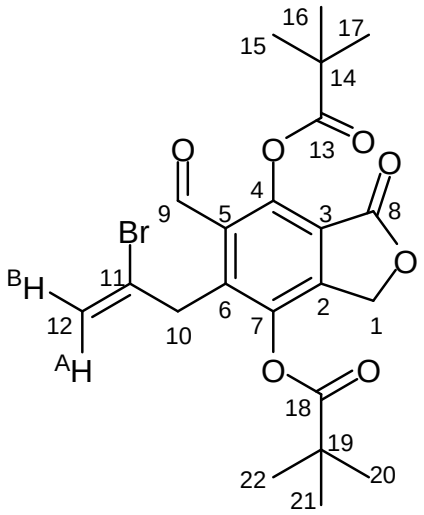
δ_C: (126 MHz, $CDCl_3$): 190.8 (CH, C9), 167.0 (C8), 158.9 (C4), 148.9 (C7), 143.7 (C2), 138.5 (C5), 130.5 (C11), 129.6 (C6), 118.3 (C8), 117.4 (CH_2, C12), 67.5 (CH_2, C1), 64.6 (CH_3, C13), 60.9 (CH_3, C14), 37.1 (CH_2, C10).

R_f: (CH_2Cl_2) = 0.56

m.p.: 90-92 °C

NMR Data appended (Appendix B).

(2.163) 5-(2-Bromo-2-propenyl)-7-[(2,2-dimethylpropanoyl)oxy]-6-formyl-1-oxo-1,3-dihydro-2-benzofuran-4-yl pivalate



6-(2-Bromo-2-propenyl)-4,7-dihydroxy-3-oxo-1,3-dihydro-2-benzofuran-5-carbaldehyde **(2.90)** (65 mg, 0.21 mmol) was dissolved in pyridine (3 mL), to this solution pivaloyl chloride (1 mL, excess) was added dropwise over 5 minutes. The RM was allowed to stir at rt for 3 hours before the solvent was removed under reduced pressure to leave an oily residue. This residue was redissolved in dichloromethane (10 mL) before being washed with water (10 mL), aqueous sodium bicarbonate solution (sat., 10 mL) and a further portion of water (10 mL). The solution was dried over anhydrous sodium sulfate before the solvent was removed under reduced pressure to give an off white solid. This solid was further purified by column chromatography eluting with 20% diethyl ether in hexane to give the title compound as a white solid (79 mg, 79%).

HRMS: (ESI+) Calculated for $C_{22}H_{25}O_7{}^{79}BrNa$, *m/z* 503.0676 found 503.0711

IR: (neat, ν cm^{-1}) 2984, 1782, 1757, 1701, 1625, 1075.

δ_H: (500 MHz, $CDCl_3$): 10.34 (1H, s, 9-H), 5.45 (1H, d, *J* = 2.1 Hz, 12-H^A), 5.18 (1H, d, *J* = 2.0 Hz, 12-H^B), 5.12 (2H, s, 1-H), 4.19 (2H, s, 10-H), 1.46 (9H, s, 15-H, 16-H & 17-H), 1.40 (9H, s, 20-H, 21-H & 22-H).

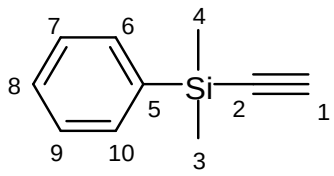
δ_C: (126 MHz, $CDCl_3$): 187.7 (CH, C9), 175.9 (C18), 175.3 (C13), 166.0 (C8), 150.2 (C4), 145.4 (C2), 142.1 (C7), 138.4 (C6), 129.2 (C5), 128.2 (C11), 119.9 (C3), 118.3 (CH_2, C12), 67.4 (CH_2, C1), 39.8 (C19), 39.7 (C14), 37.5 (CH_2, C10), 27.3 (CH_3, C15, C16, C17, C18, C19 & C20).

R_f: (CH_2Cl_2) = 0.45

m.p.: 106-109 °C

NMR Data appended (Appendix B).

(2.146) Ethynyl(dimethyl)phenylsilane



Prepared by a modification of the method of Hasegawa et al.[244a]

Chlorodimethylphenylsilane **(2.148)** (4.50 g, 26.6 mmol) was added to a stirred solution of ethynylmagnesium bromide in tetrahydrofuran (0.5M, 53.3 mL, 26.6 mmol) at 0 °C. The mixture was stirred for 1 hr before being allowed to warm to rt and then stirred for a further 24 hours. The reaction was quenched with water (100 mL) and then extracted with diethyl ether (3 x 75 mL). The combined organic extracts were washed with water (100 mL) and aqueous sodium chloride solution (sat., 100 mL) before being dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give a crude yellow oil which was further purified by column chromatography eluting with 1% diethyl ether in hexane. This gave the title compound as a colourless oil (3.42 g, 81%). Spectra were consistent with those previously reported.[244a]

HRMS: (ESI+) Ion not found.

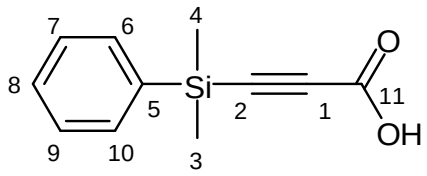
IR: (neat, ν cm^{-1}) 3275, 2963, 2035, 1429, 1250, 1117.

δ_H: (500 MHz, $CDCl_3$): 7.70 - 7.62 (2H, m, 7-H & 9-H), 7.43 - 7.37 (3H, m, 6-H, 8-H & 10-H), 2.53 (1H, s, 1-H), 0.47 (6H, s, 3-H & 4-H).

δ_C: (126 MHz, $CDCl_3$): 136.4 (C5), 133.8 (CH, C7 & C9), 129.8 (CH, C8), 128.1 (CH, C6 & C10), 94.9 (CH, C1), 88.3 (C2), -1.0 (CH_3, C3 & C4).

R_f: (5% Diethyl Ether in Hexane) = 0.89

(2.145) 3-[Dimethyl(phenyl)silyl]-2-propynoic acid



Prepared by a modification of the method of Fleming et al.[246]

Ethynyl(dimethyl)phenylsilane **(2.146)** (2.20 g, 13.7 mmol) was dissolved in tetrahydrofuran (5 mL) and this was added in one portion to a solution of methylmagnesium bromide in diethyl ether (3M, 9.1 mL, 27.4 mmol) at 0 °C. This mixture was allowed to warm to rt and stirred for a further 2 hours, developing a thick white precipitate. The precipitate was redissolved by the addition of further tetrahydrofuran (10 mL) and then solid carbon dioxide (large excess) added over 1 hour. The reaction was quenched with aqueous ammonium chloride solution (sat., 20 mL) before being extracted with ethyl acetate (3 x 25 mL). The combined organics were washed with water (25 mL) and aqueous sodium chloride solution (sat., 25 mL) before being dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to leave a crude yellow oil which was further purified by column chromatography eluting with dichloromethane, this gave a pale yellow oil that solidified in the freezer to give the title compound as an off-white solid (2.20 g, 79%). Spectra were consistent with those previously reported.[246]

HRMS: (ESI+) Calculated for $C_{11}H_{12}O_2SiNa$, *m/z* 227.0499 found 227.0498

IR: (neat, ν cm^{-1}) 3250-2500 (v br), 2964, 2632, 2167, 1674, 1406, 1253.

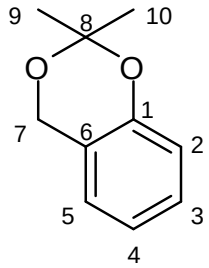
δ_H: (500 MHz, $CDCl_3$): 9.40 (1H, v.br s, 11-O*H*), 7.62 (2H, d, *J* = 7.4 Hz, 6-H & 10-H), 7.47 - 7.38 (3H, m, 7-H, 8-H & 9-H), 0.53 (6H, s, 3-H & 4-H).

δ_C: (126 MHz, $CDCl_3$): 157.0 (C11), 134.3 (C5), 133.9 (CH, C6 & C10), 130.3 (CH, C8), 128.3 (CH, C7 & C9), 95.5 (C2), 95.13 (C1), -1.7 (CH_3, C3 & C4).

R_f: (CH_2Cl_2) = 0.45

m.p.: 30-35 °C

(2.120) 2,2-Dimethyl-4H-1,3-benzodioxine



2-(Hydroxymethyl)phenol **(1.491)** (25.0 g, 200 mmol) was dissolved in acetone (500 mL) and to this solution was added 2,2-dimethoxypropane (123 mL, 1000 mmol) and one crystal of *para*-toluenesulfonic acid. The RM was stirred for 2 days at rt. The solvent was then removed under reduced pressure to give a dark orange oil. This oil was redissolved in diethyl ether (200 mL) and then washed with aqueous sodium hydroxide solution (2M, 3 x 200 mL), water (200 mL) and aqueous sodium chloride solution (sat., 200 mL). The organics were dried over anhydrous sodium sulfate before the solvent was removed under reduced pressure to give the title compound as a pale yellow oil (27.1 g, 83%). Spectra were consistent with those previously reported.[263]

HRMS: (ESI+) Ion not found.

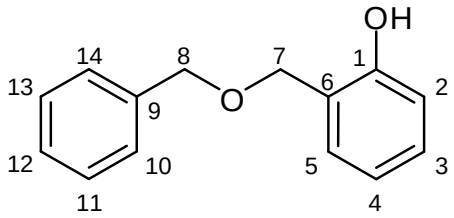
IR: (neat, ν cm^{-1}) 2994, 2857, 1590, 1490, 1459, 1268.

δ_H: (500 MHz, $CDCl_3$): 7.17 (1H, app t, *J* = 7.7 Hz, 3-H), 6.97 (1H, app d, *J* = 7.4 Hz, 5-H), 6.90 (1H, app t, *J* = 7.4 Hz, 4-H), 6.84 (1H, app d, *J* = 8.2 Hz, 2-H), 4.86 (2H, s, 7-H), 1.56 (6H, s, 9-H & 10-H).

δ_C: (126 MHz, $CDCl_3$): 151.3 (C1), 128.2 (CH, C3), 124.7 (CH, C5), 120.4 (CH, C4), 119.6 (C6), 117.2 (CH, C2), 99.6 (C8), 61.0 (CH_2, C7), 24.9 (CH_3, C9 & C10).

R_f: (20% Diethyl Ether in Hexane) = 0.80

(2.127) 2-[(Benzyloxy)methyl]phenol



2,2-Dimethyl-4H-1,3-benzodioxine **(2.120)** (2.48 g, 15.1 mmol) was dissolved in benzyl alcohol **(2.117)** (10 mL), the RM was then heated in the microwave to 180 °C for 30 minutes. When complete the solvent was removed under reduced pressure to give a yellow oil. This oil was further purified by column chromatography eluting with 1% formic acid in dichloromethane, to give the title compound as a pale yellow solid (2.82 g, 87%). Spectra were consistent with those previously reported.[264]

HRMS: (ESI+) Calculated for $C_{14}H_{14}O_2Na$, *m/z* 237.0886 found 237.0882

IR: (neat, ν cm^{-1}) 3249 (br), 2945, 2887, 1612, 1596, 1499, 1081.

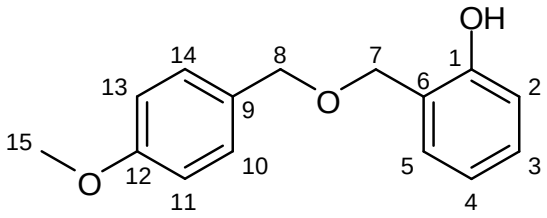
δ_H: (500 MHz, $CDCl_3$): 7.47 (1H, s, 1-O*H*), 7.41 - 7.31 (5H, m, 10-H, 11-H, 12-H, 13-H & 14-H), 7.23 (1H, td, *J* = 8.0 & 1.6 Hz, 3-H), 7.01 (1H, dd, *J* = 7.5 & 1.4 Hz, 5-H), 6.91 (1H, dd, *J* = 8.1 & 0.9 Hz, 2-H), 6.85 (1H, td, *J* = 7.4 & 1.1 Hz, 4-H), 4.75 (2H, s, 7-H), 4.60 (2H, s, 8-H).

δ_C: (126 MHz, $CDCl_3$): 156.4 (C1), 137.0 (C9), 129.7 (CH, C3), 128.8 (CH, C11 & C13), 128.5 (CH, C12), 128.4 (CH, C5), 128.3 (CH, C10 & C14), 122.2 (C6), 120.1 (CH, C4), 116.7 (CH, C2), 72.6 (CH_2, C8) 71.6 (CH_2, C7).

R_f: (CH_2Cl_2) = 0.71

m.p.: 53-54 °C (Lit: 55-56 °C)[264]

(2.128) 2-{[(4-Methoxybenzyl)oxy]methyl}phenol



2,2-Dimethyl-4H-1,3-benzodioxine **(2.120)** (2.48 g, 15.1 mmol) was dissolved in molten *para*-methoxybenzyl alcohol **(2.122)** (10 mL), the RM was then heated in the microwave to 180 °C for 30 minutes. When complete the RM was diluted with methanol (20 mL) and to this solution was added Amberlyst® A21 resin (10 g). The mixture was stirred for 10 minutes at rt before the resin was isolated by filtration. The resin was washed with methanol (3 x 100 mL) before being added to a solution of formic acid in methanol (5% v/v, 50 mL), this was stirred for 10 minutes before the resin was filtered off. This was repeated twice more before the filtrates were combined and the solvent removed under reduced pressure. The resulting solid was further purified by column chromatography, eluting with 1% formic acid in dichloromethane. This gave the title compound as a white solid (3.13 g, 85%). Spectra were consistent with those previously reported.[265]

HRMS: (ESI+) Calculated for $C_{15}H_{16}O_3Na$, *m/z* 267.0992 found 267.0988

IR: (neat, ν cm^{-1}) 3293 (br), 2924, 2866, 1610, 1513.

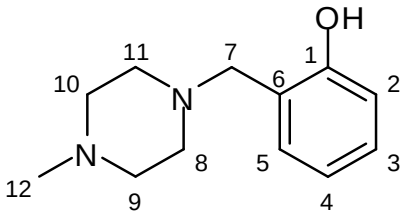
δ_H: (500 MHz, $CDCl_3$): 7.53 (s, 1H), 7.27 (2H, d, *J* = 8.7 Hz, 10-H & 14-H), 7.22 (1H, td, *J* = 7.9 & 1.7 Hz, 3-H), 7.00 (1H, dd, *J* = 7.5 & 1.6 Hz, 5-H), 6.92 - 6.89 (3H, m, 11-H, 13-H & 2-H), 6.85 (1H, td, *J* = 7.4 & 1.2 Hz, 4-H), 4.72 (2H, s, 7-H), 4.53 (2H, s, 8-H), 3.82 (3H, s, 15-H).

δ_C: (126 MHz, $CDCl_3$): 159.7 (C12), 156.3 (C1), 129.8 (CH, C10 & C14), 129.5 (CH, C3), 128.8 (C9), 128.2 (CH, C5), 122.1 (C6), 119.8 (CH, C4), 116.5 (CH, C2), 114.0 (CH, C11 & C13), 72.1(CH_2, C8), 71.2 (CH_2, C7), 55.3 (CH_3, C15).

R_f: (CH_2Cl_2) = 0.75

m.p.: 40-42 °C

(2.129) 2-[(4-Methyl-1-piperazinyl)methyl]phenol



2,2-Dimethyl-4H-1,3-benzodioxine **(2.120)** (2.48 g, 15.1 mmol) was dissolved in *N*-methylpiperazine **(2.123)** (10 mL), the RM was then heated in the microwave to 180 °C for 10 hours. When complete the RM was diluted with methanol (20 mL) to this was added Amberlyst® A21 resin (10 g). The mixture was stirred for 10 minutes at rt before the resin was isolated by filtration. The resin was washed with methanol (3 x 100 mL) before being added to a solution of formic acid in methanol (5% v/v, 50 mL), this was stirred for 10 minutes before the resin was filtered off. This was repeated twice more before the filtrates were combined and the solvent removed under reduced pressure. The resulting solid was further purified by column chromatography, eluting with 2% methanol in dichloromethane. This gave the title compound as a red solid (2.36 g, 76%). Spectra were consistent with those previously reported.[266]

HRMS: (ESI+) Calculated for $C_{12}H_{18}ON_2Na$, *m/z* 229.1311 found 229.1317

IR: (neat, ν cm^{-1}) 2944, 2803, 2550 (v br), 1593, 1457.

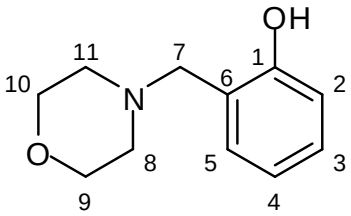
δ_H: (500 MHz, $CDCl_3$): 7.17 (1H, td, *J* = 8.0 & 1.5 Hz, 3-H), 6.98 (1H, d, *J* = 7.4 Hz, 5-H), 6.82 (1H, d, *J* = 8.1 Hz, 2-H), 6.78 (1H, td, *J* = 7.4 & 1.1 Hz, 4-H), 3.71 (2H, s, 7-H), 2.58 (8H, br s, 8-H, 9-H, 10-H & 11-H), 2.32 (3H, s, 12-H).

δ_C: (126 MHz, $CDCl_3$): 157.9 (C1), 129.0 (CH, C3), 128.8 (CH, C5), 121.3 (C6), 119.3 (CH, C4), 116.2 (CH, C2), 61.5 (CH_2, C7), 55.0 (CH_2, C9 & C10), 52.5 (CH_2, C8 & C11), 45.9 (CH_3, C12).

R_f: (5% MeOH in CH_2Cl_2) = 0.24

m.p.: 41-43 °C (Lit: 42-45 °C)[266]

(2.130) 2-(4-Morpholinylmethyl)phenol



2,2-Dimethyl-4H-1,3-benzodioxine **(2.120)** (2.48 g, 15.1 mmol) was dissolved in morpholine **(2.124)** (10 mL), the RM was then heated in the microwave to 180 °C for 12 hours. The resulting mixture was separated by column chromatography, eluting with 0.5% methanol in dichloromethane. This gave the title compound as a yellow solid (2.29 g, 79%). Spectra were consistent with those previously reported.[267]

HRMS: (ESI+) Calculated for $C_{11}H_{15}O_2NH$, *m/z* 194.1176 found 194.1173

IR: (neat, ν cm^{-1}) 2823, 2800 (v br), 1585, 1455.

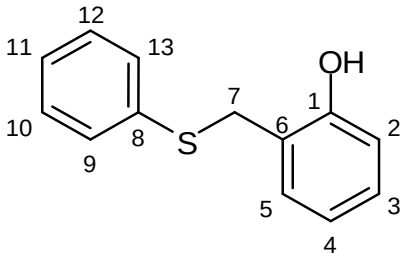
δ_H: (500 MHz, $CDCl_3$): 10.62 (1H, s, 1-O*H*), 7.18 (1H, t, *J* = 7.7 Hz, 3-H), 6.98 (1H, d, *J* = 7.4 Hz, 5-H), 6.83 (1H, d, *J* = 8.1 Hz, 2-H), 6.79 (1H, t, *J* = 7.4 Hz, 4-H), 3.75 (4H, s, 9-H & 10-H), 3.71 (2H, s, 7-H), 2.57 (4H, s, 8-H & 11-H).

δ_C: (126 MHz, $CDCl_3$): 157.7 (C1), 129.2 (CH, C3), 129.0 (CH, C5), 120.8 (C6), 119.5 (CH, C4), 116.3 (CH, C2), 67.0 (CH_2, C9 & C10), 62.0 (CH_2, C7), 53.1 (CH_2, C8 & C11).

R_f: (5% MeOH in CH_2Cl_2) = 0.41

m.p.: 92-94 °C (Lit: 91-92 °C)[268]

(2.132) 2-[(Phenylsulfanyl)methyl]phenol



2,2-Dimethyl-4H-1,3-benzodioxine **(2.120)** (2.48 g, 15.1 mmol) was dissolved in thiophenol **(2.126)** (10 mL), the RM was then heated to 170 °C for 12 hours. When complete the solvent was removed under reduced pressure to give a yellow oil. This oil was further purified by column chromatography eluting with 0.5% methanol in dichloromethane, to give the title compound as a colourless oil (2.77 g, 85%). Spectra were consistent with those previously reported.[122b]

HRMS: (ESI+) Calculated for $C_{13}H_{12}OSNa$, *m/z* 239.0501 found 239.0500

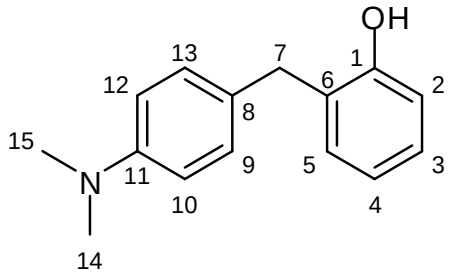
IR: (neat, ν cm^{-1}) 3390 (v br), 3056, 1582, 1455, 736.

δ_H: (500 MHz, $CDCl_3$): 7.38 (m, 2H), 7.29 (m, 3H), 7.18 (1H, app t, *J* = 7.6 Hz, 3-H), 7.09 (1H, m, 5-H), 6.88 (2H, m, 2-H & 4-H), 6.05 (1H, s, 1-O*H*), 4.20 (2H, s, 7-H).

δ_C: (126 MHz, $CDCl_3$): 154.6 (C1), 134.9 (C8), 130.8 (CH, C10 & C12), 130.7 (CH, C5), 129.2 (CH, C3), 129.0 (CH, C9 & C13), 127.1 (CH, C11), 122.9 (C6), 120.9 (CH, C4), 116.7 (CH, C2), 35.4 (CH_2, C7).

R_f: (CH_2Cl_2) = 0.64

(2.131) 2-[4-(Dimethylamino)benzyl]phenol



2,2-Dimethyl-4H-1,3-benzodioxine **(2.120)** (2.48 g, 15.1 mmol) was dissolved in *N*,*N*-dimethylaniline **(2.125)** (10 mL), the RM was then heated in the microwave to 180 °C for 2 hours. When complete the remaining *N*,*N*-dimethylaniline was removed under reduced pressure to give a red oil. This oil was further purified by column chromatography eluting with dichloromethane, to give the title compound as a pale orange oil (2.33 g, 68%). Spectra were consistent with those previously reported.[269]

HRMS: (ESI+) Calculated for $C_{15}H_{17}ONNa$, *m/z* 250.1202 found 250.1209

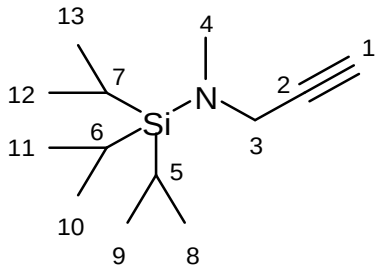
IR: (neat, ν cm^{-1}) 3336 (v br), 2888, 1499, 1614, 1516, 1454.

δ_H: (500 MHz, $CDCl_3$): 7.17-7.10 (4H, m, 3-H, 5-H, 9-H & 13-H), 6.90 (1H, t, *J* = 7.4 Hz, 4-H), 6.79 (1H, d, *J* = 8.3 Hz, 2-H), 6.72 (2H, d, *J* = 8.5 Hz, 10-H & 12-H), 4.79 (1H, v.br s, 1-O*H*), 3.93 (2H, s, 7-H), 2.93 (6H, s, 14-H & 15-H).

δ_C: (126 MHz, $CDCl_3$): 154.2 (C1), 149.6 (C2), 130.9 (CH, C5), 129.4 (CH, C9 & C13), 127.8 (CH, C3) 127.7 (C6), 127.4 (C8), 120.9 (CH, C4), 116.0 (CH, C2) 113.4 (CH, C10 & C12), 40.9 (CH_3, C14 & C15), 35.9 (CH_2, C7).

R_f: (CH_2Cl_2) = 0.35

(2.154) 1,1,1-Triisopropyl-*N*-methyl-*N*-(prop-2-ynyl)silanamine



Prepared according to the method of Faggiani.[82]

N-Methylpropargylamine **(1.380)** (5.0 g, 72.4 mmol) was dissolved in dichloromethane (50 mL) and this solution was cooled to 0 °C and to this was added triethylamine (15.1 mL, 108.5 mmol) followed by the dropwise addition of triisopropylsilyl triflate (23.3 g, 76.0 mmol). The RM was allowed to stir for 30 minutes before being allowed to warm to rt. The RM was stirred for a further 16 hours before being quenched with aqueous potassium carbonate solution (10% w/w, 50 mL), separated and then washed with further potassium carbonate solution (50 mL). The organics were dried over anhydrous sodium sulfate before removal of the solvent under reduced pressure gave a crude yellow oil. This oil was further purified by distillation under reduced pressure (85 °C at 2.1 mbar) to give the title compound as a colourless oil (14.4 g, 88%). Spectra were consistent with those previously reported.[82]

HRMS: (ESI+) Calculated for $C_{13}H_{27}NH$, *m/z* 226.1986 found 226.1982

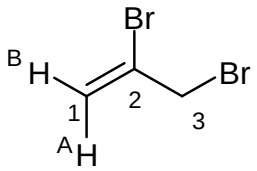
IR: (neat, ν cm^{-1}) 3311, 2944, 2865, 1463, 1142.

δ_H: (500 MHz, $CDCl_3$): 3.56 (2H, d, *J* = 2.3 Hz, 3-H), 2.60 (3H, s, 4-H), 2.13 (1H, t, *J* = 2.3 Hz, 1-H), 1.21 - 1.08 (3H, m, 5-H, 6-H & 7-H), 1.06 (18H, d, *J* = 8.2 Hz, 8-H, 9-H, 10-H, 11-H, 12-H & 13-H).

δ_C: (126 MHz, $CDCl_3$): 83.4 (C2), 70.2 (CH, C1), 40.8 (CH_2, C3), 36.3 (CH_3, C4), 18.5 (CH_3, C8, C9, C10, C11, C12 & C13), 12.3 (CH, C5, C6 & C7).

R_f: Decomposes on silica.

(1.370) 2,3-Dibromopropene



Prepared by a modification of the method of Chin-Hsien.[199]

1,2,3-Tribromopropane **(2.63)** (80.0 g, 284.8 mmol) and hexadecylpyridinium chloride monohydrate (4.0 g, 5% wt.) were added to a solution of potassium hydroxide (19.2 g, 341.8 mmol) in water (100 mL) the RM was heated at reflux for 2 hours before being allowed to cool to rt. The organic layer was separated and washed with water (3 x 100 mL) before being dried over anhydrous magnesium sulfate. This crude oil was then distilled under reduced pressure (89 °C at 5.3 mbar) to give the title compound as a colourless oil (38.0 g, 66%). Spectra were consistent with those previously reported.[270]

IR: (neat, ν cm^{-1}) 1620, 1189, 900.

δ_H: (500 MHz, $CDCl_3$): 6.01 (1H, d, *J* = 2.0 Hz, 1-H^A), 5.62 (1H, d, *J* = 2.2 Hz, 15-H^B), 4.15 (2H, s, 1-H).

δ_C: (126 MHz, $CDCl_3$): 127.5 (C2), 121.1 (CH_2, C1), 36.8 (CH_2, C3).

4. References

"I think that I shall never see
A study as muddled as chemistry
A study hidden in pondrous books,
Where only a chemist ever looks!" [271]

(1) "L.J.B" *Proc. Chem. Soc.* **1963**, 1.

(2) (a) Fleming, A. *Br. J. Exp. Pathol.* **1929**, *10*, 226; (b) Chain, E.; Florey, H. W.; Gardner, A. D.; Heatley, N. G.; Jennings, M. A.; Orr-Ewing, J.; Sanders, A. G. *Lancet* **1940**, *236*, 226.

(3) Domagk, G. *Deutsch. Med. Wschr* **1935**, *61*, 250.

(4) Luckey, T. D. *Am. J. Clin. Nutr.* **1972**, *25*, 1292.

(5) Mason, M. M. *J. Bacteriol.* **1935**, *29*, 103.

(6) Frère, J.-M. *Molecular Microbiology* **1995**, *16*, 385.

(7) Smith, A. M.; Klugman, K. P. *Antimicrob. Agents Chemother.* **2005**, *49*, 4622.

(8) Fan, H.; Brunham, R. C.; Mcclarty, G. *J. Clin. Invest.* **1992**, *90*, 1803.

(9) Kishii, R.; Takei, M. *J. Infect. Chemother.* **2009**, *15*, 361.

(10) Kaatz, G. W.; Seo, S. M.; Ruble, C. A. *Antimicrob. Agents Chemother.* **1993**, *37*, 1086.

(11) Jevons, M. P. *Br. Med. J.* **1961**, *1*, 124.

(12) Neu, H. C. *Science* **1992**, *257*, 1064.

(13) Lyon, B. R.; Skurray, R. *Microbiol. Mol. Biol. Rev.* **1987**, *51*, 88.

(14) Blumberg, H. M.; Rimland, D.; Carroll, D. J.; Terry, P.; Wachsmuth, I. K. *J. Infect. Dis.* **1991**, *163*, 1279.

(15) (a) Watanakunakorn, C. *Ann. Intern. Med.* **1982**, *97*, 376; (b) Kucers, A. *Lancet* **1982**, *2*, 425; (c) Geraci, J. E.; Hermans, P. E. *Mayo Clin. Proc.* **1983**, *58*, 88.

(16) (a) Weigel, L. M.; Clewell, D. B.; Gill, S. R.; Clark, N. C.; Mcdougal, L. K.; Flannagan, S. E.; Kolonay, J. F.; Shetty, J.; Killgore, G. E.; Tenover, F. C. *Science* **2003**, *302*, 1569; (b) Chang, S.; Sievert, D. M.; Hageman, J. C.; Boulton, M. L.; Tenover, F. C.; Downes, F. P.; Shah, S.; Rudrik, J. T.; Pupp, G. R.; Brown, W. J.; Cardo, D.; Fridkin, S. K. *N. Engl. J. Med.* **2003**, *348*, 1342.

(17) Matsumoto, N.; Tsuchida, T.; Maruyama, M.; Sawa, R.; Kinoshita, N.; Homma, Y.; Takahashi, Y.; Iinuma, H.; Naganawa, H.; Sawa, T.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1996**, *49*, 953.

(18) Kieser, T.; John Innes Foundation. *Practical Streptomyces Genetics*; John Innes Foundation: Norwich, 2000.

(19) Matsumoto, N.; Tsuchida, T.; Nakamura, H.; Sawa, R.; Takahashi, Y.; Naganawa, H.; Iinuma, H.; Sawa, T.; Takeuchi, T.; Shiro, M. *J. Antibiot.* **1999**, *52*, 276.

(20) Matsumoto, N.; Tsuchida, T.; Maruyama, M.; Kinoshita, N.; Homma, Y.; Iinuma, H.; Sawa, T.; Hamada, M.; Takeuchi, T.; Heida, N.; Yoshioka, T. *J. Antibiot.* **1999**, *52*, 269.

(21) Holtzel, A.; Dieter, A.; Schmid, D. G.; Brown, R.; Goodfellow, M.; Beil, W.; Jung, G.; Fiedler, H. P. *J. Antibiot.* **2003**, *56*, 1058.

(22) Machida, K.; Kikuchi, M. *Chem. Pharm. Bull.* **1994**, *42*, 1388.

(23) Zhang, X.; Alernany, L. B.; Fiedler, H. P.; Goodfellow, M.; Parry, R. J. *Antimicrob. Agents Chemother.* **2008**, *52*, 574.

(24) Rafanan, E. R.; Hutchinson, C. R.; Shen, B. *Org. Lett.* **2000**, *2*, 3225.

(25) Hutchinson, C. R. *Chem. Rev.* **1997**, *97*, 2525.

(26) Udvarnoki, G.; Wagner, C.; Machinek, R.; Rohr, J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 565.

(27) Cox, C.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 3493.

(28) Wessely, F.; Sinwel, F. *Monatsh. Chem.* **1950**, *81*, 1055.

(29) Yates, P.; Auksi, H. *J. Chem. Soc., Chem. Commun.* **1976**, 1016.

(30) Napolitano, E. S., G; Fiaschi, R; Marsili, A. *Synthesis* **1985**, 38.

(31) Danishefsky, S.; Kitahara, T.; Schuda, P. F.; Etheredge, S. J. *J. Am. Chem. Soc.* **1976**, *98*, 3028.

(32) Reich, H. J.; Peake, S. L. *J. Am. Chem. Soc.* **1978**, *100*, 4888.

(33) Cox, C.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2899.

(34) Aldersley, M. F.; Dean, F. M.; Mann, B. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2217.

(35) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943; (b) Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947; (c) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.

(36) Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, *38*, 5027.

(37) Riediker, M.; Duthaler, R. O. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 494.

(38) (a) Cox, C. D.; Siu, T.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 5625; (b) Siu, T.; Cox, C. D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 5629.

(39) Pinnick, H. W.; Kochlar, K. S. *J. Org. Chem.* **1989**, *54*, 3222.

(40) Allevi, P.; Anastasia, M.; Bingham, S.; Ciuffreda, P.; Fiecchi, A.; Cighetti, G.; Muir, M.; Scala, A.; Tyman, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 575.

(41) Kraus, G. A.; Chen, L.; Jacobson, R. A. *Synth. Commun.* **1993**, *23*, 2041

(42) Corey, E. J.; Sarshar, S.; Azimioara, M. D.; Newbold, R. C.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 7851.

(43) Bertucco, A.; Brennan, J.; Fachini, M.; Kluge, S.; J. Murphy, P.; Pasutto, F.; Signorini, R.; Lloyd Williams, H. *Tetrahedron* **1994**, *50*, 8237.

(44) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.

(45) Deville, J. P.; Behar, V. *Org. Lett.* **2002**, *4*, 1403.

(46) Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. *Tetrahedron Lett.* **1969**, *10*, 4555.

(47) Couladouros, E. A.; Strongilos, A. T. *Tetrahedron Lett.* **2000**, *41*, 535.

(48) Kelly, T. R.; Xu, D. C.; Martinez, G.; Wang, H. X. *Org. Lett.* **2002**, *4*, 1527.

(49) J. Bingham, S.; H. P. Tyman, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3637.

(50) Makhlouf, M. A.; Rickborn, B. *J. Org. Chem.* **1981**, *46*, 4810.

(51) Buff, H.; Kuckländer, U. *Tetrahedron* **2000**, *56*, 5137.

(52) Kelly, T. R.; Cai, X. L.; Tu, B.; Elliott, E. L.; Grossmann, G.; Laurent, P. *Org. Lett.* **2004**, *6*, 4953.

(53) (a) Kim, B. M.; Bae, S. J.; So, S. M.; Yoo, H. T.; Chang, S. K.; Lee, J. H.; Kang, J. *Org. Lett.* **2001**, *3*, 2349; (b) Mash, E. A.; Nelson, K. A.; Van Deusen, S.; Hemperly, S. B. *Org. Synth.* **1990**, *68*, 92.

(54) (a) Naef, R.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 1030; (b) Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. *J. Am. Chem. Soc.* **1994**, *116*, 12111; (c) Evans, D. A.; Wesley Trotter, B.; Barrow, J. C. *Tetrahedron* **1997**, *53*, 8779.

(55) Van Heeswijk, W. a. R.; Goedhart, J. B.; Vliegenthart, J. F. G. *Carbohydr. Res.* **1977**, *58*, 337.

(56) Trewartha, G.; Burrows, J. N.; Barrett, A. G. M. *Tetrahedron Lett.* **2005**, *46*, 3553.

(57) Schlessinger, R. H.; Graves, D. D. *Tetrahedron Lett.* **1987**, *28*, 4381.

(58) Nef, J. U. *Liebigs Ann.* **1894**, 264.

(59) Steliou, K.; Poupart, M. A. *J. Org. Chem.* **1985**, *50*, 4971.

(60) Henderson, D. A.; Collier, P. N.; Pave, G.; Rzepa, P.; White, A. J. P.; Burrows, J. N.; Barrett, A. G. M. *J. Org. Chem.* **2006**, *71*, 2434.

(61) Sudini, R. R.; Khire, U. R.; Pandey, R. K.; Kumar, P. *Ind. J. Chem. Sect. B.* **2000**, *39*, 738.

(62) Barton, D. H. R.; Elliott, J. D.; Gero, S. D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2085.

(63) Plietker, B.; Niggemann, M.; Pollrich, A. *Org. Biomol. Chem.* **2004**, *2*, 1116.

(64) Hunsdiecker, H.; Hunsdiecker, C. *Ber. Dtsch. Chem. Ges* **1942**, *75*, 291.

(65) Simonini, A. *Monatsh. Chem.* **1892**, *13*, 320.

(66) Wehlan, H.; Jezek, E.; Lebrasseur, N.; Pave, G.; Roulland, E.; White, A. J. P.; Burrows, J. N.; Barrett, A. G. M. *J. Org. Chem.* **2006**, *71*, 8151.

(67) King, A. O.; Okukado, N.; Negishi, E.-I. *J. Chem. Soc., Chem. Commun.* **1977**, 683.

(68) Kozhinov, D. V.; Behar, V. *J. Org. Chem.* **2004**, *69*, 1378.

(69) Moran, W. J.; Schreiber, E. C.; Engel, E.; Behn, D. C.; Yamins, J. L. *J. Am. Chem. Soc.* **1952**, *74*, 127.

(70) Devos, A.; Remion, J.; Frisque-Hesbain, A.-M.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* **1979**, 1180.

(71) Le Vezouet, R.; White, A. J. P.; Burrows, J. N.; Barrett, A. G. M. *Tetrahedron* **2006**, *62*, 12252.

(72) Frey, B. W., A. P.; Roden, F.; Au, T. D.; Hockless, D. C.; Willis, A. C.; Mander, L.N. *Aust. J. Chem* **2000**, *53*, 819.

(73) Watanabe, K.; Iwata, Y.; Adachi, S.; Nishikawa, T.; Yoshida, Y.; Kameda, S.; Ide, M.; Saikawa, Y.; Nakata, M. *J. Org. Chem.* **2010**, *75*, 5573.

(74) Takemura, S.; Hirayama, A.; Tokunaga, J.; Kawamura, F.; Inagaki, K.; Hashimoto, K.; Nakata, M. *Tetrahedron Lett.* **1999**, *40*, 7501.

(75) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561 ; (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, *1996*, 521.

(76) Tamura, Y.; Fukata, F.; Sasho, M.; Tsugoshi, T.; Kita, Y. *J. Org. Chem.* **1985**, *50*, 2273.

(77) (a) Kato, K.; Nishimura, A.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2001**, *42*, 4203; (b) Kato, K.; Nishimura, A.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 643.

(78) Tatsuta, K.; Tanaka, H.; Tsukagoshi, H.; Kashima, T.; Hosokawa, S. *Tetrahedron Lett.* **2010**, *51*, 5546.

(79) Patten, A. D.; Nguyen Nhan, H.; Danishefsky, S. J. *J. Org. Chem.* **1988**, *53*, 1003.

(80) Board, J., DPhil Thesis, University of Sussex, 2007.

(81) Waters, A. J., DPhil Thesis, University of Sussex, 2008.

(82) Faggiani, D., DPhil Thesis, University of Sussex, 2012.

(83) (a) Parsons, P. J.; Board, J.; Waters, A. J.; Hitchcock, P. B.; Wakenhut, F.; Walter, D. S. *Synlett* **2006**, 3243; (b) Parsons, P. J.; Waters, A. J.; Walter, D. S.; Board, J. *J. Org. Chem.* **2007**, *72*, 1395; (c) Parsons, P. J.; Board, J.; Faggiani, D.; Hitchcock, P. B.; Preece, L.; Waters, A. J. *Tetrahedron* **2010**, *66*, 6526.

(84) Cope, A. C.; Hardy, E. M. *J. Am. Chem. Soc.* **1940**, *62*, 441.

(85) (a) Bowers, A. H., T. G.; Jones, E. R. H.; Lemin, A. J. *J. Chem. Soc.* **1953**, 2548; (b) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39; (c) Hermeling, D.; Schafer, H. J. *Chem. Ber./Recl.* **1988**, 1151; (d) Fleming, I. G., S.; Sarkar, A. K.; Schmidlin, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3351; (e) Kruithof, K. J. H.; Mateboer, A.; Schakel, M.; Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, 62; (f) Wilson, S. R.; Grandi, M. J. D. *J. Org. Chem.* **1991**, 4766; (g) Cunico, R. F.; Lee, H. M. *J. Am. Chem. Soc.* **1977**, 7613; (h) Saito, S. N., S.; Koizumi, T.; Hirayama, K.; Yamamoto, Y. *J. Org. Chem.* **1999**, 3975; (i) Petrow, E., Al. *Izv. Akad. Nauk SSSR Ser. Khim.* **1958**, 954; (j) Mironow, E. A. *Izv. Akad. Nauk SSSR Ser. Khim.* **1959**, 1954.

(86) Bazant, V.; Capka, M.; Cerny, M.; Chvalovs.V; Kochloef.K; Kraus, M.; Malek, J. *Tetrahedron Lett.* **1968**, 3303.

(87) Hermeling, D.; Schafer, H. J. *Angew. Chem. Int. Ed. Engl.* **1984**, 233.

(88) Harris, T., D.; Roth, G. P. *J. Org. Chem.* **1979**, 2004.

(89) Corriu, R. P.; Mix, A.; Lanneau, F. G. *J. Organomet. Chem.* **1998**, 183.

(90) Salerno, A. C., C.; Perillo, I. A. *Synth. Commun.* **2000**, *30*, 3369.

(91) Sibi, M. P.; Miah, M. J.; Snieckus, V. *J. Org. Chem.* **1984**, 737.

(92) (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636; (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4981; (c) Milstein, D.; Stille, J. K. *J. Org. Chem.* **1979**, *44*, 1613; (d) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992; (e) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.

(93) Corey, E. J.; Yu, C. M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495.

(94) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

(95) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434.

(96) Burton, G. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 6472.

(97) (a) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopalan, B.; Larsen, S. D.; Siret, P.; Gras, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 8034; (b) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Gras, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 8031.

(98) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660.

(99) (a) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 9130; (b) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057.

(100) Nagata, R.; Yamanaka, H.; Okazaki, E.; Saito, I. *Tetrahedron Lett.* **1989**, *30*, 4995.

(101) Schmittel, M.; Strittmatter, M.; Kiau, S. *Tetrahedron Lett.* **1995**, *36*, 4975.

(102) (a) Nicolaou, K. C.; Ogawa, Y.; Zuccarello, G.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866; (b) Nicolaou, K. C.; Ogawa, Y.; Zuccarello, G.; Kataoka, H. *J. Am. Chem. Soc.* **1988**, *110*, 7247; (c) Nicolaou, K. C.; Hwang, C. K.; Smith, A. L.; Wendeborn, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 7416; (d) Nicolaou, K. C.; Dai, W. M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387.

(103) (a) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694; (b) Tamao, K.; Akita, M.; Kumada, M. *J. Organomet. Chem.* **1983**, *254*, 13; (c) Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* **1983**, *39*, 983; (d) Tamao, K.; Ishida, N. *J. Organomet. Chem.* **1984**, *269*, c37; (e) Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4249; (f) Tamao, K.; Kumada, M.; Maeda, K. *Tetrahedron Lett.* **1984**, *25*, 321.

(104) (a) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29; (b) Fleming, I.; Hill, J. H. M.; Parker, D.; Waterson, D. *J. Chem. Soc., Chem. Commun.* **1985**, 318; (c) Chow, H.-F.; Fleming, I. *Tetrahedron Lett.* **1985**, *26*, 397; (d) Fleming, I.; Kilburn, J. D. *J. Chem. Soc., Chem. Commun.* **1986**, 1198; (e) Fleming, I.; Sanderson, P. E. J. *Tetrahedron Lett.* **1987**, *28*, 4229.

(105) Dhar, R. K.; Clawson, D. K.; Fronczek, F. R.; Rabideau, P. W. *J. Org. Chem.* **1992**, *57*, 2917.

(106) Linderberg, M.; Hellberg, S.; Bjork, S.; Gotthammar, B.; Hogberg, T.; Persson, K.; Schwarcz, R.; Luthman, J.; Johansson, R. *Eur. J. Med. Chem.* **1999**, *34*, 729.

(107) Witiak, D. T.; Kamat, P. L.; Allison, D. L.; Liebowitz, S. M.; Glaser, R.; Holliday, J. E.; Moeschberger, M. L.; Schaller, J. P. *J. Med. Chem* **1983**, *26*, 1679.

(108) Fries, K. *Liebigs Ann.* **1907**, *353*, 335.

(109) (a) Gardner, P. D.; Sarrafizadeh R, H.; Brandon, R. L. *J. Am. Chem. Soc.* **1959**, *81*, 5515; (b) Merijan, A.; Shoulders, B. A.; Gardner, P. D. *J. Org. Chem.* **1963**, *28*, 2148.

(110) (a) Turner, A. B. *Q. Rev. Chem. Soc* **1964**, *18*, 347; (b) Schleigh, W. R. *Eastman Org. Chem. Bull.* **1971**, *43*, 1; (c) Boger, D.; Weinreb, S. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; (d) Wan, P. B.,

B.; Diao, L.; Fischer, M.; Shi, Y.; Yang, C. *Can. J. Chem.* **1996**, *74*, 465; (e) Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367.

(111) Rokita, S. E. *Quinone Methides*; John Wiley & Sons, Inc.: Hoboken, NJ, 2009.

(112) Gaudiano, G.; Resing, K.; Koch, T. H. *J. Am. Chem. Soc.* **1994**, *116*, 6537.

(113) Kassahun, K.; Pearson, P. G.; Tang, W.; Mcintosh, I.; Leung, K.; Elmore, C.; Dean, D.; Wang, R.; Doss, G.; Baillie, T. A. *Chem. Res. Toxicol.* **2000**, *14*, 62.

(114) Clausen, T. P.; Koller, J. W.; Reichardt, P. B. *Tetrahedron Lett.* **1990**, *31*, 4537.

(115) (a) Leary, G.; Porter, G. *J. Chem. Soc. A* **1970**, 2273; (b) Leary, G. *J. Chem. Soc. A* **1971**, 2248; (c) Balakrishnan, G.; Umapathy, S. *J. Mol. Struct.* **1999**, *475*, 5.

(116) (a) Jurd, L.; Roitman, J. N. *Tetrahedron* **1978**, *34*, 57; (b) Jurd, L. *Aust. J. Chem* **1978**, *31*, 347.

(117) (a) Hultzsch, K. *Chem. Ber.* **1941**, *74*, 898; (b) Schmidt, R. R. *Tetrahedron Lett.* **1969**, *10*, 5279; (c) Dorrestijin, E.; Epema, O. J.; Van Scheppingen, W. B.; Mulder, P. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1173; (d) Sprengling, G. R. *J. Am. Chem. Soc.* **1952**, *74*, 2937.

(118) (a) Decodts, G.; Wakselman, M.; Vilkas, M. *Tetrahedron* **1970**, *26*, 3313; (b) Dorrestijin, E., ; Kranenburg., M.; Ciriano, M. V.; Mulder, P. *J. Org. Chem.* **1999**, *64*, 3012; (c) Britt, P., F.; Buchanan, A. C.; Cooney, M. J.; Martineau, D. R. *J. Org. Chem.* **2000**, *65*, 1376.

(119) Loubinoux, B.; Miazimbakana, J.; Gerardin, P. *Tetrahedron Lett.* **1989**, *30*, 1939.

(120) (a) Von Strandtmann, M.; Cohen, M. P.; Shavel, J. *Tetrahedron Lett.* **1965**, *6*, 3103; (b) Strandtmann, M. V.; Cohen, M. P.; Shavel, J. *J. Org. Chem.* **1965**, *30*, 3240; (c) Büyükkıdan, B.; Bilgiç, S.; Bilgiç, O. *Synth. Commun.* **2001**, *31*, 1263

(121) Breuer, E.; Melumad, D. *Tetrahedron Lett.* **1969**, *10*, 1875.

(122) (a) Chiba, K. S., J.; Tada, M. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1381; (b) Chiba, K.; Sonoyama, J.; Tada, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1435.

(123) Rosenau, T. H., W. D. *Tetrahedron* **1995**, *51*, 7919.

(124) Hansen, H. J. *Helv. Chim. Acta* **1977**, *60*, 2007.

(125) (a) Lau, C. K. W., H. W. R.; Tardiff, S.; Dufresne, C.; Scheigetz, J.; Bélanger, P. C. *Can. J. Chem.* **1989**, *67*, 1384; (b) Chambers, J. D. C., J.; Williams, H. W. R.; Dufresne, C.; Scheigetz, J.; Bernstein, M. A.; Lau, C. K. *Can. J. Chem.* **1992**, *70*, 1717.

(126) Sheppard, W. A. *J. Org. Chem.* **1968**, *33*, 3297.

(127) (a) Yato, M.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1990**, *112*, 5341; (b) Goldschmidt, Z.; Levinger, S.; Gottlieb, H. E. *Tetrahedron Lett.* **1994**, *35*, 7273.

(128) (a) Heaney, H. J., J. M. *J. Chem. Soc., Chem. Commun.* **1968**, 1139; (b) Heaney, H.; Jablonski, J. M.; Mccarty, C. T. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2903; (c) Adam, W.; Hadjiarapoglou, L.; Peters, K.; Sauter, M. *J. Am. Chem. Soc.* **1993**, *115*, 8603.

(129) (a) Paul, G. C.; Gajewski, J. J. *J. Org. Chem.* **1993**, *58*, 5060; (b) Yamato, T.; Matsumoto, J.-I.; Sato, M.; Fujita, K.; Nagano, Y. *J. Chem. Res. (S)* **1997**, 74.

(130) Chiang, Y.; Kresge, A. J.; Zhu, Y. *J. Am. Chem. Soc.* **2001**, *123*, 8089.

(131) Dorrestijn, E.; J. Epema, O.; B. Van Scheppingen, W.; Mulder, P. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1173.

(132) Khasanova, T.; Sheridan, R. S. *J. Am. Chem. Soc.* **2000**, *122*, 8585.

(133) Miyazaki, H.; Honda, K.; Asami, M.; Inoue, S. *J. Org. Chem.* **1999**, *64*, 9507.

(134) (a) Inoue, T. I., S.; Sato, K. *Chem. Lett.* **1990**, *19*, 55; (b) Chiba, K.; Hirano, T.; Kitano, Y.; Tada, M. *Chem. Commun.* **1999**, 691.

(135) Smith, L. I.; Tess, R. W. H.; Ullyot, G. E. *J. Am. Chem. Soc.* **1944**, *66*, 1320.

(136) Wenderski, T. A.; Marsini, M. A.; Pettus, T. R. R. *Org. Lett.* **2011**, *13*, 118.

(137) Li, T.; Rokita, S. E. *J. Am. Chem. Soc.* **1991**, *113*, 7771.

(138) Karabelas, K.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 5372.

(139) Moore, R. F.; Waters, W. A. *J. Chem. Soc.* **1954**, 243.

(140) Boldron, C.; Ozalp-Yaman, S.; Gamez, P.; Tooke, D. M.; Spek, A. L.; Reedijk, J. *Dalton Trans.* **2005**, 3535.

(141) (a) Bolon, D. A. *J. Org. Chem.* **1970**, *35*, 715; (b) Bolon, D. A. *J. Org. Chem.* **1970**, *35*, 3666.

(142) Cook, C. D.; Butler, L. C. *J. Org. Chem.* **1969**, *34*, 227.

(143) (a) Kasturi, T. R.; Rajasekhar, B.; Raju, G. J.; Reddy, G. M.; Sivaramakrishnan, R.; Ramasubbu, N.; Venkatesan, K. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2375; (b) Kasturi, T. R.; Jayaram, S. K. *Ind. J. Chem. Sect. B.* **1988**, *27B*, 714; (c) Kasturi, T. R.; Jayaram, S. K.; Sattigeri, J. A.; Pragnacharylu, P. V. P.; Row, T. N. G.; Renuka, K.; Venkatesan, K.; Begum, N. S.; Munirathinam, N. *Tetrahedron* **1993**, *49*, 7145.

(144) Chiba, K.; Yamaguchi, Y.; Tada, M. *Tetrahedron Lett.* **1998**, *39*, 9035.

(145) (a) Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318; (b) Wittig, G.; Haag, W. *Chem. Ber.* **1955**, *88*, 1654.

(146) (a) Parrick, J. *Can. J. Chem.* **1964**, *42*, 190; (b) Sullivan, W. W.; Ullman, D.; Schechter, H. *Tetrahedron Lett.* **1969**, *10*, 457.

(147) Verboom, W.; Bos, H. J. *Tetrahedron Lett.* **1978**, *19*, 1229.

(148) Da Silva, M. N.; Ferreira, S. B.; Jorqueira, A.; De Souza, M. C. B. V.; Pinto, A. V.; Kaiser, C. R.; Ferreira, V. F. *Tetrahedron Lett.* **2007**, *48*, 6171.

(149) Cavitt, S. B.; R, H. S.; Gardner, P. D. *J. Org. Chem.* **1962**, *27*, 1211.

(150) René, L. *Synthesis* **1989**, *1989*, 69.

(151) Van De Water, R. W.; Magdziak, D. J.; Chau, J. N.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2000**, *122*, 6502.

(152) Lukyanov, S. M. E., L. N.; Dorofeenko, G. N. *Russ. J. Org. Chem.* **1978**, *14*, 2148.

(153) Katada, T.; Eguchi, S.; Esaki, T.; Sasaki, T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2649.

(154) Attwood, M. R.; Brown, B. R.; Lisseter, S. G.; Torrero, C. L.; Weaver, P. M. *J. Chem. Soc., Chem. Commun.* **1984**, 177.

(155) Angle, S. R.; Yang, W. *J. Am. Chem. Soc.* **1990**, *112*, 4524.

(156) Mcloughlin, B. J. *J. Chem. Soc. D* **1969**, 540.

(157) Borchardt, R. T.; Sinhababu, A. K. *J. Org. Chem.* **1981**, *46*, 5021.

(158) Tolmach, E. L. K., A. B.; Zheltov, A. Y.; Stepanov, B. I. *Russ. J. Org. Chem.* **1989**, *25*, 1764.

(159) Fanghänel, E.; Böckelmann, J.; Grossmann, N.; Pfeifer, D. *J. Prakt. Chem.* **1986**, *328*, 724.

(160) Adam, W.; Sauter, M. *Chem. Ber.* **1993**, *126*, 2697.

(161) Pisova, M.; Soucek, M. *Coll. Czech. Chem. Comm.* **1982**, *47*, 838.

(162) Samarakoon, T. B.; Hur, M. Y.; Kurtz, R. D.; Hanson, P. R. *Org. Lett.* **2010**, *12*, 2182.

(163) Adlington, R. M.; Baldwin, J. E.; Pritchard, G. J.; Williams, A. J.; Watkin, D. J. *Org. Lett.* **1999**, *1*, 1937.

(164) Lawrence, A. L.; Adlington, R. M.; Baldwin, J. E.; Lee, V.; Kershaw, J. A.; Thompson, A. L. *Org. Lett.* **2010**, *12*, 1676.

(165) Chapman, O. L.; Engel, M. R.; Springer, J. P.; Clardy, J. C. *J. Am. Chem. Soc.* **1971**, *93*, 6696.

(166) Penttila, A.; Kapadia, G. J.; Fales, H. M. *J. Am. Chem. Soc.* **1965**, *87*, 4402.

(167) Wenderski, T. A.; Huang, S.; Pettus, T. R. R. *J. Org. Chem.* **2009**, *74*, 4104.

(168) Hoffmann, R. *The Same and Not the Same*; Columbia University Press: New York, NY, 1997.

(169) Comins, D. L.; Hong, H.; Jianhua, G. *Tetrahedron Lett.* **1994**, *35*, 5331.

(170) Kumar, S. K.; Amador, M.; Hidalgo, M.; Bhat, S. V.; Khan, S. R. *Bio. Med. Chem.* **2005**, *13*, 2873.

(171) Magnus, P.; Eisenbeis, S. A.; Magnus, N. A. *J. Chem. Soc., Chem. Commun.* **1994**, 1545.

(172) (a) Duan, J.; Zhang, L. H.; Dolbier Jr, W. R. *Synlett* **1999**, *1999*, 1245; (b) Carreno, M. C.; Garcia Ruano, J. L.; Sanz, G.; Toledo, M. A.; Urbano, A. *J. Org. Chem.* **1995**, *60*, 5328.

(173) Bloomer, J. L.; Lankin, M. E. *Tetrahedron Lett.* **1992**, *33*, 2769.

(174) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899.

(175) Schoenberg, A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 7761.

(176) (a) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7175; (b) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 452.

(177) (a) Pri-Bar, I.; Buchman, O. *J. Org. Chem.* **1984**, *49*, 4009; (b) Misumi, Y.; Ishii, Y.; Hidai, M. *Organometallics* **1995**, *14*, 1770.

(178) Kotsuki, H.; Datta, P. K.; Suenaga, H. *Synthesis* **1996**, *1996*, 470.

(179) (a) Ito, Y.; Hirao, T.; Ohta, N.; Saegusa, T. *Tetrahedron Lett.* **1977**, *18*, 1009; (b) Kosugi, M. O., T.; Tamura, H.; Sano, H.; Migita, T. *Chem. Lett.* **1986**, *15*, 1197; (c) Saluste, C. G.; Whitby, R. J.; Furber, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 4156; (d) Saluste, C. G.; Whitby, R. J.; Furber, M. *Tetrahedron Lett.* **2001**, *42*, 6191; (e) Whitby,

R. J.; Gustaf Saluste, C.; Furber, M. *Org. Biomol. Chem.* **2004**, *2*, 1974.

(180) Olah, G. A.; Ohannesian, L.; Arvanaghi, M. *Chem. Rev.* **1987**, *87*, 671.

(181) Gattermann, L.; Koch, J. A. *Ber. Dtsch. Chem. Ges* **1897**, *30*, 1622.

(182) Gattermann, L.; Berchelmann, W. *Ber. Dtsch. Chem. Ges* **1898**, *31*, 1765.

(183) Vilsmeier, A.; Haack, A. *Chem. Ber.* **1927**, *60*, 119.

(184) (a) Duff, J. C.; Bills, E. J. *J. Chem. Soc.* **1932**, 1987; (b) Duff, J. C.; Bills, E. J. *J. Chem. Soc.* **1934**, 1305; (c) Duff, J. C. *J. Chem. Soc.* **1941**, 547; (d) Duff, J. C. *J. Chem. Soc.* **1945**, 276.

(185) (a) Henry, P. M. *Tetrahedron Lett.* **1968**, *9*, 2285; (b) Baird, W. C.; Hartgerink, R. L.; Surridge, J. H. *J. Org. Chem.* **1985**, *50*, 4601; (c) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5546.

(186) (a) Somei, M. K., T.; Ohta, T. *Heterocycles* **1988**, *27*, 2363; (b) Yamada, F., ; Somei, M., *Heterocycles* **1987**, *26*, 1173; (c) Antus, S.; Snatzke, G.; Steinke, I. *Liebigs Ann.* **1983**, *1983*, 2247.

(187) Whitmore, F. C.; Middleton, E. B. *J. Am. Chem. Soc.* **1921**, *43*, 619.

(188) Mckillop, A.; Fowler, J. S.; Zelesko, M. J.; Hunt, J. D.; Taylor, E. C.; Mcgillivray, G. *Tetrahedron Lett.* **1969**, *10*, 2423.

(189) Von Euler, H.; Adler, E.; Gie, G. J. *Ark. Kemi., Mineral., Geol.* **1940**, *B14*, 1.

(190) Wegner, G.; Nakabayashi, N.; Cassidy, H. G. *J. Org. Chem.* **1967**, *32*, 3155.

(191) (a) Wuts, P. G. M.; Greene, T. W. "Protection for the Hydroxyl Group, Including 1,2- and 1,3-Diols" In *Greene's Protective Groups in Organic Synthesis*; 4th ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2006, p 16; (b) Evans, M. E.; Parrish, F. W.; Long, L. *Carbohydr. Res.* **1967**, *3*, 453.

(192) Sakamoto, S.; Sakazaki, H.; Hagiwara, K.; Kamada, K.; Ishii, K.; Noda, T.; Inoue, M.; Hirama, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 6505.

(193) (a) Schmidt, O. T. *Methods Carbohydr. Chem.* **1963**, ***II***, 318; (b) De Belder, A. N. *Adv. Carbohydr. Chem.* **1965**, *20*, 219.

(194) Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072.

(195) Zuo, L.; Yao, S.; Wang, W.; Duan, W. *Tetrahedron Lett.* **2008**, *49*, 4054.

(196) Evans, G. E.; Staunton, J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 755.

(197) Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G. *Synthesis* **1980**, *1980*, 124.

(198) Sayigh, A. a. R.; Ulrich, H.; Green, M. *J. Chem. Soc.* **1964**, 3482.

(199) Chin-Hsien, W., A., N., G. *Synthesis* **1982**, *1982*, 494.

(200) (a) Powell, S. G.; Adams, R. *J. Am. Chem. Soc.* **1920**, *42*, 646; (b) Nazarov, S. I.; Magerramov, M. N.; Mamedov, S. M.; Akhmedov, S. T.; Namazova, E. N. *Russ. J. Org. Chem.* **1989**, *25*, 1680 ; (c) Nazarov, S. I.; Magerramov, M. N.; Mamedov, S. M.; Akhmedov, S. T.; Namazova, E. N. *Russ. J. Org. Chem.* **1989**, *25*, 1510.

(201) Goundry, W. R. F.; Lee, V.; Baldwin, J. E. *Synlett* **2006**, *2006*, 2407.

(202) Ndungu, J. M.; Larson, K. K.; Sarpong, R. *Org. Lett.* **2005**, *7*, 5845.

(203) (a) Caddick, S. *Tetrahedron* **1995**, *51*, 10403; (b) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem* **1995**, *48*, 1665; (c) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.

(204) (a) Brower, K. R. *J. Am. Chem. Soc.* **1961**, *83*, 4370; (b) Walling, C.; Naiman, M. *J. Am. Chem. Soc.* **1962**, *84*, 2628.

(205) (a) Binner, J. G. P.; Hassine, N. A.; Cross, T. E. *J. Mater. Sci.* **1995**, *30*, 5389; (b) Berlan, J.; Giboreau, P.; Lefeuvre, S.; Marchand, C. *Tetrahedron Lett.* **1991**, *32*, 2363; (c) Langa, F.; De La Cruz, P.; De La Hoz, A.; Diaz-Ortiz, A.; Diez-Barra, E. *Contemp. Org. Syn.* **1997**, *4*, 373.

(206) (a) Ichikawa, H.; Maruoka, K. "Aliphatic and Aromatic Claisen Rearrangement" In *The Claisen Rearrangement*; Wiley-VCH: Weinheim, 2007, p 45; (b) Hiersemann, M. N., U. *The Claisen Rearrangement*; Wiley-VCH: Weinheim, 2007.

(207) Khan, M. A. *Bull. Chem. Soc. Jap.* **1991**, *64*, 3682.

(208) Boeckman, R. K.; Perni, R. B. *J. Org. Chem.* **1986**, *51*, 5486.

(209) Riedel, J. D.; De Haen, E., Patent, DE1929R077572D 19290316 Reichspatentamt, 1929.

(210) Rehbein, J.; Hiersemann, M. "Mechanistic Aspects of the Aliphatic Claisen Rearrangement" In *The Claisen Rearrangement*; Wiley-VCH: Weinheim, 2007, p 525.

(211) (a) Goering, H. L.; Jacobson, R. R. *J. Am. Chem. Soc.* **1958**, *80*, 3277; (b) White, W. N.; Gwynn, D.; Schlitt, R.; Girard, C.; Fife, W. *J. Am. Chem. Soc.* **1958**, *80*, 3271.

(212) (a) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205; (b) Majumdar, K. C.; Alam, S.; Chattopadhyay, B. *Tetrahedron* **2008**, *64*, 597; (c) Martín Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939.

(213) Svanholm, U.; Parker, V. D. *J. Chem. Soc., Chem. Commun.* **1972**, 645.

(214) Wipf, P.; Ribe, S. *Org. Lett.* **2001**, *3*, 1503.

(215) White, W. N.; Wolfarth, E. F. *J. Org. Chem.* **1970**, *35*, 2196.

(216) Robertson, D. W.; Lacefield, W. B.; Bloomquist, W.; Pfeifer, W.; Simon, R. L.; Cohen, M. L. *J. Med. Chem* **1992**, *35*, 310.

(217) (a) Grieco, P. A.; Brandes, E. B.; Mccann, S.; Clark, J. D. *J. Org. Chem.* **1989**, *54*, 5849; (b) Bagnell, L.; Cablewski, T.; Strauss, C. R.; Trainor, R. W. *J. Org. Chem.* **1996**, *61*, 7355.

(218) Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219.

(219) Yoo, S. E.; Lee, S. H.; Kim, S. K.; Lee, S. H. *Bio. Med. Chem.* **1997**, *5*, 445.

(220) Liazid, A.; Palma, M.; Brigui, J.; Barroso, C. G. *J. Chromatogr. A* **2007**, *1140*, 29.

(221) (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885; (b) Oikawa, Y.; Tanaka, T.; Horita, K.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1984**, *25*, 5393; (c) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

(222) Nakajima, N. A., R.; Yonemitsu, O. *Chem. Pharm. Bull.* **1988**, *36*, 4244.

(223) Hurd, C. D.; Webb, C. N. *J. Am. Chem. Soc.* **1936**, *58*, 2190.

(224) (a) Iwanami, K.; Yano, K.; Oriyama, T. *Chem. Lett.* **2007**, *36*, 38; (b) Wada, M.;

Nagayama, S.; Mizutani, K.; Hiroi, R.; Miyoshi, N. *Chem. Lett.* **2002**, *31*, 248.

(225) Sullivan, B.; Djura, P.; Mcintyre, D. E.; Faulkner, D. J. *Tetrahedron* **1981**, *37*, 979.

(226) Raber, D. J.; Gariano, P.; Brod, A. O.; Gariano, A.; Guida, W. C.; Guida, A. R.; Herbst, M. D. *J. Org. Chem.* **1979**, *44*, 1149.

(227) Presser, A.; Hüfner, A. *Monatsh. Chem.* **2004**, *135*, 1015.

(228) Brandes, E.; Grieco, P. A.; Gajewski, J. J. *J. Org. Chem.* **1989**, *54*, 515.

(229) Chumachenko, N., V.; Kolesnikov, V., T.; Novikov, V. P. *Russ. J. Org. Chem.* **1991**, *27*, 846.

(230) Fixler, N.; Salez, H.; Demeunynck, M.; Lhomme, J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1649.

(231) Wang, P.; Hu, H.; Wang, Y. *Org. Lett.* **2007**, *9*, 1533.

(232) Wang, P.; Hu, H.; Wang, Y. *Org. Lett.* **2007**, *9*, 2831.

(233) Sugimoto, H.; Nakamura, S.; Ohwada, T. *J. Org. Chem.* **2007**, *72*, 10088.

(234) Castro, E. A.; Ureta, C. *J. Org. Chem.* **1989**, *54*, 2153.

(235) Stewart, E. T.; De La Mare, P. B. D.; Pritchard, J. G.; Buckingham, A. D.; Holland, H. G.; Le Fevre, R. J. W.; Davidson, G. F.; Lynch, B. M.; Pausacker, K. H.; Barduhn, A. J.; Kobe, K. A.; Whalley, W. B. *J. Chem. Soc* **1954**, 1643.

(236) Cowley, E. G. *J. Chem. Soc* **1952**, 3557.

(237) Partington, J. R.; Coomber, D. I. *Nature* **1938**, *141*, 918.

(238) Hunter, E. C. E.; Partington, J. R. *J. Chem. Soc* **1932**, 2812.

(239) Allinger, N. L.; Carpenter, J. G. D.; Karkowski, F. M. *J. Am. Chem. Soc.* **1965**, *87*, 1232.

(240) Williams, J. W. *J. Am. Chem. Soc.* **1928**, *50*, 2350.

(241) Weinert, E. E.; Dondi, R.; Colloredo-Melz, S.; Frankenfield, K. N.; Mitchell, C. H.; Freccero, M.; Rokita, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 11940.

(242) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317.

(243) (a) Sunderhaus, J. D.; Lam, H.; Dudley, G. B. *Org. Lett.* **2003**, *5*, 4571; (b) Fleming, I.; Ghosh, S. K. *J. Chem. Soc., Chem. Commun.* **1992**, 1775; (c) Fleming, I.; Ghosh, S. K. *J. Chem. Soc., Chem. Commun.* **1992**, 1777; (d) Corey, E. J.; Chen, Z. *Tetrahedron Lett.* **1994**, *35*, 8731; (e) Fleming, I.; Winter, S. B. D. *Tetrahedron Lett.* **1993**, *34*, 7287; (f) Stork, G. *Pure Appl. Chem.* **1989**, *61*, 439; (g) Hunt, J. A.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 501; (h) Landais, Y.; Planchenault, D.; Weber, V. *Tetrahedron Lett.* **1995**, *36*, 2987; (i) Angelaud, R.; Landais, Y.; Maignan, C. *Tetrahedron Lett.* **1995**, *36*, 3861; (j) Chan, T. H.; Pellon, P. *J. Am. Chem. Soc.* **1989**, *111*, 8737; (k) Delft, F. L. V.; Marel, G. a. V. D.; Boom, J. H. V. *Synlett* **1995**, *1995*, 1069; (l) Itami, K.; Mitsudo, K.; Yoshida, J.-I. *J. Org. Chem.* **1999**, *64*, 8709.

(244) (a) Hasegawa, M.; Murakami, M. *J. Org. Chem.* **2007**, *72*, 3764; (b) Denmark, S. E.; Habermas, K. L.; Hite, G. A.; Jones, T. K. *Tetrahedron* **1986**, *42*, 2821 ; (c) Fleming, I.; Takaki, K.; Thomas, A. P. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2269

(245) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

(246) Fleming, I.; D. Kilburn, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2663.

(247) Bradbury, B. J.; Baumgold, J.; Jacobson, K. A. *J. Med. Chem* **1990**, *33*, 741.

(248) Dominguez, D.; Cava, M. P. *J. Org. Chem.* **1983**, *48*, 2820.

(249) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227.

(250) Jacob, P.; Callery, P. S.; Shulgin, A. T.; Castagnoli, N. *J. Org. Chem.* **1976**, *41*, 3627.

(251) Larsen, D. S.; O'shea, M. D. *J. Org. Chem.* **1996**, *61*, 5681.

(252) Kim, A. I.; Rychnovsky, S. D. *Angew. Chem. Int. Ed.* **2003**, *42*, 1267.

(253) (a) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968; (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M. *J. Org. Chem.* **1992**, *57*, 2768.

(254) Morikawa, K.; Park, J.; Andersson, P. G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 8463.

(255) Yu, L.; Chen, D.; Li, J.; Wang, P. G. *J. Org. Chem.* **1997**, *62*, 3575.

(256) Shing, T. K. M.; Luk, T. *Tetrahedron: Asymmetry* **2009**, *20*, 883.

(257) Larock, R. C.; Fellows, C. A. *J. Am. Chem. Soc.* **1982**, *104*, 1900.

(258) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731.

(259) Smith, M.; Boundy, C. *Ind. Eng. Chem., News Ed.* **1930**, *8*, 18.

(260) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512.

(261) Magnus, P.; Eisenbeis, S. A.; Fairhurst, R. A.; Iliadis, T.; Magnus, N. A.; Parry, D. *J. Am. Chem. Soc.* **1997**, *119*, 5591.

(262) Witiak, D. T.; Loper, J. T.; Ananthan, S.; Almerico, A. M.; Verhoef, V. L.; Filppi, J. A. *J. Med. Chem* **1989**, *32*, 1636.

(263) Choudhury, P. K.; Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1997**, *53*, 17373.

(264) De Jonge, J.; Bibo, B. H. *Recl. Trav. Chim. Pays-Bas* **1955**, *74*, 1448.

(265) Johnsson, R.; Olsson, D.; Ellervik, U. *J. Org. Chem.* **2008**, *73*, 5226.

(266) Hodgkin, J. H. *Aust. J. Chem* **1984**, *37*, 2371.

(267) Hwang, D.-R.; Uang, B.-J. *Org. Lett.* **2002**, *4*, 463.

(268) Katritzky, A. R.; Zhang, Z.; Lan, X.; Lang, H. *J. Org. Chem.* **1994**, *59*, 1900.

(269) Toshihiro, N.; Nobuhiko, F.; Hideki, F.; Masayuki, I.; Takeshi, N.; Kazuya, T.; Minoru, F., Patent, EP20020701540 20020213, Kissei Pharmaceutical Co. Ltd., 2003.

(270) (a) Bollinger, J. M.; Brinich, J. M.; Olah, G. A. *J. Am. Chem. Soc.* **1970**, *92*, 4025; (b) Crowder, G. A. *J. Mol. Spec.* **1967**, *23*, 103.

(271) Halbach, M. J. *Ind. Eng. Chem., News Ed.* **1932**, *10*, 257.

Appendix A: Crystallographic Data

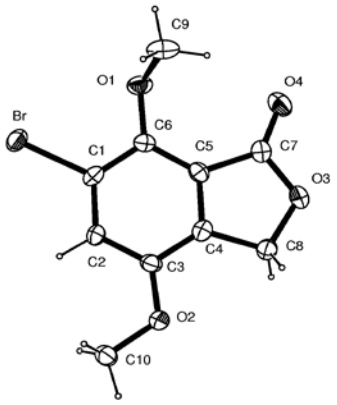


Table 1. Crystal data and structure refinement .

Identification code	Compound **(2.13)**	
Empirical formula	$C_{10}H_9BrO_4$	
Formula weight	273.08	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	Pn (No.7)	
Unit cell dimensions	a = 10.5872(8) Å	□= 90°.
	b = 3.9457(3) Å	□= 94.092(5)°.
	c = 11.8125(8) Å	□= 90°.
Volume	492.20(6) $Å^3$	
Z	2	
Density (calculated)	1.84 Mg/m^3	
Absorption coefficient	4.17 mm^{-1}	
F(000)	272	
Crystal size	0.35 x 0.35 x 0.20 mm^3	
Theta range for data collection	3.46 to 25.95°.	
Index ranges	-13<=h<=13, -4<=k<=4, -14<=l<=14	
Reflections collected	4146	
Independent reflections	1748 [R(int) = 0.052]	
Reflections with I>2sigma(I)	1704	
Completeness to theta = 25.95°	99.6 %	
Tmax. and Tmin.	0.3865 and 0.2003	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1748 / 2 / 138	
Goodness-of-fit on F^2	1.085	
Final R indices [I>2sigma(I)]	R1 = 0.045, wR2 = 0.107	
R indices (all data)	R1 = 0.046, wR2 = 0.109	

Absolute structure parameter	0.009(15)
Largest diff. peak and hole	1.16 and -1.27 e.Å^{-3} (near Br)

Data collection KappaCCD , Program package WinGX , Abs correction MULTISCAN Refinement using SHELXL-97, Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for dec1007. U (eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br	6140	4439(1)	2152	27(1)
O(1)	7441(4)	857(10)	4193(4)	28(1)
O(2)	2592(5)	5064(11)	5043(4)	26(1)
O(3)	5295(4)	-415(10)	7229(4)	27(1)
O(4)	7209(4)	-1824(13)	6694(4)	34(1)
C(1)	5493(5)	3555(14)	3573(4)	22(1)
C(2)	4269(6)	4622(13)	3742(6)	22(1)
C(3)	3761(5)	4113(12)	4777(5)	23(1)
C(4)	4504(5)	2444(12)	5611(4)	21(1)
C(5)	5708(4)	1403(14)	5427(4)	20(1)
C(6)	6256(4)	1948(13)	4407(4)	20(1)
C(7)	6213(6)	-419(13)	6469(5)	24(1)
C(8)	4182(5)	1402(15)	6781(5)	25(1)
C(9)	8471(5)	2568(16)	4798(6)	36(1)
C(10)	1796(5)	6773(17)	4182(4)	26(1)

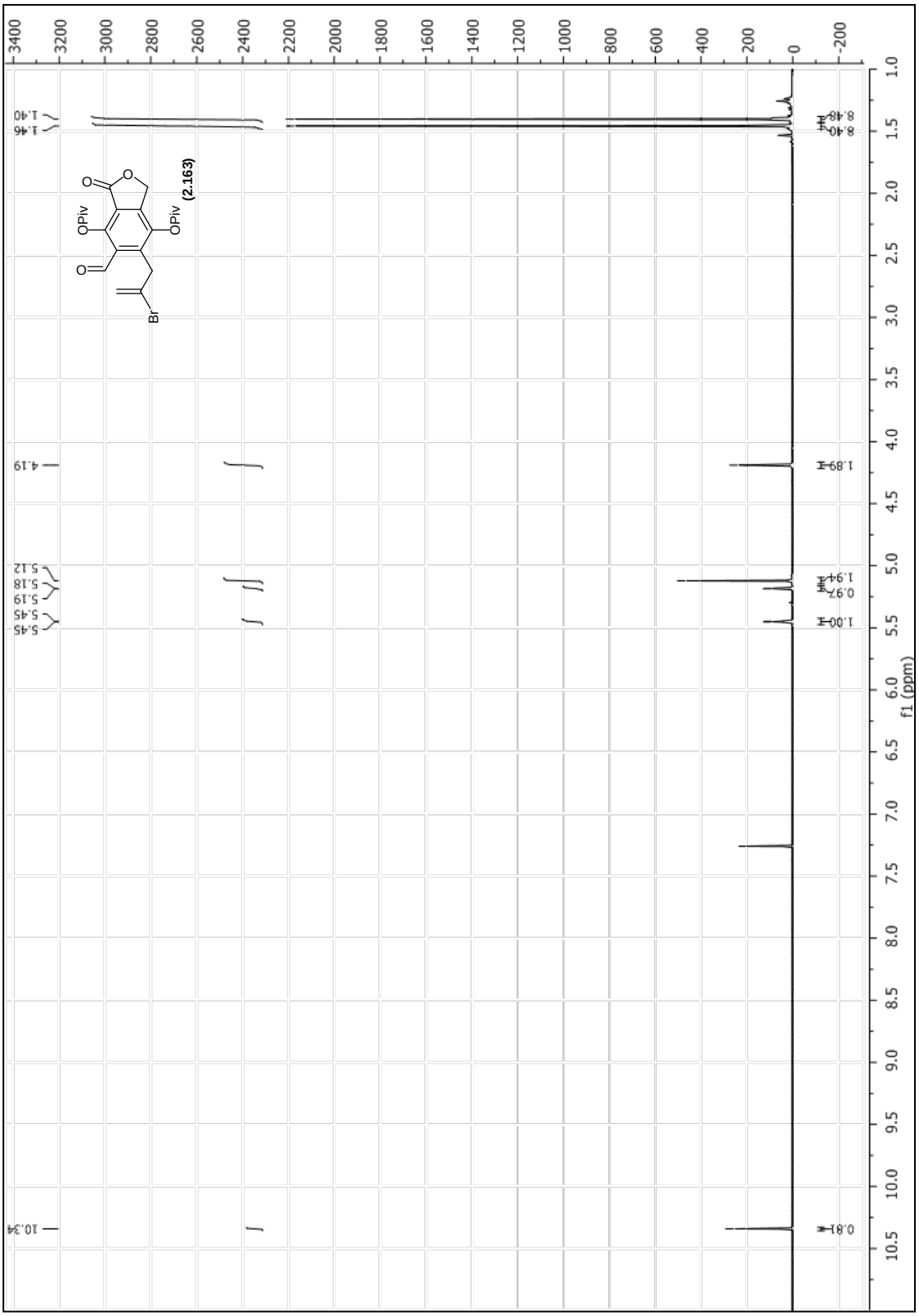
Table 3. Bond lengths [Å] and angles [°] for dec1007.

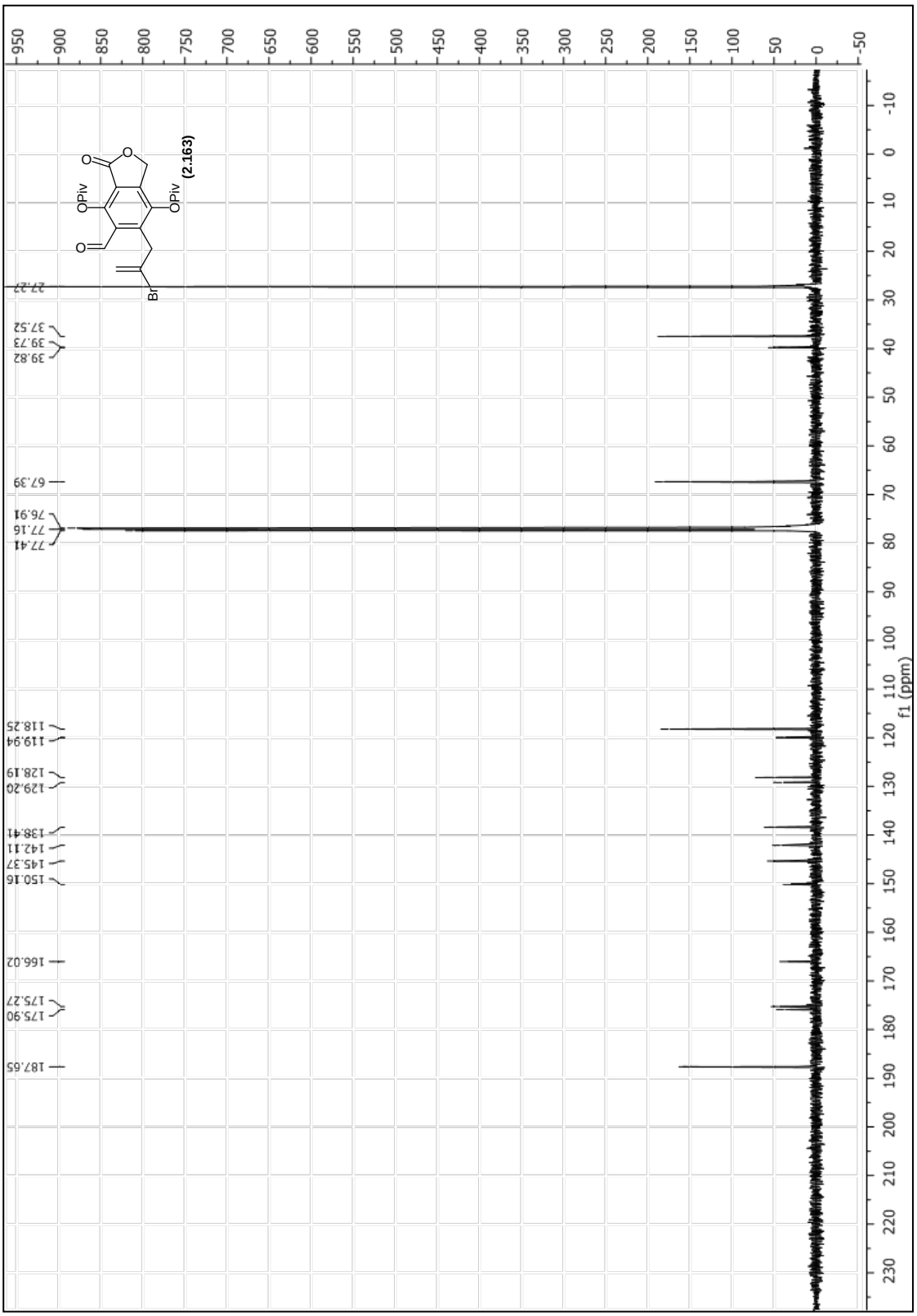
Br-C(1)	1.890(5)
O(1)-C(6)	1.367(6)
O(1)-C(9)	1.430(7)
O(2)-C(3)	1.351(7)
O(2)-C(10)	1.441(7)
O(3)-C(7)	1.369(8)

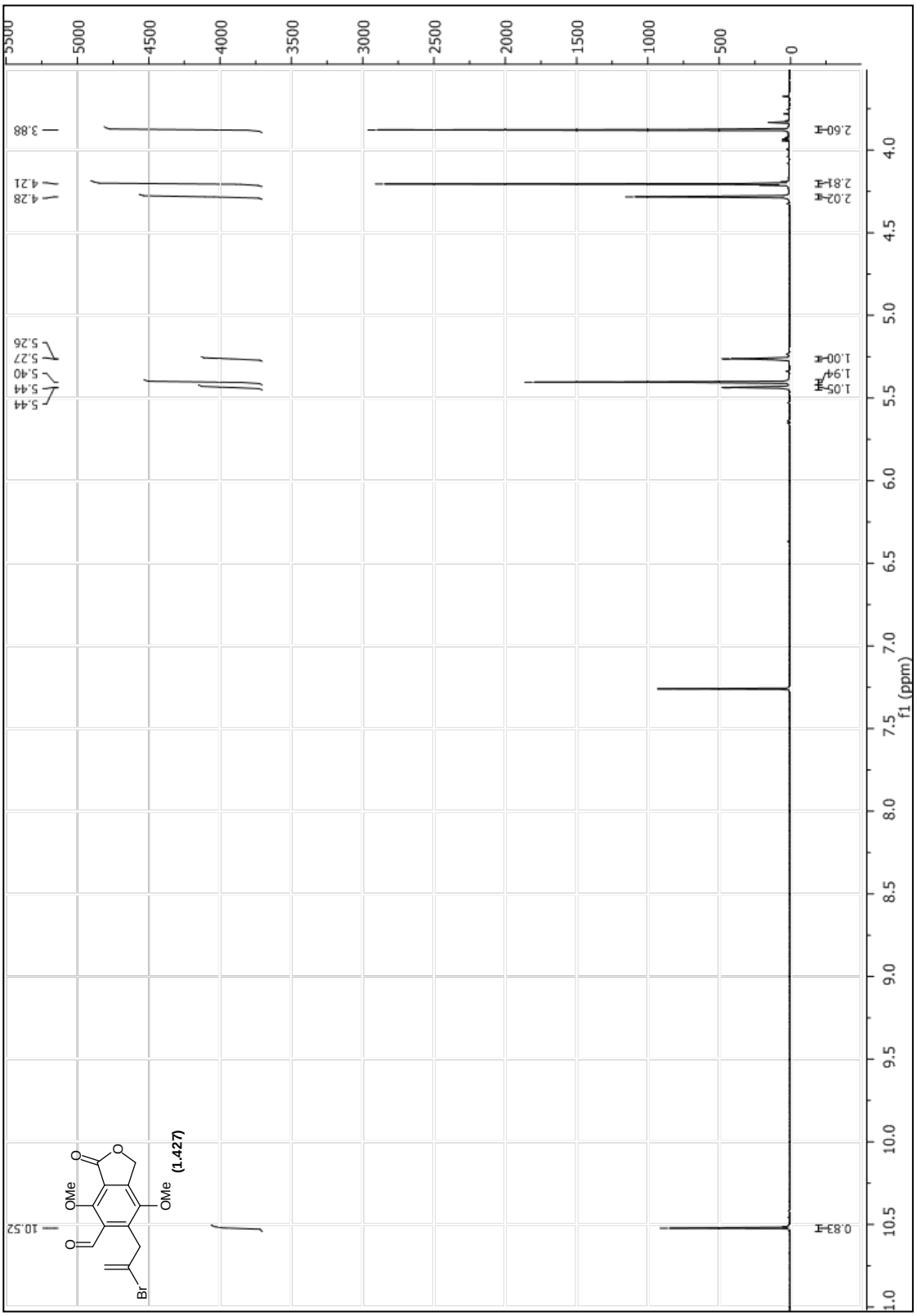
O(3)-C(8)	1.446(7)
O(4)-C(7)	1.204(7)
C(1)-C(6)	1.383(7)
C(1)-C(2)	1.389(8)
C(2)-C(3)	1.385(9)
C(3)-C(4)	1.383(7)
C(4)-C(5)	1.372(7)
C(4)-C(8)	1.504(7)
C(5)-C(6)	1.391(7)
C(5)-C(7)	1.491(8)

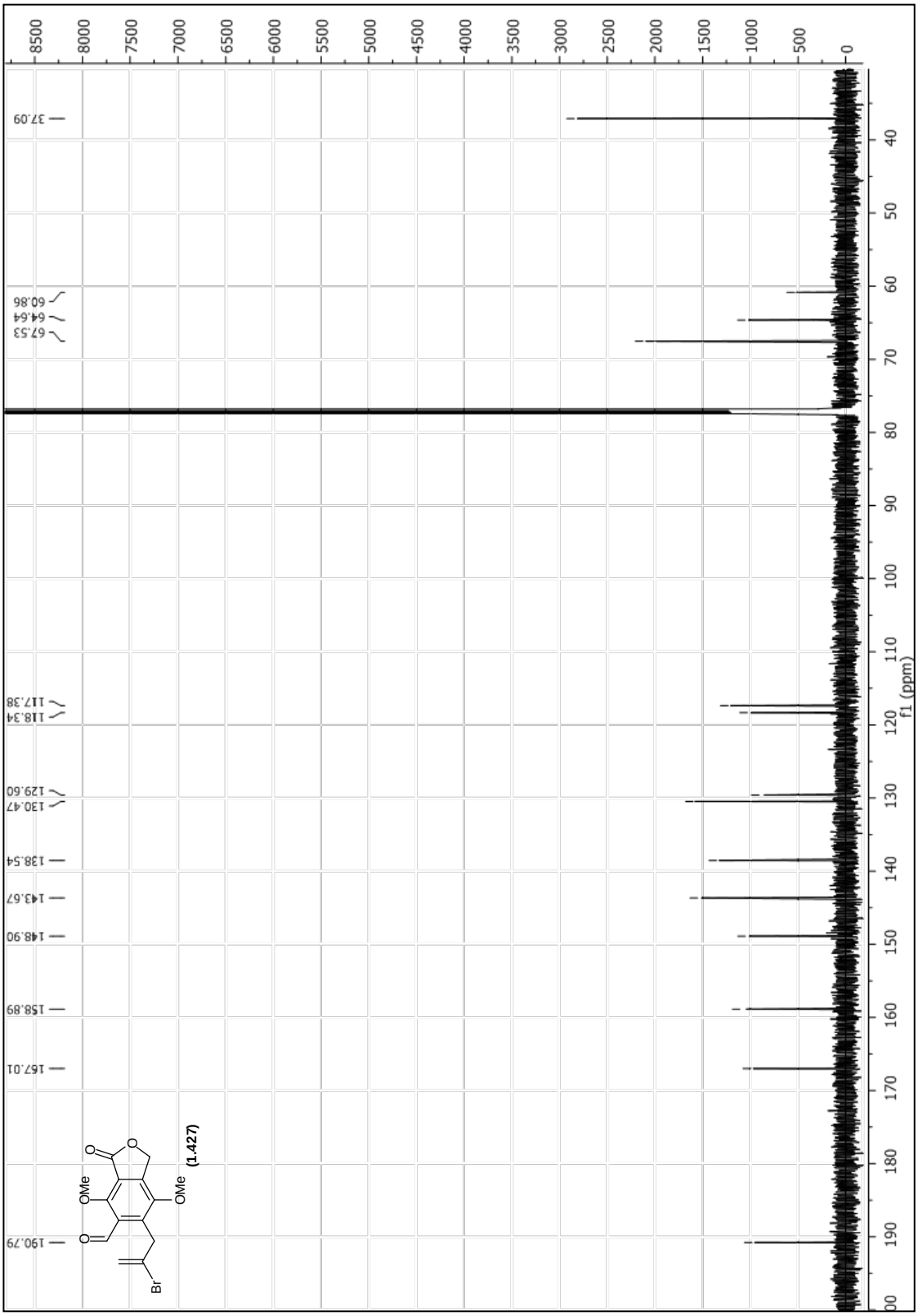
C(6)-O(1)-C(9)	115.9(4)
C(3)-O(2)-C(10)	117.7(5)
C(7)-O(3)-C(8)	111.0(5)
C(6)-C(1)-C(2)	122.7(5)
C(6)-C(1)-Br	119.1(4)
C(2)-C(1)-Br	118.2(4)
C(3)-C(2)-C(1)	120.5(6)
O(2)-C(3)-C(4)	116.8(5)
O(2)-C(3)-C(2)	125.8(5)
C(4)-C(3)-C(2)	117.4(5)
C(5)-C(4)-C(3)	121.2(5)
C(5)-C(4)-C(8)	109.7(4)
C(3)-C(4)-C(8)	129.1(5)
C(4)-C(5)-C(6)	122.7(5)
C(4)-C(5)-C(7)	107.2(5)
C(6)-C(5)-C(7)	130.0(5)
O(1)-C(6)-C(1)	120.7(5)
O(1)-C(6)-C(5)	123.8(5)
C(1)-C(6)-C(5)	115.4(4)
O(4)-C(7)-O(3)	120.5(5)
O(4)-C(7)-C(5)	131.3(5)
O(3)-C(7)-C(5)	108.2(5)
O(3)-C(8)-C(4)	103.9(4)

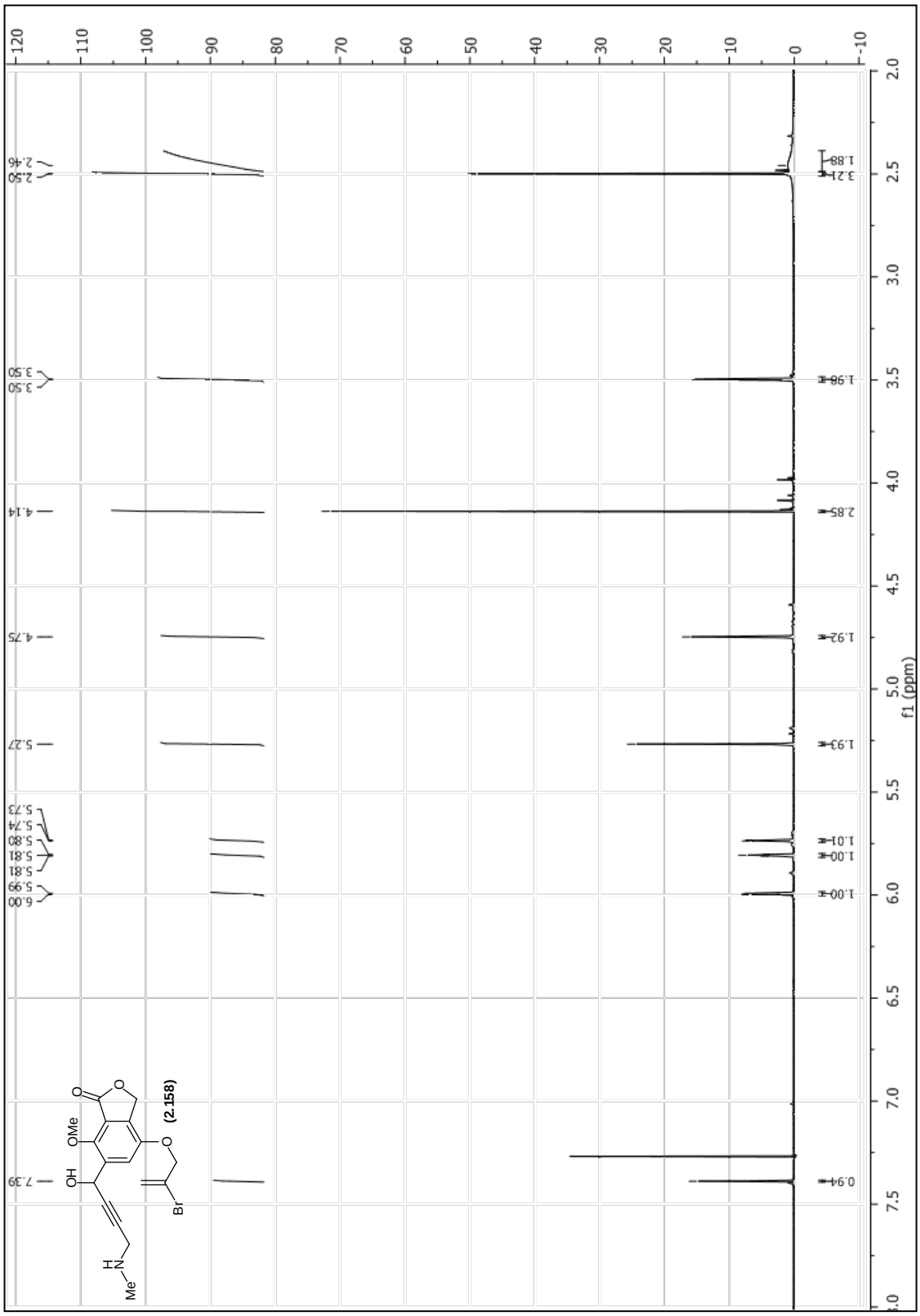
Appendix B: NMR Spectra

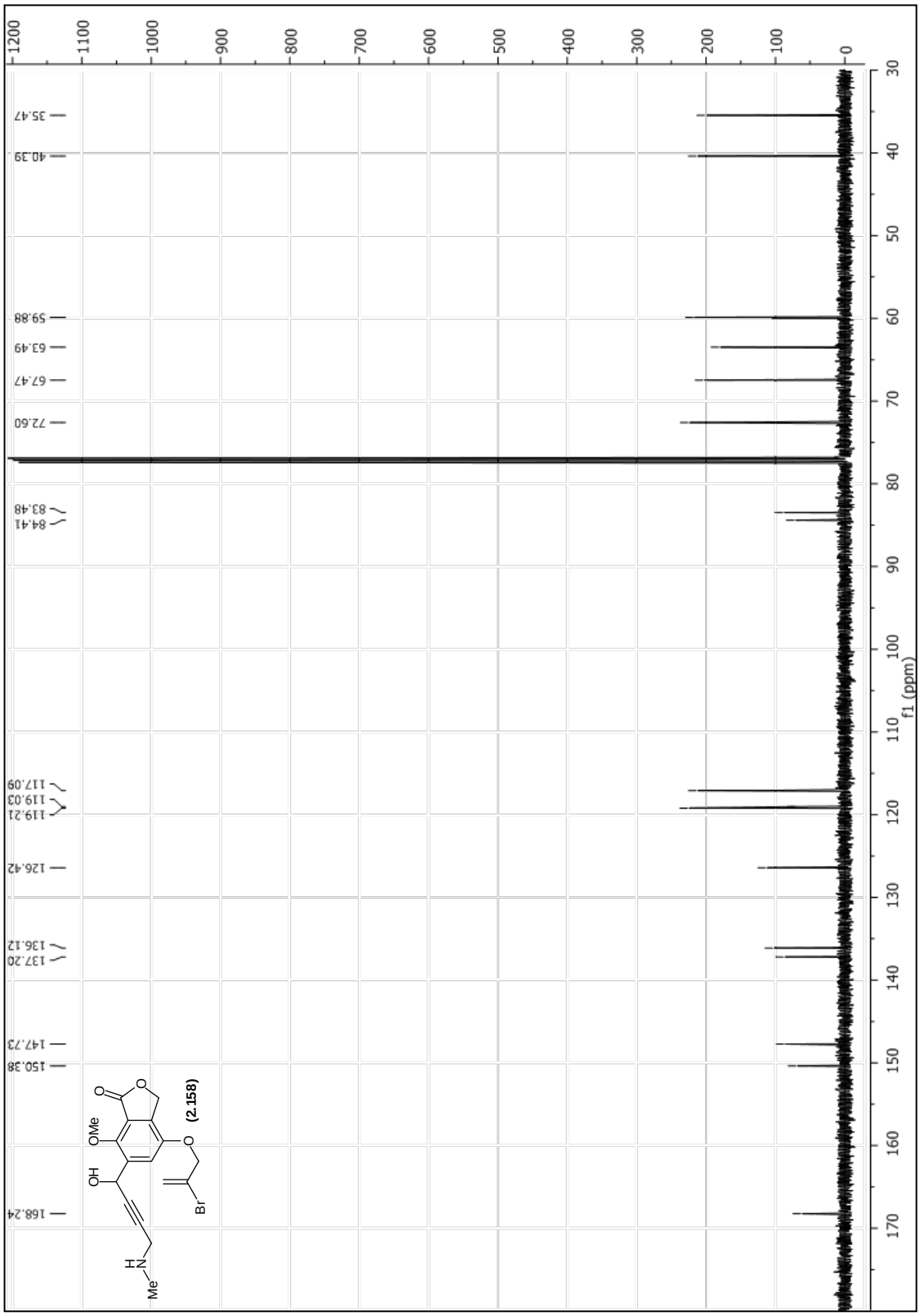

(2.163)
OPiv
OPiv
Br
f1 (ppm)

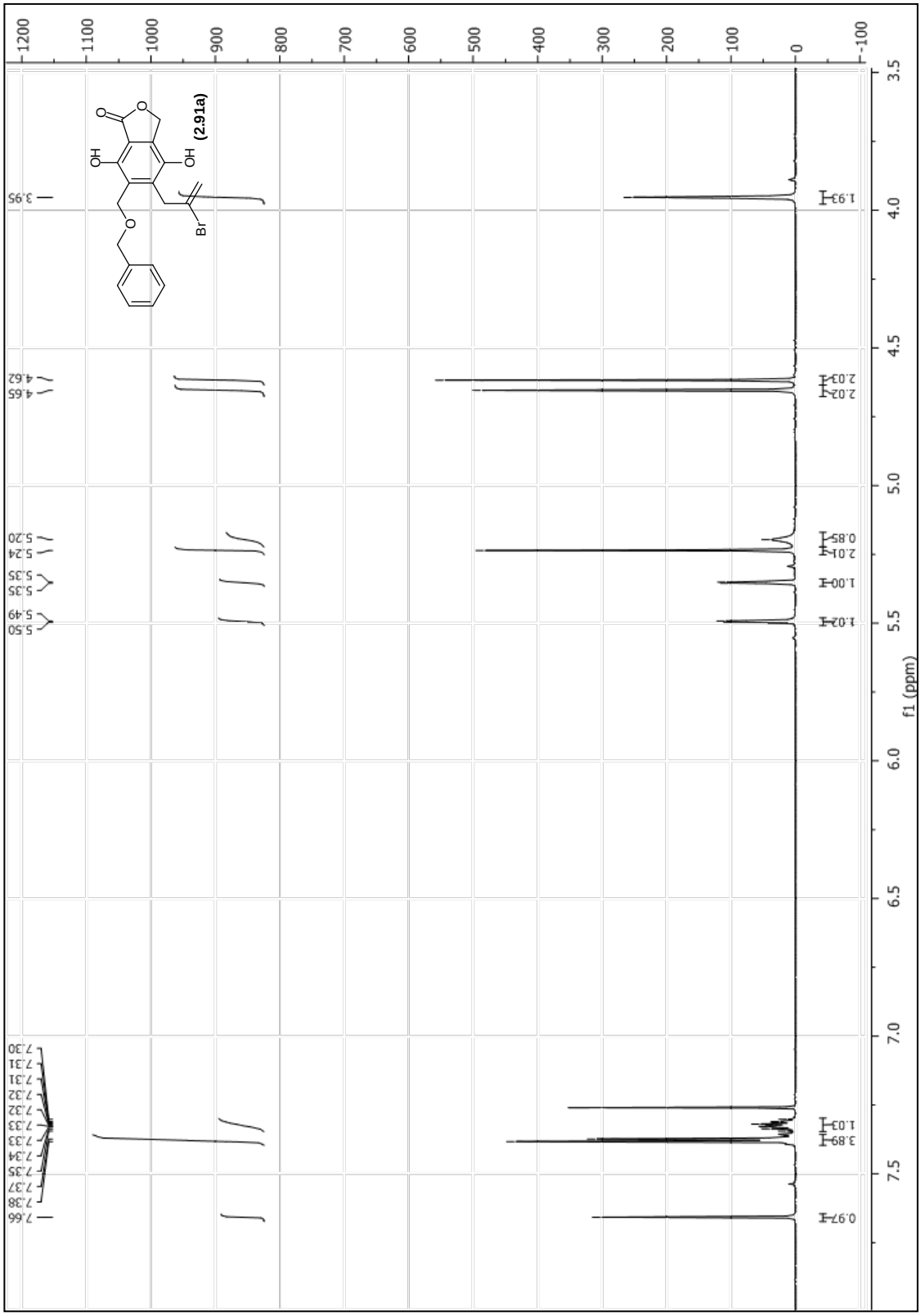

(2.163)
OPiv
OPiv
Br
27.27
37.52
39.73
39.82
67.39
76.91
77.16
77.41
118.25
119.94
128.19
129.20
138.41
142.11
145.37
150.16
166.02
175.27
175.90
187.65
f1 (ppm)

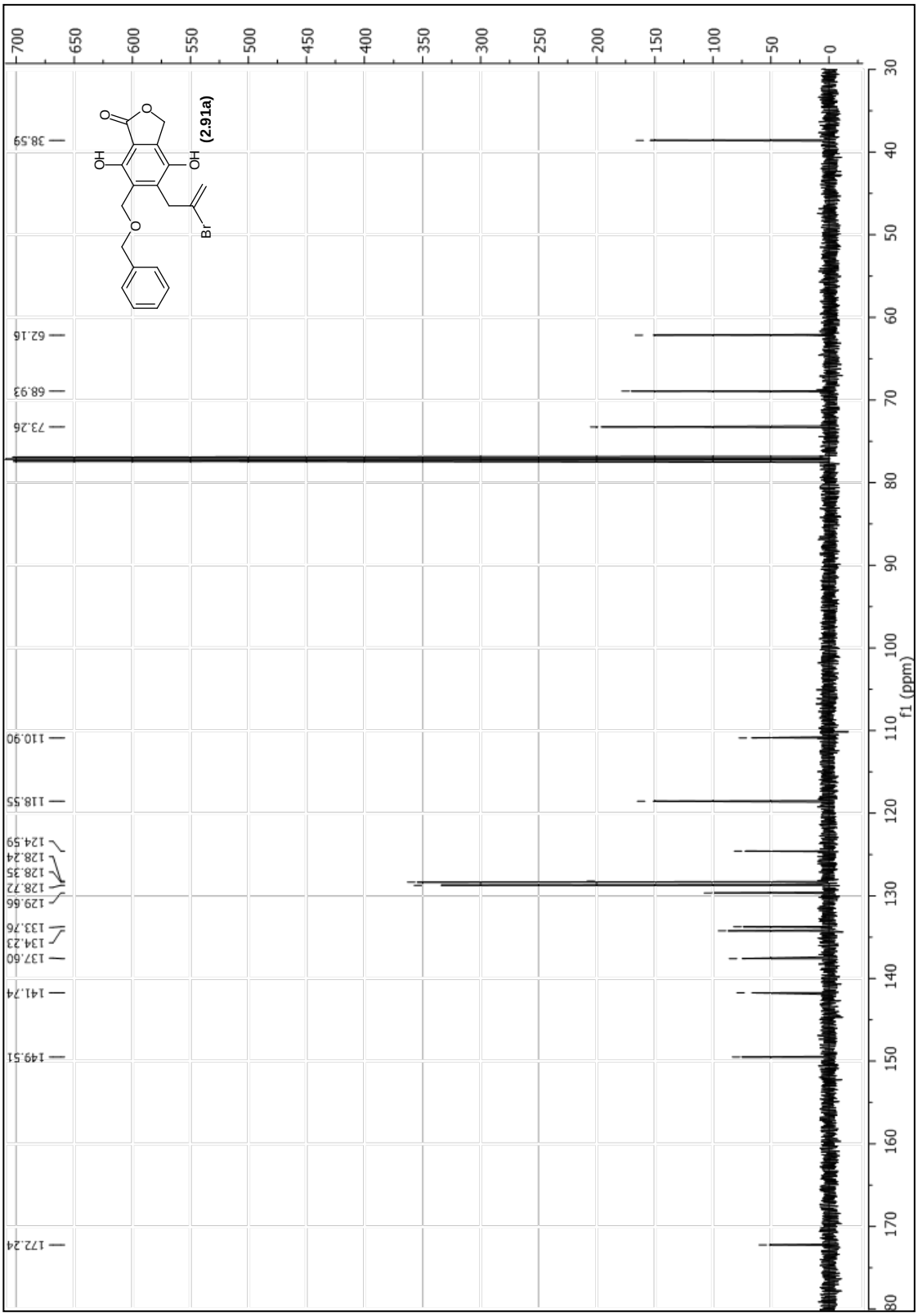

10.52
5.44
5.44
5.40
5.27
5.26
4.28
4.21
3.88
2.60
2.81
2.02
1.94
1.05
1.00
0.83
f1 (ppm)
OMe
OMe
Br
(1.427)


37.09
60.86
64.64
67.53
117.38
118.34
129.60
130.47
138.54
143.67
148.90
158.89
167.01
190.79
OMe
OMe
Br
O
O
O
(1.427)
f1 (ppm)


f1 (ppm)
(2.158)
OMe
OH
Br
Me
N
H


35.47
40.39
59.88
63.49
67.47
72.60
83.48
84.41
117.09
119.03
119.21
126.42
136.12
137.20
147.73
150.38
168.24
OMe
OH
Br
(2.158)
Me
f1 (ppm)


(2.91a)
OH
OH
O
O
Br
f1 (ppm)


(2.91a)
OH
OH
Br
O
O
O
38.59
62.16
68.93
73.26
110.90
118.55
124.59
128.24
128.35
128.72
129.66
133.76
134.23
137.60
141.74
149.51
172.24
f1 (ppm)