UNIVERSITY OF CALGARY

Preparation of Two Key Intermediates Towards the Synthesis of Viridin

by

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Preparation of Two Key Intermediates Towards the Synthesis of Viridin" submitted by Kristine M. Muller in partial fulfillment of the requirements for the degree of Master of Science.

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Abstract

The asymmetric construction of natural products continues to be a challenge for synthetic chemists. This dissertation describes the research pertaining to the synthesis of two key intermediates needed in the total synthesis of viridin.

The first key intermediate, a furan derivative, was synthesized in 8 steps in 30% overall yield. This synthesis employs methodology developed in the Keay laboratory, which uses a single silicon protecting group that is migrated multiple times throughout the synthesis for various purposes. The second key intermediate, an indane derivative, was synthesized convergently, in 10 steps with 5.8% overall yield. The key step in this synthesis is an Intramolecular Diels-Alder reaction of a Furan Diene in which the bridged Diels-Alder adduct aromatizes *in situ* to form an indane species in 54% yield.

Preface

The synthesis of enantiomerically pure natural products for their use as therapeutic agents still remains a challenge for the synthetic organic chemist. The Keay group has recently been interested in the biologically active, secondary metabolite viridin and its assembly through an asymmetric palladium-catalyzed polyene cyclization as the key step. This thesis will discuss the synthetic attempts that have been made towards this natural product.

Chapter one is divided into three sections. The first section will provide background on viridin including its discovery and biological properties. The second section will provide a review of the previous synthetic efforts on viridin and some related natural products. The third section will describe the project's objectives and illustrate the retrosynthetic approach that will be taken towards the synthesis of viridin.

Chapter two is divided into seven sections. Sections one and two will describe the two different approaches that were taken in the synthesis of a furan-containing key intermediate. Section three will describe the future work that still needs to be done on the furan portion of the molecule. Section four deals with the previous synthetic efforts towards an indane key intermediate. Section five explains the retrosynthetic approach that will be used in the synthesis of a similar indane derivative, literature precedence for the key step and the first approach that was used in the synthesis of a second key intermediate. Section six describes the alternative approach that was successful in the

synthesis of the key intermediate indane derivative while section seven provides conclusions and future work that needs to be completed.

Chapter three provides the experimental methods and procedures and also contains relevant characterization data.

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List of Abbreviations

δ	chemical shift
*	carbon-14 labeled
°C	degrees Celsius
^{13}C	carbon-13
^{19}F	fluorine-19
^{1}H	proton
9-BBN	9-borabicyclo[3.3.1]nonane
Å	angstrom
Ac	acetyl
amu	atomic mass unit
anal.	analysis
Ar	aryl group
atm	atmosphere
ATP	adenosine triphosphate
B	base
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
Bn	benzyl
bp	boiling point
bs	broad singlet
BTIB	bistrifluoroacetoxy iodobenzene
Bu	butyl
Bz	benzoyl

CAN	ceric ammonium nitrate
cat.	catalytic
CM	complex mixture
cm^{-1}	wavenumbers
conc.	concentrated
CSA	camphor sulphonic acid
d	days, doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
dec	decomposition
DEPT	distortionless enhancement by polarization transfer
DHP	dihydropyran
DHQ	dihydroquinone
DIBAL-H	diisobutylaluminum hydride
dioxane	1,4-dioxane
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dppf	bis(diphenylphosphino)ferrocene

ee	enantiomeric excess
equiv.	equivalents
Et	ethyl
g	grams
GC	gas chromatography
h	hours
H_o	Hammett acidity function
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
Hz	hertz
i	iso
IMDAF	intramolecular Diels-Alder of a furan diene
imid	imidazole
IR	infrared
J	coupling constant
k_1	first order rate constant
KHMDS	potassium hexamethyldisilazide
L	liters
LAH	lithium aluminum hydride
LDA	lithium diidopropylamide
LHMDS	lithium hexamethyldisilazide
LTBA	tri-*tert*-butoxyaluminohydride
LUMO	lowest unoccupied molecular orbital

m	*meta*
m	multiplet
M	molar
m/z	mass-to-charge ratio
MCC	multi component coupling
*m*CPBA	meta-chloroperoxybenzoic acid
Me	methyl
min	minutes
mol	moles
mp	melting point
MS	mass spectroscopy, molecular sieves
N	normal
n/a	not applicable
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*
p	pentet
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl

PI-3K	phosphatidylinositol-3-kinase
PM3	third parameterization of the modified neglect of differential overlap semiempirical modeling method
PMP	1,2,2,6,6-pentamethylpiperidine
PP	pyrophosphate
ppm	parts per million
PPTS	pyridinium paratoluenesulfonate
Pr	propyl
psi	pounds per square inch
py	pyridine
q	quartet
R	alkyl group
rt	room temperature
rxn	reaction
s	singlet
s^{-1}	reciprocal seconds
SEM	2-(trimethylsilyl)ethoxymethyl
SM	starting material
t	triplet, tertiary
TBAF	*tert*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Temp.	temperature
THF	tetrahydrofuran
THP	tetrahydropyran

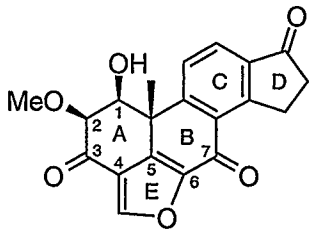
TIPS	triisopropylsilyl
TLC	thin layer chromatography
tm	transition metal
TMEDA	tetramethylethylene diamine
TMP	tetramethylpiperidine
TMS	trimethylsilyl
tol	toluene
TPAP	tetrapropylammonium perruthenate
Ts	toluenesulfonyl
vs.	versus
X	halide
	live long and prosper

Chapter 1

1.1.1 Introduction to Viridin

All organisms, plant and animal, need to synthesize, transform and interconvert a wide variety of organic compounds in order to live, grow and reproduce.[1] These processes can be divided into two metabolic pathways: primary metabolism and secondary metabolism. Primary metabolism, which is responsible for the production of carbohydrates, proteins, fats and nucleic acids, is essentially the same in all organisms and therefore demonstrates the fundamental similarity of all living matter. Secondary metabolism, in contrast, produces compounds that are limited to specific organisms or groups of organisms. These compounds are called secondary metabolites and define the individuality of the species. The purposes of these unique compounds are not always clear. However, some of them have shown significant physiological activity when introduced to other organisms such as humans. Secondary metabolites from fungal species are a source of structurally diverse and biologically active compounds. One such example is viridin (**1**), a secondary metabolite produced by the fungal species *Gliocladium virens*. This natural product was found to possess a pentacyclic steroidal framework containing a fused furan moiety. Other interesting characteristics include an angular methyl group, an aromatic C ring and a highly oxygenated A ring (Figure 1.1).

Figure 1.1 The Structure of Viridin



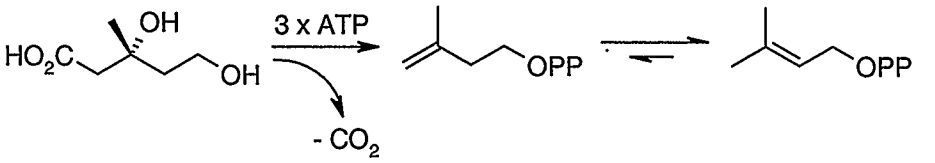
1

Due to its potent biological activity and distinctiveness of structure, viridin has been the focus of many studies. These include elucidation of the biosynthetic pathway,[2] biological testing[3] and, although a total synthesis has never been reported, several synthetic approaches have been published.[4,5] These topics will be discussed in the following sections.

1.1.2 Biosynthesis of Viridin

Formation of the dimethylallyl pyrophosphate (**4**) required in the biosynthesis of both steroids and terpenes, occurs by way of mevalonic acid (**2**), which is sequentially phosphorylated by ATP. This facilitates decarboxylation-elimination which produces isopentenyl pyrophosphate (**3**). Allylic isomerization of **3** provides dimethylallyl pyrophosphate (**4**) (Scheme 1.1).

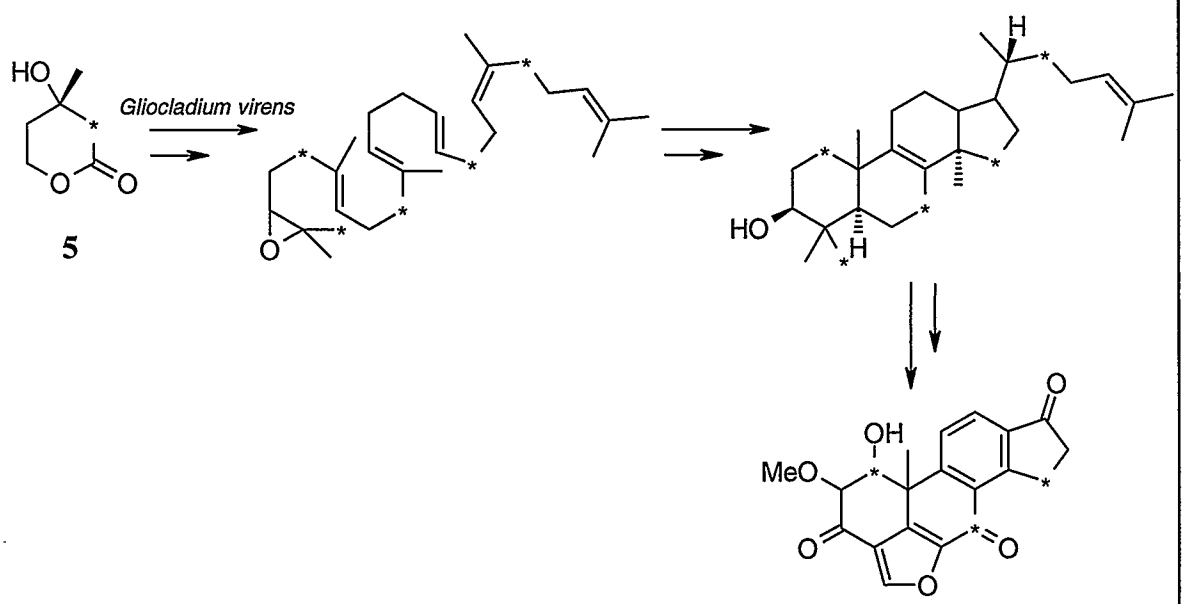
Scheme 1.1



2 **3** **4**

The biosynthesis of **1** was determined to be consistent with a triterpenoid/steroidal rather than a diterpenoid pathway.[2] [^{14}C]Viridin **6**, derived from [2-^{14}C] melvalonate (**5**) by a tail-to-tail condensation of two farnesyl units through a triterpenoid pathway (Scheme 1.2) would be expected to have a labeling pattern consistent with that of structure **6**. This labeling pattern was confirmed by oxidative degradation studies.[6]

Scheme 1.2



* = ^{14}C

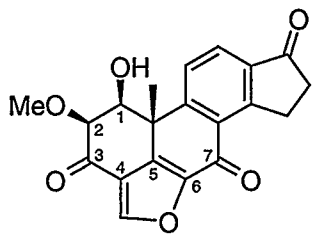
6

1.1.3 Viridin- Discovery and Biological Properties

Viridin was first isolated in 1945 from the fungal species *Gliocladium virens* by McGowan and Brian.[7] This was accomplished by first extracting the culture with chloroform. The organic extracts were concentrated *in vacuo* to produce an oily residue which was then recrystallized from methanol. The natural product was then purified by column chromatography using a strongly acidic alumina column to give both α and β-viridin. The α-isomer isolated from the benzene-ether eluant was recrystallized from methanol, then acetone and finally dilute acetic acid to yield fine colorless needles.[8]

Since its discovery, viridin has also been found in *Gliocladium flavofuscum*[9] and *Trichoderma viride.*[10] Its structure was first determined through nuclear magnetic resonance spectroscopy as well as unpublished chemical degradations.[11] Relative and absolute stereochemistries were later confirmed through x-ray crystallography.[12] Viridin has been classified as a furanosteroid and thus, has an IUPAC name of 1β-hydroxy-2β-methoxy-18-norandrosta-5,8,11,13-tetraeno(6,5,4-*bc*)furan-3,7,17-trione.

Figure 1.2 The IUPAC Name of Viridin

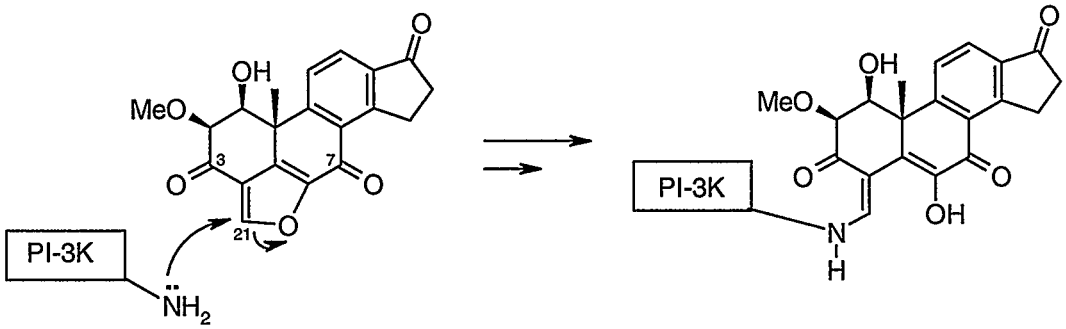


1-1β-hydroxy-2β-methoxy-18-norandrosta-5,8,11,13-tetraeno(6,5,4-*bc*)furan-3,7,17-trione

Viridin has been shown to exhibit both antibiotic and antifungal properties; however, much of the current research has been focused on its ability to act as a potent inhibitor of

the cell signaling enzyme phosphatidylinositol-3-kinase (PI-3K).[13] Excessive PI-3K activity has been associated with certain types of cancer including leukemia,[14] ovarian, and lung cancer.[15] This activity is believed to be due to a number of factors. First, it is believed that viridin inhibits PI-3K by covalent modification of the active site. This occurs by Michael addition of the ε-amino group of lysine-802 to the C21 position of the furan moiety of viridin, which has increased electrophilicity due to the presence of the carbonyl groups at the C3 and C7 positions. The furan ring is then opened to relieve the increased ring strain of the system.[13,16]

Scheme 1.3

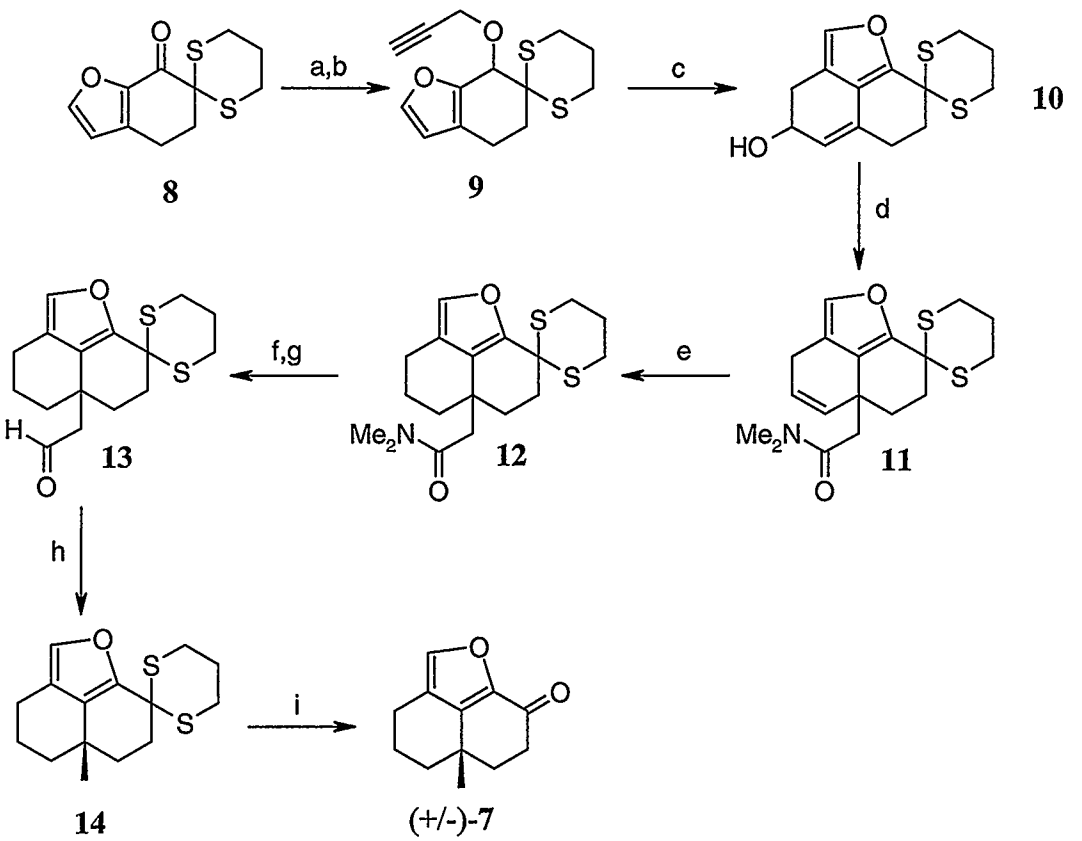


1.2.1 Previous Synthetic Efforts Towards Viridin

Viridin has been shown to exhibit extremely important biological activity and it is because of this that it has been the focus of much research attention. Although a total synthesis of viridin has continued to elude chemists, it still continues to be the focus of several synthetic attempts. Kanematsu *et al.*[4] published the synthesis of key intermediate **7**, which contains both the fused furan moiety and the angular methyl group. This synthesis was achieved starting from the dithioacetal derivative of 7-oxo-4,5,6,7-tetrahydro-1-benzofuran (**8**). The ketone was first reduced using LAH and subsequently

alkylated to yield **9**, which then underwent a furan ring transfer reaction[17] by treatment with excess KO*t*Bu in refluxing *t*BuOH. This resulted in the formation of an allenic intermediate (not shown) that underwent an intramolecular Diels-Alder reaction with the already present furan ring. The tricyclic intermediate **10**, containing the fused furan moiety, was obtained in 92% yield. The angular methyl group was then introduced into the system *via* a Claisen rearrangement. Treatment of allylic alcohol **10** with *N,N*-dimethylacetamide dimethyl acetal in refluxing xylenes gave rise to a [3,3]-sigmatropic rearrangement leading to **11** in 60% yield. The double bond was then reduced to yield **12**, with diimide formed from 2,4,6-triisopropylphenylsulphonylhydrazine.[18] The amide was reduced to the primary alcohol with Super-Hydride, and subsequently oxidized to aldehyde **13** using Collins reagent.[19] Decarbonylation was achieved using Wilkinson's catalyst[20] to obtain intermediate **14** containing the angular methyl group in 92% yield. Finally, oxidative cleavage of the dithioketal yielded the target compound **7** (Scheme 1.4).

Scheme 1.4



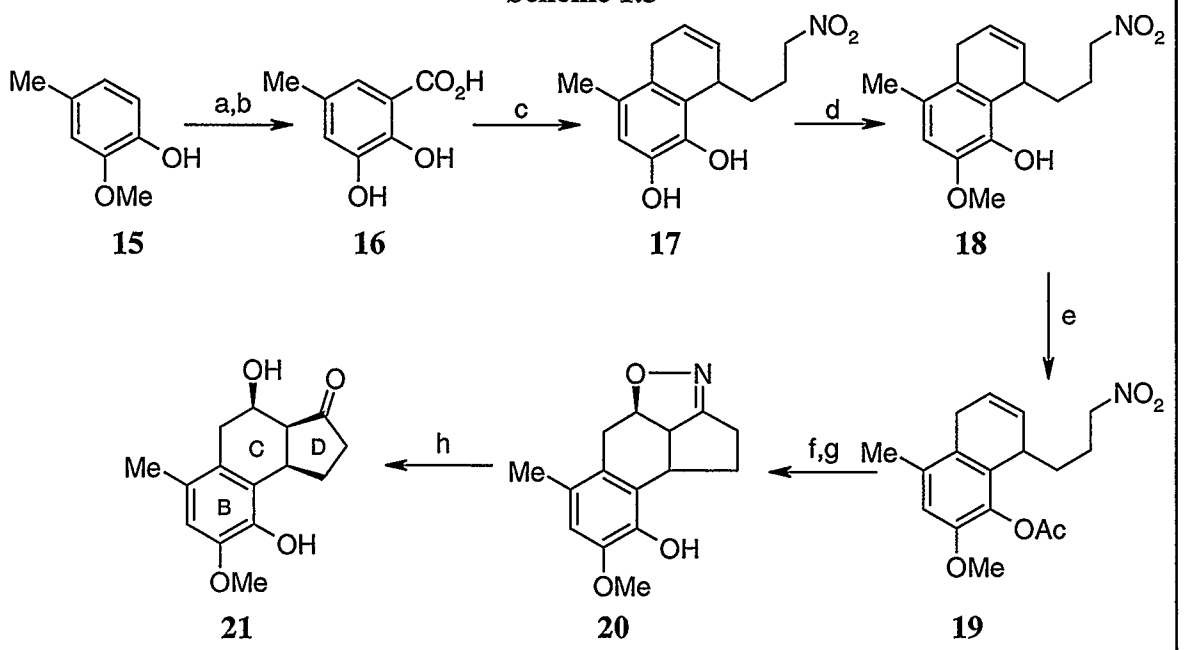
Conditions: a) LAH, THF, rt (>95%); b) *n*BuLi, HMPA, THF, then $CH{\equiv}CCH_2Br$ (82%); c) 10 equiv. KO*t*Bu, *t*BuOH, 83 °C, 30 min (92%); d) $Me_2NC(OMe)_2Me$, xylene, 140 °C, 30 min (60%); e) 2,4,6-triisopropylphenylsulphonylhydrazine, NEt_3, THF/MeOH, rt (100%); f) $LiEt_3BH$, THF, rt (90%); g) Collins reagent, CH_2Cl_2 (31%); h) $(Ph_3P)_3RhCl$, C_6H_6, 80 °C (92%); i) $Hg(ClO_4)_2$, THF (40%).

The synthesis of key intermediate **7**, which was prepared with nine steps in an overall yield of 4.4%, provided a fast and easy route to the fused furan ring system. This synthetic route incorporated both the fused furan moiety and the angular methyl group. It also incorporated novel key steps such as the furan ring transfer reaction. Unfortunately, this synthesis was not asymmetric and provided **7** as a racemic mixture.

Recently, Souza and Rodrigo[5] reported the synthesis of **26** containing the pentacyclic steroidal framework of viridin (Scheme 1.6). This synthesis involved nine

linear steps from 4-methylguaicol (**15**) (Scheme 1.5) and, unlike the previous approach, utilized successive cycloadditions involving *o*-benzoquinoid intermediates which are generated *in situ*. Carboxylic acid **16** was prepared from **15** using Kolbe-Schmitt carboxylation conditions[21] followed by demethylation. Upon treatment of **16** with an excess of 1-nitrohepta-4,6-diene in the presence of BTIB the intermediate (not shown) underwent a series of reactions. The compound was first oxidized to the *o*-quinone by BTIB, which then underwent a regiospecific Diels-Alder reaction. Decarboxylation of the β-keto acid adduct, followed by re-aromatization, produced dihydronaphthalene **17**. Compound **17** was selectively methylated to yield **18**, and the remaining hydroxyl group was acetylated to yield **19**. Compound **19** was then converted to the nitrile oxide, which underwent an intramolecular 1,3-dipolar cycloaddition[22] to produce isoxazoline **20**. The isoxazoline moiety was then catalytically hydrogenated to generate benzindanone **21**, an intermediate containing the B, C and D rings of Viridin (Scheme 1.5).

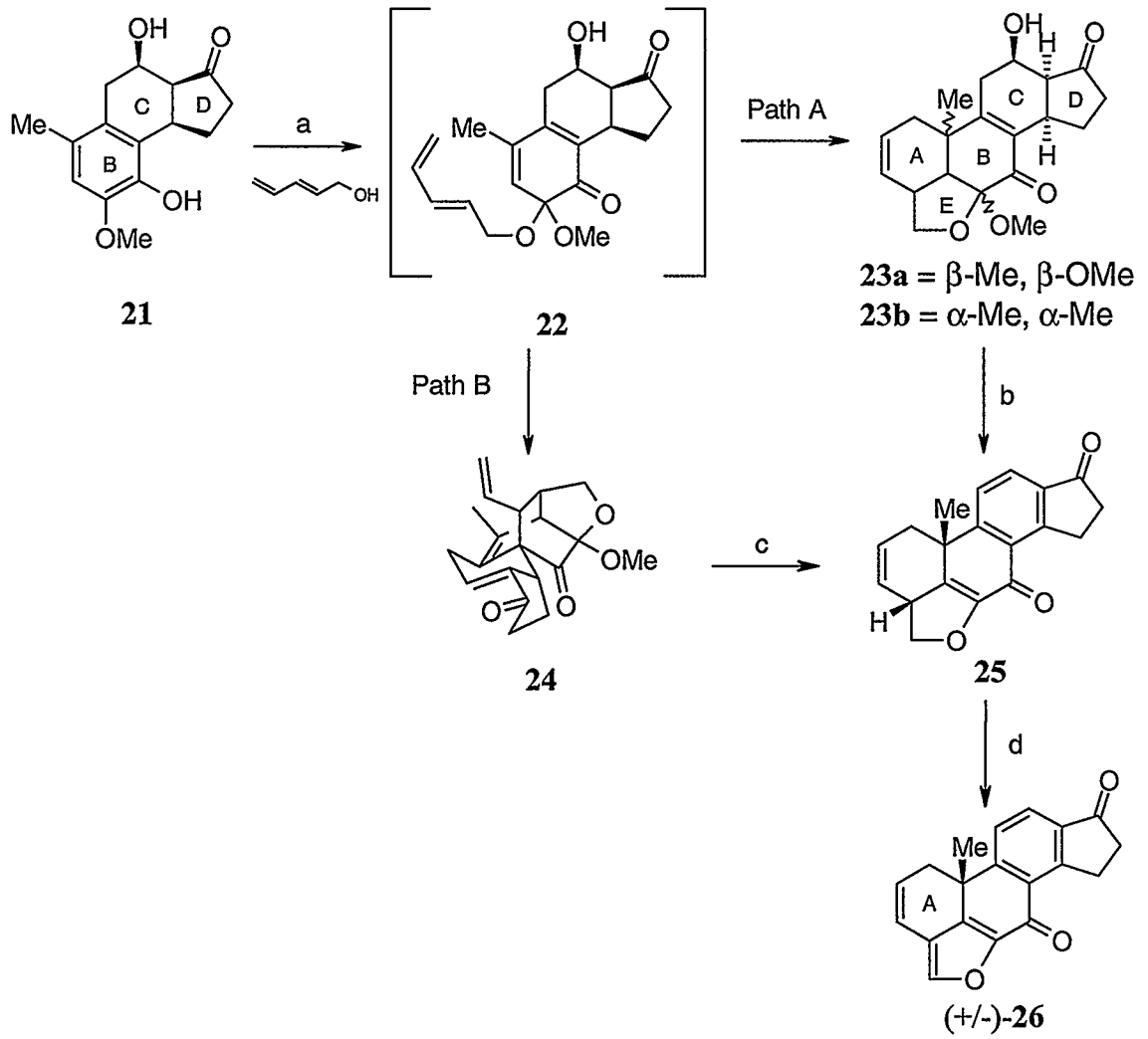
Scheme 1.5



Conditions: a) K_2CO_3, CO_2, 800 psi, 200 °C, 4 h; b) BBr_3, CH_2Cl_2, -78 °C to rt (72%, 2 steps); c) 5 equiv. 1-nitrohepta-4,6-diene, BTIB, THF (86%); d) K_2CO_3, Me_3OBF_4, CH_2Cl_2 (100%); e) Ac_2O, py; f) *p*-ClC_6H_4NCO, NEt_3, C_6H_6, rt, 36 h; g) NaOH, THF/H_2O (84%, 3 steps); h) H_2, Pd/C, H_3BO_3, $MeOH/THF/H_2O$ (100%).

The A and E rings of the pentacyclic steroidal framework were then introduced *via* the *o*-benzoquinone monoketal procedure; a method developed by Rodrigo *et al.*[23] Treatment of **21** with BTIB followed by the addition of excess penta-2,4-dienol produced monoketal **22** *in situ*, which subsequently reacted by both possible intramolecular Diels-Alder pathways to produce a 1:1 mixture of inseparable *endo* adducts **23a** and **23b** as well as bridged adduct **24**. The *endo* adducts **23a** and **23b** were aromatized upon treatment with *p*-TsOH in benzene with exposure to air to form **25**. The bridged adduct **24** was also easily converted to **25** *via* a Cope rearrangement. Finally, dehydrogenation of the dihydrofuran moiety was achieved by refluxing in xylenes in the presence of *p*-chloranil (Scheme 1.6).

Scheme 1.6

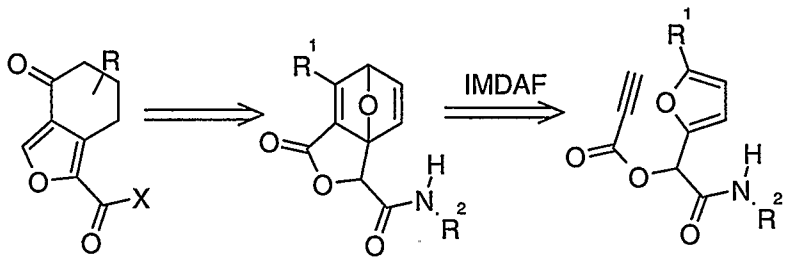


Conditions: a) BTIB, THF (Path A: 33%, Path B: 31%); b) *p*-TsOH, C_6H_6, 45 °C, 4 h (50%); c) $Cl_2CHCHCl_2$, reflux, 2 d (65%); d) *p*-chloranil, xylenes, reflux, 36 h (60%).

This synthesis of **26** is an extremely important contribution to the assembly of the pentacyclic steroidal framework of viridin simply because it was the first successful attempt reported in the literature. In addition to making **25** available in sufficient quantity, it was a fast and simple synthesis; however many problems still must be overcome. The authors reported that functionalization of the A ring in **26** could not be achieved using the double bond. This synthesis was also plagued by low diastereoselectivities and, most importantly, it only provided **26** as a racemic mixture.

Wright *et al.*[24] recently completed the synthesis of oxabicyclo[2.2.1]heptadiene derivatives containing the fused furan moiety **27** (Scheme 1.7). These studies were directed toward the synthesis of simplified analogues of viridin, similarly deactivated by carbonyl groups at C3 and C7, and only incorporated the features required to covalently modify the active site of the PI-3K enzyme. The retrosynthesis of **27** provided **29a-e** as a starting material for the preparation of **27** through an intramolecular Diels-Alder reaction of a furan diene (IMDAF).

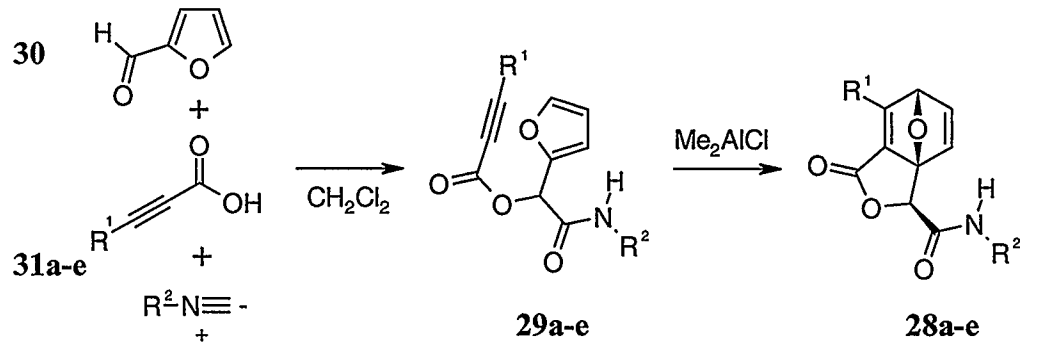
Scheme 1.7



27 **28a-e** **29a-e**

These analogues were prepared using a modified Passerini multi-component coupling (MCC) approach which involved mixing furfural (**30**), acetylenic acid **31a-e** and an isonitrile (**32**).[25] This approach efficiently generated acetylenic esters **29a-e** which underwent IMDAF to produce bicyclic fused systems **28a-e**. The results of the various oxabicyclo[2.2.1]heptadiene products are displayed in Table 1.1. These results indicate that there was moderate to good yield of all the MCC products and subsequent IMDAF reactions. A notable exception was product **29e** which underwent decomposition upon treatment with Me_2AlCl.

Table 1.1: Synthesis and Yields of Oxabicyclo[2.2.1]heptadiene Derivatives



SM	R^1	R^2	MCC Product	MCC Yield (%)	IMDAF Product	IMDAF Yield (%)
31a	Me	Bn	**29a**	86	**28a**	77
31b	Ph	*t*Bu	**29b**	79	**28b**	72
31c	Ph	*t*Bu	**29c**	69	**28c**	68
31d	Me	*t*Bu	**29d**	82	**28d**	72
31e	H	Bn	**29e**	79	**28e**	dec.

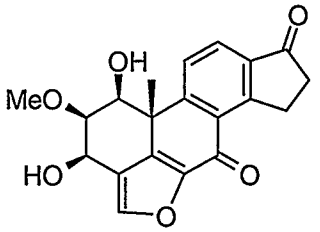
IMDAF products **28a-e** were synthesized with the intent of forming simplified analogues of viridin by aromatization to generate **27**. To date, these attempts have been unsuccessful and are currently under investigation.

1.2.2 Related Natural Products

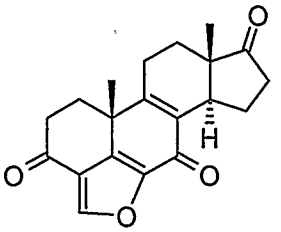
A number of natural products containing similar ring skeletons to viridin have been isolated from the various fungal species previously mentioned. Some of these natural products included viridiol (**33**),[26] virone (**34**),[27] and wortmannin (**35**),[28] which are shown in Figure 1.2. Viridiol, which differs from viridin only by the presence of the β-hydroxy group at the C3 position, is a phytotoxin and, when employed in small quantities, has been used to treat various plant and tree diseases.[29] Wortmannin, in addition to being an anti-fungal metabolite, has also shown very strong anti-inflammatory properties;[30]

however, its high toxicity in humans has limited its development clinically.[31] Recently, wortmannin has also shown powerful inhibition of the PI-3K enzyme. The activity of wortmannin is even more potent than that of viridin. Due to this increased biological activity, wortmannin has also been the target of syntheses.[32,33]

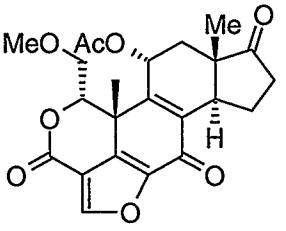
Figure 1.2 Related Natural Products



33 viridiol



34 virone



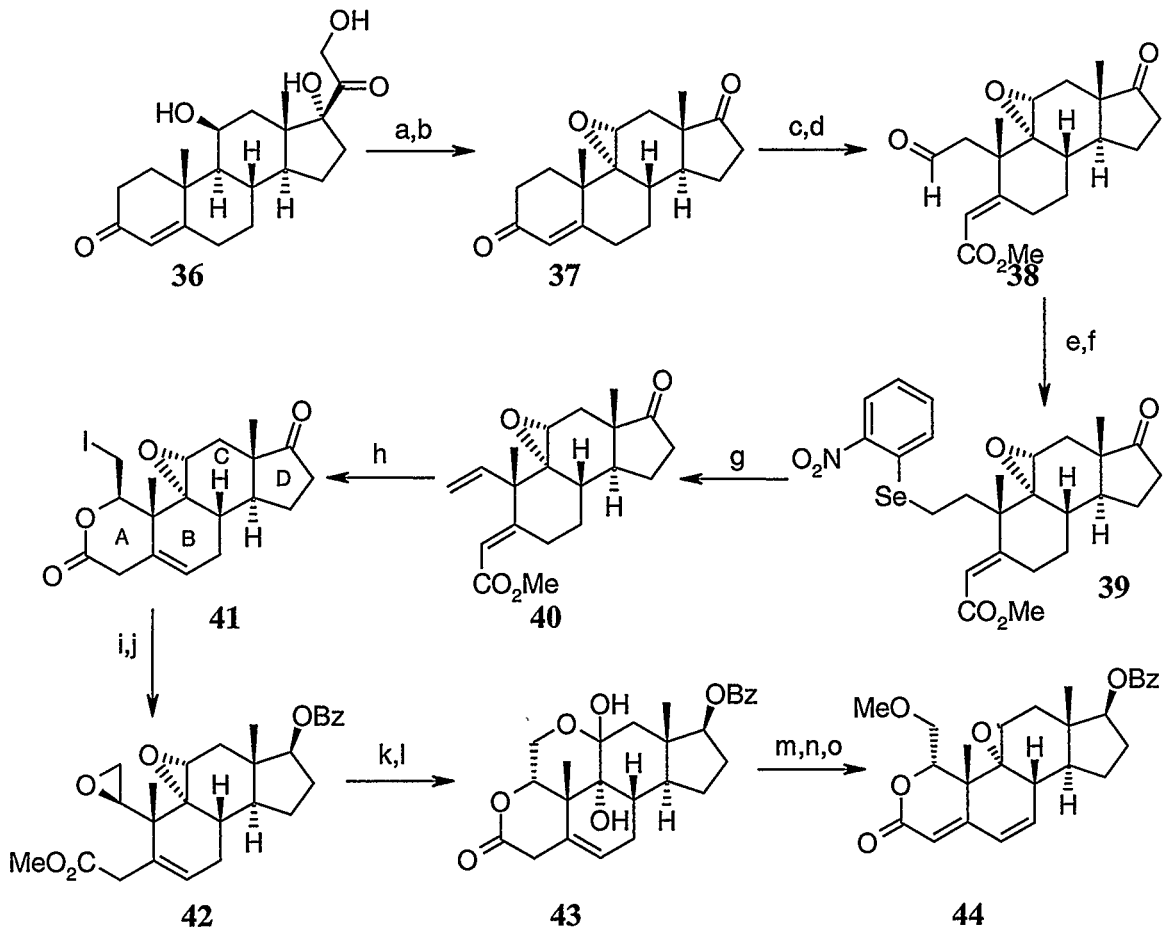
35 wortmannin

1.2.3 Synthesis of Related Natural Products

Attempts at synthesizing wortmannin have fared better than the efforts towards the synthesis of viridin. The first chemical synthesis of wortmannin was published in 1996 by Shibasaki *et al.*[32] The synthesis of **35** was achieved starting from commercially available, optically pure hydrocortisone (**36**) and was carried out in thirty-four linear steps with 0.12% overall yield. Highlights of this synthesis include conversion of **36** to produce **40**, the precursor to their key step, a stereoselective lactonization to construct the lactone functionality of the A ring. Compound **40**, when treated with I_2 and $NaHCO_3$ generated the undesired β-iodolactone **41** quantitatively. As a result, the iodolactone was treated with NaOMe and MeOH to create epoxide **42**, and the ketone functionality was reduced and protected as the benzoate to produce **42**. The stereochemistry at the chiral center was then inverted by treatment of **42** with DHQ and CSA in refluxing benzene.

This yielded the unsaturated cyclic ether containing the correct stereocenter, which was then hydroxylated to give **43**. The first 21steps of the synthesis are shown in Scheme 1.8.

Scheme 1.8

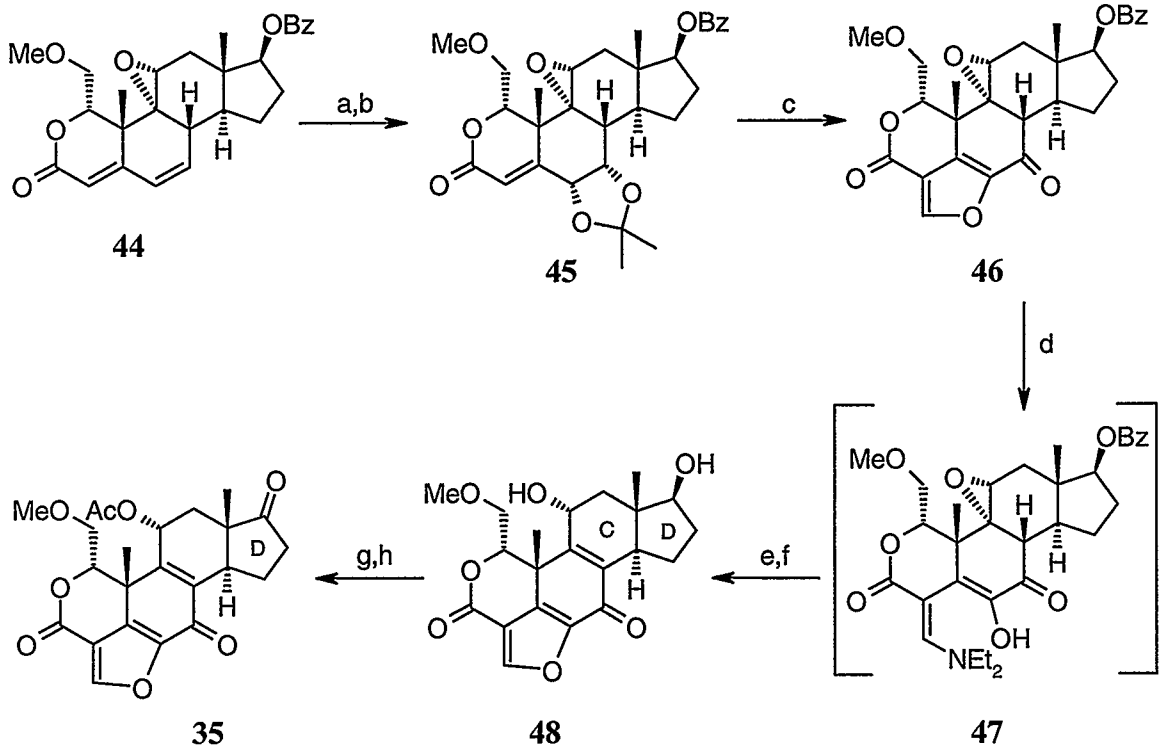


Conditions: a) (i) $NaBH_4$, CH_2Cl_2/EtOH(1:1), -10 °C then $NaIO_4$, rt, 1 d; (ii) TsOH, C_6H_6, reflux, 1 d (90%, 2 steps); b) *m*CPBA, CH_2Cl_2, -20 °C to 0 °C, 1 d (80%); c) (i) TMSOTf, iPr_2NEt, CH_2Cl_2, -78 °C, 30 min; (ii) *m*CPBA, $KHCO_3$, CH_2Cl_2, -25 °C, 1 h; (iii) citric acid, MeOH, 0 °C to rt, 1 h (55%, 3 steps); d) (i) $NaIO_4$, MeOH/H_2O (1:2), 0 °C, 12 h; (ii) CH_2N_2, $CHCl_3$, rt (83%, 2 steps); e) LTBA, THF, -78 °C to –35 °C, 4 h (71%); f) *o*-nitrophenyl selenocyanate, PBu_3, THF, 0 °C to rt, 1 h (89%); g) 30% H_2O_2, THF, 0 °C to rt, 18 h (85%); h) I_2, $NaHCO_3$, CH_2Cl_2, rt, 2 d (100%); i) NaOMe, MeOH, 0°C to rt, 4 h (90%); j) (i) LTBA, THF, 0 °C, 3 h; (ii) BzCl, py, 0 °C to rt, 2 h (94%, 2 steps); k) CSA, DHQ, C_6H_6, reflux, 3 h (56%); l) (i) *m*CPBA, CH_2Cl_2, -30 °C, 20 h; (ii) 2N HCl, THF, rt, 16 h (61%, 2 steps); m) (i) $Me_4NBH(OAc)_3$, AcOH/CH_3CN (1:1), 0 °C, 2 h; (ii) DDQ, dioxane, 80 °C, 4 h (68%, 2 steps); n) Ag_2O, MeI/CH_3CN (2:1), rt, 1 d (94%); o) MsCl, NEt_3, CH_2Cl_2, rt (92%).

With **44** in hand, the highly reactive furanocyclohexadienone moiety was then constructed. Epoxide **44** was subjected to dihydroxylation followed by the protection as

the acetal to produce **45**. Subsequent treatment of **45** with tris(dimethylamino)methane in the presence of DBU and N,N-dimethylformamide dimethyl acetal gave the aminomethylene-lactone, which was subjected to hydrolysis and subsequent oxidation to produce **46**. Compound **46** was again transformed into the aminomethylene-lactone upon treatment with $NHEt_2$ to give **47,** which was then treated *in situ* with DBN and hydrolyzed. The furan ring was again opened with $NHEt_2$ and the benzoate functionality removed with K_2CO_3 in MeOH. Exposure to 1N HCl gave intermediate **48**. The hydroxyl moiety on the C ring was then acetylated and the remaining hydroxyl group on the D ring oxidized by PCC to produce target compound **35**. This synthetic sequence is depicted in Scheme 1.9.

Scheme 1.9



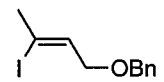
44 **45** **46** **47** **48** **35**

Conditions: a) OsO_4, DABCO, THF, -40 °C, 1 d (47%); b) PPTS, 2,2-dimethoxypropane, CH_2Cl_2, rt, 16 h (92%); c) (i) DBU, $Me_2NCH(OMe)_2/CH(NMe_2)_3$ (1:4), 100 °C, 1 h; (ii) 2N HCl, THF, rt, 20 h; (iii) PCC, CH_2Cl_2, rt, 5 h (11%, 3 steps); d) $NHEt_2$, CH_2Cl_2, rt, 20 min; e) (i) DBN, CH_2Cl_2, rt, 6 h; (ii) 1N HCl, THF, rt, 14 h (36%, 3 steps); f) (i) $NHEt_2$, CH_2Cl_2, rt, 10 min; (ii) K_2CO_3, MeOH, rt, 5 h; (iii) 1N HCl, THF, rt, 12 h (64%, 3 steps); g) Ac_2O, py, -20 °C, 12 h (49%); h) PCC, CH_2Cl_2, rt, 2 h (72%).

This synthesis has several obvious drawbacks. First, it is extremely impractical since it is a long multi-step linear sequence. It also has a very low overall yield (*vide supra*). Second, it is not a true total synthesis as it employs hydrocortisone as the starting material. Finally, it is not asymmetric in nature. This method of synthesis employs the "Chiral Pool"[34] approach which uses commercially available optically pure starting materials and transforms them through diastereoselective reactions to enantiopure product.

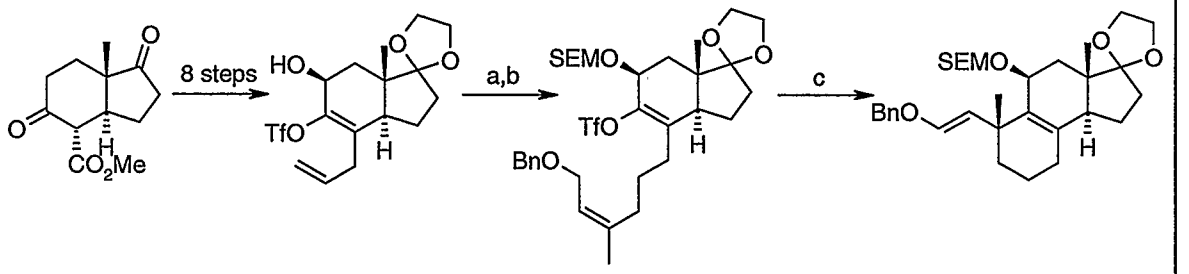
The first total asymmetric synthesis of (±)-wortmannin was achieved in 2002 by Shibasaki *et al.*[33] This approach employed an intramolecular Heck reaction to form an allylic quaternary carbon center and a diosphenol Claisen rearrangement as the two primary key steps. The total synthesis began with compound **50** which was obtained as a racemate in eight steps from **49**.[35] The secondary alcohol was first protected as the SEM ether and the resulting protected ether was coupled *via* an *in situ* Suzuki reaction with vinyl iodide **51** (Figure 1.3) to produce **52**. The first key step, the intramolecular Heck reaction, was carried out by treatment of **52** with 10 mol% $Pd(OAc)_2$, 22 mol% 1,3-bis(diphenylphosphanyl)propane, 1.0 equiv. Bu_2NBr, and 2.5 equiv. K_2CO_3. Enol ether **53** was obtained in 65% yield with an excellent diastereoselectivity of 18:1 β-Me:α-Me (Scheme 1.10).

Figure 1.3 Vinyl Iodide 51



51

Scheme 1.10



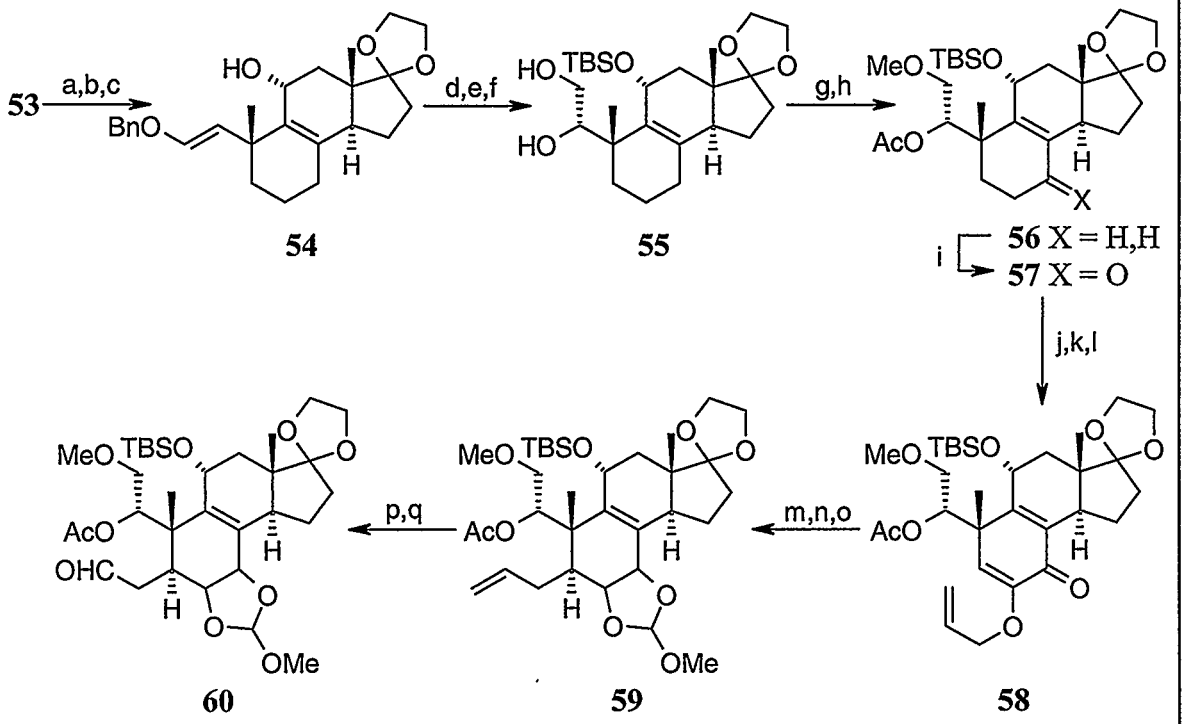
49 **50** **52** **53**

Conditions: a) SEMCl, 2,6-lutidine, Bu_4NI, CH_2Cl_2, 40 °C (87%); b) 9-BBN, THF, rt then **51**, $[PdCl_2(dppf)]$, K_2PO_4, THF/DMF, 60 °C (64%); c) 10 mol% $Pd(OAc)_2$, 22 mol% 1,3-bis(diphenylphosphanyl)propane, 1.0 equiv. Bu_2NBr, 2.5 equiv. K_2CO_3, tol., 100 °C, 17 h (65%).

Removal of the SEM group followed by oxidation and stereoselective reduction produced the α-allylic alcohol **54**. The allylic alcohol was then protected as the TBS ether. Treatment of the silyl ether with OsO_4 yielded the hydroxyaldehyde, which was reduced *in situ* with LAH to generate the desired diol **55**. The primary alcohol was then selectively methylated, and the remaining secondary alcohol was acetylated to produce **56**. Allylic oxidation of **56** was achieved using 15 equiv. CrO_3 in the presence of 3,5-dimethylpyrazole to generate α,β-unsaturated ketone **57**. A diosphenol-Claisen rearrangement was then used to introduce a carbon unit at the sterically hindered neopentyl position. Enone **57** was converted to **58** via five successive transformations. The enone was first converted to the silyl enol ether, which was in turn oxidized using dimethyldioxirane. The TMS group was then removed to give the α-hydroxyketone. The α-hydroxyketone was oxidized to a mixture of diosphenol and α-diketone which was allylated using allyl bromide. The Claisen rearrangement then proceeded smoothly under thermal conditions to yield the α-diketone as a single diastereomer. The α-diketone was reduced to the diol as an inseparable mixture of diastereomers which were then protected

as the cyclic acetal **59**. The terminal olefin of **59** was then cleaved *via* formation of the diol, followed by oxidative cleavage to generate aldehyde **60** (Scheme 1.11).

Scheme 1.11

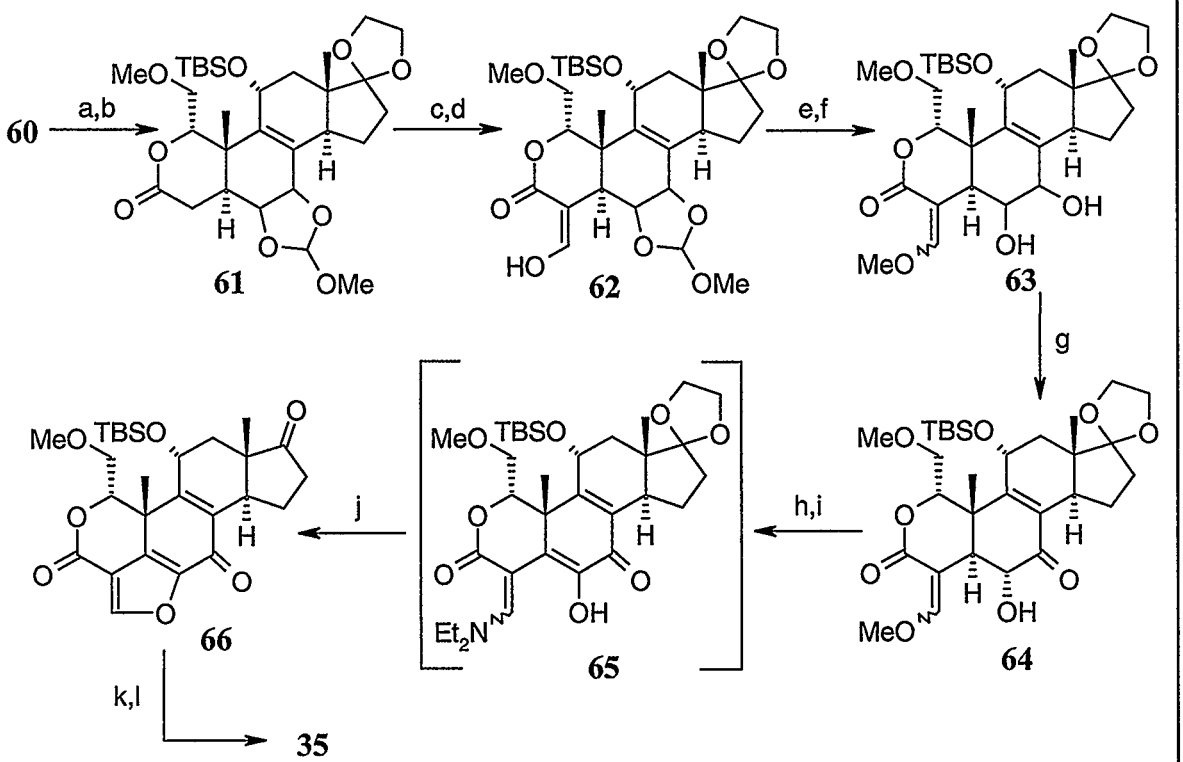


Conditions: a) CsF, DMF, 130 °C; b) PDC, NaOAc, CH_2Cl_2, rt; c) DIBAL-H, tol, -78 °C (45%, 3 steps); d) TBSCl, imid., DMF, rt; e) OsO_4, NMO, acetone/H_2O, rt; f) LAH, THF, -40 °C (42%, 2 steps); g) MeI, Ag_2O, rt; h) Ac_2O, DMAP, py., CH_2Cl_2, rt (90%, 2 steps); i) CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, -20 °C; j) i) TMSOTf, Hunig base, CH_2Cl_2, -78 °C; ii) dimethyldioxirane, acetone, rt; iii) PPTS, MeOH, rt; k) $(COCl)_2$, DMSO, CH_2Cl_2, NEt_3, -40 °C; l) allyl bromide, K_2CO_3, acetone, 40 °C (67%, 3 steps); m) xylene, 200 °C, 50 min; n) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C; o) $CH(OMe)_3$, PPTS, rt (67%, 3 steps); p) OsO_4, NMO, CH_3CN/H_2O, rt; q) Bu_4NIO_4, $CHCl_3$, 40 °C (59%, 2 steps).

The acetyl group of **60** was then removed, leading to formation of the hemi-acetal intermediate (not shown). This intermediate was subsequently oxidized to lactone **61**. The carbon unit needed for the formation of the furan ring was then introduced using the same method used as the previously described synthesis of **35** (Scheme 1.9). Treatment of **61** with $HC(NMe_2)_3$ followed by aqueous acidic workup produced β-hydroxyenone **62** in good yield. Conversion of the enol to the methyl ether and deprotection of the 1,2-diol occurred simultaneously to yield **63**, which was subsequently oxidized to **64**. A

Swern oxidation of the major diastereomer produced the diosphenol which was then treated with Et_2NH. These conditions not only promoted the desired cyclization to form the furan ring, but also simultaneously deprotected the acetal to yield **66**. The final step in the synthetic sequence was cleavage of the TBS ether, followed by treatment with Ac_2O to form **35** (Scheme 1.12).

Scheme 1.12



Conditions: a) K_2CO_3, MeOH, rt; b) TPAP, NMO, 4Å MS, CH_2Cl_2, rt (75%, 2 steps); c) $HC(OMe)_3$, DMF, 100 °C; d) phosphate buffer (pH 4 –5), THF, rt (72%, 2 steps); e) Me_2SO_4, K_2CO_3, acetone, rt; f) 1N NaOH, THF, rt (78%, 2 steps); g) PDC, NaOAc, CH_2Cl_2, rt, (71%); h) $(COCl)_2$, DMSO, CH_2Cl_2, NEt_3, -20 °C (75%); i) Et_2NH, CH_2Cl_2, rt; j) 1N HCl, THF, rt (60%); k) $3HF{\cdot}NEt_3$, THF, 40 °C; l) Ac_2O, py., rt (31%, 2 steps).

This synthesis was the first total synthesis of a natural product from the viridin family; however, several issues must still be addressed. This is an extremely long and linear synthesis containing over forty steps with an overall yield of 0.016%. Also,

several of the steps have low stereoselectivities which must be improved before this synthesis could be practical.

1.2.4 Conclusions

When reviewing all of the previous attempts at the syntheses of the natural products in the viridin family, it can be seen that there is much need for a synthesis that is convergent, shorter in length and, most importantly, asymmetric. Previous attempts at the synthesis of viridin have all been directed towards the synthesis of key intermediates. In addition, all attempts have been racemic. The syntheses directed towards the related natural product wortmannin have been long and intensive. Since there is so much room for improvement in the synthesis of these natural products and because of their biological importance, their continued study certainly worthwhile.

1.3.1 Project Objectives

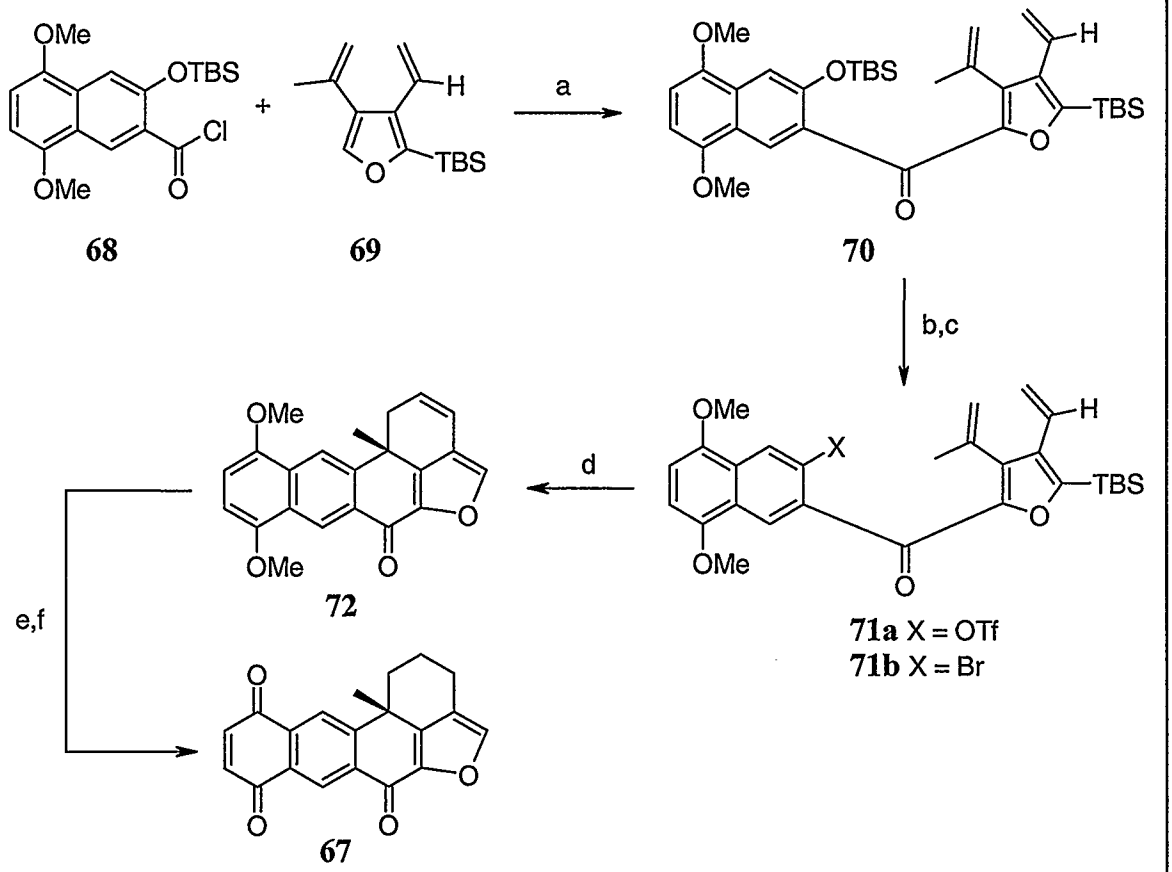
This project encompassed two main objectives. The first was to synthesize two key intermediates needed for the synthesis of viridin. These intermediates are presented in the retrosynthetic approach (*vide infra*). The second objective was to perform model asymmetric palladium catalyzed polyene cyclization studies with one of the key intermediates to determine whether the system would behave according to previous examples from the Keay lab.[36] Progress toward the synthesis of these key intermediates

and model studies are presented in chapter two. This thesis concludes with the experimental methods and pertinent data which are presented in chapter three.

1.3.2 Retrosynthetic Approach

The approach that will be used in the synthesis of viridin will be similar to that employed in the first total asymmetric synthesis of (+)-xestoquinone (**67**) shown in Scheme 1.13.[37] This approach employed an asymmetric palladium catalyzed polyene cyclization to form the angular methyl group and construct two of the five rings of viridin. This was accomplished through the synthesis of two novel intermediates, **68** and **69**, which were coupled through lithiation at the α-site of the furan ring to produce compound **70**. Deprotection of **70** using TBAF followed by formation of the triflate using NaH and $PhNTf_2$ yielded precursor **71a** for the key step. Treatment of the triflate with catalytic $Pd_2(dba)_3$ using the chiral ligand, (*S*)-BINAP afforded the pentacyclic ring structure **72** of xestoquinone with 68% ee. Hydrogenation of the double bond followed by aromatization of the quinone ring produced xestoquinone (**67**) without any loss of optical activity. Cyclization of bromide **71b** was also attempted. Unfortunately, even in the presence of silver salts, the resulting %ee was poor. In 1998, the synthesis of **67** was repeated by Shibasaki *et al.*[38] using compound **71b** in the presence of silver zeolites. The yield in this case was very poor and the %ee of the cyclization was only 63% (Scheme 1.13).

Scheme 1.13

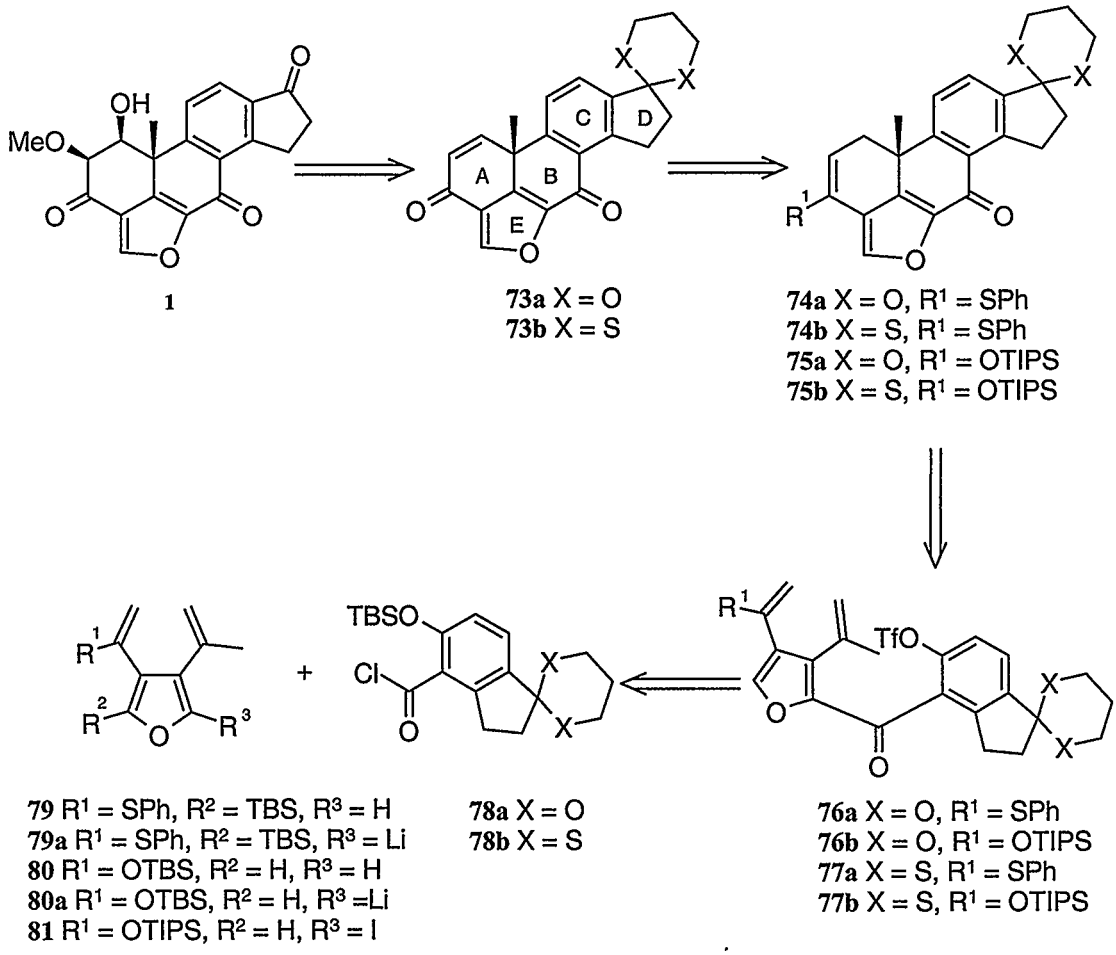


Conditions: a) *n*BuLi, HMPA, THF (64%); b) TBAF, THF (80%); c) NaH, $PhNTf_2$, THF; d) 2.5 mol% $Pd_2(dba)_3$, 10 mol% (*S*)-BINAP, PMP, tol (82%, 2 steps with **70a**); e) H_2, Pd/C, EtOAc (99%); f) CAN, CH_3CN/H_2O (55%).

In the retrosynthetic analysis of **1**, it is hoped that oxygenation of the A ring could be achieved using an enone. Through functional group interconversion, the carbonyl group of the D ring (which is the most reactive center of the molecule) could be protected as either a ketal **73a**, or a thioketal **73b**. The enone could be easily formed from either a vinyl sulfide **74a** or **74b**, or a silyl enol ether **75a** or **75b**. By disconnection of the bonds in a retro-polyene cyclization, the precursor to the key step would be obtained (**76** or **77**). This could then be further simplified by disconnection of the bond between the furan and carbonyl group. This would generate two sets of novel compounds; indane derivatives **78**

and trisubstituted furans containing either a vinyl sulfide **79**, or a silyl enol ether **80** (Scheme 1.14).

Scheme 1.14



1

73a X = O
73b X = S

74a X = O, R^1 = SPh
74b X = S, R^1 = SPh
75a X = O, R^1 = OTIPS
75b X = S, R^1 = OTIPS

79 R^1 = SPh, R^2 = TBS, R^3 = H
79a R^1 = SPh, R^2 = TBS, R^3 = Li
80 R^1 = OTBS, R^2 = H, R^3 = H
80a R^1 = OTBS, R^2 = H, R^3 =Li
81 R^1 = OTIPS, R^2 = H, R^3 = I

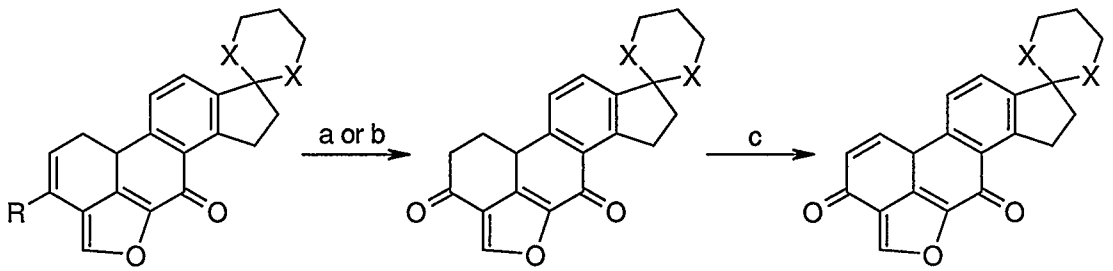
78a X = O
78b X = S

76a X = O, R^1 = SPh
76b X = O, R^1 = OTIPS
77a X = S, R^1 = SPh
77b X = S, R^1 = OTIPS

There are a number of reasons why either a vinyl sulfide or silyl enol ether is required in the synthesis of viridin. The first reason for this was described by Rodrigo *et al.*[5] They reported that the A ring of the pentacyclic structure **26** (Scheme 1.15) could not be functionalized when a double bond was present in ring A. Therefore, it becomes necessary to have a group other than a double bond in the A ring of the molecule. This should allow for functionalization of the A ring later in the synthesis. The use of either a

vinyl sulfide or silyl enol ether should allow this. Hydrolysis of vinyl sulfide **74a** or **74b**,[39] or silyl enol ether **75a** or **75b**,[40] will generate ketones **82a** and **82b**. Formation of an enone can then be achieved *via* conventional methods to give enones **73a** or **73b** (Scheme 1.15).[41]

Scheme 1.15



74a X = O, R^1 = SPh
74b X = S, R^1 = SPh
75a X = O, R^1 = OTIPS
75b X = S, R^1 = OTIPS

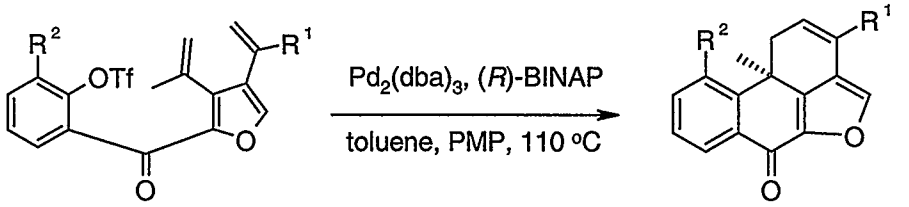
82a X = O
82b X = S

73a X = O
73b X = S

Conditions: a)$TiCl_4$, AcOH; b) HF, CH_3CN; c) LDA, PhSeCl, 30% H_2O_2

The second reason for the need of either the vinyl sulfide or the silyl enol ether in **76** and **77** can be explained by the results obtained by Lau and Keay.[36] Model compounds **83-86** were synthesized and subjected to an intramolecular palladium-catalyzed polyene cyclization. Their results showed that remote substituents have a profound influence on the %ee of the intramolecular palladium-catalyzed polyene cyclization. As can be seen in Scheme 1.16, when the steric bulk of the R^1 group was increased from a hydrogen atom **84**, to a methyl group **83**, the enantioselectivity of the reaction also increased from 71% to 90% respectively. Similarly, when the steric bulk of the R^2 group was increased from a hydrogen atom **84**, to a methyl group **85**, the enantioselectivity of the cyclization rose from 71% to >96% respectively.

Scheme 1.16



83	R^1 = Me, R^2 = H	**87** (90% ee)
84	R^1 = R^2 = H	**88** (71% ee)
85	R^1 = H, R^2 = Me	**89** (>96% ee)
86	R^1 = R^2 = Me	**90** (71% ee)

This increase in enantioselectivity can be attributed to a number of reasons. Semi-empirical $PM3_{(TM)}$ calculations[42] performed on the two transition states indicated that as the steric bulk of the R^1 group increased, the hydrogen atom *ortho* to palladium moved closer to the hydrogen in the 3 position of (*R*)-BINAP, creating a significant steric interaction. This steric interaction was not observed when palladium coordinated to the other enantiotopic face of the double bond. These interactions created enough difference in energy between the transition states to increase the enantioselectivity of the reaction. The same effect was observed when the steric bulk of the R^2 group was increased, and can be attributed to the same reasons. Surprisingly, increasing the steric bulk in both R^1 and R^2 was found to be counter-productive and resulted in a decrease in enantioselectivity (**86** → **90**). Using these studies as a basis for our synthetic design, it seems reasonable that by incorporating either a bulky vinyl sulfide or silyl enol ether into the R^1 position of the furan (**77-79**), we can use the steric bulk of these moieties in their remote position to have a positive effect on the enantioselectivity of the reaction.

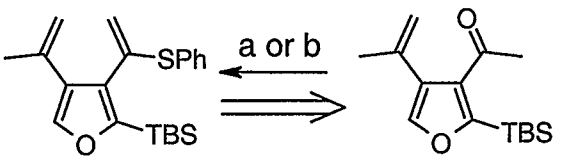
The next chapter provides a detailed description of the research done towards the synthesis of viridin.

Chapter 2

2.1.1 Introduction and Retrosynthesis of Vinyl Sulfide 79

Vinyl sulfide **79**, has never before been synthesized in the literature. Significant progress has now been made towards its synthesis in the Keay lab. A number of examples in the literature indicate that a vinyl sulfide can be easily prepared either directly[43,44] or indirectly[45] from methyl ketones under Lewis acidic conditions (Scheme 2.1).

Scheme 2.1



79 **91**

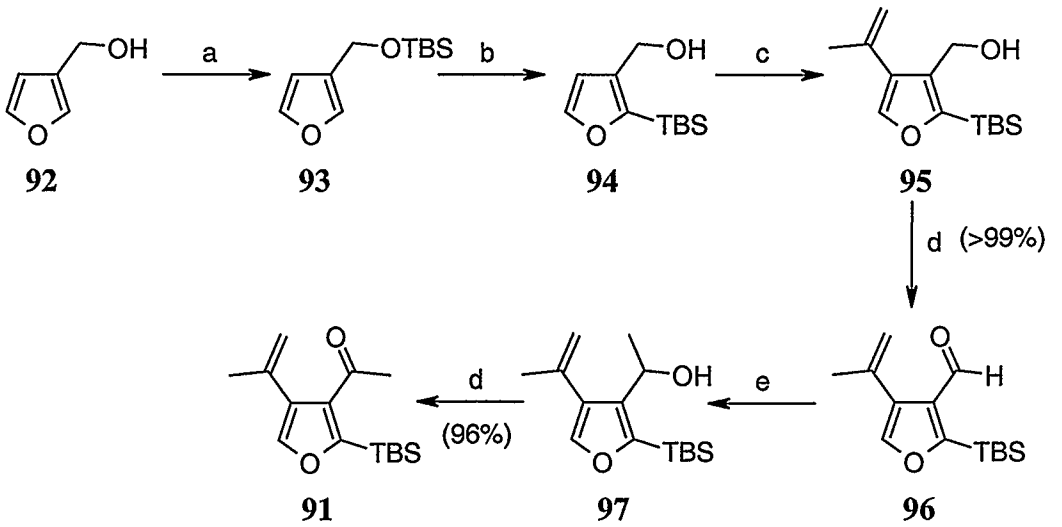
Conditions: a) $TiCl_4$, PhSH, NEt_3, CH_2Cl_2 b) i) 2,6-di-*t*-butyl-4-methylpyridine, Tf_2O, CH_2Cl_2; ii) NaH, PhSH

2.2.1 Synthetic Attempts Toward Key Intermediate 79

The synthesis of vinyl sulfide **79** (Scheme 2.2), began with 3-furanmethanol (**92**), a compound that is commercially available. Alcohol **92** was protected as the TBS ether using standard conditions. Silyl ether **93**, was generated in >99% yield. The silyl group of the protected alcohol was then migrated to the 2-position of the furan ring. This was accomplished using a method developed by Keay *et al.*[46a] Treatment of **93** with *n*BuLi and HMPA for 12 h produced migrated product **94** in excellent yield. The 4-position of

the furan ring was then functionalized with an isopropenyl unit using the *in situ* Suzuki method, a modified version of the classic Suzuki reaction, which was developed by Keay and coworkers in 1994.[47] Alcohol **94** was treated with 2.2 equiv. *n*BuLi in DME for 2 h at –78 °C. These conditions facilitated an alkoxide-directed *ortho*-lithiation at the 4-position of the furan ring. The resulting dianion was treated with triisopropylborate at –78 °C and allowed to warm to rt overnight. The resulting borate was treated with 2 M Na_2CO_3 to promote formation of the boronic acid. The boronic acid intermediate (not shown) was treated with 2-bromopropene and 5 mol% $Pd(PPh_3)_4$. The mixture was heated to 40 °C for 24 h to afford trisubstituted furan **95**. The yields obtained from this reaction were very inconsistent, ranging from 45% to 96%. They seemed to vary by reagent bottles and by the batches of starting material. Alcohol **95** was oxidized to the aldehyde using a highly efficient TPAP/NMO oxidation.[48] Compound **95** was first dissolved in methylene chloride and treated with catalytic TPAP in the presence of the stoichiometric re-oxidant NMO. This gave aldehyde **96** in quantitative yield which was treated with MeLi in THF to produce secondary alcohol **97**, also in quantitative yield. Alcohol **97** was converted to methyl ketone **91**, using another TPAP/NMO oxidation. This was accomplished in 96% yield. The synthesis of **91** through **92** depicted in Scheme 2.2 was originally performed by S.Y.W. Lau.[49]

Scheme 2.2



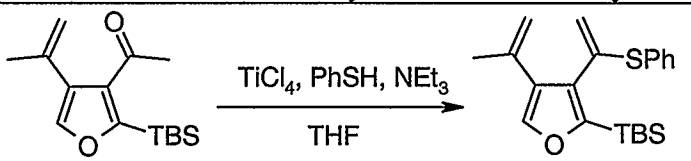
Conditions: a) TBSCl, imid., DMF, rt, 8 h (>99%); b) *n*BuLi, HMPA, THF, 0 °C, 12 h (96%); c) i) 2.2 equiv. *n*BuLi, DME, -78 °C, 2 h; ii) $(iPrO)_3B$, -78 °C to rt overnight; iii) 2-bromopropene, $Pd(PPh_3)_4$, 2 M Na_2CO_3, 40 °C, 24 h (75%); d) 5 mol% TPAP, NMO, 4Å MS, CH_2Cl_2, rt, 1 h; e) MeLi, THF, 0 °C, 2h (>99%).

S.Y.W.Lau

Relatively little work has been done involving the formation of a vinyl sulfide from a carbonyl compound. Consequently, there are only two procedures reported in the literature for the direct conversion of a methyl ketone to a vinyl sulfide. The first of these procedures involves treatment of a methyl ketone with 2 equiv. of a Lewis Acid, most commonly $TiCl_4$, followed by addition of a THF solution containing 2 equiv. of a thiol and 2 equiv. NEt_3.[43] Attempts at formation of vinyl sulfide **79** from methyl ketone **91** under these conditions were unsuccessful. This transformation was attempted under a variety of conditions, varying both temperature and concentration of reagents, which are summarized in Table 2.1. In entry 1, methyl ketone **91** was dissolved in THF at 0 °C. Titanium tetrachloride (1.1 equiv.) was added the solution, followed by thiophenol, and NEt_3. Work-up after fifteen minutes revealed only starting material by ^{1}H-NMR spectral analysis. The same result was observed when the reaction time was extended for up to

four days (entry 2). In entry 3, the reaction mixture was concentrated. No reaction was also observed under these conditions. The temperature was then raised to determine whether this would increase the reactivity of the system. Refluxing the solution for 1 d produced a complex mixture of products that could not be identified either by ^{1}H-NMR spectroscopy or GC/MS analysis. As a result, this method was abandoned due to the fact that preliminary studies did not show promising results.

Table 2.1: Attempts at Conversion of Methyl Ketone 91 to Vinyl Sulfide 79



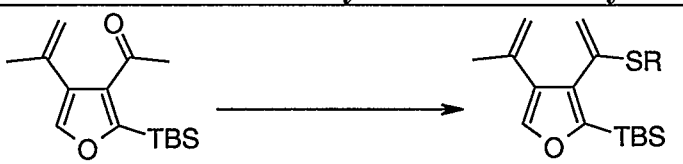
91 **79**

Entry	SM	Concentration (M)	Reaction Time	Temperature (°C)	Yield 79
1	**91**	0.11	15 min	0 °C to rt	no rxn
2	**91**	0.11	4 d	0 °C to rt	no rxn
3	**91**	0.378	4 d	0 °C to rt	no rxn
4	**91**	0.378	1 d	reflux	CM

Villeman *et al's*[44] method for the direct conversion of a methyl ketone to a vinyl sulfide was then attempted. This method involved the use of acidic clays such as Montmorillonite KSF, K10SF, and K10 which are relatively inexpensive, stable, non-hazardous and non-corrosive acid catalysts. Methyl ketone **91** was dissolved in toluene, and in that mixture was suspended Montmorillonite K10. Thiophenol (1 equiv.) was added, and the mixture was refluxed overnight with a Dean-Stark apparatus. After TLC analysis showed that the starting material had been consumed, the reaction was filtered through Celite. Unfortunately, ^{1}H-NMR and GC/MS spectral analysis of the crude product revealed a complex mixture of unidentifiable products. The absence of vinyl peaks from 5.0-6.0 ppm indicated vinyl sulfide **79** was not formed. Reducing the

temperature by refluxing in benzene produced similar results (entry 2). The reaction was also attempted using a more reactive clay, Montmorillonite KSF, (entry 3).[44] This also produced a complex mixture, even when a less sterically demanding thiol was employed (entry 4). Use of a more polar solvent was also tested in the formation of the vinyl sulfide (entry 5). These modifications were unsuccessful, no reaction was observed.

Table 2.2: Attempts at Conversion of Methyl Ketone 91 to Vinyl Sulfide 79

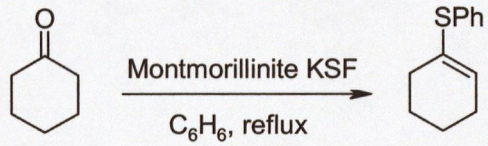


91 **79** R = Ph
79a R = iPr

Entry	SM	R	Acid Catalyst	Conditions	Product	Yield
1	**91**	Ph	Mont. K10	tol., reflux, 1 d	**79**	CM
2	**91**	Ph	Mont. K10	C_6H_6, reflux, 1 d	**79**	CM
3	**91**	Ph	Mont. KSF	tol., reflux, 1 d	**79**	CM
4	**91**	iPr	Mont. KSF	tol., reflux, 1 d	**79a**	CM
5	**91**	Ph	Mont. K10	CH_2Cl_2, 4Å MS, reflux, 1 d	**79**	no rxn

To test the validity of the method and the reactivity of the reagents, a test reaction was performed. The transformation of cyclohexanone to vinyl sulfide **98** (Scheme 2.3) was attempted by refluxing cyclohexanone and thiophenol in the presence of Montmorillonite KSF in a Dean-Stark apparatus. The following day the reaction was cooled, filtered and concentrated *in vacuo*. ^{1}H-NMR spectral analysis revealed the complete disappearance of the starting material, cyclohexanone, and revealed the presence of vinyl peaks in the vinyl region of the spectrum (5.0-6.0 ppm). This confirmed that both the reagents were reliable and the method was sound. This also confirmed that the inability of methyl ketone **91** to react to form either **79** or **79a** was due to reasons specific to that of the substrate.

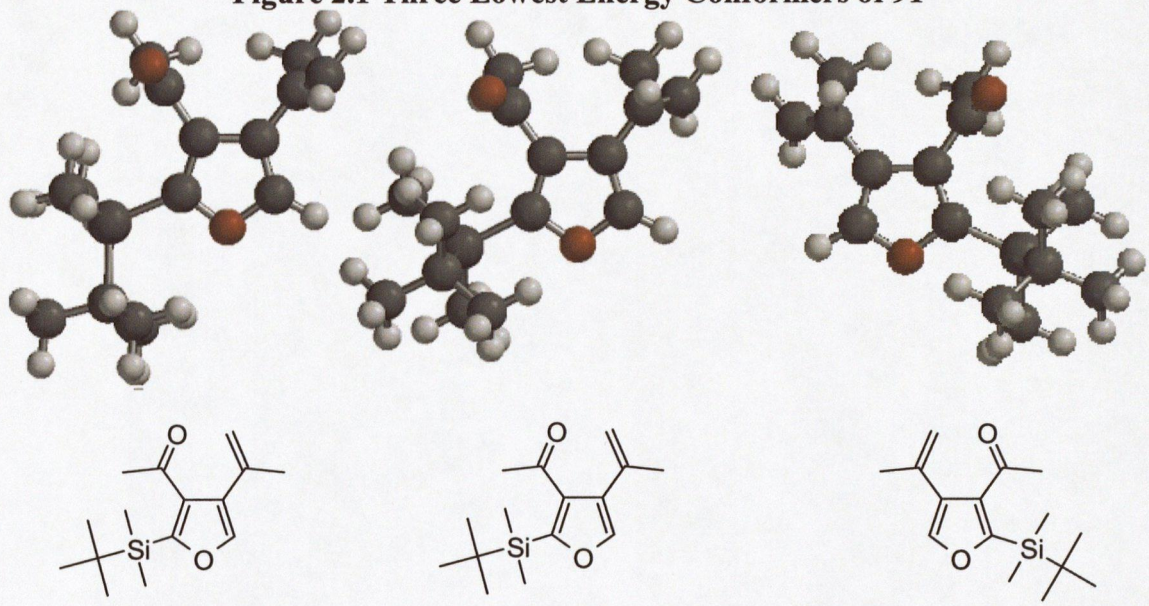
Scheme 2.3



98

Using Spartan Pro,[42] a conformer search at the semi-empirical PM3 level was conducted in hopes of gaining insight as to why the transformation from **91** to **79** would not occur. This conformer search generated 12 conformers; the three which were lowest in energy are shown in Figure 2.1.

Figure 2.1 Three Lowest Energy Conformers of 91

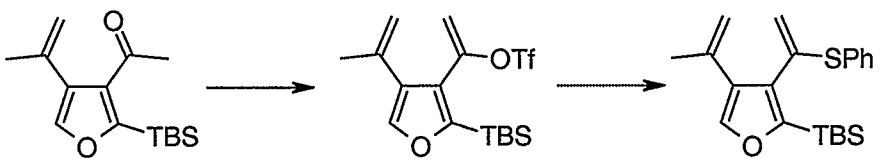


In the first attempts at synthesizing the vinyl sulfide, $TiCl_4$ coordinates to the carbonyl group, effectively activating it. The thiophenol must approach the carbonyl group in roughly an orthogonal manner in order to react, to form the vinyl sulfide. It can be seen from these conformers that both faces of the carbonyl group are effectively

blocked. On one side the bulky *t*-butyldimethylsilyl group prevents the thiophenol approach and, on the other, the isopropenyl unit does the same. It is thus impossible for the thiophenol to approach the carbonyl group close enough to react. This effectively explains why only starting material was observed in entries 1 through 3 in Table 2.1. In entry 4, the complex mixture observed was probably due to decomposition of the starting material in the presence of $TiCl_4$ at elevated temperatures. In Table 2.2, complex mixtures were observed under all conventional reaction conditions (entries 1-4). This could be due to both decomposition of starting material and to formation of 1,4-diketones by acid-catalyzed opening of the furan ring under extremely acidic conditions. The acidic clays, Montmorillonite KSF and Montmorillonite K10 have respective Hammett acidities of $H_o = -7$ and $H_o = -6.6$.[44]

As the route involving the formation of a vinyl sulfide directly from a methyl ketone proved to be unsuccessful, preparation of the vinyl sulfide directly from vinyl triflate **99** was investigated (Scheme 2.4).[45]

Scheme 2.4

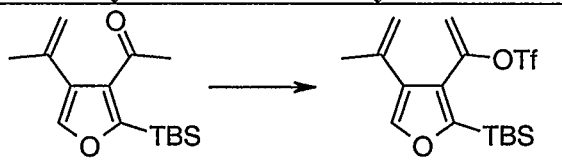


91 **99** **79**

Starting from methyl ketone **91**, the synthesis of vinyl triflate **99** was attempted following a literature procedure published by Faul *et al.*[50] Methyl ketone **91** was dissolved in CH_2Cl_2, and 2 equiv. of Na_2CO_3 were added in one portion at room temperature with vigorous stirring (entry 1, Table 2.3). A solution containing 3 equiv. of

triflic anhydride was added dropwise. After 15 min, analysis by TLC revealed the consumption of starting material. The mixture was filtered through Celite and concentrated *in vacuo*. Analysis of the crude product by ^{1}H-NMR spectroscopy revealed complete decomposition of the starting material; none of the desired vinyl triflate was observed. The reaction was also attempted at a reduced temperature (entry 2). Under these conditions the starting methyl ketone did not completely decompose. By ^{1}H-NMR spectral analysis, a complex mixture was observed and no additional peaks were visible in the vinyl region of the spectrum. Utilizing a procedure published by Stang *et al.*,[51] the methyl ketone was dissolved in CCl_4 and cooled to -22 °C. Pyridine was added (1.2 equiv.), and the mixture stirred for 15 min. Triflic anhydride was added, and the mixture stirred for 2 h after warming to rt (entry 3). After work-up, ^{1}H-NMR spectral analysis revealed only starting material indicating that a longer reaction time may be required. The final method that was attempted in the formation of vinyl triflate **99** was a method employing the use of 2,6-di-*t*-butyl-4-methylpyridine, a reagent specifically used for the formation of vinyl triflates from methyl ketones.[52] This reagent, a non-nucleophilic, sterically hindered base, eliminates the formation of anhydride salts allowing the base to react exclusively with the ketone. Methyl ketone **91** was dissolved in CH_2Cl_2 and to the solution was added 2,6-di-*t*-tbutyl-4-methylpyridine. The mixture was stirred for 15 min, after which triflic anhydride was added and stirred for an additional 1 h at rt (entry 4). ^{1}H-NMR spectral analysis of the crude reaction mixture revealed complete decomposition of the substrate.

Table 2.3: Conversion of Methyl Ketone 91 to Vinyl Triflate 99



91 **99**

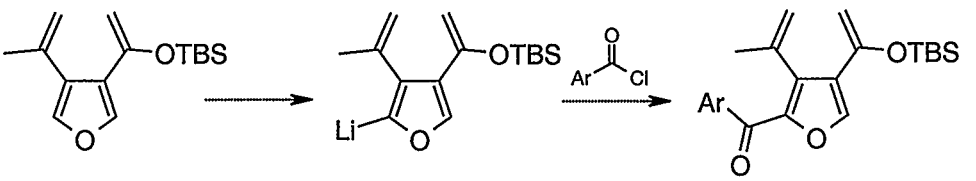
Entry	Base Used	Equiv. Tf_2O	Temperature (°C)	Solvent	Yield 99
1	2 equiv. Na_2CO_3	3	rt	CH_2Cl_2	dec
2	1.2 equiv. Na_2CO_3	1.2	-78	CH_2Cl_2	CM
3	1.2 equiv. pyridine	1.2	-22	CCl_4	no rxn
4	1.2 equiv. 2,6-di-tertbutyl-4-methylpyridine	1.2	rt	CH_2Cl_2	dec

In light of the unsuccessful attempts at conversion of methyl ketone **91** to either the vinyl sulfide **79** or vinyl triflate **99**, this approach was abandoned and attempts were made to synthesize the silyl enol ether.

2.3.1 Introduction and Rationale for the Synthesis of Silyl Enol Ethers 80 and 81

A silyl enol ether, as previously mentioned, can be converted to an enone functionality, which is needed to functionalize the A ring of the pentacyclic system. It was also hoped that the steric bulk of the silyl group could be used to selectively lithiate the opposite side of the furan ring in order to couple it to the aromatic portion of the molecule (Scheme 2.5).

Scheme 2.5



80 **80a**

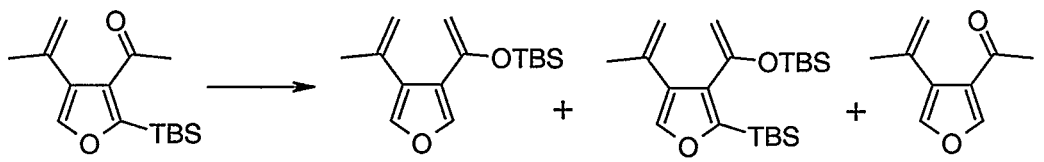
The silyl migrations used in the synthetic approach toward viridin are extremely useful for a number of reasons. First, they demonstrate the use of atom economy. The same silyl group serves a multitude of functions throughout the synthesis. It is originally used to protect the alcohol of 3-furanmethanol (**92**). It then migrates to the 2-position of the furan ring, blocking that side. This allows the 4-position to be selectively lithiated in the presence of the *ortho*-lithiation director and subsequently functionalized. Finally, the formation of the enolate and subsequent migration to form the silyl enol ether serves dual purposes. First, the steric bulk allows selective lithiation, and the TBS enol ether can be later converted to the enone (*vide supra*). The silyl migrations are driven by a number of factors. In the conversion of **93** to **94**, the migration is driven by the instability of the carbanion formed relative to an alkoxide upon treatment of **93** with *n*BuLi. To stabilize the charge on the carbanion, the silyl group migrates down to the 2-position, creating a significantly more stable alkoxy anion. In the transformation of **91** to **80**, an enolate is formed upon treatment of **91** with a base. The silyl group then migrates to form the silyl enol ether driven by the strength of the silicon-oxygen bond, which is significantly stronger then the corresponding silicon-carbon bond. A full explanation on the mechanism has been published by Bures *et al.*[46b]

2.3.2 Synthesis of Silyl Enol Ethers 80 and 81

The [1,4] C $\rightarrow$ O migration of methyl ketone **91** to form silyl enol ether **80** was attempted following modified procedures published by Keay *et al.*[46a] Not surprisingly, the desired product **80** was not the only product obtained in the many cases (Table 2.4).

By ^{1}H-NMR spectral analysis, mixtures of identifiable products were obtained. These mixtures contained the desired product **80**, in which silyl migration had occurred in an intramolecular fashion, disilylated product **100**, in which silyl migration had occurred intermolecularly, and desilylated starting material **101**, was also obtained as a result of the intermolecular silyl migration (Scheme 2.6).

Scheme 2.6



91 **80** **100** **101**

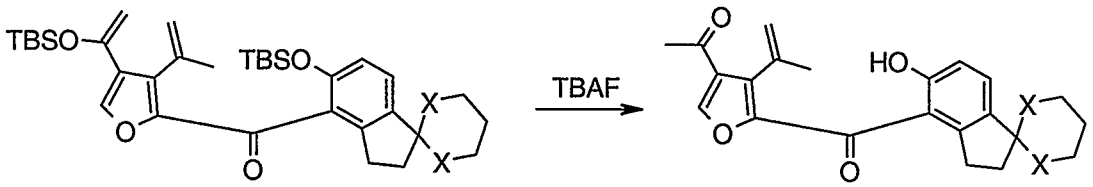
The use of NaH as a base was unsuccessful. No reaction was observed in THF, DME, Et_2O or toluene at ambient temperature (entries 2, 3, 5, 6, 7). In DMF, NaH gave exclusively desilylated starting material **101** (entry 1). The use of LHMDS as a base gave more promising results. By varying both the concentration of starting material and the amount of base, optimum conditions were obtained. Treatment of a 0.05 M solution of **91** in DMF with 1.5 equiv. of a 1.0 M solution of LHMDS in THF at rt (entry 8) gave 7% of **91**, 60% of **80** and 33% of **100**. Dilution of the reaction did not eliminate formation of the disilylated product (entry 12). Instead, primarily starting material **101**, and small amounts of **100** were isolated. Increasing the amount of base used in the reaction did not appear to counter act the dilution problem (entry 13). Instead, when a large excess of base was used, the sample decomposed, producing a complex mixture of unidentifiable products. These results are summarized in Table 2.4.

Table 2.4: Conversion of Methyl Ketone 91 to Silyl Enol Ether 80

Entry	Base (equiv.)	Solvent	Concentration of 91 (M)	Temperature (°C)	% Product Mixture 91:80:100:101
1	1.2 NaH	DMF	0.05	rt	0:0:0:100
2	1.2 NaH	THF	0.05	rt	100:0:0:0
3	1.2 NaH	DME	0.04	rt	100:0:0:0
4	1.2 NaH	DME	0.04	Reflux	CM
5	1.2 NaH	Et_2O	0.04	Reflux	100:0:0:0
6	1.2 NaH	tol	0.04	rt	100:0:0:0
7	1.2 NaH	tol	0.04	Reflux	100:0:0:0
8	1.2 LHMDS	DMF	0.05	rt	7:60:33:0
9	1.2 LHMDS	DMF	0.05	-78 to rt	2:42:15:40
10	1.2 LHMDS	THF	0.05	-78 to rt	100:0:0:0
11	1.2 LHMDS	DMF	0.04	-78 to rt	4:51:17:28
12	1.5 LHMDS	DMF	0.02	-78 to rt	88:0:1:11
13	5 LHMDS	DMF	0.02	-78 to rt	CM

One potential problem must now be addressed. Coupling of **80a** to the aromatic portion of the molecule would give either **102** or **103**. These compounds contain both a TBS enol ether and a TBS phenolic ether (Scheme 2.7). The TBS phenolic ether however, must be removed in order to make the triflate needed for the polyene cyclization. Upon treatment with TBAF, both the TBS phenolic ether and the TBS enol ether would be removed, generating either **104** or **105** (Scheme 2.7). It is necessary to be able to deprotect the phenol in the presence of the silyl enol ether. Therefore, it becomes necessary to be able to differentiate between the two protecting groups. A solution to this problem is to form the silyl enol ether using a less labile protecting group such that the TBS phenolic ether can be selectively cleaved.

Scheme 2.7

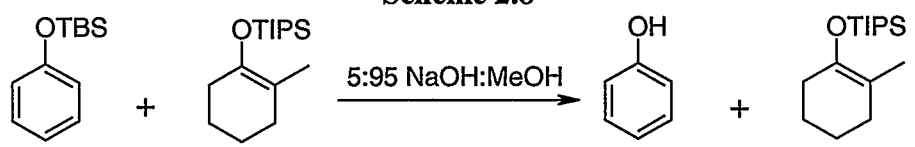


102 X = O
103 X = S

104 X = O
105 X = S

The TIPS protecting group was chosen to serve this purpose as it is more base stable than the TBS group.[53] A model system was prepared by A. Mroch,[54] in which both *t*-butyldimethylphenoxy silane (**106**) and triisopropyl-(2-methyl-cyclohex-1-enyloxy)silane (**107**) were synthesized. Treatment of a 1:1 mixture of **106** and **107** with a 5% NaOH solution in MeOH at ambient temperature gave a 1:1 mixture of **108** and **107**. Thus, the TBS phenolic ether could be selectively removed in the presence of the TIPS enol ether (Scheme 2.8).

Scheme 2.8



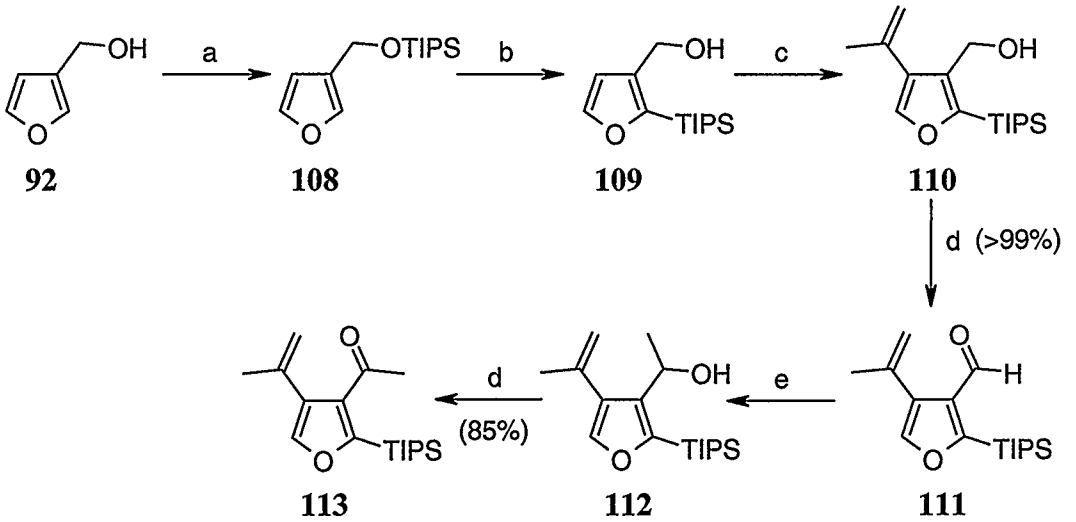
106 **107** **108** **107**

A. Mroch

The synthetic sequence of Scheme 2.9 was originally performed by A. Mroch.[54] The following modifications were done by myself: the conversion of **110**→**111** and **112**→**113**, which was originally a PDC oxidation, was changed to a TPAP/NMO oxidation. 3-Furanmethanol (**92**) was therefore protected as TIPS enol ether **108** and carried through to methyl ketone **113**. The previously described conditions were used in

the preparation of these compounds, no unexpected problems were encountered with the change of protecting group, and comparable yields were obtained for each step. The preparation of these compounds is shown in Scheme 2.9.

Scheme 2.9

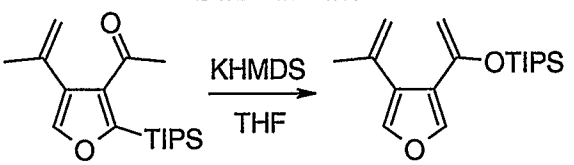


Conditions: a) TIPSCl, imid., DMF, rt, 8 h (95%); b) *n*BuLi, HMPA, THF, 0 °C, 12 h (90%); c) i) 2.2 equiv. *n*BuLi, DME, -78 °C, 2 h; ii) $(iPrO)_3B$, -78 °C to rt overnight; iii) 2-bromopropene, $Pd(PPh_3)_4$, 2 M Na_2CO_3, 40 °C, 24 h (61%); d) 5 mol% TPAP, NMO, 4Å MS, CH_2Cl_2, rt, 1 h; e) MeLi, THF, 0 °C, 2h (>99%).

A. Mroch

The work pertaining to both Scheme 2.10 and Scheme 2.11 was also performed by A. Mroch.[54] After compound **113** was obtained, the TIPS silyl group was migrated to form the silyl enol ether. Treatment of **113** with KHMDS in THF (Scheme 2.10) gave only desired product **114**, and unreacted starting material, which could be recovered by flash chromatography. None of the undesired disilylated or desilylated byproducts were observed under these conditions.

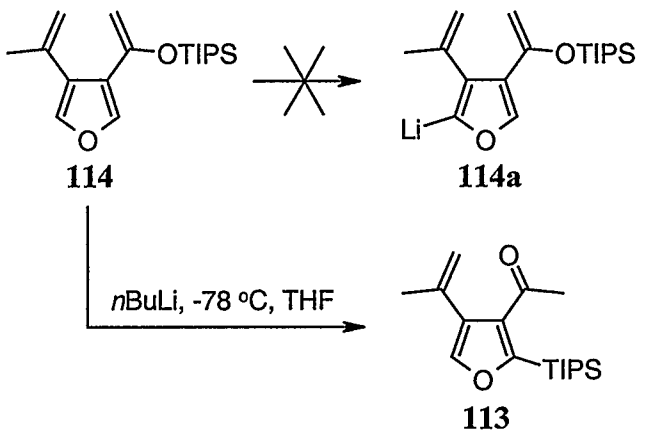
Scheme 2.10



	113	**114**
A. Mroch		

Compound **114** was isolated and purified by flash chromatography. Selective lithiation studies were carried out by treatment of silyl enol ether **114** with *n*BuLi in THF at -78 °C. These studies proved to be inconclusive. It could not be determined which side of the furan ring was being selectively lithiated. The only discernable product that could be observed by ^{1}H-NMR spectroscopy was **113**, which results from the formation of the more thermodynamically favored anion, the anion α to the silyl enol ether. When this anion was formed, the silyl group migrated back down to the α-position to stabilize the carbanion to produce the starting methyl ketone **113**. This is shown in Scheme 2.11.

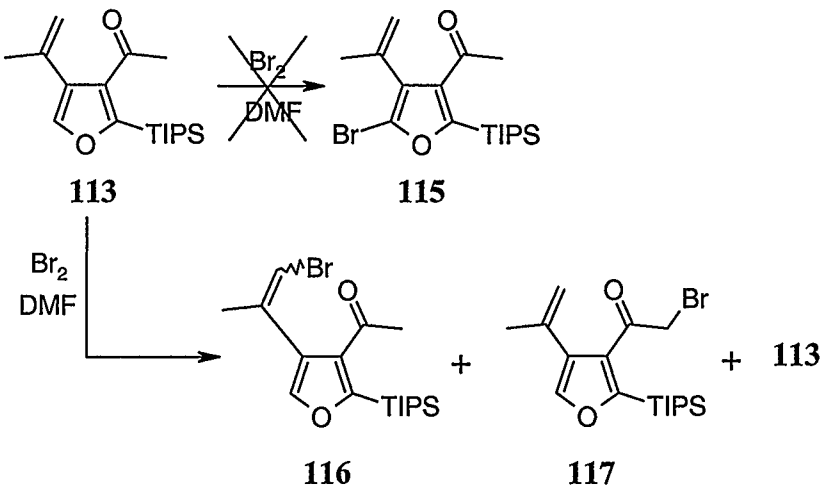
Scheme 2.11



A. Mroch

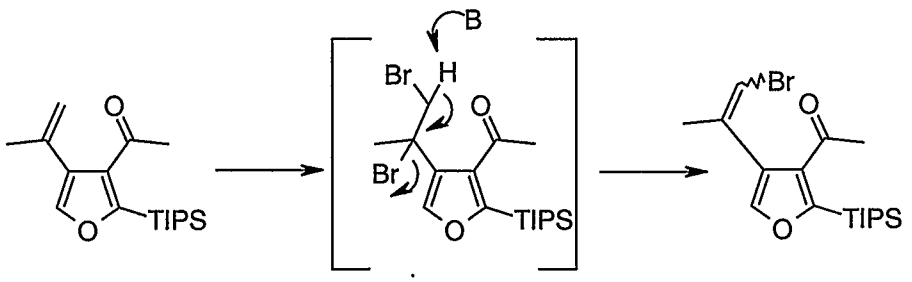
Following the unsuccessful attempts at selective lithiation of **114** to produce **114a**, it was decided that functionalizing the α-position of the furan ring with either bromine or iodine might be helpful. This should allow a halogen-metal exchange prior to coupling with the aromatic portion of the molecule. Following a literature procedure published by Brandsma *et al.*[55] the transformation was first attempted by treating **113** with bromine in a solution of DMF in hopes of producing compound **115** (Scheme 2.12).

Scheme 2.12



After work-up, ^{1}H-NMR spectral analysis revealed a mixture of three distinct species. The three species were isolated by preparative TLC and characterized by ^{1}H-NMR spectral analysis. Spectral analysis revealed that, in addition to starting material, compounds **116** and **117** were also present. Compound **117** arose from bromination at the most acidic site of the molecule which has a pKa of approximately 20. Addition of bromine across the terminal double bond would produce intermediate **118**, which was subsequently eliminated to yield vinyl bromide **116** (Scheme 2.13). Although only one isomer of **116** was obtained, it was not determined whether **116** had either *E*, or *Z* geometry.

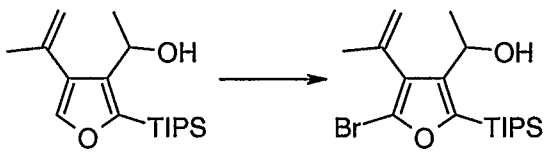
Scheme 2.13



113	118	116

Halogenations at the α-site were also attempted using secondary alcohol **112**. It was hoped that by using **112** instead of methyl ketone **113,** there would be less reactive sites on the starting material and as a result, the desired product, either **119** or **120** would be obtained. A solution of **112** and Br_2 in DMF was stirred at rt for 2 h.[55] The reaction was quenched with a saturated solution of $Na_2S_2O_3$ (Entry 1). ^{1}H-NMR spectral and TLC analysis revealed a mixture of three species, one of which was starting material. In this case, the species were not isolated and identified due to the fact that ^{1}H-NMR analysis showed 2 additional peaks in the 7.0-8.0 ppm region. This indicated that whatever the undesired by-products were, they were not the desired product as the last furyl hydrogen should be replaced by a halogen. Treatment of **112** with both NBS and NIS[56] also produced complex mixtures of products which were not isolated or identified. The results of these trials are summarized in Table 2.5.

Table 2.5: Attempted Halogenation at the α-site of 112



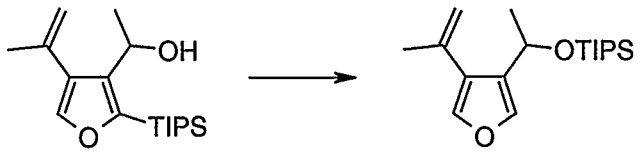
112 **119** X = Br
120 X = I

Entry	Electrophile	Solvent	Product	Yield
1	Br_2	DMF	**119**	CM
2	NBS	98:2 THF:H_2O	**119**	CM
3	NIS	98:2 THF:H_2O	**120**	CM

The approach toward the functionalization of the α-site was modified for a third time following these bromination attempts. As an alternative, **112** was treated with a number of bases in a variety of solvents (Table 2.6). This was performed in order to form the

dianion *in situ*. Quenching with D_2O allowed the determination of the % incorporation of deuterium into the α-site of the compound. This would reveal the optimum conditions for complete lithiation of the α-site of the furan. There were a number of problems associated with this reaction. First, in diethyl ether, the monoanion was insoluble and precipitated, preventing lithiation at the α-site (entry 10). Second, to obtain incorporation of deuterium at high levels, the reaction had to be warmed to 0 °C. After 2 h at this temperature, the silyl group on the 2-position of the furan ring migrated to the alkoxy anion, producing silyl ether **121** (Scheme 2.14). This was observed in entries 3, 4 and 7.

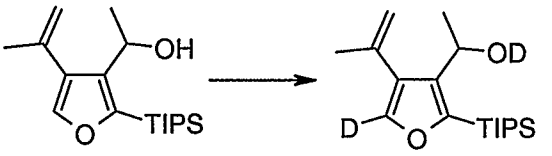
Scheme 2.14



112 **121**

Third, warming to temperature above 0 °C for long periods allowed the anion at the α-site of **112** to react with THF when used as the solvent. Thus, the anion is quenched (entries 1, 2, 5, 6 and 8).

Table 2.6: Lithiation Conditions for the Dilithiation of 112

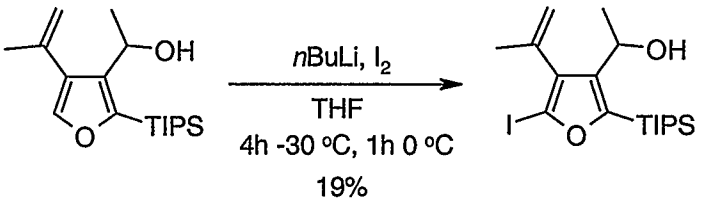


112 **112a**

Entry	Equiv. Base	Base	Solvent	Time (h)	Temp. (°C)	% D Incorporation
1	2.2	*t*BuLi	THF	1	-78	21
				2	-78	15
2	5	*n*BuLi	THF	4	-30	50
				5	0	85
				6	0	dec
3	2.5	*n*BuLi/HMPA	THF	1	-78	5
				2	0	dec
4	2.5	*n*BuLi/TMEDA	THF	1	-78	10
				2	0	50
				4	0	70
5	2.5	LDA	THF	1	-78	20
				2	0	20
				4	0	0
6	3	KHMDS	THF	2	0	dec
7	1.2	LiTMP	THF	1	-78	18
				2	0	40
8	2.5	*n*BuLi	DME	1	-78	7
				2	0	0
9	2.5	*n*BuLi	Et_2O	2	-78	25
				3	0	18

The best results were obtained when **112** was treated with *n*BuLi in THF and stirred for 4 h at -30 °C then 1 h at 0 °C (entry 2). Under these conditions 85% deuterium incorporation was observed. Using these lithiation conditions, iodination was attempted by adding sublimed I_2 to the mixture. After purification by flash chromatography, only 19% of desired tetrasubstituted furan **122** was obtained (Scheme 2.15).

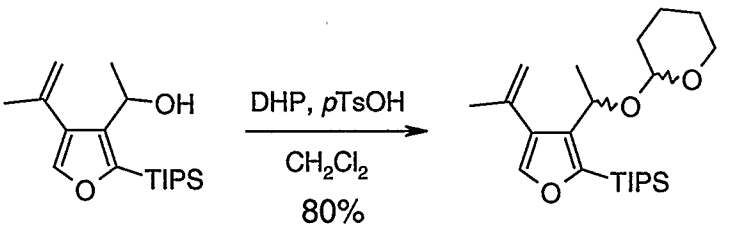
Scheme 2.15



112 **122**

To eliminate problems associated with formation of the dianion. Alcohol **112** was protected with the THP ether to yield **123**. By treating **112** with dihydropyran (DHP) in the presence of catalytic quantities of *p*TsOH in CH_2Cl_2 at 0 °C for 15 min, **123** was obtained in 80% yield as a 50:50 mixture of diastereomers (Scheme 2.16).[57]

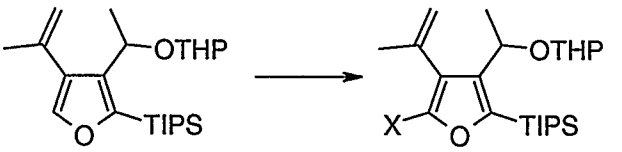
Scheme 2.16



112 **123**

Attempts at functionalizing the α-site of the furan ring were unsuccessful upon treatment with both NBS and NIS.[56] Complex mixtures were obtained, which were not isolated or characterized. The results from these attempts are summarized in Table 2.7.

Table 2.7: Attempted Halogenation at the α-site of 122

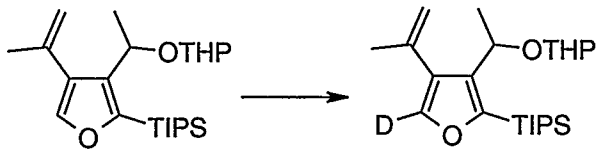


122 **124** X = Br
125 X = I

Entry	Electrophile	Solvent	Product	Yield
1	NBS	49:1 THF:H_2O	**124**	CM
2	NIS	49:1 THF:H_2O	**125**	CM

Lithiation of the α-site of **122** was attempted under a variety of conditions summarized in Table 2.8. Having the alcohol protected as the THP ether incorporated higher levels of deuterium then previously observed (*vide supra*). In general it was found that employing *t*BuLi as a base achieved far greater lithiation. The levels of deuterium incorporation also increased significantly when the reaction was warmed to -40 °C (entry 2). Optimum conditions were achieved when **122** was treated with 1.4 equiv. of *t*BuLi in THF and stirred for 3 h at –40 °C. Under these conditions >95% deuterium incorporation was observed, (entry 4).

Table 2.8: Lithiation Conditions for the Lithiation of 122

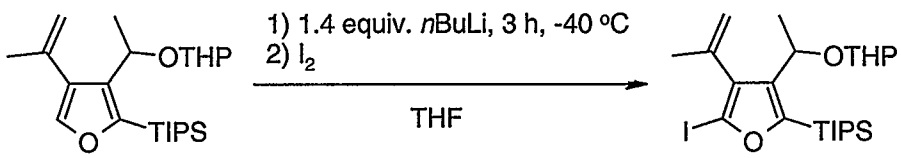


122 **126**

Entry	Equiv. Base	Base	Solvent	Time (h)	Temp (°C)	% D Incorporation
1	1.2	*n*BuLi	THF	1	0	70
				2.5	0	50
2	1.1	*t*BuLi	THF	1	-78	20
				2	-40	90
3	1.2	*t*BuLi	THF	1.5	-40	40
				3	-40	50
				6	-40	65
4	1.4	*t*BuLi	THF	1	-40	50
				2	-40	80
				3	-40	>95

Once optimum lithiation conditions were achieved (Entry 4), sublimed iodine was added to the anion. The reaction was quenched with a solution of saturated $Na_2S_2O_3$ and extracted with Et_2O. ^{1}H-NMR spectroscopy and GC/MS analysis revealed an 80:20 mixture of **125** to **122** (Scheme 2.17). Purification was attempted by flash chromatography, however, the retention factors for **122** and **125** were extremely similar and it was found that these two compounds could not be separated. In addition, the compounds were also liquid in nature and as a result, could not be purified by fractional recrystallization.

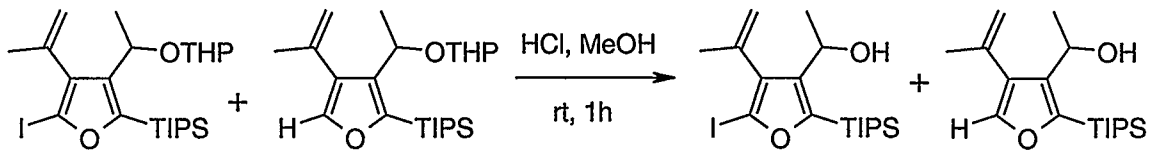
Scheme 2.17



122 **125**

As a solution to this problem, the mixture of **125** and **122** was dissolved in MeOH, and a drop of concentrated HCl was added to the solution and stirred for 4 h at ambient temperature. Under these conditions the THP group was removed from both **125** and **122**, producing a mixture of **112** and **126** (Scheme 2.18). A significant difference in retention factors was created in the free alcohols which made it possible to separate the desired tetrasubstituted furan derivative **126** from **112**. The tetrasubstituted furan **126** was isolated in 90% yield after flash chromatography.

Scheme 2.18



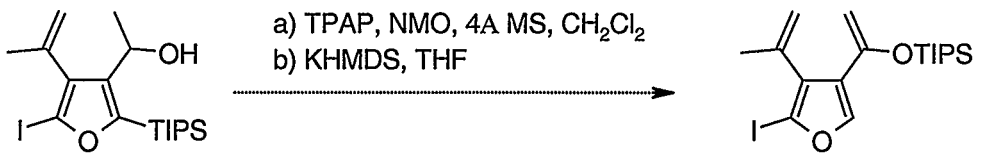
125 **122** **126** **112**

2.3.3 Conclusions and Future Work on the Furan Portion of the Molecule

In conclusion, the tetrasubstituted furan **126** can be synthesized in eight steps in 30% overall yield. Although the desired target **81** was not achieved, many of the potential problems for its synthesis have been resolved. This includes the selective deprotection of the TBS phenolic ether in the presence of the TIPS enol ether (Scheme 2.8), and the introduction of the halogen at the α-site of the furan, which was not a trivial transformation.

Future work on this portion of the molecule will involve oxidation of alcohol **126** to the methyl ketone (not shown), followed by migration of the TIPS protecting group to provide the target compound **81** (Scheme 2.19).

Scheme 2.19

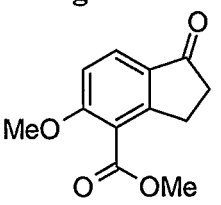


126 **81**

2.4.1 Previous Syntheses of Indane Derivatives

There have been 3 previous syntheses reported in the literature of the indane derivative **127** (Figure 2.1)[58,59,60]

Figure 2.1

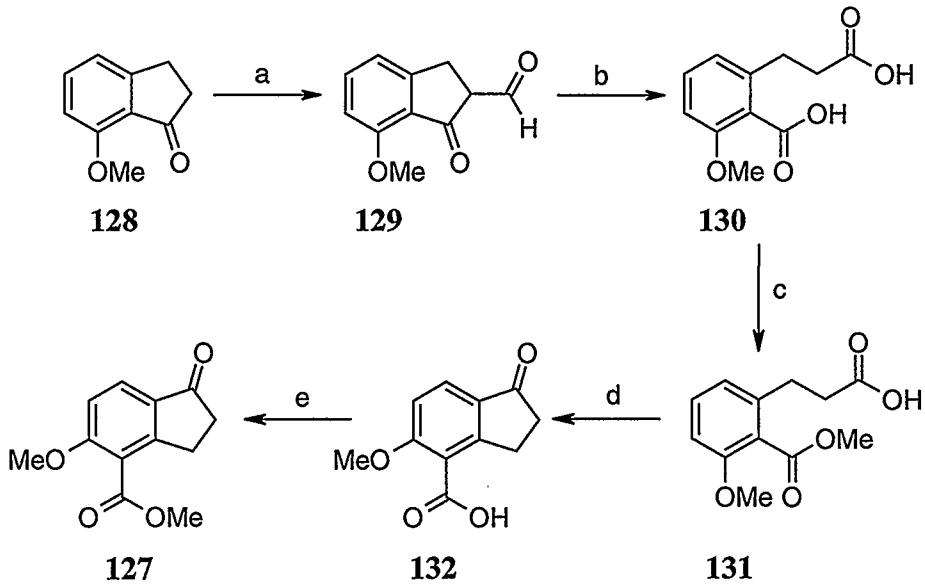


127

The first synthesis of **127**, reported in 1972 by Loewenthal and Schatzmiller,[58] began with 7-methoxyindan-1-one (**128**) which was first formylated using conditions not given in the paper. This generated α-formyl ketone **129**. The α-formyl ketone **129**, was treated with hydrogen peroxide in refluxing *t*BuOH to yield dicarboxylic acid **130**. The aromatic carboxylic acid was then selectively methylated, using conditions not given to generate the mono-carboxylic acid **131**. The carboxylic ester was treated with aluminum trichloride in 1,2-dichlorethane to produce the acid chloride (not shown), which

underwent a Friedel-Crafts acylation to produce indanone derivative **132**. Finally, the acid was converted to the methyl ester **127**, using dimethyl sulfate in a NaOH/THF solution. This is shown in Scheme 2.20.

Scheme 2.20

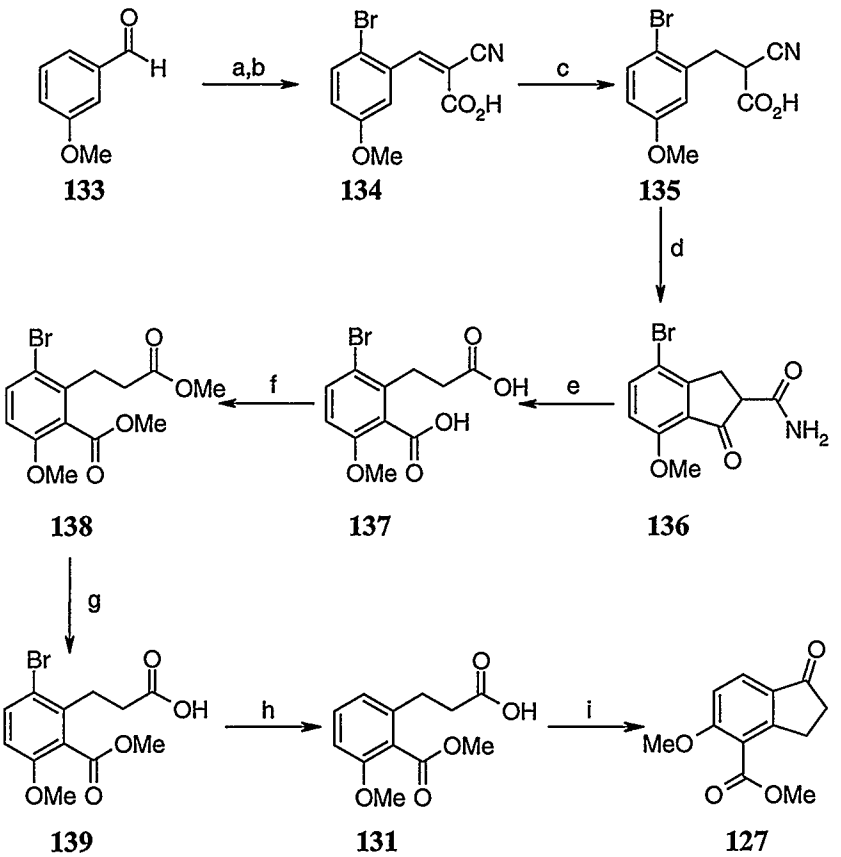


Conditions: a) not given; b) H_2O_2, *t*BuOH, reflux; c) not given; d) $AlCl_3$, CH_2Cl_2; e) Me_2SO_4, NaOH, THF.

The second synthesis of **127**, published in 1975 by Kametani *et al.*[59] used an approach similar to that previously published.[58] 3-Methoxy-benzaldehyde (**133**), was first brominated and the aldehyde was condensed with cyanoacetic acid in the presence of pyridine and ammonium acetate to yield cinnamic acid, **134**. The double bond of **134** was reduced with $NaBH_4$ to yield **135**, which was cyclized with polyphosphoric acid to yield 4-bromo-2-carbamoyl-7-methoxyindan-1-one (**136**). Acid hydrolysis of **136** gave dicarboxylic acid **137**, which was subsequently methylated with diazomethane to yield di ester **138**. Compound **138** was selectively hydrolyzed to yield mono-acid **139**, and subsequently debrominated by hydrogenolysis with palladium on carbon to yield 2-carbomethoxy-3-methoxyphenylpropionicacid (**131**). Finally, intermediate **131** was

cyclized with polyphosphoric acid to yield indanone **127**. This synthetic sequence is summarized in Scheme 2.21.

Scheme 2.21

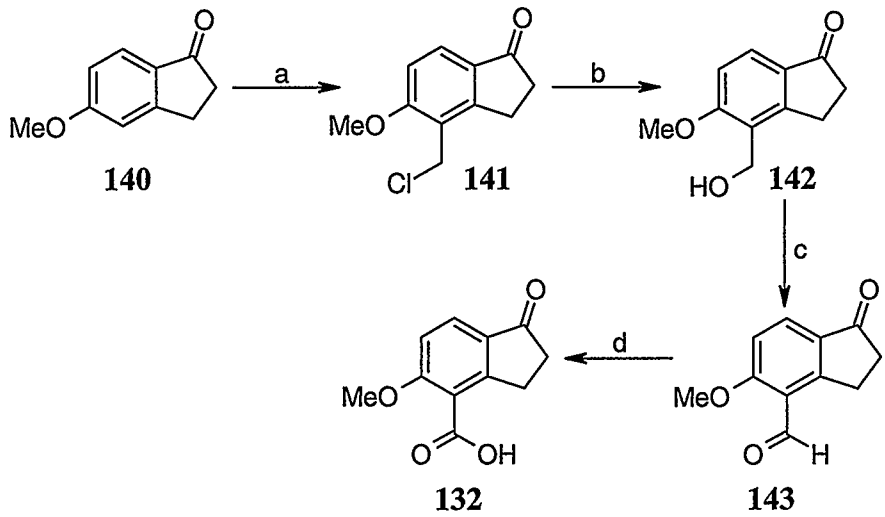


Conditions: a) not given; b) CH_3COCN, py, NH_4OAc (85%); c) $NaBH_4$, $NaHCO_3$, MeOH (73%); d) polyphosphoric acid, 100 °C, 30 min (79%); e) 10% KOH; f) CH_2N_2; g) 2.5% NaOH/MeOH (80%); h) Pd/C, NaOAc, AcOH (90%); i) polyphosphoric acid, 110 °C, 10 min (72%).

This synthesis of **127** was carried out in 20% overall yield over 9 linear steps. This value however, is inaccurate due to the fact that not all yields were reported for this synthesis. The total synthesis is long and impractical. It also uses an approach similar to that previously employed.

A third approach, also published by Loewenthal and Schatzmiller,[60] synthesizes carboxylic acid derivative **132**, and does not proceed to the methyl ester derivative **127**. Starting with 5-methoxy-indan-1-one (**140**), the compound was first chloromethylated using gaseous HCl, $ZnCl_2$ and conc. HCl, which occurred in high selectivity. The 4-chloromethyl derivative **141**, was obtained in a 6:1 ratio to the 6-chloromethyl byproduct (not shown). Compound **141** was converted to alcohol **142**, by treatment with a 10% solution of NaOH in MeOH. Alcohol **142** was oxidized to aldehyde **143** by treatment of the primary alcohol with chromic acid in acetone. The authors reported that conversion to the carboxylic acid **132** was not achieved under these conditions, and **143** had to be treated with chromic acid containing trace amounts of cerium(IV). The synthetic sequence is summarized in Scheme 2.22.

Scheme 2.22



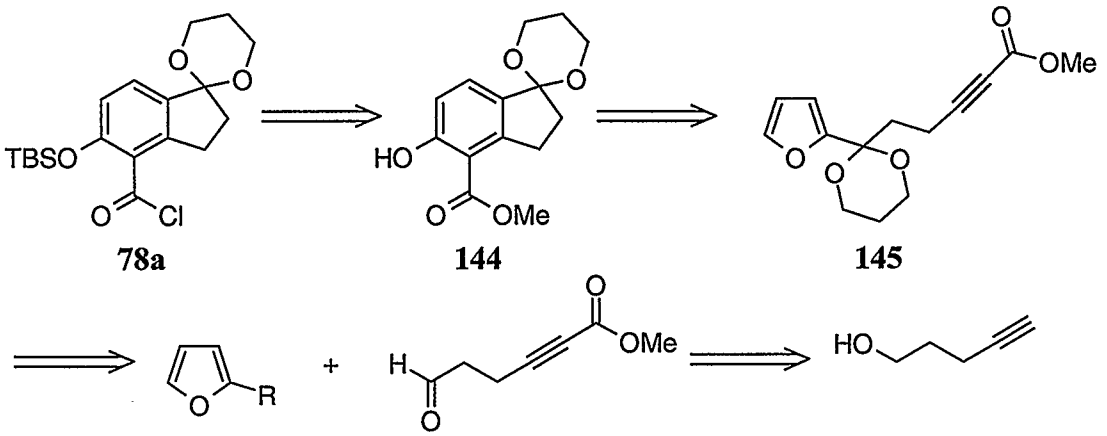
Conditions: a) HCl (g), $ZnCl_2$, conc. HCl, 45 °C, 8 h (21%); b) 10% NaOH/MeOH, rt, 15 min (85%); c) Chromic acid, acetone, 0 °C, 15 min (72%); d) Chromic acid, acetone, Cerium ammonium sulphate, rt, 12 h (75%).

This synthesis was performed in 10% overall yield over four steps. The overall yield in this synthesis is quite low. The formation of **141** occurred in 21% yield which contributes to this poor overall yield.

2.5.1 Retrosynthetic Analysis of Indane Derivative 78a

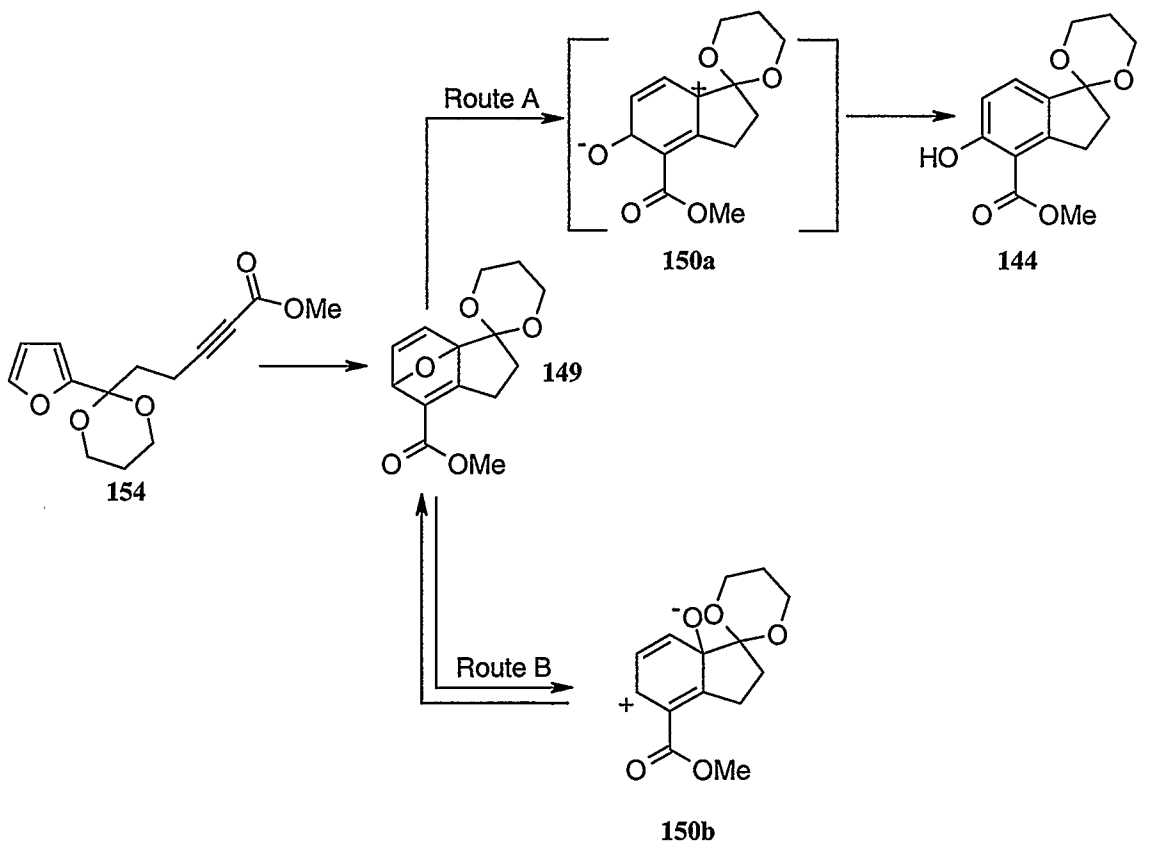
Through functional group interconversion, the acid chloride **78a** can be made indirectly from the corresponding methyl ester, and the TBS ether can be formed by protection of the phenol. This gives compound **144**, the IMDAF product of **145**, in which the bridged Diels-Alder adduct (not shown) has undergone aromatization. IMDAF precursor **145** can be synthesized by reacting lithiated furan **146b** with known aldehyde **147**. Aldehyde **147** can in turn be made through known reactions in the literature from 4-pentynol (**148**), a compound commercially available from Aldrich. This retrosynthetic analysis is depicted in Scheme 2.23.

Scheme 2.23



The key step in this synthetic sequence is the IMDAF reaction of intermediate **145**. When cyclized, bridged adduct **149** is produced, which must then be opened and aromatized to produce **144**. There are two possible r outes by which the bridged Diels-Alder adduct can be opened (Scheme 2.24). In route A, the bridged adduct can open to form intermediate **150a** which contains a tertiary carbocation at a doubly allylic site. This intermediate can undergo a loss of H^+ to produce aromatized species **144** after protonation of the alkoxide. In route B, bridged adduct **149** can open to form **150b** which contains a secondary carbocation at a doubly allylic site. This intermediate cannot undergo aromatization due to the fact that a tertiary alkoxy anion is formed, and there is no proton *ipso* to the alkoxide to allow for elimination. Instead, **150b** could reclose to reform **149**. Route A is more likely to occur due to a number of factors. First, intermediate **150a** is more stable then the corresponding intermediate **150b**. Second, route A is driven by aromatization of the intermediate species. Compound **150b** is incapable of aromatization, making route A preferred.

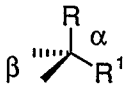
Scheme 2.24



There are a number of factors affecting the rate of ring closure in the IMDAF reaction. It has been recognized that alkyl substituents attached to the alkyl tether between the diene and dieneophile promote the rate of ring formation. This effect has been termed the gem-dialkyl effect.[61] The effect of these alkyl groups is two-fold and is influenced by both enthalpy and entropy. By changing the number of gauche interactions from reactants to products, the enthalphy of the reaction is made more favorable. By increasing the energy barriers required for internal rotations in the acyclic precursor, the entropy of the reaction is also improved. The alkyl groups also invoke the Thorpe-Ingold effect.[62] Mutual repulsion of the gem-dialkyl groups R and R^1 creates an increase in

angle β and a simultaneous decrease in angle α (Figure 2.2). This decrease in angle α pushes the diene and dieneophile together and makes the substrate more likely to undergo an IMDAF reaction.

Figure 2.2 Thorpe-Ingold Effect

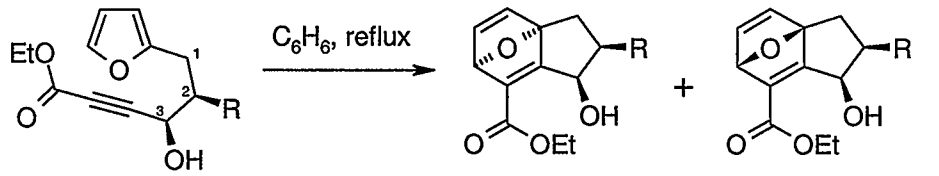


IMDAF precursor **144** contains either a ketal or a thioketal functionality (*vide infra*) which is expected to act similarly to a gem-dialkyl functionality and make cyclization to bridged adduct **148** more probable.

2.5.2 Literature Precedence for the IMDAF Key Step

Previous work indicated that the key step has the potential to be successful. In 1988, Cauwberghs and De Clercq[63] synthesized IMDAF precursors **151** and **152**. The first order rate constants of the IMDAF cycloadditions were then determined at 80 °C in benzene. It was found that the IMDAF of **151** was extremely slow ($t_{½}$ = 100 h), and gave both diastereomers **153a** and **153b**, of which the former predominated. The analogous reaction of **152** had a $t_{½}$ of 0.43 h and led to the single diastereomer **154a** (Scheme 2.25). From this example it can be seen that by placing an alkyl substituent on the tether results in a dramatic rate enhancement. Incorporating a *t*Bu group increased the rate by a factor of 240 due to both gem-dialkyl and Thorpe-Ingold effects.

Scheme 2.25



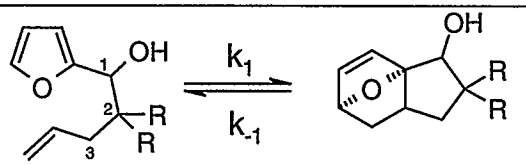
151 R = H
152 R = *t*Bu

153a **153b** $k_1 = 1.9 \times 10^4\ s^{-1}$
154a **154b** $k_1 = 4.5 \times 10^6\ s^{-1}$

There are both similarities and differences between this system and the proposed IMDAF. Like **145**, IMDAF precursors **151** and **152** contain electron withdrawing esters attached to the dieneophile. These serve to lower the energy of the LUMO, thereby increasing the rate of reaction. IMDAF precursor **145** however does not have a hydroxyl group on the tether. The proximity of this electron donating group to the dieneophile does not seem to be counter productive and does not impede the reaction. Instead, **145** contains a cyclic ketal at the 1-position which should aid cyclization (*vide supra*).

In 1985, Sternbach and Rossana[64] synthesized IMDAF precursors **155-161**. These compounds contained a hydroxyl group at the 1-position of the alkyl chain and an unactivated double bond as the dieneophile. It was found that the acyclic geminal substituted precursors led to improved yield of products in less time. This can be seen when comparing entry 3 vs. 4 and entry 5 vs. 6 in Table 2.9. As the steric bulk of the R group increased from a methyl group to a propyl group (entry 2 and 4) the yield increased by a factor of 10. In summary, Sternbach and Rossana[65] noted that the yield of IMDAF products was dependant on both the nature and position of substituents on the alkyl chain (Table 2.9).

Table 2.9: IMDAF Reaction of Precursors 155-161



155-161 162-168

Entry	SM	R	$k_1 \times 10^6$ (s^{-1})	t ½ (h)	Product	% Yield
1	**155**	H	n/a	n/a	**162**	no rxn
2	**156**	Me	n/a	n/a	**163**	<5
3	**157**	$-(CH_2)_3-$	1.46	131	**164**	47
4	**158**	Pr	2.73	71	**165**	58
5	**159**	$-S(CH_2)_3S-$	5.95	32	**166**	76
6	**160**	SEt	6.94	28	**167**	85
7	**161**	OEt	14.3	13	**168**	82

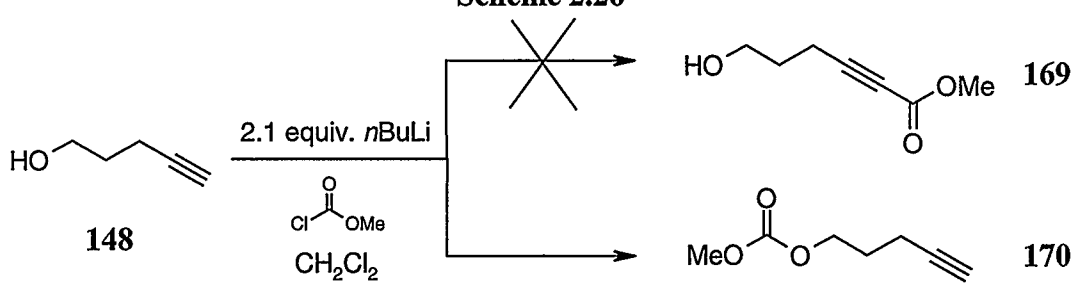
There has also been mention in the literature of similar IMDAF reactions performed under a variety of other conditions in an attempt to increase the rate and yield of the reaction. These conditions include the use of more polar solvents,[66a] β-cyclodextrin[66b] and elevated pressure.[67]

2.5.3 Synthesis of Indane Derivative 78a

The synthesis of indane derivative **78a** began with 4-pentyn-1-ol (**148**). Alcohol **148** was first treated with 2.1 equiv. of *n*BuLi then, after 1.5 h, 1.1 equiv. of methyl chloroformate was added in hopes of generating ester **169**. By forming the dianion, it was hoped that the more reactive carbanion would react faster to produce **169** preferentially over undesired carbonate **170** (Scheme 2.26). After work-up, ^{1}H-NMR analysis revealed that it was in fact the undesired by-product **170**, which had formed (Scheme 2.26). ^{1}H-NMR spectral analysis revealed a fine triplet present at approximately 2.0 ppm. This indicated that the acetylenic proton was still present. Formation of **170**

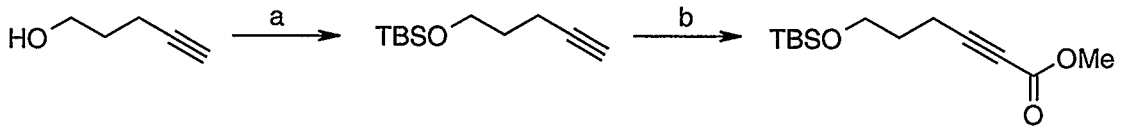
was also observed when freshly distilled methyl chloroformate was added to the dianion. This could be attributed to small quantities of HCl present in the methyl chloroformate that cannot be removed by distillation. This HCl was quenching both the acetylenic and alkoxy anion. Thus the alcohol of **147** was reacting directly with the electrophile.

Scheme 2.26



As a solution, the alcohol was protected as the TBS ether. Following a literature procedure published by Piers *et al.*,[68] a solution of TBSCl in CH_2Cl_2 was added slowly to a solution of **147** and NEt_3 in CH_2Cl_2 at 0 °C. The mixture was slowly warmed to rt over 4 h. After work-up and purification by flash chromatography, **171** was obtained in quantitative yield. Optimum yield of acetylenic ester **172** was obtained following a modified literature procedure by Piers *et al.*[69] To a solution of **171** in THF at -78 °C was added *n*BuLi. The solution was stirred at -78 °C for 15 min and then -20 to -30 °C for 1 h. Freshly distilled methyl chloroformate was then added to the resulting anion. The crude mixture was purified by distillation under reduced pressure to provide a clear, colorless oil in 70% yield. This sequence is shown in Scheme 2.27.

Scheme 2.27

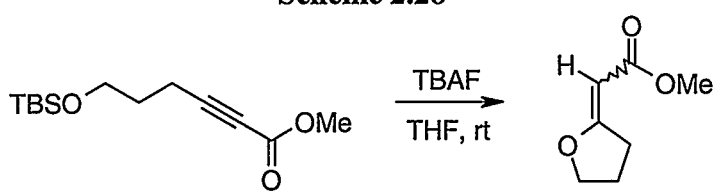


147 **171** **172**

Conditions: a) TBSCl, NEt_3, CH_2Cl_2, 0 °C (>99%); b) *n*BuLi, -78 °C, 15 min, -25 °C, 1 h then methyl chloroformate (70%).

Cleavage of the TBS ether to produce **169** was attempted by treating **172** with a 1.0 M solution of TBAF in THF. The solution was stirred at rt until TLC analysis showed the complete disappearance of starting material. ^{1}H-NMR spectral analysis of the crude mixture was not consistent with formation of **169**. Instead, it revealed a triplet at 5.4 ppm and a doublet of triplets present at 3.2 ppm. The unknown product was isolated and partially characterized in order to elucidate its structure. Surprisingly, the IR spectrum did not show a broad absorption in the 3300 cm^{-1} region. This indicated one of two things: either the TBS group had not been removed, which was unlikely, or the alcohol functionality was no longer present. It was finally determined that the sole product was **173**; however, the stereochemistry of the double bond was not established (Scheme 2.28). This can be rationalized by assuming that the acetylenic ester is a Michael acceptor. Treatment of the TBS ether with TBAF gives an alkoxy anion that can perform an intramolecular Michael addition to produce **173**.

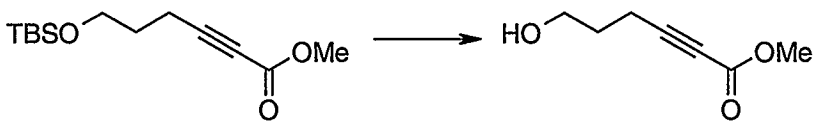
Scheme 2.28



172 **173**

A variety of alternative deprotection conditions were attempted and are summarized in Table 2.10. Even in the presence of a proton source (entry 2), treatment with TBAF gave **173** as the major product. In entry 3, deprotection was attempted following a modified literature procedure published by Wilson and Keay.[70] Compound **172** was dissolved in reagent grade acetone and H_2O. The solution was treated with 5 mol% $PdCl_2(CH_3CN)_2$ and refluxed overnight. After work-up, ^{1}H-NMR spectral analysis revealed quantitative yield of cyclized product **173**. By performing this transformation under strongly acidic conditions (entry 4),[71] a complex mixture was observed by ^{1}H-NMR spectroscopy. Deprotection to obtain **169** was finally achieved using a method published by Kawai *et al.*[72] Compound **172** was dissolved in a 20:1 mixture of THF:H_2O. One portion of 0.15 mol% *p*TsOH was added and the mixture was allowed to stir at rt overnight. After work-up, ^{1}H-NMR spectral analysis revealed the presence of only **169**. After purification by flash chromatography, alcohol **169** was obtained in 96% yield.

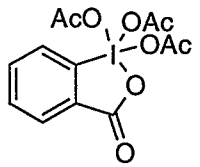
Table 2.10: Deprotection Attempts of 172



172 **169**

Entry	Conditions	Product Obtained
1	2.2 equiv. TBAF, THF	**173**
2	1.5 equiv. TBAF, 1.5 equiv. H_2O, THF	**173**
3	5 mol% $PdCl_2(CH_3CN)_2$	**173**
4	1.2 equiv. TBAF, 1.2 equiv. AcOH, THF	CM
5	0.15 mol% *p*TsOH, 20:1 THF:H_2O	**169**

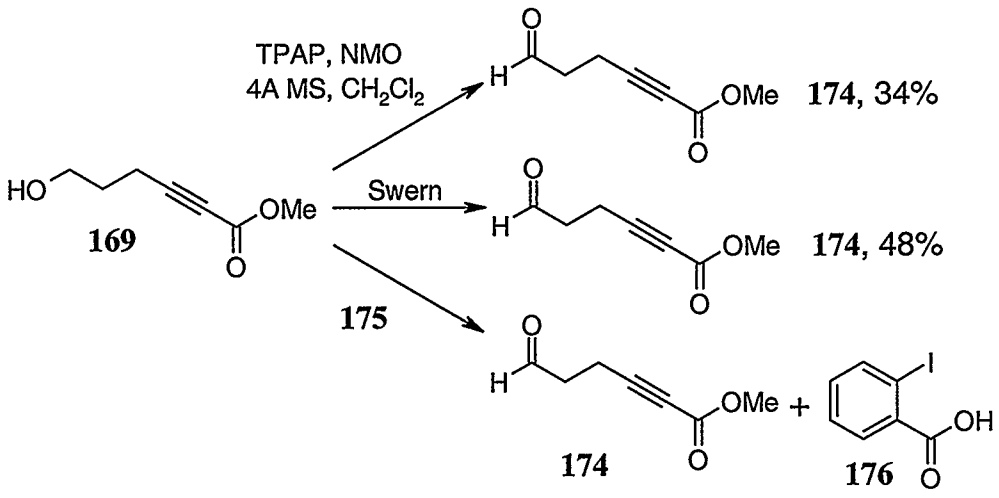
Figure 2.3 Dess-Martin Reagent



175

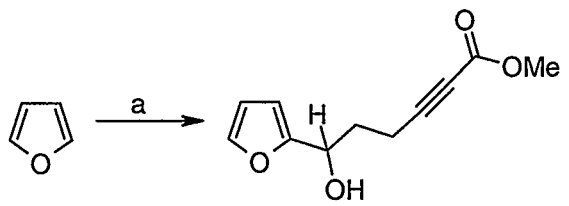
Aldehyde **174** was prepared via a Swern oxidation according to a literature procedure published by Trost and Shi.[73] To a solution of oxalyl chloride in CH_2Cl_2 at –55 °C was added DMSO and the mixture was stirred for 15 min. A solution of **169** in CH_2Cl_2 was added and stirred for an additional 15 min at which point NEt_3 was added. The mixture was allowed to warm to rt (Scheme 2.29). After work-up and purification by flash chromatography, aldehyde **174** was obtained in 48% yield. Alternative oxidation methods were undertaken in an attempt optimize the yield of this reaction. These methods included the TPAP/NMO method[48] and the Dess-Martin method.[74] Oxidation with TPAP/NMO gave a much lower yield, affording 34% of **174** after flash chromatography. Oxidation using Dess-Martin periodinane **175** (Figure 2.3) also gave poor yields and, in addition, by-product *o*-iodobenzoic acid (**176**), which could not be separated from **174** by flash chromatography. In the end, the synthesis was continued with crude product from the Swern oxidation since it gave crude yields >70%. The crude product was clean by ^{1}H-NMR spectral analysis.

Scheme 2.29



Compound **177** was prepared by treating furan with *n*BuLi at –78 °C, then quenching with aldehyde **174**. The mixture was allowed to stir for 2.5 h at –78 °C then quenched with H_2O (Scheme 2.30). ^{1}H-NMR analysis revealed a triplet at 3.5 ppm for the furylic hydrogen atom indicating that **177** was present in the crude product. Purification by preparative TLC produced clean **177** in 25% yield.

Scheme 2.30

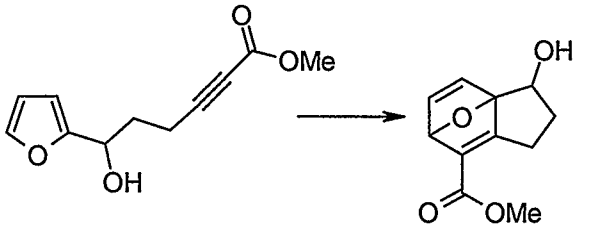


145a **177**

Conditions: a) i) *n*BuLi, -78 °C, 1 h; ii) **174**, -78 °C, 2 h (25%).

The IMDAF reaction was then attempted on compound **177** to produce the bridged Diels-Alder adduct **178** (Table 2.11). Literature precedent[64] indicated that similar IMDAF reactions proceeded when the dieneophile was a simple double bond (*vide supra*). In this case **177** contained an activated acetylenic dieneophile which should make cyclization more likely. Refluxing IMDAF precursor **177** in both benzene and toluene (entries 1 and 2) for up to 3 d produced no reaction. The only signals observable by ^{1}H-NMR belonged to compound **177**. Treatment of **177** with excess Me_2AlCl at –50 °C (entry 3) also gave no reaction. Treatment with 3.0 equiv. Me_2AlCl at –30 °C followed by warming to 0 °C over 2 h gave a black solution. ^{1}H-NMR analysis showed complete decomposition of **177**. As a result, the reaction was abandoned.

Table 2.11: IMDAF Attempts on Precursor 177

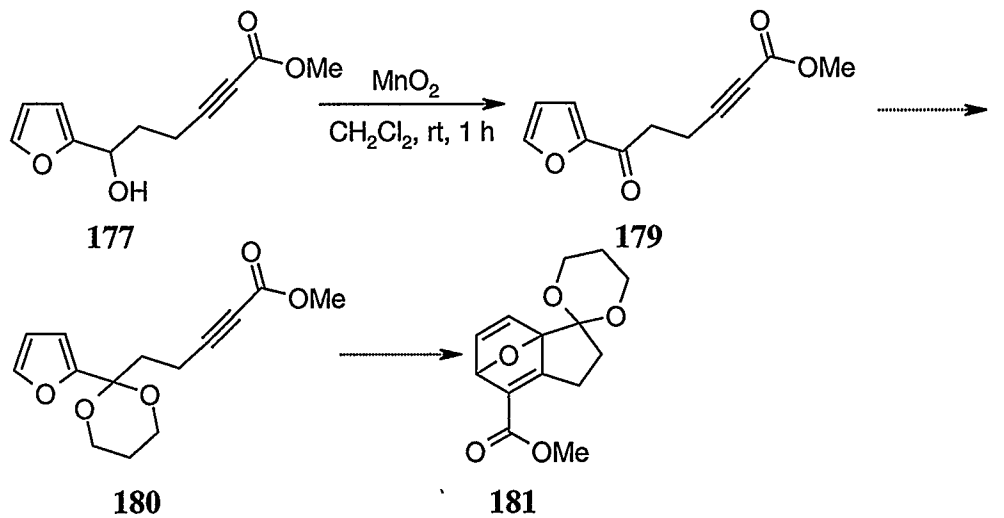


177 **178**

Entry	SM	Equiv. LA	Temperature	Time	Solvent	Expected Product	Yield
1	**177**	n/a	reflux	3 d	C_6H_6	**178**	no rxn
2	**177**	n/a	reflux	3 d	tol	**178**	no rxn
3	**177**	2.2	-50 °C	2 h	CH_2Cl_2	**178**	no rxn
4	**177**	3.0	-30 – 0 °C	2 h	CH_2Cl_2	**178**	dec

Compound **177** was oxidized to ketone **179** following a literature procedure published by Eberbach *et al.*[75] To a stirred solution of **177** in Et_2O was added a 50-fold excess of MnO_2. The mixture was stirred for 1 h at rt then filtered through a pad of Celite. ^{1}H-NMR spectroscopy indicated the absence of the triplet at 3.5 ppm confirming that the α,β-unsaturated ketone was present. The plan was to convert ketone **179** to cyclic ketal **180**. It was hoped that gem-dialkyl effects would make **180** cyclize more readily to **181** than **177** to **178**. This is shown in Scheme 2.31.

Scheme 2.31

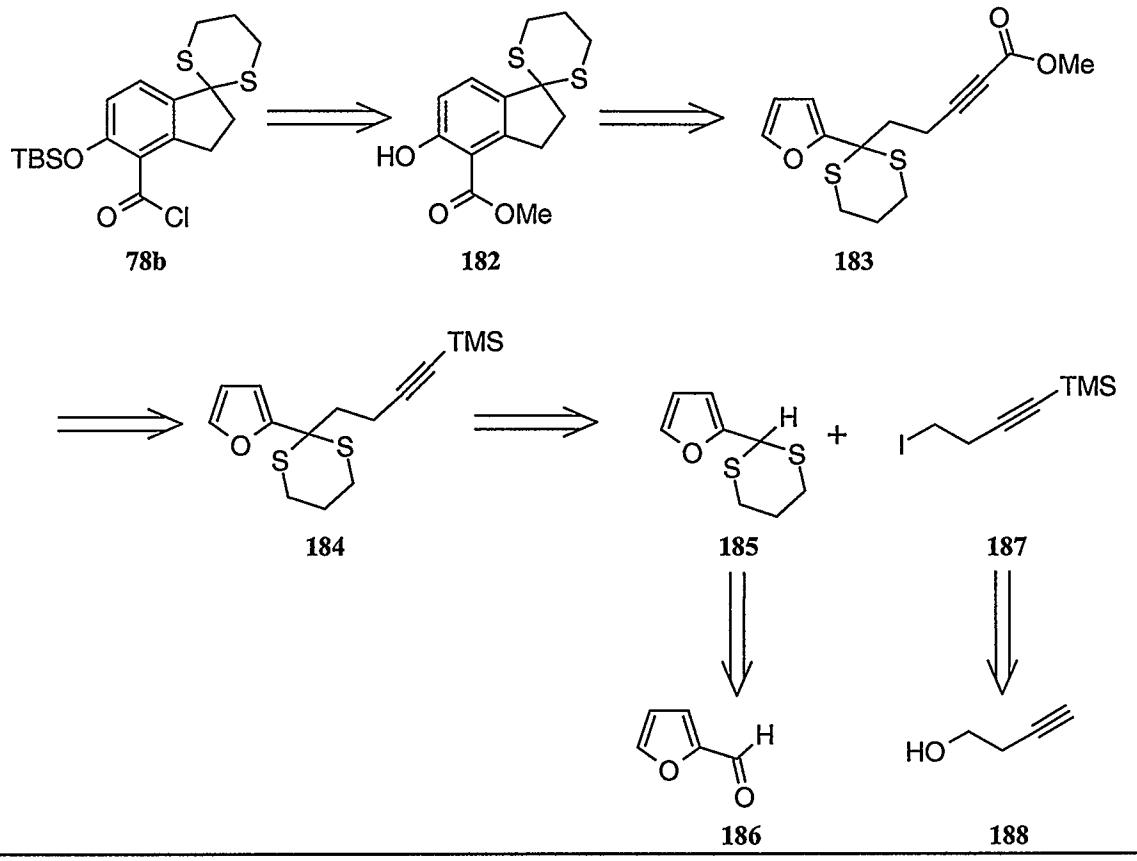


At this time, oxidations of **177** were being performed on <30 mg of substrate. This was deemed inadequate as it is impossible to perform a total synthesis using only small quantities of starting materials. Also, as the yields on some of the steps (**169**→**174** and **145a**→**177**) were extremely low and some of the transformations were problematic, the synthesis of **78a** was abandoned, and the synthesis of **78b** was designed as an alternative.

2.6.1 Retrosynthetic Analysis of Indane Derivative 78b

Through functional group interconversion, the acid chloride **78b** can be made indirectly from a methyl ester and TBS ether formed by protecting the phenol (Scheme 2.32). This gives **182**, which is the IMDAF product of **183** in which the bridged Diels-Alder adduct (not shown) has undergone aromatization. IMDAF precursor **183** can be made by functional group interconversion from **184**. Compound **184** is simply the product of coupling thioketal **185**, and iodide **187**. Thioketal **185** can be made from 2-furfural (**186**) a commercially available starting material. Iodide **187** can be made from 4-butyn-1-ol (**188**), a compound that is also commercially available. The synthesis has a number of advantages. The use of the dithiane allowed for a shorter synthesis and the presence of the dithiane should favor the IMDAF reaction due to increased gem-dialkyl[61] and Thorpe-Ingold[62] effects.

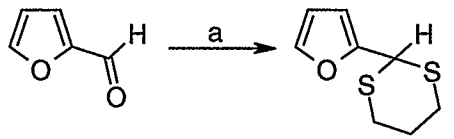
Scheme 2.32



2.6.2 Synthesis of Indane Derivative 78b

The aldehyde of 2-furfural (**186**) was protected as a thioketal to give compound **185** (Scheme 2.33). This was accomplished following a literature procedure published by Ramos *et al.*[76] To a solution of **186** in $CHCl_3$ at 0 °C was added 1,3-propanedithiol followed by TMSCl. The reaction was stirred overnight, allowing warming to rt. Quenching with 4% NaOH, extraction and concentration *in vacuo* provided crude thioketal **185** which was purified by distillation to provide a white, fluffy solid in 97% yield.

Scheme 2.33

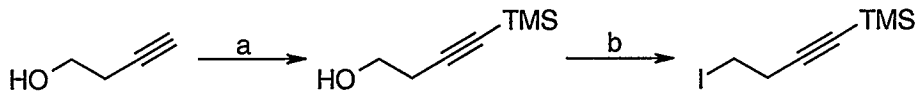


186 **185**

Conditions: a) 1,3-propanedithiol, TMSCl, $CHCl_3$, 0 °C, 12 h (97%).

Compound **187**, shown in Scheme 2.34, was prepared according to modified procedures provided by Rawal *et al.*[77] Alcohol **188** was dissolved in THF and cooled to –78 °C. *n*BuLi (2.2 equiv.) was added dropwise, and the mixture was stirred for 1.5 h before adding freshly distilled TMSCl. The mixture was stirred for an additional 1.5 h, allowing warming to 0 °C. Quenching with 2 M HCl, extraction and concentration *in vacuo* provided protected TMS-acetylene **189** in quantitative yield. Compound **189** was used without further purification. Compound **189** was dissolved in CH_2Cl_2, and PPh_3 was added followed by imidazole. The reaction mixture was placed in an ice bath, and I_2 was added in small portions. The reaction was stirred for 4 h at 0 °C then quenched with a saturated $Na_2S_2O_3$ solution. After purification, iodide **187** was obtained in 77% yield.

Scheme 2.34



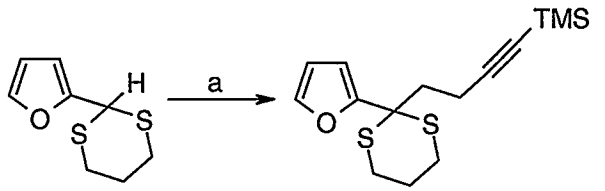
188 **189** **187**

Conditions: a) i) 2.2 equiv. *n*BuLi, TMSCl, -78 °C, THF; ii) 2 M HCl (>99%, 2 steps); b) PPh_3, imid., I_2, CH_2Cl_2, 0 °C (77%).

Dithiane **185** and iodide **187** were coupled by treatment of **185** with *n*BuLi at -78 °C. The anion of **185** was allowed to form over 1 h then treated with a solution of **187** in THF. ^{1}H-NMR spectral analysis of the crude product revealed the disappearance of the

singlet at 5.2 ppm, due to the thioacetal hydrogen. Alkylated product **184** was obtained in 82% yield after recrystallization from hexanes (Scheme 2.35).

Scheme 2.35

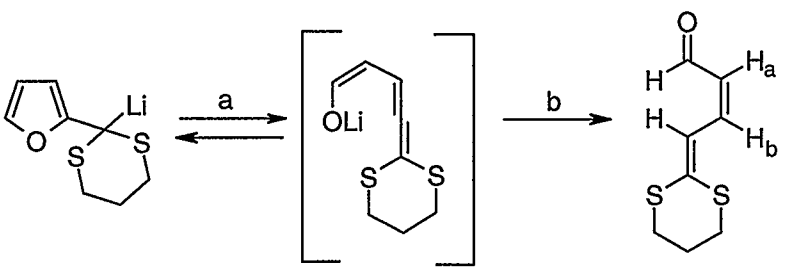


185 **184**

Conditions: a) *n*BuLi, THF, -78 °C, 1 h then **187** (82%).

Precautions had to be taken in formation of anion **190** (Scheme 2.36). Previous studies[78] have indicated that a temperature-dependent rearrangement of **190** to allene **191** occurs at temperatures above -20 °C. This rearrangement was confirmed through low temperature ^{1}H-NMR studies. Species **190** and **191** exist in equilibrium. At -78 °C, the equilibrium lies largely towards **190**. At temperatures above -20 °C, only **191** exists in solution. If the solution was recooled to -78 °C, only compound **190** was observed again. Once **191** is formed, it can react with water to give aldehyde **192**, a highly colored species (Scheme 2.36). The stereochemistry of **192** was determined through ^{1}H-NMR spectral analysis. The coupling constant between H_a and H_b was J_{ab} = 6.8 Hz which is indicative of a *Z*-substituted double bond.

Scheme 2.36

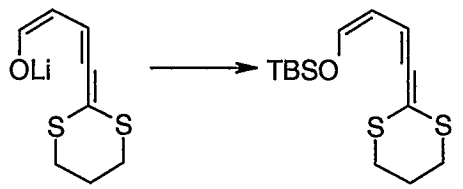


190 **191** **192**

Conditions: a) *n*BuLi, THF, 1 h, -20 °C; b) H_2O

The formation of **191** was also confirmed by trapping as the TBS enol ether **193** (Scheme 2.37). Intermediate **193** formed upon addition of freshly sublimed TBSCl. ^{13}C-NMR spectral analysis confirmed the presence of **193** by the signal at 220 ppm which is characteristic of an allenic carbon. This phenomenon of ring opening has been observed in similar heterocyclic compounds such as thiadiazoles and oxadiazoles.[79]

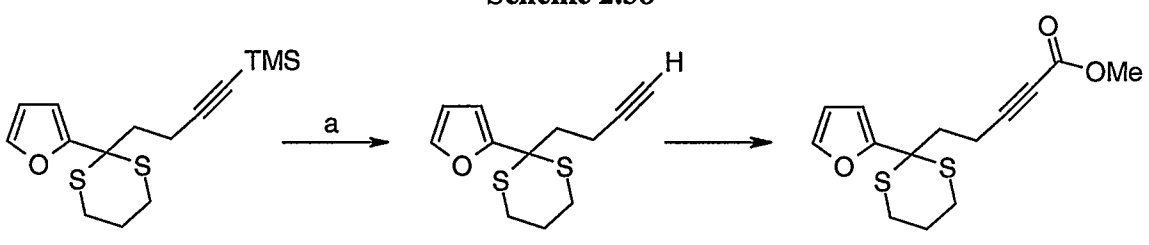
Scheme 2.37



191 **193**

Removal of the TMS group in **184** was first accomplished using TBAF in THF at rt. Acetylene **194** was isolated after flash chromatography in 65% yield. Optimal deprotection conditions were achieved following a modified procedure published by Cai and Vasella.[80] By treatment of **184** with solid K_2CO_3 in MeOH, acetylene **194** was isolated in 94% yield after purification by flash chromatography (Scheme 2.38).

Scheme 2.38



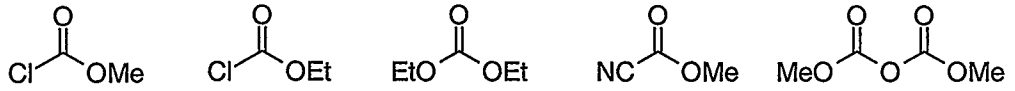
184 **194** **183**

Conditions: a) K_2CO_3, MeOH, rt, 4 h (94%).

Formation of the acetylenic ester **183** in good yield proved to be a challenge. Acetylene **194** was treated with *n*BuLi at -78 °C. ^{1}H-NMR spectral analysis revealed that after 1 h, the lithiation of **194** was complete. Lithiated acetylene **194a** was treated with

electrophiles **195-199** shown in Figure 2.4, giving a variety of results summarized in Table 2.12.

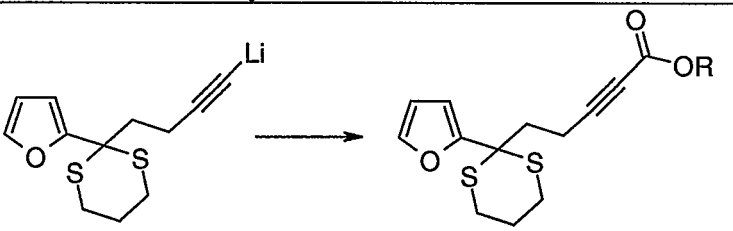
Figure 2.4 Electrophiles Used in the Formation of Acetylenic Ester 183 and 199



195 **196** **197** **198** **199**

Upon treatment of lithiated species **194** with methyl chloroformate (**195**) only starting material was observed by ^{1}H-NMR spectral analysis of the crude product (entry 1). This result was probably due to the MeOH and HCl present from decomposition of **195**. These by-products effectively quenched the acetylenic anion. The low yield observed when employing ethyl chloroformate (**196**) as an electrophile was probably due to similar decomposition products (entry 2). In this case, 20% of acetylenic ester **200** was isolated after flash chromatography. A complex mixture was observed by ^{1}H-NMR spectral analysis when either diethyl carbonate (**197**) or methyl cyanoformate (**198**) was employed as the electrophile (entries 3 and 4). Optimal conditions were finally achieved using dimethyl pyrocarbonate (**199**) to quench the electrophile. Product **182** was obtained in 74% yield after purification by flash chromatography. Acetylenic ester **183** was an extremely reactive compound that had to be used immediately after purification. The silica gel used for purification of **183** was pretreated with a solvent system made basic by the addition of 2% NEt_3. The addition of NEt_3 neutralized the acidic silica gel reducing the decomposition observed when using untreated silica gel. The acid present in the silica gel catalyzes Michael additions onto the activated acetylene producing a complex mixture of decomposition products.

Table 2.12: Formation of the Acetylenic Ester 183 and 200

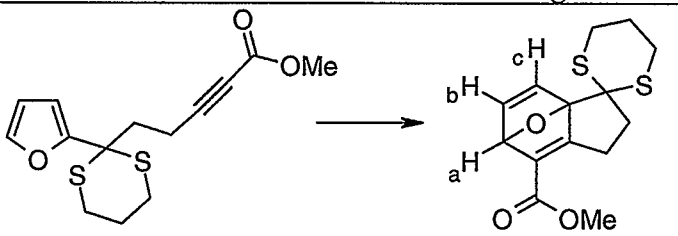


194a **183** R = Me
200 R = Et

Entry	Electrophile	Product	Yield
1	**195**	**183**	SM
2	**196**	**200**	20%
3	**197**	**200**	dec
4	**198**	**183**	dec
5	**199**	**183**	74%

Having a sufficient quantity of precursor **183**, the Diels-Alder reaction of **183** to produce bridged adduct **201** was attempted (Table 2.13). Acetylenic ester **183** was dissolved in benzene and heated in a sealed vial. After 24 h (entry 1), ^{1}H-NMR analysis revealed a 6:1 ratio of starting ester **183** to bridged adduct **201**. Refluxing for 3 d (entry 2) provided a 2:1 ratio of **183**:**201**. The best results in benzene were observed when **183** was refluxed for 12 d (entry 3). This produced a 1:2 mixture of **183**:**201**. In entry 4, the higher boiling solvent toluene was used; however, after refluxing for 2 d the substrate decomposed. ^{1}H-NMR spectroscopy did not show peaks related to that of **183** or **201**. When dioxane, a more polar solvent was used (entry 5) a 1.5:1 mixture of **183**:**201** was seen after 1 d. Refluxing for 4 d in either dioxane (entry 6) or H_2O (entry 7) produced a complex mixture due to decomposition of both **183** and **201**.

Table 2.13: IMDAF Conditions for the Formation of Bridged Adduct 201



183 **201**

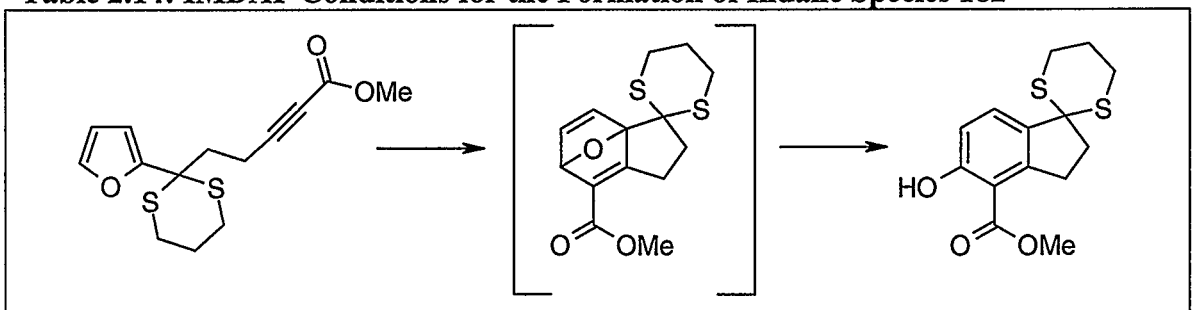
Entry	Solvent	Temperature	Time	Ratio 183:201 by ^{1}H-NMR
1	C_6H_6	reflux	1 d	6:1
2	C_6H_6	reflux	3 d	2:1
3	C_6H_6	reflux	12 d	1:2
4	tol	reflux	1 d	dec
5	dioxane	reflux	1 d	1.5:1
6	dioxane	reflux	4 d	CM
7	H_2O	reflux	4 d	CM

As an alternative, the Diels-Alder was attempted at low temperature with the use of Lewis acid Me_2AlCl (Table 2.14). Acetylenic ester **183** was dissolved in CH_2Cl_2 and cooled to -78 °C. In entry 1, 0.1 equiv. Me_2AlCl was added, and in entry 2, 1.5 equiv. of Me_2AlCl was added. Both reactions were monitored by TLC at -78 °C for 2 h, -40 °C for 1 h then 0 °C for 1 h. This did not reveal any additional spots corresponding to the bridged adduct so the reactions were stirred overnight, allowing the mixture to warm to rt. The following day, ^{1}H-NMR spectral analysis of the crude product of entry 1 showed only recovered starting material.

Interestingly, ^{1}H-NMR spectral analysis of the product obtained from entry 2 after flash chromatography (isolated in 54% yield.) indicated the product was not bridged adduct **201**. The ^{1}H-NMR spectrum showed two doublets at 6.90 and 7.59 ppm with a coupling constant of $J = 7.3$ Hz while the two vinyl signals in **201** were a doublet at 7.26 ppm corresponding to H_c and the doublet of doublets at 7.35 ppm corresponding to H_b.

In addition, the doublet at 5.86 ppm corresponding to bridge hydrogen (H_a) in **201** was absent. This indicated that the bridged compound **201** was not the product from the reaction involving 1.5 equiv. of Me_2AlCl. Further analysis of the product by IR showed the presence of an OH stretch from 3500-3000 cm^{-1} and a carbonyl stretch at 1670 cm^{-1}. That the carbonyl stretch was due to a methyl ester was confirmed by a 3 hydrogen singlet at 3.94 ppm in the ^{1}H-NMR spectrum. A sharp singlet at 11.2 ppm integrating for one hydrogen atom was also observed in the ^{1}H-NMR spectrum. This peak was indicative of an ortho substituted phenolic ester in which the hydrogen atom of the hydroxyl group is hydrogen bonding to the ester.[49] Proof that the bridged compound had aromatized was found upon examination of the ^{13}C-NMR spectrum. The ^{13}C-NMR spectrum of **182** showed six aromatic signals while that of **183** showed four characteristic furan signals. So, given the above data and the fact that the ^{1}H-NMR spectrum did not match that of bridged compound **201**, it was concluded that **201** had aromatized *in situ* to form desired indane **182** in the presence of excess Lewis acid. Unfortunately, mass spectrometry was not useful in determining the structure of **182** as **183**, **201** and **182** had identical masses. Thus, key intermediate **182** was finally synthesized!

Table 2.14: IMDAF Conditions for the Formation of Indane Species 182

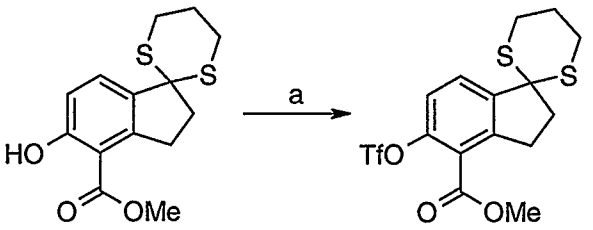


183 **201** **182**

Entry	equiv. LA	Solvent	Temperature	Product
1	0.1 Me_2AlCl	CH_2Cl_2	-78 °C to rt	**183**
2	1.5 Me_2AlCl	CH_2Cl_2	-78 °C to rt	**182**

In the synthesis of xestoquinone (Scheme 1.13),[37] the aromatic portion of the molecule was coupled to the furan portion through an acid chloride. It was hoped that in the synthesis of viridin, the indane portion of the molecule could be coupled to the furan portion through a methyl ester. By doing this, two steps would be eliminated in the total synthesis. Phenol **182** was converted to triflate **202** by treatment of **182** with Tf_2O and NEt_3 (Scheme 2.39). Triflate **202** was isolated in 65% yield after purification by flash chromatography.

Scheme 2.39

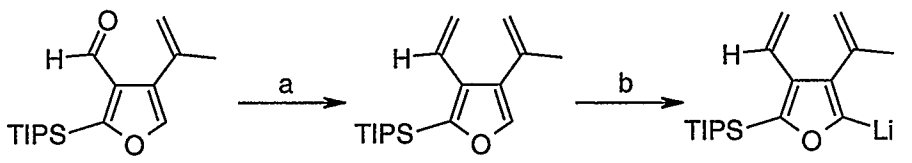


182 **202**

Conditions: a) Tf_2O, NEt_3, CH_2Cl_2, 0 °C, 15 min (65%).

The model furan system **203** was prepared by treatment of aldehyde **111** with an ylid prepared by treatment of methyl triphenylphosphonium bromide with *n*BuLi. Wittig product **203** was isolated in 89% yield after purification by flash chromatography. Furan **203** was lithiated using *n*BuLi to produce **203a**.

Scheme 2.40

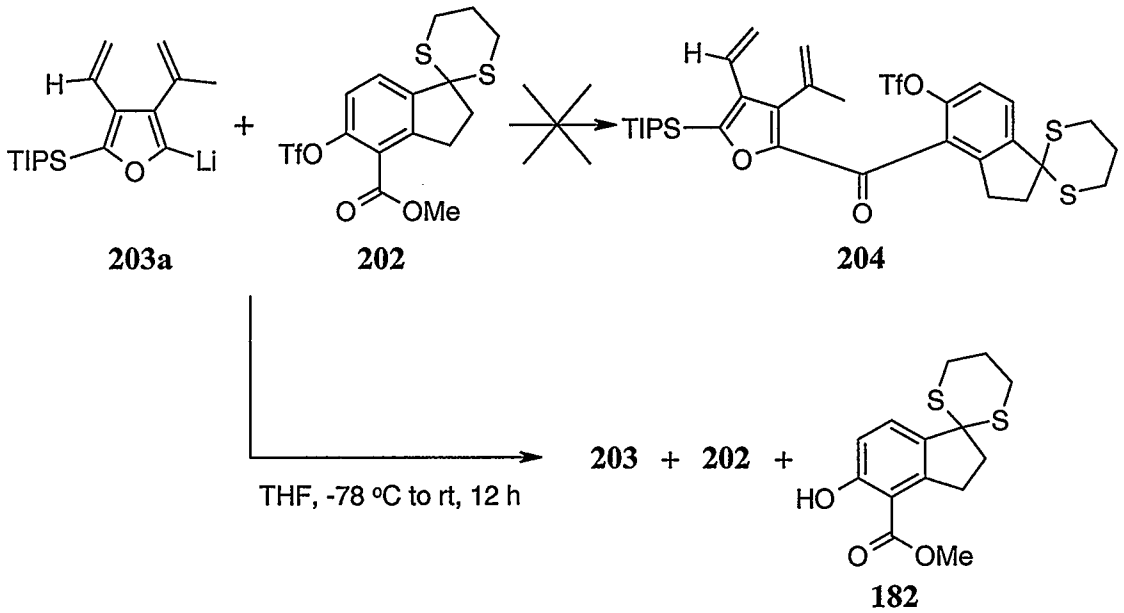


111 **203** **203a**

Conditions: a) Ph_3PCH_2Br, *n*BuLi, THF, -78 °C to 0 °C 2 h (89%); b) *n*BuLi, THF, -78 °C, 1 h then 0 °C, 1 h.

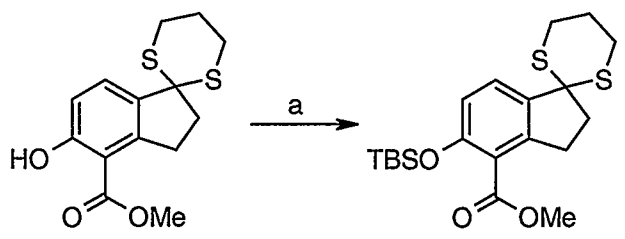
Lithiated furan **203a** was treated with triflate **202** in a solution of THF at –78 °C and stirred overnight. Coupled product **204** was not observed in the crude reaction mixture. Instead, ^{1}H-NMR spectroscopy showed a mixture of furan **203**, triflate **202** and phenol **182** (Scheme 2.41).

Scheme 2.41



Phenol **182** was protected by treating **182** with TBSCl and NEt_3 to produce TBS ether **205** (Scheme 2.42). It was hoped that the TBS ether would be less reactive and couple to the furan successfully through the methyl ester.

Scheme 2.42

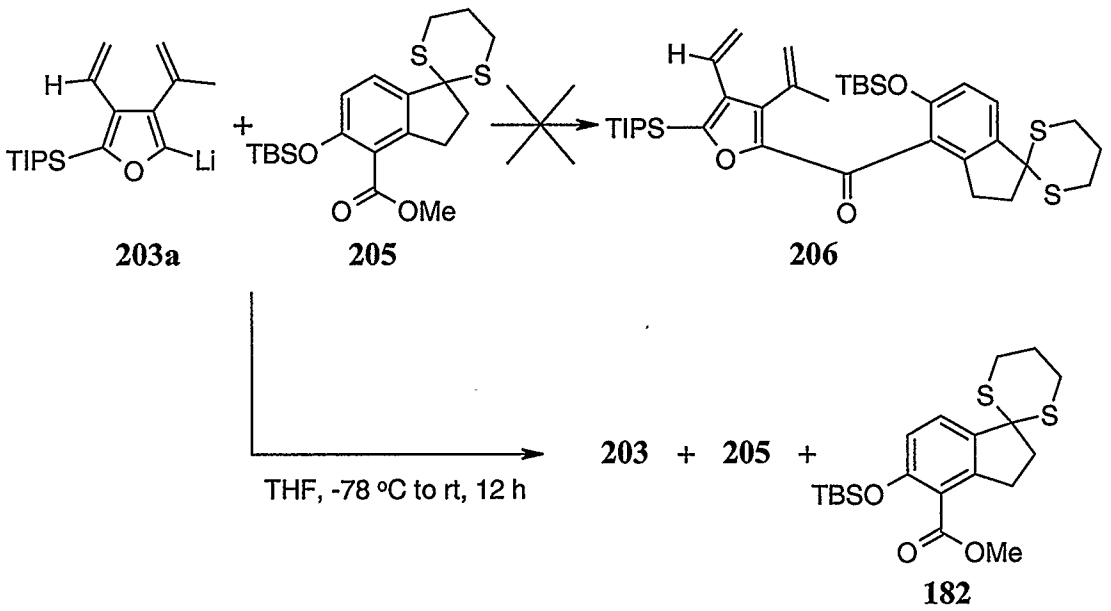


182 **205**

Conditions: a) TBSCl, NEt_3, CH_2Cl_2 (75%).

Lithiated furan **203a** was treated with TBS ether **205** in a solution of THF at –78 °C and stirred overnight The desired coupled product **206,** was not observed in the crude reaction mixture. By ^{1}H-NMR spectroscopy, a similar mixture containing furan **203**, triflate **205** and phenol **182** was observed (Scheme 2.43). It was concluded that the methyl ester of the aromatic portion was not reactive enough to couple with lithiated furan **203a**. As such, the methyl ester of **182** had to be converted to acid chloride **78b** (Scheme 2.44).

Scheme 2.43

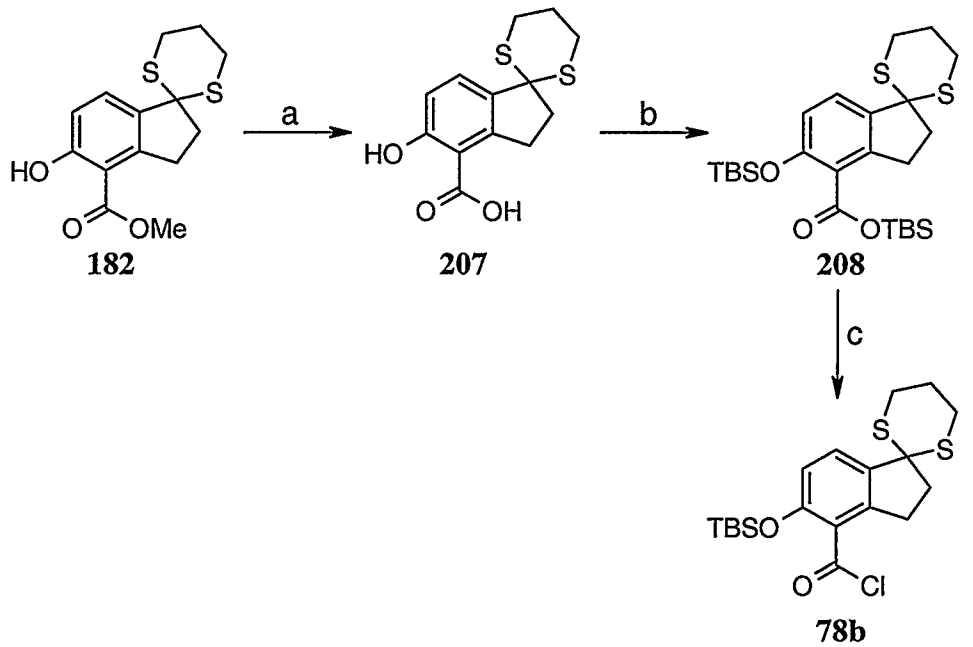


203a **205** **206** **182**

Methyl ester **182** was converted to carboxylic acid **207** by refluxing in a 2.5% NaOH solution in MeOH. Acid **207** was isolated in 54% yield after purification by flash chromatography. Both the acid and phenol of **207** were protected by treatment of **207** with a solution of TBSCl and NEt_3 to produce the di-TBS indane derivative **208**. Finally, di-TBS indane derivative **208** was converted to acid chloride **78b** by stirring **208** in neat

thionyl chloride overnight. Acid chloride **78b** was isolated in 63% yield after purification by distillation over anhydrous K_2CO_3.

Scheme 2.44



Conditions: a) 2.5% NaOH in MeOH, reflux 24 h (54%); b) TBSCl, NEt_3, CH_2Cl_2 (75%); c) $SOCl_2$, rt, 24 h (63%).

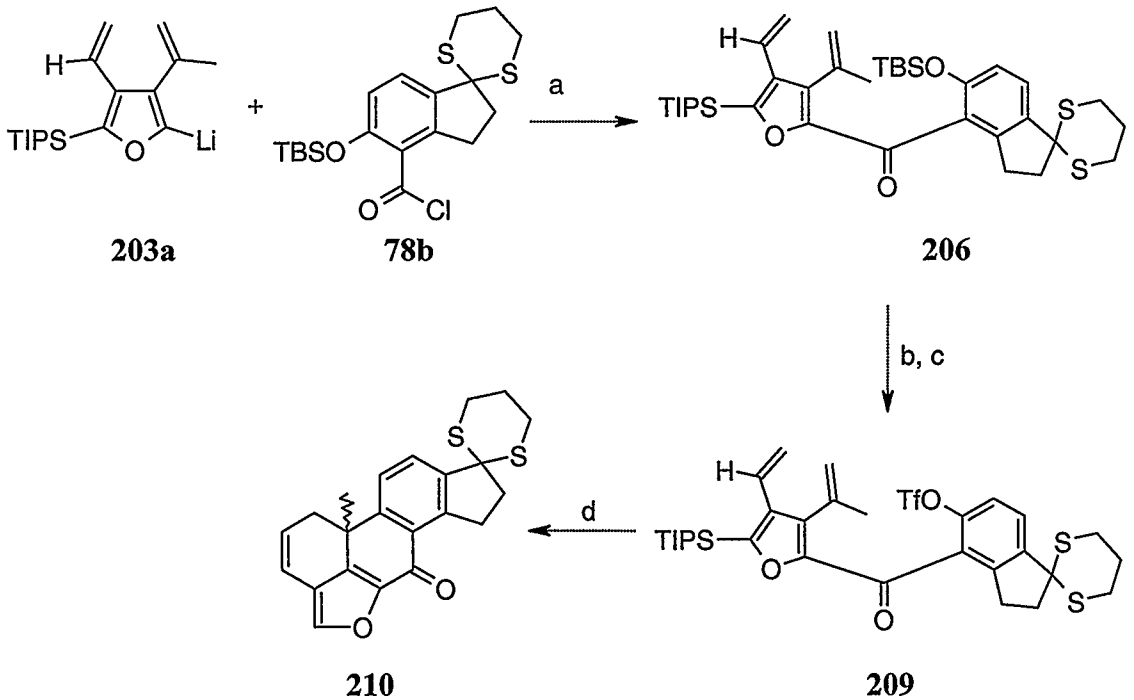
Progress towards to total synthesis of viridin (**1**) was stopped at key intermediate **78b**. This was done mainly due to time constraints but can also be attributed to the lack of substantial quantities of precursors **207** – **78b**. Not enough of acid chloride **78b** could be obtained to effectively carry of the coupling of **78b** with furan **203a** (Scheme 2.45).

2.7.1 Conclusions and Future Work

The objective of synthesizing indane derivative **78b** was achieved via a convergent synthesis in 10 steps with 5.8% overall yield. Reactions at the beginning of the synthesis including the coupling of thioketal **185** and iodide **187**, deprotection of TMS-acetylene **184** and formation of the acetylenic ester **183** were fully optimized. Later synthetic steps

such as the Diels-Alder reaction and saponification still require optimization to increase yields above 50%. The synthesis of tetra-substituted furan derivative **126** (Scheme 2.18) was accomplished in 8 linear steps with 30% overall yield. Future Work on this project will involve two things. First, the reaction of **78b** with furan **203a** must be done to produce a model system **206**. After modifications to produce **209**, polyene cyclization studies will be done to make sure **209** will behave properly with the new aromatic triflate (Scheme 2.45).

Scheme 2.45



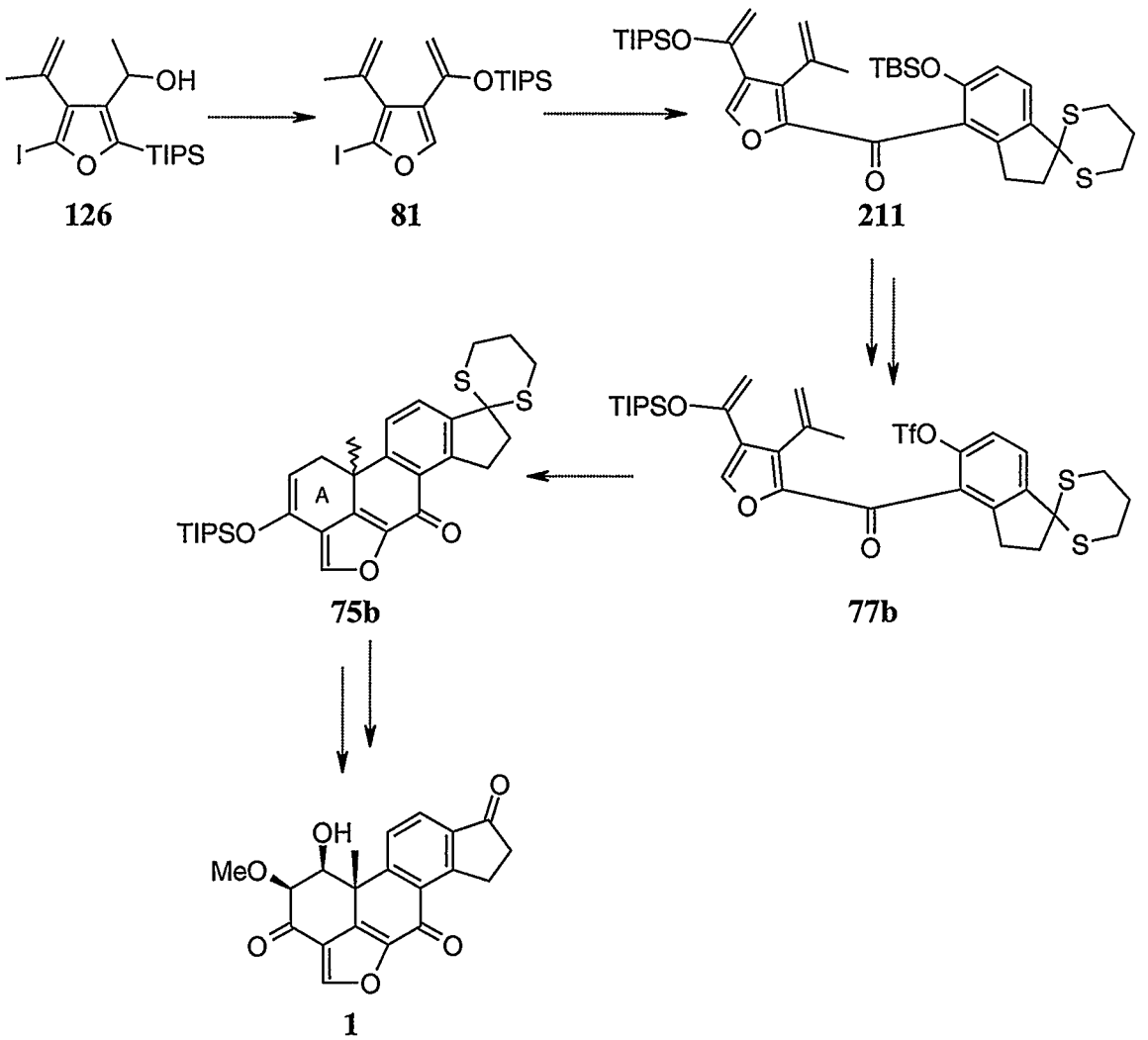
203a **78b** **206** **209** **210**

Conditions: a) THF, -78 °C, 10 h; b) TBAF, THF, 0 °C; c) Tf_2O, NEt_3, 0 °C, CH_2Cl_2; d) (*R*)-BINAP, $Pd(PPh_3)_4$, PMP, toluene.

Second, furan **126** must be oxidized and migrated to form silyl enol ether **81**. In doing this, furan **81** can be coupled to indane **78b** to produce **211**. The TBS phenolic ether of **211** can then be deprotected and transformed to form triflate **77b**. Triflate **77b** can be used in an asymmetric polyene cyclization to form pentacyclic system **75b**. The A

ring of the **75b** can then be manipulated to form **1** and the first total asymmetric synthesis of viridin can be achieved (Scheme 2.46).

Scheme 2.46



Chapter 3

3.1.1 General Experimental

All glassware used in anhydrous reactions was either flame dried prior to use or dried overnight in a 120 °C oven and subsequently cooled under the flow of N_2. All reactions were performed under an atmosphere of N_2 unless otherwise stated.

Tetrahydrofuran was freshly distilled prior to use from sodium benzophenone ketyl. Dimethoxyethane, methylene chloride, chloroform and triethylamine were distilled before use from calcium hydride. All other solvents and reagents were purified using standard methods when required.[81] *n*-Butyllithium and *t*-butyllithium were titrated before use using *N*-benzylbenzamide as an indicator.[82]

The following cooling baths were prepared to maintain sub-ambient temperature: dry ice/acetone (-78 °C), dry ice/chloroform (-60 °C), dry ice/ 1:1 Ethylene glycol:H_2O (-40 °C), and dry ice/MeOH (-20 - -30 °C).[83]

All reactions were monitored via thin layer chromatography (TLC) using aluminum-backed silica gel plates (E. Merck, 0.2 mm silica gel 60, F_{254}). The plates were visualized under UV light at 254 nm and/or by immersing in a stain solution (0.56 g *p*-anisaldehyde, 180 mL 95% EtOH, 4 mL conc. H_2SO_4, 0.2 mL glacial acetic acid) followed by heat development. Flash chromatography was executed using silica gel 60 (E. Merck, 0.04-0.063 mm, 230-400 mesh).[84] Solvent systems refer to mixtures, by ratio, of hexanes to ethyl acetate unless otherwise stated.

Aqueous solutions of NH_4Cl, NaCl (brine), NaS_2O_3, and Na_2CO_3 used either for quenching or for washing the organic phase during extraction were saturated unless otherwise stated.

3.1.2 Compound Characterization and Identification

Melting points were obtained using an Electrothermal® melting point apparatus in a sealed capillary tube and are uncorrected. Boiling points are also uncorrected and refer to measured air-bath temperatures using a Kugelrohr short path distillation apparatus.

Infrared spectra were acquired using a Nicolet Nexus 470 FT-IR E.S.P. spectrophotometer. Solid samples were prepared as $CHCl_3$ thin films and liquid samples were analyzed neat between KBr plates. Characteristic absorptions are listed in wavenumbers (cm^{-1}) followed by the assignment in parentheses.

Routine proton spectra were obtained on a Bruker ACE 200 (^1H 200 MHz) while proton and carbon spectra for the purposes of characterization were obtained on a Bruker DRX 400 (^1H 400 MHz, ^{13}C 100 MHz). For ^1H-NMR and ^{13}C-NMR, deuteriochloroform was used as the NMR solvent and the residual chloroform signal used as the internal standard for chemical shift referencing.^{19}F-NMR spectra were obtained using a Bruker AMX 300 (^{19}F 282 MHz). ^{19}F-NMR spectra were referenced externally to C_6F_6 at -163 ppm relative to $CFCl_3$ at 0 ppm. ^1H-NMR spectra are listed in the format: chemical shift in ppm (multiplicity, coupling constant, number of protons, assignment). DEPT 90 and

DEPT 135 experiments determine the signals assigned to ^{13}C-NMR spectra, either methyl (CH_3), methylene (CH_2), methine (CH) or quaternary carbon (C). ^{13}C-NMR spectra are listed in the following format: chemical shift in ppm (methyl (CH_3), methylene (CH_2), methine (CH) or quaternary carbon (C), assignment). The numbering of atoms for the purpose of spectral assignment does not necessary follow IUPAC rules and are numbered for convenience only.

Low resolution mass spectra were acquired by Ms. Q. Wu at the University of Calgary using a VG 7070 or a Kratos MS80 mass spectrometer using 70 eV ionization with direct probe sample introduction. Mass spectral data is listed in the format: mass (assignment, relative intensity). High resolution mass spectrometry was performed by Ms. D. Fox at the University of Calgary on a Kratos MS80 spectrometer. Elemental analysis was performed by Ms. R. Simank using a Control Equipment Corporation 440 Elemental Analyzer.

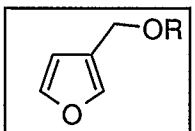
3.1.3 Naming Conventions

Structures presented in this chapter are numbered for convenience only and do not follow IUPAC rules. Names for complex chemical compounds were generated either by the Beilstein AutoNom program[85] or by the Chemical Abstract naming system for polycyclic ring systems and do not follow IUPAC rules.

3.2.1 Experimental Conditions Pertaining to Chapter 2

3.2.2 General Procedures

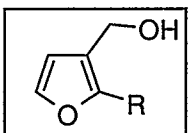
General Procedure 1 for the Protection of 3-Furanmethanol



93 R = TBS
107 R = TIPS

Imidazole (0.255 mol) was dissolved in DMF (20 mL). To this solution was added a solution of the desired silyl chloride (0.153 mol) in DMF (50 mL). The mixture was then stirred at rt for 1 h. A solution of **92** (0.102 mol) in DMF (20 mL) was added to the imidazole/silyl chloride mixture and stirred for 48 h. The reaction mixture was diluted with Et_2O (3 x 25 mL) and the organic layer washed with 0.1 M HCl (3 x 25 mL) followed by brine (3 x 25 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a yellow oil. The crude product was purified by distillation *via* air bath under reduced pressure to afford a clear, colorless oil.

General Procedure 2 for the Migration of Silyl Protected 3-Furanmethanol

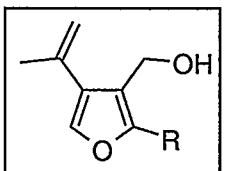


94 R = TBS
108 R = TIPS

The silyl protected 3-furanmethanol (0.100 mol) was dissolved in THF (50 mL) and the solution was cooled to 0 °C. Hexamethylphosphoramide (0.150 mol) was added to the solution and the mixture stirred for 2 h. *n*BuLi (0.140 mol) was added dropwise, and the mixture stirred overnight, allowing to warm to rt. The mixture was quenched with NH_4Cl (40 mL) and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over $MgSO_4$, filtered and concentrated *in*

vacuo to provide an orange oil. The crude product was then purified by distillation under reduced pressure to yield a white solid.

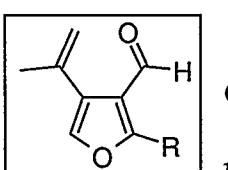
General Procedure 3 for the Preparation of 4-Isopropenyl Substituted Furans



95 R = TBS
109 R = TIPS

The product obtained from the silyl migration (24.0 mmol) was dissolved in DME (50 mL) and cooled to –78 °C. *n*-Butyllithium (48.0 mmol) was added slowly to the reaction mixture and was stirred for 2 h. Triisopropylborate (48.0 mmol) was then added to the mixture at –78 °C and the mixture stirred overnight, allowing to warm to rt. A solution of 2 M Na_2CO_3 (48.0 mmol) was added and stirred for 20 min. Tetrakis(triphenylphosphine) palladium(0) (1.20 mmol) was added, followed by 2-bromopropene (24.0 mmol). The mixture was heated at 50 °C for 24 h. The reaction was cooled to rt and the aqueous layer extracted with Et_2O. The aqueous layer was acidified with 10% HCl and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (3 x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford a brown oil which was purified by flash chromatography.

General Procedure 4 for the Oxidation of 3-(1-Hydroxyalkyl)furans to the Corresponding 3-(1-Oxoalkyl)furans

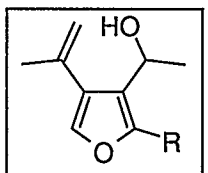


96 R = TBS
110 R = TIPS

To a solution of the isopropenyl-substituted furan (4.00 mmol) in CH_2Cl_2 (10 mL) was suspended NMO (6.00 mmol), and powdered 4Å molecular sieves (2.00 g). Solid TPAP (0.199 mmol) was added in one portion and the mixture was allowed to stir at rt for 1.5 h. The mixture was filtered through a plug of silica gel, eluting with CH_2Cl_2. The solution was

concentrated *in vacuo* to yield a black oil. The crude product was purified by distillation under reduced pressure to provide a clear, colorless oil.

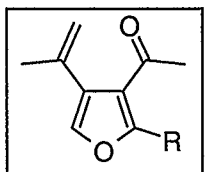
General Procedure 5 for the Alkylation of 3-(1-Oxoalkyl)furans



97 R = TBS
111 R = TIPS

To a solution of the furaldehyde (1.51 mmol) in THF (5 mL) at 0 °C was added dropwise, a solution of MeLi (1.81 mmol). The reaction was stirred for 2 h at 0 °C then subsequently quenched with NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a pale yellow solid. If needed, the crude product was purified by flash chromatography to provide a colorless solid.

General Procedure 6 for the Oxidation of 3-(1-Hydroxyalkyl)furans to the Corresponding 3-(1-Oxoalkyl)furans

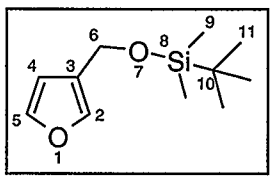


98 R = TBS
112 R = TIPS

To a solution of 3-(1-hydroxyalkyl)furan (4.00 mmol) in CH_2Cl_2 (10 mL) was suspended NMO (6.00 mmol), and powdered 4Å molecular sieves (2.00 g). Solid TPAP (0.199 mmol) was added in one portion and the mixture was allowed to stir at rt for 1.5 h. The mixture was filtered through a plug of silica gel, eluting with CH_2Cl_2. The solution was concentrated *in vacuo* to yield a black oil. The crude product was purified by distillation under reduced pressure to provide a clear, colorless oil.

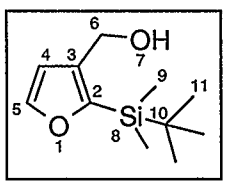
3.2.3 Experimental Methods Pertaining to Section 2.2

Preparation of *t*-Butyl(3-furylmethoxy)dimethylsilane (93)



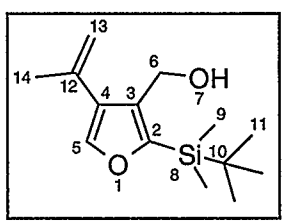
Compound **93** was prepared according to General Procedure 1 utilizing **92** (10.0 g, 0.102 mol) as the starting material. The distilled product (bp 55-60 °C, 0.08 Torr) was a clear, colorless oil (21.2 g, 0.100 mol, 98%). ^{1}H-NMR (200 MHz) δ -0.04 (s, 6H, H-9), 0.81 (s, 9H, H-11), 4.54 (s, 2H, H-6), 6.42 (d, J = 1.1 Hz, 1H, H-4), 1.50-1.55 (m, 2H, H-2 and H-5) ppm. Spectral and physical data corresponded to those reported in the literature.[46a]

Preparation of 2-(*t*-Butyldimethylsilyl)-3-furanmethanol (94)



Compound **94** was prepared according to General Procedure 2 utilizing **93** (10.0 g, 47.1 mmol) as the starting material. The crude product was purified by distillation under reduced pressure (bp 85-90 °C, 0.06 Torr) to afford a white slushy solid (9.62 g, 45.2 mmol, 96.2%). ^{1}H-NMR (200 MHz) δ 0.01 (s, 6H, H-9), 0.89 (s, 9H, H-11), 1.58 (s, 1H, H-7), 4.57 (s, 2H, H-6), 6.46 (d, J = 1.8 Hz, 1H, H-4), 7.57 (d, J = 1.8 Hz, 1H, H-5) ppm. Spectral and physical data corresponded to those reported in the literature.[46a]

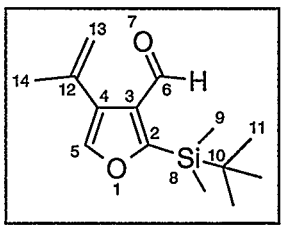
Preparation of 2-(*t*-Butyldimethylsilyl)-4-isopropenyl-3-furanmethanol (95)



Compound **95** was prepared according to General Procedure 3 utilizing **94** (1.00 g, 4.72 mmol) as the starting material. The crude product was purified by flash chromatography (100:1) to

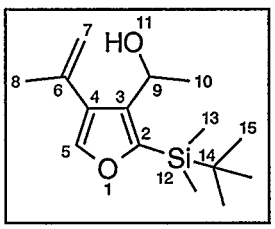
afford a pale yellow solid (0.714 g, 2.84 mmol, 60.2%). ^{1}H-NMR (200 MHz) δ 0.33 (s, 6H, H-9), 0.93 (s, 9H, H-11), 1.55 (s, 1H, H-7), 2.05-2.10 (m, 3H, H-14), 4.63 (2, 2H, H-6), 5.05-5.10 (m, 1H, H-13a), 5.35-5.45 (m, 1H, H-13b), 7.60 (s, 1H, H-5) ppm. Spectral and physical data corresponded to those reported in the literature.[37]

Preparation of 2-(*t*-Butyldimethylsilyl)-4-isopropenyl-3-furaldehyde (96)



Compound **96** was prepared according to General Procedure 4 employing **95** (1.07 g, 4.25 mmol) as the starting 3-(1-hydroxyalkyl)furan. The crude product was purified by distillation under reduced pressure (bp 65-70 °C, 0.06 Torr) to yield a clear, colorless oil (1.06 g, 4.25 mmol, >99.0%). ^{1}H-NMR (200 MHz) δ 0.37 (s, 6H, H-9), 0.95 (s, 9H, H-11), 2.00-2.10 (m, 3H, H-14), 5.10-5.15 (m, 1H, H-13a), 5.20-5.30 (m, 1H, H-13b), 7.57 (s, 1H, H-5), 10.1 (s, 1H, H-6) ppm. Spectral and physical data corresponded to those reported in the literature.[37]

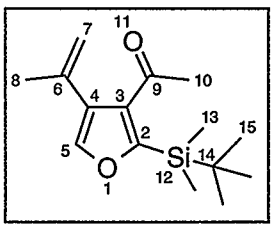
Preparation of 1-(2-(*t*-Butyldimethylsilyl)-4-isopropenyl-3-furan)ethanol (97)



Compound **97** was prepared according to General Procedure 5 utilizing **96** (1.00 g, 4.00 mmol) as the starting 3-(1-oxoalkyl)furan and MeLi (3.40 mL, 1.40 M in Et_2O, 4.80 mmol) as the alkyllithium. The crude product was purified by flash chromatography (50:1) to provide a white solid (1.06 g, 3.96 mmol, 99.0%). ^{1}H-NMR (200 MHz) δ 0.30 (s, 3H H-13a), 0.32 (s, 3H, H-13b), 0.95 (s, 9H, H-15), 1.52 (d, J = 1.8 Hz, 3H, H-10), 2.05-2.15 (m, 3H, H-8), 5.05-5.15 (m, 2H, H-7a and H-9), 5.40-5.45 (m,

1H, H-7b), 7.52 (s, 1H, H-5) ppm. Spectral and physical data corresponded to those reported in the literature.[49]

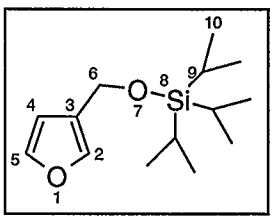
Preparation of 1-(2-(*t*-Butyldimethylsilyl)-4-isopropenyl-3-furan)ethanone (91)



Compound **91** (0.400 g, 1.51 mmol) was prepared according to General Procedure 6 utilizing **97** as the starting 3-(1-hydroxyalkyl)furan. The crude product was purified *via* distillation under reduced pressure (bp 85-90 °C, 0.1 Torr) to yield a yellow oil (0.363 g, 1.37 mmol, 90.7%). ^{1}H-NMR (200 MHz) δ 0.24 (s, 6H, H-13), 0.95 (s, 9H, H-15), 2.03-2.05 (m, 3H, H-8), 2.41 (s, 3H, H-10), 4.90-4.95 (m, 1H, H-7a), 5.09-5.11 (m, 1H, H-7b), 7.51 (s, 1H, H-5) ppm. Spectral and physical data corresponded to those reported in the literature.[49]

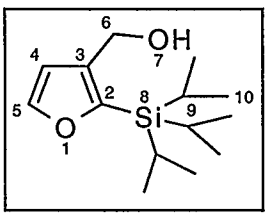
3.2.4 Experimental Methods Pertaining to Section 2.3

Preparation of (3-furylmethoxy)triisopropyl silane (108)



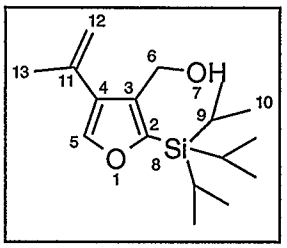
Compound **108** was prepared according to General Procedure 1 utilizing 3-furanmethanol (10.0 g, 0.0394 mol) as the starting material. The distilled product (bp 95-98 °C, 20 Torr) was a clear, colorless oil (15.3 g, 0.0374 mol, 94.9%). ^{1}H-NMR (200 MHz) δ 1.03-1.15 (m, 21H, H-10 and H-9), 4.66 (s, 2H, H-6), 6.32 (d, 1H, J = 1.3 Hz, H-4), 7.35-7.40 (m, 2H, H-2 and H-5) ppm. Spectral and physical data corresponded to those reported in the literature.[46b]

Preparation of 2-(Triisopropylsilyl)-3-furanmethanol (109)



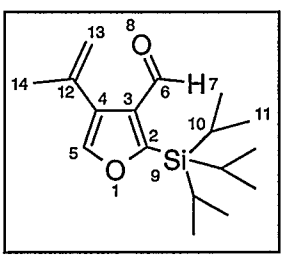
Compound **109** was prepared according to General Procedure 2 utilizing **108** (10.0 g, 39.4 mmol) as the starting material. The crude product was purified by distillation under reduced pressure (bp 124-126 °C, 0.08 Torr) to afford a white slushy solid (9.87 g, 38.9 mmol, 98.7%). ^{1}H-NMR (200 MHz) δ 1.09 (d, 18H, J = 7.3 Hz, H-10), 1.40 (septet, 3H, H-9), 1.56 (bs, 1H, exchanges with D_2O, H-7), 4.68 (s, 2H, H-6), 7.32 (d, J = 4.7 Hz, 1H), 7.57 (d, J = 4.7 Hz, 1H, H-5). Spectral and physical data corresponded to those reported in the literature.[46b]

Preparation of 2-(Triisopropylsilyl)-4-isopropenyl-3-furanmethanol (110)



Compound **110** was prepared according to General Procedure 3 utilizing **109** (2.04 g, 7.87 mmol) as the starting material. The crude product was purified by flash chromatography (20:1) to provide a white solid (1.41 g, 4.80 mmol, 61.0%). mp 60.0-61.5 °C; IR (KBr) 3317 (OH) cm^{-1}; ^{1}H-NMR (200 MHz) δ 1.10 (d, J = 7.3 Hz, 18H, H-10), 1.35 (septet, J = 7.3 Hz, 3H, H-9), 2.08 (s, 3H, H-13), 4.6 (s, 2H, H-6), 5.08 (t, J = 1.6 Hz, 1H, H-12a), 5.45 (t, J = 1.6 Hz, 1H, H-12b), 7.64 (s, 1H, H-5) ppm; ^{13}C-NMR (50 MHz) δ 11.5 (CH, C-9), 18.6 (CH_3, C-10), 23.5 (CH_3, C-13), 56.0 (CH_2, C-6), 112.7 (CH_2, C-12), 126.5 (C, C-2), 133.4 (C, C-3), 135.4 (C, C-4), 145.1 (CH, C-5), 156.0 (C, C-11) ppm; mass spectrum, *m/z* (relative intensity, %) 251 (M^+-C_3H, 70) amu; Exact mass for $C_{14}H_{23}O_2Si$ (M^+ - C_3H_7): calcd 251.1468, found 251.1467 amu.

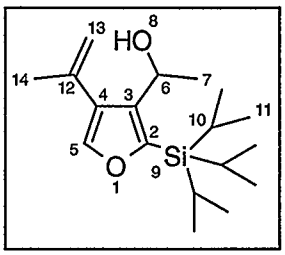
Preparation of 4-Isopropenyl-2-triisopropylsilanyl-furan-3-carbaldehyde (111)



Compound **111** was prepared according to General Procedure 4 employing **110** (1.07 g, 3.66 mmol) as the starting 3-(1-hydroxyalkyl)furan. The crude product was purified by distillation under reduced pressure (bp 80-82 °C, 8.0 x 10^{-2} Torr) to yield a clear, colorless oil (1.06 g, 3.66 mmol, >99.0%). IR (KBr) 1689 (C=O) cm^{-1}; ^{1}H-NMR (200 MHz) δ 1.09 (d, J = 7.3 Hz, 18H, H-11), 1.50 (septet, J = 7.3 Hz, 3H, H-10), 2.07 (s, 3H, H-14), 5.15 (t, J = 1 Hz, 1H, H-13a), 5.27 (t, J = 0.6 Hz, 1H, H-13b), 7.60 (s, 1H, H-5), 10.28 (s, 1H, H-7) ppm; ^{13}C-NMR (50 MHz) δ 11.6 (CH, C-10), 18.5 (CH_3, C-11), 23.3 (CH_3, C-14), 115.9 (CH_2, C-13), 127.2 (C, C-12), 134.8 (C, C-2),

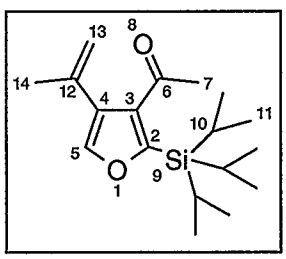
136.1 (C, C-4), 145.0 (CH, C-5), 170.8 (C, C-3), 186.8 (C, C-6) ppm; mass spectrum, *m/z* (relative intensity, %) 249 (M^+-iPr, 100) amu; Exact mass for $C_{14}H_{21}O_2Si$ (M^+ - C_3H_7): calcd 249.1301, found 249.1311 amu.

Preparation of 1-(2-(Triisopropylsilyl)-4-isopropenyl-3-furan)ethanol (112)



Compound **112** was prepared according to General Procedure 5 utilizing **111** (1.40 g, 4.80 mmol) as the starting 3-(1-oxoalkyl)furan and MeLi (4.11 mL, 1.40 M in Et_2O, 5.75 mmol) as the alkyllithium. The crude product was purified by flash chromatography (12:1) to provide a white solid (1.48 g, 4.80 mmol, >99.0%). mp 57.5-59.0 °C; IR (KBr) 3305 (OH) cm^{-1}; ^{1}H-NMR (400 MHz) δ 1.11 (d, J = 7.4 Hz, 18H, H-11), 1.39 (p, J = 7.4 Hz, 3H, H-10), 1.54 (d, J = 8.8 Hz, 3H, H-7), 2.12 (s, 3H, H-14), 5.04 (q, J = 7.2 Hz, 1H, H-6), 5.13 (s, 1H, H-13b), 5.50 (s, 1H, H-13a), 7.54 (s, 1H, H-5) ppm; ^{13}C-NMR (100 MHz) δ 12.0, 18.9, 22.4, 25.0, 64.1, 116.1, 127.1, 136.7, 138.1, 145.7, 154.5 ppm; mass spectrum, *m/z* (relative intensity, %) 265 (M^+-C_3H_7) amu; Exact mass for $C_{15}H_{25}O_2Si$ (M^+ - C_3H_7): calcd 265.1632, found 265.1624 amu.

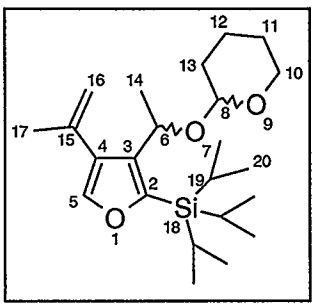
Preparation of 1-(2-(triisopropylsilyl)-4-isopropenyl-3-furan)ethanone (113)



Compound **113** was prepared according to General Procedure 6 utilizing **112** (1.00 g, 3.24 mmol) as the starting 3-(1-hydroxyalkyl)furan. The crude product was purified *via* distillation under reduced pressure (bp 88-90 °C, 7.0 x 10^{-2} Torr) to yield a clear, colorless oil (0.795 g, 2.75 mmol, 86.0%). IR (KBr) 1683 (C=O) cm^{-1};

^{1}H-NMR (400 MHz) δ 1.07 (d, J = 7.6 Hz, 18H, H-11), 1.41 (septet, J = 7.6 Hz, 3H, H-10), 2.04 (s, 3H, H-7), 2.41 (s, 3H, H-14), 4.95 (s, 1H, H-13a), 5.11 (s, 1H, H-13b), 7.52 (s, 1H, H-5) ppm; ^{13}C-NMR (50 MHz) δ 11.5 (CH, C-10), 18.7 (CH_3, C-11), 23.9 (CH_3, C-7), 30.7 (CH_3, C-14), 115.3 (CH_2, C-13), 126.8 (C, C-12), 135.4 (C, C-3), 137.8 (C, C-4), 143.6 (C, C-2), 160.5 (CH, C-5), 198.9 (C, C-6) ppm; mass spectrum, *m/z* (relative intensity, %) 263 (M^+ -C_3H_7, 100) amu; Exact mass for $C_{115}H_{23}O_2Si$ (M^+ - C_3H_7): calcd 263.1455, found 263.1467 amu.

Preparation of (4-Isopropenyl-3-[1-(tetrahydro-pyran-2-yloxy)-ethyl]-furan-2-yl-triisopropylsilane (123)

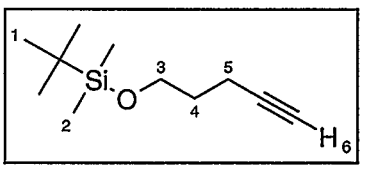


Compound **112** (0.154 g, 0.487 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. Dihydropyran (0.0500 mL, 0.536 mmol) was added to the solution followed by *p*TsOH (9.30 mg, 0.0487 mmol). The mixture was stirred for 10 min at 0 °C at which point the ice bath was removed, and stirred for an additional 5 min. The reaction was quenched with brine (5 mL) and washed with Et_2O (2 x 10 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to provide a yellow oil. The crude product was purified by flash chromatography (20:1) to provide a yellow oil (0.150 g, 0.384 mmol, 78.9%) that was isolated as a 50:50 mixture of diastereomers. IR (KBr) 1629 (C=C), 1014 (CO) cm^{-1}; ^{1}H-NMR (400 MHz) δ 1.11 (m, 36H, H-20), 1.38 (m, 6H, H-19), 1.40 (d, J = 5.4 Hz, 3H, H-14), 1.44 (d, J = 5.4 Hz, 3H, H-14), 1.60-1.80 (m, 12H, H-11, H-12, H-13), 2.11 (s, 6H, H-17), 3.43 (m, 2H, H-10), 3.78-3.96 (m, 2H, H-10), 4.57 (m, 1H, H-6), 4.87 (m, 1H, H-6), 5.04 (m, 4H, H-16), 5.50

(s, 1H, H-8), 5.53 (s, 1H, H-8), 7.53 (s, 1H, H-5), 7.55 (s, 1H, H-5) ppm; ^{13}C-NMR (100 MHz) δ 11.9 (CH, C-19), 12.0 (CH, C-19), 18.8 (CH_3, C-20), 18.9 (CH_3, C-20), 19.4 (CH_2, C-12), 19.8 (CH_2, C-12), 20.1 (CH_2, C-11), 22.2 (CH_2, C-11), 24.6 (CH_3, C-14), 24.7 (CH_3, C-14), 30.9 (CH_2, C-13), 31.1 (CH_2, C-13), 62.0 (CH_2, C-10), 62.8 (CH_2, C-10), 67.1 (CH, C-8), 67.5 (CH, C-8), 95.7 (CH, C-6), 96.6 (CH, C-6), 115.3 (CH_2, C-16), 115.5 (CH_2, C-16), 127.1 (C, C-2), 127.4 (C, C-2), 136.0 (C, C-3), 136.2 (C, C-3), 136.7 (C, C-4), 137.2 (C, C-4), 145.1 (CH, C-5), 145.5 (CH, C-5), 153.9 (C, C-15), 155.4 (C, C-15) ppm; mass spectrum, *m/z* (relative intensity, %) 392 (M^+, 1) amu, Exact mass for $C_{23}H_{40}O_3Si$: calcd 392.6471, found 392.6486 amu.

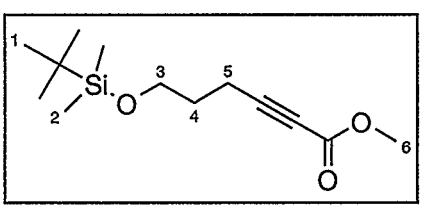
3.2.5 Experimental Methods Pertaining to Section 2.5

Preparation of *t*-Butyl-dimethyl-pent-4-ynyloxy-silane (171)



Following a literature procedure published by Piers *et al.*[68] a solution of TBSCl (5.25 g, 35.0 mmol) in dry CH_2Cl_2 (5 mL) was added slowly to a solution of 4-pentynol (1.68 g, 20.0 mmol) and NEt_3 (3.78 g, 27.2 mmol) in CH_2Cl_2 (25 mL) at 0 °C. The mixture was stirred for 4 h, allowing to warm to rt. Water (30 mL) was added to the mixture, and the organic layer was washed with a 1:1 solution of hexanes:EtOAc (3 x 30 mL). The combined organic layers were washed with brine (1 x 25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a yellow oil. The crude product was purified by flash chromatography (9:1) to provide a clear colorless oil (3.43 g, 17.3 mmol, 86.5%). ^{1}H-NMR (200 MHz) δ 0.064 (s, 6H, H-2), 0.90 (s, 9H, H-1), 1.63-1.83 (m, 2H, H-4), 1.93 (t, J = 2.6 Hz, 1H, H-6), 2.27 (dt, $J_{5,4}$ = 6 Hz, $J_{5,6}$ = 2.6 Hz, 2H, H-5), 3.70 (t, J = 6 Hz, 2H, H-3) ppm. Spectral and physical data corresponded to those reported in the literature.[68]

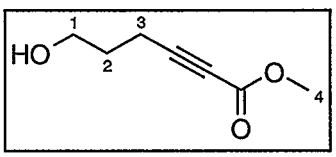
Preparation of 6-(*t*-Butyl-dimethyl-silanyloxy)-hex-2-ynoic Acid, Methyl Ester (172)



Compound **172** was prepared according to a literature procedure published by Piers *et al.*[69] Acetylene **171** (0.500 g, 2.53 mmol) was dissolved in THF (15 mL) and cooled to -78 °C. *n*BuLi (1.84 mL, 1.51 M in hexanes, 2.78 mmol) was added dropwise. The mixture was stirred at -78 °C for 15 min then stirred at -25 °C

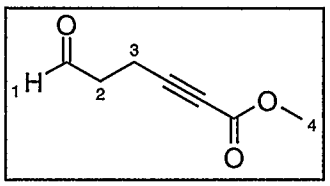
for 1 h. Methyl chloroformate (0.263 g, 2.78 mmol) was then added and the mixture stirred for 1 h at -20 °C followed by 1 h at rt. The reaction was quenched with $NaHCO_3$ (20 mL) and extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a pale yellow oil. The crude oil was purified by distillation (70-75 °C, 8 x 10^{-2} torr) to provide a clear, colorless oil (0.452 g, 1.77 mmol, 70.0%). ^{1}H-NMR (200 MHz) δ 0.060 (s, 6H, H-2), 0.90 (s, 9H, H-1), 1.78 (p, J = 7 Hz, 2H, H-4), 2.44 (t, J = 7 Hz, 2H, H-5), 3.69 (t, J = 5.6 Hz, 2H, H-3), 3.77 (s, 3H, H-6) ppm. Spectral and physical data corresponded to those reported in the literature.[69]

Preparation of 6-Hydroxy-hex-2-ynoic Acid, Methyl Ester (169)



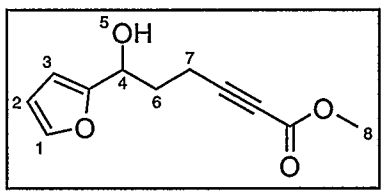
The deprotection of **172** was achieved following a literature procedure published by Kawai *et al.*[72] Compound **172** (2.27 g, 8.91 mmol) was dissolved in a 20:1 mixture of THF:H_2O (40 mL:2 mL) and to that solution, solid *p*TsOH (0.254 g, 1.34 mmol) was added. The mixture was stirred overnight at rt. The reaction was treated with $NaHCO_3$ (30 mL) and concentrated *in vacuo*. Water (30 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a pale yellow oil. The crude product was purified by flash chromatography (4:1) to afford a clear and colorless oil (1.22 g, 8.59 mmol, 96.4%). ^{1}H-NMR (200 MHz) δ 1.84 (p, J = 7 Hz, 2H, H-2), 2.49 (t, J = 7 Hz, 2H, H-3), 3.76 (t, J = 6.6 Hz, 2H, H-1), 3.76 (s, 3H, H-4) ppm. Spectral and physical data corresponded to those reported in the literature.[72]

Preparation of 6-Oxo-hex-2-ynoic Acid, Methyl Ester (174)



Aldehyde **174** was prepared according to a literature procedure provided by Trost and Shi.[73] DMSO (0.110 mL, 1.55 mmol) was added dropwise to a solution of oxalyl chloride (68.0 μL, 0.774 mmol) in CH_2Cl_2 (1.7 mL) at -55 °C and the mixture stirred for 5 min. A solution of **169** (0.100 g, 0.704 mmol) in CH_2Cl_2 (1 mL) was added to the mixture and stirred for 15 min. Triethylamine (0.480 mL, 3.52 mmol) was then added and the reaction stirred for an additional 15 min at -55 °C then 1 h at rt. The reaction was treated with H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a dark red oil. The crude product was purified by flash chromatography (1:1 hexanes:Et_2O) to give a pale yellow solid (0.0471 g, 0.336 mmol, 47.7%). ^{1}H-NMR (200 MHz) δ 2.69 (m, 4H, H-2 and H-3), 3.76 (s, 3H, H-4), 9.80 (s, 1H, H-1) ppm. Spectral and physical data corresponded to those reported in the literature.[73]

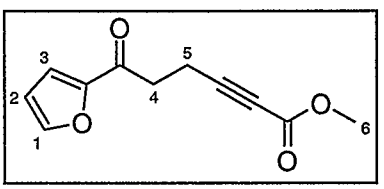
Preparation of 6-Furan-2-yl-6-hydroxy-hex-2-ynoic Acid, Methyl Ester (177)



Compound **177** was prepared according to a modified procedure published by Eberbach *et al.*[75] To a solution of furan (0.0110 g, 0.162 mmol) in Et_2O (0.5 mL) at -78 °C was added *n*BuLi (0.100 mL, 1.60 M in hexanes, 0.160 mmol) dropwise. The mixture was stirred for 15 min at -78 °C, warmed to 0 °C and stirred for an additional 1.5 h. The

mixture was recooled to -78 °C and a solution of **174** (0.0251 g, 0.179 mmol) in Et_2O (0.25 mL) was added. The mixture was stirred for 2.5 h at -78 °C. The reaction was quenched with H_2O (2.5 mL) and extracted with Et_2O (3 x 5 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a brown/orange oil. The crude product was purified by flash chromatography (50:1) to provide a yellow oil (0.00931g, 0.0448 mmol, 25.0%) ^{1}H-NMR (200 MHz) δ 2.07-2.18 (m, 2H, H-6), 2.39-2.60 (m, 2H, H-7), 3.77 (s, 3H, H-8), 4.83 (dt, J = 6.8 Hz, J = 4.7 Hz, 1H, H-4), 6.27 (dd, J = 3.3 Hz, J = 0.8 Hz, 1H, H-2), 6.34 (dd, J = 3.3, J = 1.8 Hz, 1H, H-3), 7.39 (dd, J = 1.8 Hz, J = 0.8 Hz, 1H, H-1) ppm. Spectral and physical data corresponded to those reported in the literature.[75]

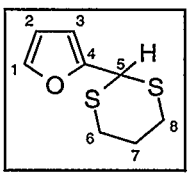
Preparation of 6-Furan-2-yl-6-oxo-hex-2-ynoic Acid, Methyl Ester (179)



Compound **179** was prepared according to a modified procedure published by Eberbach *et al.*[75] To a solution of **177** (0.0150 g, 0.0721 mmol) in Et_2O (2 mL) was suspended a 50-fold weight excess of MnO_2 (75.0 mg, 0.0863 mmol). The mixture was stirred for 2 h at rt, filtered through a pad of Celite and rinsed with Et_2O. The solution was then concentrated *in vacuo* to provide a yellow oil. ^{1}H-NMR (200 MHz) δ 2.73-2.80 (m, 2H, H-4), 3.13-3.21 (m, 2H, H-5), 3.77 (s, 3H, H-6), 6.57 (dd, J = 3.7 Hz, J = 1.8 Hz, 1H, H-3), 7.23 (dd, J = 3.7 Hz, J = 0.8 Hz, 1H, H-2), 7.62 (dd, J = 1.8 Hz, J = 0.8, 1H, H-1) ppm. Spectral and physical data corresponded to those reported in the literature.[75]

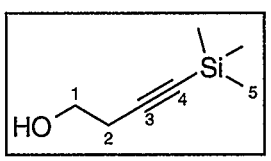
3.2.6 Experimental Methods Pertaining to Section 2.6

Preparation of 2-Furyl-1,3-dithiane (185)



Compound **185** was prepared according to the procedure published by Ramos *et al.*[76] 2-Furfural (2.02 g, 0.0200 mol) was dissolved in $CHCl_3$ (21 mL) and cooled to 0 °C. 1,3-Propanedithiol (2.48 g, 0.0230 mol) was slowly added to the solution, followed by the addition of TMSCl (4.99 g, 0.0460 mol). The mixture was stirred for 18 h, allowing to warm to rt. The reaction was quenched with 4% NaOH (80 mL) and extracted with $CHCl_3$ (3 x 30 mL). The organic layers were combined, washed with brine (3 x 30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a dark red oil. The crude product was purified by distillation under reduced pressure (80 °C, 0.1 Torr) to provide a white solid (3.58 g, 0.193 mol, 96.2%). ^{1}H-NMR (400 MHz) δ 1.97-2.14 (m, 2H, H-7), 2.96-2.98 (m, 4H, H-6 and H-8), 5.23 (s, 1H, H-5), 6.35 (s, 1H, H-2), 6.40 (d, J = 3.2 Hz, 1H, H-3), 7.38 (s, 1H, H-1) ppm. Spectral and physical data corresponded to those reported in the literature.[76]

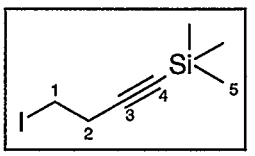
Preparation of 4-Trimethylsilanyl-but-3-yn-1-ol (189)



Compound **189** was prepared according to a modified procedure published by Rawal *et al.*[77] 4-Butynol (10.0 g, 0.143 mol) was dissolved in THF (600 mL) and the mixture cooled to –78 °C. *n*-BuLi (2.20 equiv., 226 mL, 1.39 M in hexanes, 0.314 mol) was added dropwise and the mixture stirred for 1.5 h at –78 °C. TMSCl (38.8 g, 0.357 mol) was added and the reaction stirred for 2 h, warming to 0 °C. The reaction was quenched with H_2O (200 mL) and the aqueous layer

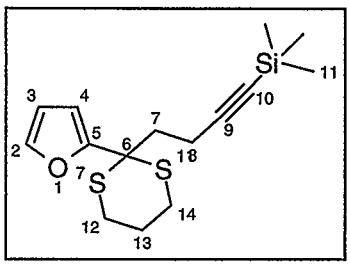
was extracted with Et_2O (3 x 200 mL). The combined organic layers were then washed with 0.1 M HCl (3 x 100 mL) followed by brine (3 x 100 mL) to provide a pale yellow oil (20.2 g, 0.143 mol, >99.0%), which was used without further purification. ^{1}H-NMR (200 MHz) δ 0.17 (s, 9H, H-5), 2.79 (t, J = 15 Hz, H-2), 3.22 (t, J = 15 Hz, H-1) ppm. Spectral and physical data corresponded to those reported in the literature.[77]

Preparation of (4-Iodo-but-1-ynyl)-trimethyl-silane (187)



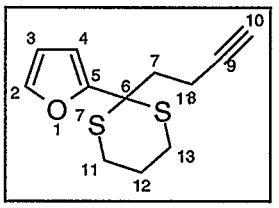
Compound **187** was prepared according to a modified literature procedure published by Rawal *et al.*[77] Compound **189** (5.00 g, 35.2 mmol) was dissolved in CH_2Cl_2 (40 mL). Triphenylphosphine (10.2 g, 38.7 mmol) was added to the mixture, followed by imidazole (3.60 g, 52.8 mmol) and the mixture was stirred until all solids had dissolved. The reaction mixture was then cooled to 0 °C and iodine (9.83 g, 38.7 mmol) was added slowly in portions. The mixture was stirred for 4 h warming to rt. The reaction was quenched with a solution of $Na_2S_2O_3$ (40 mL) and the organic layer was washed with $Na_2S_2O_3$ (3 x 40 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a brown solid. The crude product mixture was then dissolved in hexanes (100 mL) to precipitate the triphenylphosphine oxide by-product, filtered and concentrated *in vacuo* to provide a brown oil. The crude product was then further purified *via* distillation under reduced pressure to provide a clear, colorless oil (6.83 g, 27.1 mmol, 77.0%). ^{1}H-NMR (200 MHz) δ 0.18 (s, 9H, H-5), 2.80 (t, J = 13 Hz, H-2), 3.24 (t, J = 13 Hz, H-1) ppm. Spectral and physical data corresponded to those reported in the literature.[77]

Preparation of [4-(2-Furan-2-yl-[1,3]dithian-2-yl)-but-1-ynyl]-trimethyl silane (184)



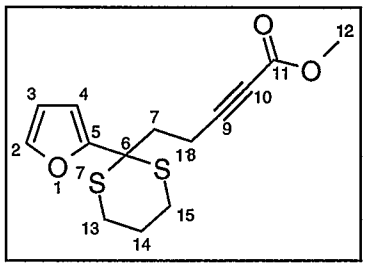
Compound **186** (1.00 g, 5.38 mmol) was dissolved in dry THF (10 mL) and cooled to –78 °C. *n*-BuLi (1.10 equiv., 3.63 mL, 1.63 M in hexanes, 5.91 mmol) was then added dropwise and stirred at this temperature for 1.5 h. A solution of **187** (1.49 g, 5.91 mmol) in THF (2.5 mL) was added slowly to the solution. The mixture was stirred overnight, warming to rt. The reaction was quenched with NH_4Cl and the aqueous layer was extracted with Et_2O (3 x 15 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to provide a brown solid. The crude product was purified by recrystallization from a minimal amount of hexanes to provide a clear, colorless solid (1.37 g, 4.43 mmol, 82.3%). mp 75-76 °C; IR (KBr) 2164 (C≡C), 1022 (C-O) cm^{-1}; ^{1}H-NMR (400 MHz) δ 0.101 (s, 9H, H-11), 1.93-2.00 (m, 2H, H-13), 2.25-2.27 (m, 2H, H-8), 2.32-2.34 (m, 2H, H-7), 2.73-2.83 (m, 4H, H-12 and H-14), 6.33 (t, J = 3 Hz, 1H, H-4), 6.50 (d, J = 3 Hz, 1H, H-3), 7.39 (d, J = 0.78 Hz, 1H, H-2) ppm; ^{13}C-NMR (100 MHz) δ 0.086 (CH_3, C-11), 15.5 (CH_2, C-8), 25.1 (CH_2, C-7), 27.8 (CH_2, C-13), 40.9 (CH_2, C-12 and C-14), 51.5 (C, C-6), 84.9 (C, C-10), 105.9 (C, C-9), 110.4 (CH, C-3), 110.8 (CH, C-4), 142.6 (CH, C-2), 153.5 (C, C-5) ppm; mass spectrum, *m/z* (relative intensity, %) 310.0 (M^+, 4.8) amu; Exact mass for $C_{15}H_{22}OS_2Si$: calcd 310.0869, found 310.0881 amu; Anal. for $C_{15}H_{22}OS_2Si$: calcd C 58.01, H 7.14; found C 58.04, H 7.10 %.

Preparation of 2-(2-But-3-ynyl-[1,3]dithian-2-yl)-furan (194)



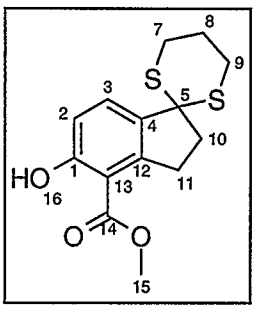
TMS-acetylene **184** (1.40 g, 4.50 mmol) was suspended in MeOH (14 mL) and 2 equiv. of solid K_2CO_3 (1.24 g, 9.00 mmol) was added in one portion. The suspension was then stirred at rt under air for 2 h or until the TLC showed complete disappearance of starting material. The mixture was then concentrated *in vacuo* and the resulting solid was dissolved in 20 mL of H_2O. The aqueous phase was extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide an off-white solid. The crude product was purified by flash chromatography (9:1) to provide a colorless solid (1.00 g, 4.21 mmol, 93.6%). mp 54.5-56 °C; IR (KBr) 3284 (C≡CH), 2115 (C≡C) cm^{-1}; ^{1}H-NMR (400 MHz) δ 1.90 (t, J = 2 Hz, 1H, H-10), 2.01-2.12 (m, 2H, C-8), 2.21-2.24 (m, 2H, C-7), 2.34-2.38 (m, 2H, C-12), 2.73-2.85 (m, 4H, C-11 and C-13), 6.33 (t, J = 3 Hz, 1H, C-3), 6.51 (d, J = 3 Hz, 1H, C-4), 7.40 (d, J = 1.7 Hz, 1H, C-2) ppm; ^{13}C-NMR (100 MHz) δ 14.3 (CH_2, C-8), 25.3 (CH_2, C-7), 27.9 (CH_2, C-12), 41.0 (CH_2, C-11 and C-13), 51.6 (C, C-6), 68.8 (CH, C-10), 88.4 (C, C-9), 110.7 (CH, C-3), 111.0 (CH, C-4), 142.8 (CH, C-2), 153.6 (C, C-5) ppm; mass spectrum, *m/z* (relative intensity, %) 238.0 (M+, 1.48) amu; Exact mass for $C_{12}H_{14}OS_2$: calcd 238.0501, found 238.0486 amu; Anal for $C_{12}H_{14}OS_2$: calcd C 60.46, H 5.92; found C 60.75, H 5.75%.

Preparation of 5-(2-Furan-2-yl-[1,3]dithian-2-yl)-pent-2-ynoic Acid, Methyl Ester (183)



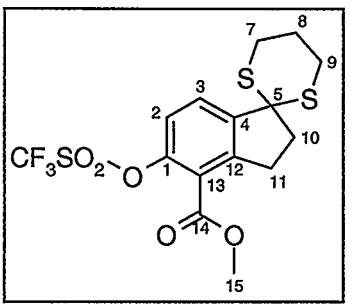
Compound **194** (0.250 g, 1.05 mmol) was dissolved in dry THF (6 mL) and cooled to –78 °C. *n*-BuLi (1.10 equiv., 0.312 mL, 1.48 M in hexanes, 1.16 mmol) was added dropwise to the solution and stirred for 1.5 h. Dimethyl pyrocarbonate was added neat at –78 °C and the mixture was stirred overnight, allowing to warm to ambient temperature. The reaction was quenched with NH_4Cl (10 mL) and the aqueous phase extracted with Et_2O (3 x 10 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide an orange oil. The crude product was purified using flash chromatography (12:1 hexanes:EtOAc with 2% NEt_3) to provide a yellow oil (0.223 g, 0.753 mmol, 71.5%). IR (KBr) 2203 (C≡C), 1711 (C=O), 1257 (C-O) cm^{-1}; ^{1}H-NMR (400 MHz) δ 1.92-1.98 (m, 2H, H-14), 2.38 (s, 4H, H-7 and H-8), 2.75 (m, 4H, H-13 and H-15), 3.70 (s, 3H, H-12), 6.32 (m, 1H, H-3), 6.50 (d, J = 0.7 Hz, 1H, H-4), 7.38 (d, J = 0.7 Hz, 1H, H-2) ppm; ^{13}C-NMR (100 MHz) δ 14.4 (CH_2, C-7), 24.9 (CH_2, C-14), 27.7 (CH_2, C-13 and C-15), 39.4 (CH_2, C-8), 51.1 (C, C-6), 52.6 (CH_3, C-12), 73.1 (C, C-9), 88.2 (C, C-10), 110.5 (CH, C-4), 111.0 (CH, C-3), 142.8 (CH, C-2), 153.0 (C, C-5), 154.0 (C, C-11) ppm; mass spectrum, *m/z* (relative intensity, %) 259.9 (M^+, 14.8) amu; Exact mass for $C_{14}H_{16}O_3S_2$: calcd 296.0518, found 296.0541 amu; Anal for $C_{14}H_{16}O_3S_2$: calcd. C 56.73, H 5.44; found C 55.89, H 5.50%.

Preparation of 2',3'-Dihydro-5'-hydroxy-spiro[1,3]-dithiane-2,1'-[1*H*]indene-4'-carboxylic Acid, Methyl Ester (182)



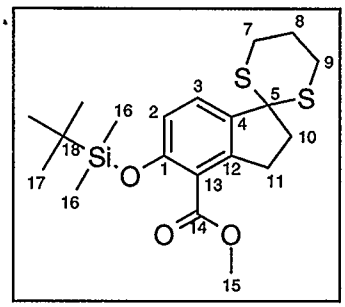
Compound **183** (0.394 g, 1.33 mmol) was dissolved in CH_2Cl_2 (25 mL) and the solution cooled to –78 °C. Dimethylaluminum chloride (1.50 equiv.) was added slowly to the solution, and the mixture stirred overnight, warming to rt. The reaction was then placed in an ice bath and H_2O (10 mL) was slowly added to the reaction. The aqueous layer was shaken gently with $CHCl_3$ (3 x 15 mL) to prevent the formation of an emulsion. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide a brown solid. The crude product was purified by flash chromatography (20:1) to provide a white solid (0.213 g, 0.720 mmol, 54.1%). mp 137-139 °C; IR (KBr) 3113 (OH), 1669 (C=O), 1222 (C-O) cm^{-1}; ^{1}H-NMR (400 MHz) δ 1.95 (m, 1H), 2.14 (m, 1H), 2.86 (m, 5H), 3.16 (t, J = 8 Hz, 2H), 3.30 (t, J = 6.0 Hz, 2H), 3.94 (s, 3H), 6.95 (d, J = 8.5 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 11.24 (s, 1H) ppm; ^{13}C-NMR (100 MHz) δ 25.0 (CH_2, C-10), 29.2 (CH_2, C-8), 32.9 (CH_2, C-7 and C-9), 43.0 (CH_2, C-11), 52.2 (CH_3, C-15), 58.4 (C, C-5), 109.8 (C, C-4), 117.0 (CH, C-3), 131.2 (CH, C-2), 136.5 (C, C-12), 145.7 (C, C-13), 163.3 (C, C-1), 171.3 (C, C-14) ppm; mass spectrum, *m/z* (relative intensity, %) 296.1 (M^+, 11.82) amu; Exact mass for $C_{12}H_{14}OS_2$: calcd 296.0555, found 296.0541 amu; Anal for $C_{14}H_{16}O_3S_2$: calcd C 56.73, H 5.44; found C 59.90, H 5.19%.

Preparation of 2',3'-Dihydro-5'-(trifluoromethylsulphonyloxy)-spiro[1,3]-dithiane-2,1'-[1*H*]indene-4'-carboxylic Acid, Methyl Ester (202)



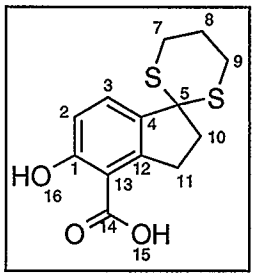
Compound **182** (0.0840 g, 0.284 mmol) was dissolved in CH_2Cl_2 (2.5 mL) and the solution was cooled to –45 °C. Triethylamine (0.0870 mL, 0.624 mmol) was added dropwise and the mixture stirred for 15 min. Triflic anhydride (0.0600 mL, 0.340 mmol) was added and the mixture was allowed to stir for an additional 20 min. The reaction was diluted with Et_2O (10 mL) and washed with 0.1 M HCl (3 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a yellow oil. The crude product was purified by flash chromatography (20:1) to provide an off-white solid (0.0782 g, 0.183 mmol, 64.4%). mp 85-87 °C; IR (KBr) 1710 (C=O), 1206 (CO) cm^{-1}; ^{1}H-NMR (400 MHz) δ 1.72 (m, 1H), 1.95 (m, 1H), 2.68 (m, 4H), 2.94 (m, 2H), 3.07 (t, J = 7 Hz, 2H), 3.73 (s, 3H), 6.95 (d, J = 8.5 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H) ppm; ^{19}F-NMR (282 MHz) δ -86.3 ppm; ^{13}C-NMR (100 MHz) δ 24.8 (CH_2, C-10), 29.7 (CH_2, C-7 and C-9), 31.3 (CH_2, C-8), 43.0 (CH_2, C-11), 52.4 (CH_3, C-15), 58.0 (C, C-5), 117.0 (CF_3, q, $J_{C,F}$ = 116 Hz), 121.5 (CH,C-3), 122.3 (C, C-4), 128.9 (CH, C-2), 146.5 (C, C-12), 147.4 (C, C-13), 147.9 (C, C-1), 164.2 (C, C-14) ppm; mass spectrum, *m/z* (relative intensity, %) 428 (M^+, 17.2) amu; Exact mass for $C_{15}H_{15}O_5S_3F_3$: calcd 428.0014, found 428.0034 amu.

Preparation of 2',3'-Dihydro-5'-(*t*-butyldimethylsilyloxy)-spiro[1,3]-dithiane-2,1'-[1*H*]indene-4'-carboxylic Acid, Methyl Ester (205)



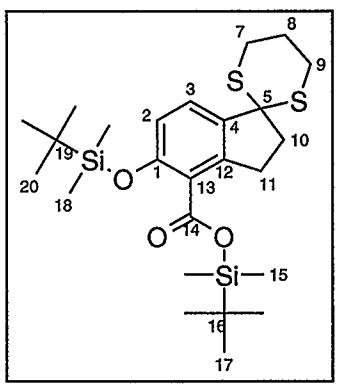
To a solution of TBSCl (0.202 g, 1.34 mmol) in CH_2Cl_2 (0.5 mL) was slowly added a premixed solution of **182** (0.221 g, 0.747 mol) and NEt_3 (0.150 mL, 1.05 mmol) in CH_2Cl_2 (3.5 mL). The mixture was stirred for 4 h then quenched with brine (5 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the organic layers combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a yellow solid. The crude product was purified by flash chromatography (20:1) to provide a white solid (0.229 g, 0.560 mmol, 75.0%). mp 122-124 °C; IR (KBr) 1725 (C=O) cm^{-1}; ^{1}H-NMR (200 MHz) δ 0.21 (s, 6H), 0.97 (s, 9H), 1.99 (m, 1H), 2.17 (m, 1H), 2.84-2.96 (m, 4H), 3.08-3.19 (m, 4H), 3.85 (s, 3H), 6.73 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H) ppm; ^{13}C-NMR (100 MHz) δ -4.4 (CH_3, C-16), 18.1 (C, C-18), 25.5 (CH_3, C-17), 29.2 (CH_2, C-7 or C-9), 29.7 (CH_2, C-8), 30.3 (CH_2, C-11), 43.2 (CH_2, C-7 or C-9), 51.8 (CH_3, C-15), 58.4 (C, C-5), 118.9 (CH, C-3), 121.5 (C, C-4), 127.3 (CH, C-2), 137.8 (C, C-12), 144.4 (C, C-1), 154.4 (C, C-13), 167.4 (C, C-14) ppm; mass spectrum, *m/z* (relative intensity, %) 433.15 (M^+ + Na, 95), 439 (M^+ + K, 25) amu; Exact mass for $C_{16}H_{21}O_3S_2Si$ (M^+ - C_4H_9): calcd 353.0706, found 353.0701 amu; Anal for $C_{20}H_{30}O_3S_2Si$: calcd C 58.49, H 7.36; found C 55.37, H 7.75%.

Preparation of 2',3'-Dihydro-5'-hydroxy-spiro[1,3]-dithiane-2,1'-[1*H*]indene-4'-Carboxylic Acid (207)



Compound **207** was prepared by dissolving **182** (0.100 g, 0.338 mmol) in a 5% NaOH solution in MeOH (5 mL). The solution was heated to 70 °C for 48 h, cooled and concentrated *in vacuo*. Water (10 mL) was added and the aqueous portion acidified with 0.1 M HCl. The acidified aqueous portion was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a brown solid. The crude product was purified by flash chromatography (3% MeOH in $CHCl_3$) to provide a yellow/brown solid (0.0515 g, 0.183 mmol, 54.1%). mp >360 °C; IR (KBr) 3223 (OH), 1661 (C=O) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.39 (t, J = 6 Hz, 2H), 3.18-3.24 (m, 4H), 3.30 (t, J = 6 Hz, 2H), 6.55 (d, J = 8.7 Hz, 1H), 7.35 (d, J = 8.7 Hz, 1H) ppm.

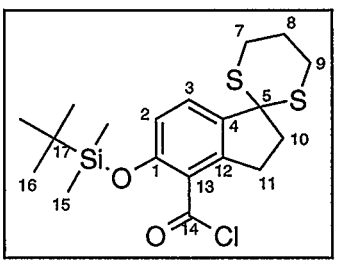
Preparation of 2',3'-Dihydro-5'-(*t*-butyldimethylsilyloxy)-Spiro[1,3]-dithiane-2,1'-[1*H*]indene-4'-carboxylic Acid, *t*-Butyldimethylsilyl Ester (208)



To a solution of TBSCl (0.0639 g, 0.425 mmol) and NEt_3 (0.0165 mL, 0.128 mmol) in CH_2Cl_2 (1 mL) was added a solution of TBSCl (0.0639 g, 0.425 mmol) and **207** (0.0400 g, 0.142 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 2 d, or until analysis by TLC showed the disappearance of starting material. The reaction was quenched with H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a brown solid. The crude product was purified by flash

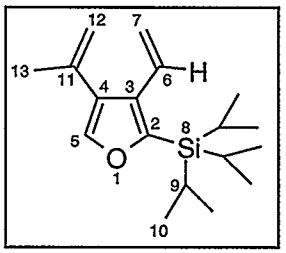
chromatography (3% MeOH in $CHCl_3$) to provide a yellow/brown solid (0.0543 g, 0.107 mmol, 75.3%). IR (KBr) 1709 (C=O) cm^{-1}; ^{1}H-NMR (400 MHz) δ 0.22 (s, 6H), 0.36 (s, 6H), 0.97 (s, 9H), 0.98 (s, 9H), 1.84 (m, 1H), 2.17 (m, 1H), 2.85 (m, 4H), 3.06 (t, J = 12 Hz, 2H), 3.16 (t, J = 7 Hz, 2H), 6.73 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H) ppm; ^{13}C-NMR (100 MHz) δ -4.5 (CH_3, C-18), -4.2 (CH_3, C-15), 17.8 (C, C-19), 18.2 (C, C-16), 25.7 (CH_3, C-20), 25.8 (CH_3, C-17), 29.3 (CH_2, C-7 and C-9), 29.7 (CH_2, C-10), 30.5 (CH_2, C-8), 43.2 (CH_2, C-11), 58.3 (C, C-5), 118.9 (CH, C-3), 123.6 (C, C-4), 126.6 (CH, C-2), 137.4 (C, C-12), 143.0 (C, C-1), 154.1 (C, C-13), 166.6 (C, C-14) ppm; mass spectrum, *m/z* (relative intensity, %) 511 (M^+, 3.4) amu; Exact mass for $C_{25}H_{42}O_3S_2Si$: calcd 510.9056, found 510.9084 amu.

Preparation of 2',3'-Dihydro-5'-(*t*-butyldimethylsilyloxy)-spiro[1,3]-dithiane-2,1'-[1*H*]indene-4'-carbonyl Chloride (78b)



Acid chloride **78b** was prepared by dissolving **208** (0.0500 g, 0.0979 mmol) in $SOCl_2$ (0.169 mL, 1.95 mmol) at rt. The mixture was stirred for 10 min after which the mixture was concentrated at reduced pressure under high vacuum. The crude product was purified by distillation (85-89 °C, 0.08 Torr) to produce a yellow oil (0.0256 g, 0.0617 mmol, 63.0%). ^{1}H-NMR (200 MHz) δ 0.08 (s, 6H), 1.29 (s, 9H), 3.38 (m, 2H), 3.91 (m, 1H), 4.06 (m, 1H), 4.25 (m, 4H), 4.34 (m, 2H), 7.68 (d, J = 7.3 Hz, 1H), 8.05 (d, J = 7.3 Hz, 1H) ppm.

Preparation of (4-Isopropenyl-3-vinyl-furan-2-yl)-triisopropylsilane (203)



Methyltriphenylphosphonium bromide (1.61 g, 4.52 mmol) was dissolved in THF (90 mL) and cooled to -78 °C. *n*BuLi (3.12 mL, 1.45 M in hexanes, 4.52 mmol) was added dropwise and the mixture stirred for 2 h allowing to warm to 0 °C. The ylid mixture was recooled to -78 °C then transferred *via* cannula to a solution of aldehyde **110** (1.10 g, 3.77 mmol) in THF (75 mL) at -78 °C. The mixture was stirred for 2 h at this temperature after which was concentrated in vacuo. The crude mixture was purified by flash chromatography using hexanes as the solvent to provide a clear, colorless oil (0.970 g, 3.34 mmol, 88.6%). bp 82-85 °C (8.0 x 10^{-2} torr); IR (KBr) 1629 (C=C) cm^{-1}; ^{1}H-NMR (400 MHz) δ 0.87 (d, J = 7.5 Hz, 18H, H-10), 1.19 (p, J = 7.5 Hz, 3H, H-9), 1.80 (s, 3H, H-13), 4.80 (s, 1H, H-12a), 4.94 (s, 1H, H-12b), 5.01 (dd, $J_{7a,7b}$= 1.8 Hz, $J_{7a,6}$ = 11 Hz, 1H, H-7a), 5.24 (dd, $J_{7a,7b}$ = 1.8 Hz, $J_{7b,6}$= 18 Hz, 1H, H-7b), 6.45 (dd, $J_{6,7a}$= 6.4 Hz, $J_{6,7b}$ = 11 Hz, 1H, H-6), 7.27 (s, 1H, H-5) ppm; ^{13}C-NMR (100 MHz) δ 11.8 (CH, C-9), 18.6 (CH_3, C-10), 23.4 (CH_3, C-13), 114.1 (CH_2, C-12), 117.1 (CH_2, C-7), 126.8 (C, C-2), 129.3 (CH, C-6), 133.8 (C, C-4), 136.8 (C, C-3), 143.9 (CH, C-5), 155.3 (C, C-11) ppm; mass spectrum, *m/z* (relative intensity, %) 290 (M^+, 4.75) amu; Exact mass for $C_{18}H_{30}OSi$: calcd 290.2051, found 290.2066 amu; Anal for $C_{18}H_{30}OSi$: calcd. C 74.42, H 10.41; found C 72.55, H 10.11%.

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