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Synthetic Approaches Toward (+)-Halenaquinone

by

Anastasia R. Mroch

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a dissertation entitled "Synthetic Approaches Toward (+)-Halenaquinone." submitted by Anastasia R. Mroch in partial fulfillment of the requirements for the degree of Master of Science.

B. A Keay

Supervisor, Dr. B.A. Keay, Department of Chemistry

Dr. W.E. Piers, Department of Chemistry

Ted Sorensen

Dr. T.S. Sorensen, Department of Chemistry

Dr. E. Donovan, Department of Physics and Astronomy

Sept 15/04

Date

Abstract

The design of novel, efficient and enantioselective routes for the laboratory preparation of structurally unique and biologically active natural products remains a fundamental interest in the field of organic synthesis. This dissertation describes synthetic approaches toward the preparation of one such compound, (+)-halenaquinone.

Retrosynthetic analysis of (+)-halenaquinone shows that its unique pentacyclic framework can be divided into two subunits of approximately equal complexity: 3-hydroxy-5,8-dimethoxy-2-naphthoic acid (**42**), or alternately 5,8-dimethoxy-3-trifluoromethanesulfonyloxy-naphthalene-2-carboxylic acid methyl ester (**122**), and 5-lithio-[1-(4-isopropenyl-furan-3-yl)-vinyloxy]-triisopropyl-silane (**55**). The bicyclic skeleton of **42** is prepared from a Diels-Alder addition between triisopropyl-(1-methylene-allyloxy)-silane and *p*-quinone. This adduct is then converted to **42** in 7 steps. Naphthol **42** is a known compound, and this route represents a substantial improvement in efficiency over the previous preparation in which **42** was constructed in 13 steps from 2,5-dimethoxy benzyl alcohol. Alternately, **42** can be replaced in the route by **122** reducing number of step required in the late stages of the synthesis by two. Naphthol triflate **122** is likewise prepared in 8 steps with an overall yield of 15%. Lithiated furan **55** is a new compound and is prepared in 8 steps from 3-furanmethanol in an overall yield of 16%.

Coupling furan **55** to a benzyl derivative, a simplified version of naphthol subunit **42**, results in the formation of a system which models the fully elaborated precursor to halenaquinone. Selective deprotection of a TIPS enol ether in the presence of a phenolic TBS ether, followed by triflate formation, yields a model upon which the key Pd-

catalyzed cyclization can be tested. Treatment of this system under cyclization conditions shows no conversion to product.

Preface

The efficient, enantioselective preparation of biologically active natural products for potential pharmaceutical use provides organic chemists with a seemingly endless supply of synthetic targets. For several years, the Keay laboratory has been active in designing synthetic routes for unique pentacyclic metabolites produced by the *Xestospongia* family of sea sponges. These biologically active compounds include (+)-xestoquinone, prepared asymmetrically in 1996 in the Keay laboratory and (+)-halenaquinone a closely related natural product. This thesis describes the strategy and rationale used to devise a synthetic route toward (+)-halenaquinone along with the practical results obtained pursuing this strategy in the laboratory.

Chapter one is an introductory chapter with six primary sections. The first section introduces the natural product and the second provides background information pertaining to the discovery, isolation and biological properties of halenaquinone. This is followed by an overview of the three previous syntheses of halenaquinone and a short section describing Keay's synthesis of a related compound, xestoquinone. The next section begins with a retrosynthetic analysis of halenaquinone, which leads to the description of two target subunits, Fragment A and Fragment B. The final section provides a rationale for the recurrent use of the triisopropyl silyl group within the context of the synthetic strategy.

Chapter two describes the preparation of naphthol subunit Fragment A and is divided into several sections. The first part of this chapter, comprised of several sections, focuses on the construction of the bicyclic skeleton of this subunit using a trimethyl silyl then phosphate substituent. The next several sections examine the construction of this

subunit with a triisopropyl silyl substituent. This is then followed by several sections, which chronologically describe the elaboration of the bicyclic system into Fragment A. The final sections in this chapter describe the preparation of Fragment A', an alternate subunit which can be used in place of Fragment A to improve the efficiency with which halenaquinone can be synthesized.

Chapter three is divided into two parts, each comprised of several sections. The first part describes the preparation of the second subunit, Fragment B. The first sections in this part describe the preparation of the key furyl intermediate. The second set of sections investigates several sets of conditions that were used to effect a [1,4] C $\rightarrow$ O silyl migration and construct the critical silyl enol ether moiety of Fragment B. The final sections in the first part of this chapter describe the spectral assignments of the silyl enol ether furyl derivative and the lithiation of this compound to complete Fragment B. The second part of this chapter describes the preparation and manipulation of a simplified system used to model the final steps in the preparation of halenaquinone. The first sections in the second part describe the preparation of a truncated version of Fragment A and its addition to Fragment B. This is followed by a description of the deprotection conditions used to selectively cleave a TIPS enol ether in the presence of a phenolic TBS group; first on a test system, then on the fully elaborated model system. The continued elaboration of the model system is then chronologically described. The final section then details failed attempts to perform the key Pd-catalyzed cyclization.

Chapter four details experimental methods and procedures used and lists relevant characterization data.

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^{13}C-NMR	carbon-13 nuclear magnetic resonance
^{1}H-NMR	proton nuclear magnetic resonance
9-BBN	9-borabicyclo[3.3.1]nonane
Å	angstrom
Ac	acetyl
AIBN	2,2'-azobis-(2-methylpropionitrile)
amu	atomic mass unit
Ar	aryl
atm	atmospheres
BHT	2,6-di-*tert*-butyl-4-methylphenol
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
bp	boiling point
br	broad
Bu	butyl
calcd	calculated
CAN	ceric ammonium nitrate
cm	centimeters
CM	complex mixture
cm^{-1}	wavenumbers
d	doublet, days
dba	dibenzylideneacetone
DCC	dicyclohexylcarbodiimide
dd	doublet of doublets

ddd	doublet of doublets of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarization transfer
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	bis(diphenylphosphino)ferrocene
dt	doublet of triplets
ee	enantiomeric excess
equiv.	equivalent
ESI	electrospray ionization
Et	ethyl
fcc	flash column chromatography
FGI	functional group interconversion
g	grams
GC	gas chromatograph
h	hours
H^+	acid
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
Hz	Hertz
i	iso
imid.	imidazole
IR	infrared
J	coupling constant
KHMDS	potassium hexamethyldisilazide
L	generic phosphine ligand, liter
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide

LRMS	low resolution mass spectroscopy
M	molar
m	multiplet, milli
m/z	mass to charge ratio
M^+	molecular ion
MCPBA	*m*-chloroperoxybenzoic acid
Me	methyl
mg	milligrams
MHz	megaHertz
min	minutes
mL	milliliters
MMC	methyl magnesium carbonate
mmol	millimoles
mol	moles
mp	melting point
MS	mass spectrometry, molecular sieves
MVK	methyl vinyl ketone
n	normal
NBS	*N*-bromosuccinimide
NGF	nerve growth factor
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NR	no reaction
o	*ortho*
[O]	oxidation
p	*para*
PDC	pyridinium dichromate
Ph	phenyl
PMP	1,2,2,6,6-pentamethylpiperidine
ppm	parts per million

Pr	propyl
PTK	protein tyrosine kinase
R`	generalized alkyl group or subsituent
rt	room temperature
s	singlet
s	secondary
sept	septet
SM	starting material
solv.	solvent
t	triplet
t	tertiary
TBAF	tetrabutylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
temp.	temperature
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
tol	toluene
Topo	topoisomerase
TPAP	tetrapropylammonium perruthenate
Ts	toluenesulfonyl
wrt	with respect to
X	halide, triflate

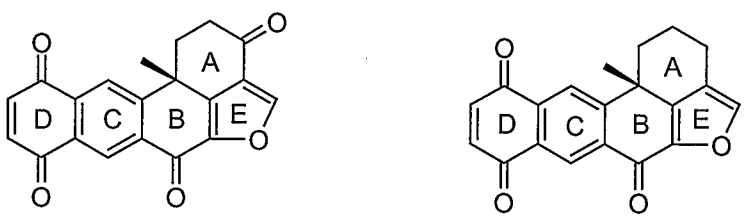
Δ	heat
δ	chemical shift
°C	degrees Celsius
*	chiral

Chapter 1

1. Introduction to Halenaquinone

Primary metabolic pathways are responsible for the synthesis, degradation and interconversion of compounds common to most organisms.[1] These metabolic processes enable growth and reproduction by synthesizing and transforming sugars, proteins, nucleic acids and other compounds necessary for life. Secondary metabolites, on the other hand, are found only in specific organisms or groups of organisms and are characteristic of a particular species or group of species. Typically, these compounds are not produced under all conditions, and often their roles within the organism are not clearly understood. Although the exact details of their function may be elusive these metabolites must serve some vital purpose within the organism and many are known to serve as components of the organism's defense systems. They are of particular scientific interest, however, because many secondary metabolites possess desirable pharmacological properties and offer a wide range of activity in the human body that may differ entirely from their role within the producing organism. Halenaquinone (**1**) is one such compound, and has been of interest to the Keay group for the past 6 years.

Figure 1.1 Halenaquinone (1) and Xestoquinone (2)



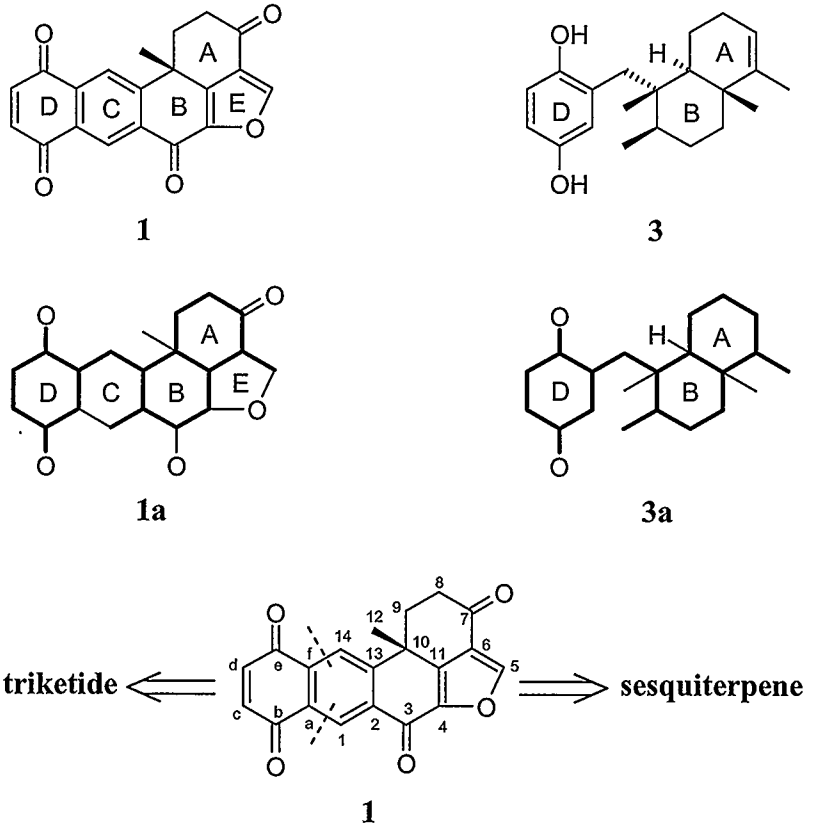
1 **2**

1.1 Discovery and Biological Properties of Halenaquinone

Halenaquinone (**1**) was first isolated from the pacific sponge *Xestospongia exigua*.[2] More recently, it was isolated from a related sponge, *Xestospongia carbonaria*,[3] establishing that halenaquinone is not unique to a single species. It does, however, appear to be unique to *Xestospongia* as it has not been observed in any organism outside this genus. The novel pentacyclic structure of this marine metabolite identifies it as a member of a discrete group of compounds, which are now considered exclusive taxonomic markers[3a] of the genus *Xestospongia*. A novel pentacyclic framework including a furan moiety and a quinone ring identifies this secondary metabolite as a member of this novel family of compounds while the A ring carbonyl function characterizes this individual compound (Figure 1.1). Xestoquinone (**2**), has also been isolated from sponges of the genus *Xestospongia*,[3,4] and shares halenaquinone's novel pentacyclic framework, angular methyl group and furan moiety (Figure 1.1).

Roll and Scheuer[2] initially identified halenaquinone as a rare pentacyclic polyketide; however, a biosynthetic link has recently been drawn between halenaquinone and compounds such as isozonarol (**3**) which are comprised of a sesquiterpene and a triketide.[5] A structural relationship between the two compounds can be seen when common connectivity is highlighted (Figure 1.2). This structural correlation is further evidenced by the relatively few transformations required to convert the framework of isozonarol (**3a**) into the framework of halenaquinone (**1a**). Demethylation of the A and B ring of **3a**, followed by C-C bond formation to close the C ring and finally ether formation to establish the E ring completes the skeletal structure of halenaquinone (**1a**).[3a] It has thus been proposed[3a] that biosynthetic construction of halenaquinone (**1**) occurs as the union of a triketide (the 6 carbons labeled a – f of the D ring), and a singly demethylated sesquiterpene (the remaining 14 carbon atoms labeled 1 – 14) (Figure 1.2).

Figure 1.2 Halenaquinone (1), Isozonarol (3) and Respective Common Framework (1a) and (3a)



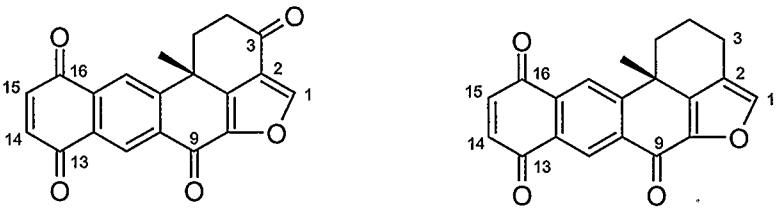
Although halenaquinone was initially reported[2] to exhibit *in vitro* antibiotic activity against *Staphylococcus aureus* and *Bacillus subtilis*, later studies uncovered far more intriguing pharmacological properties. The potential application of halenaquinone to the treatment of proliferative diseases such as cancer[3] and psoriasis[3a] is perhaps the most remarkable result of studies involving this marine natural product.

Proliferative diseases are characterized by uncontrolled cell growth. As such, one method of treatment is to retard this growth by inhibiting enzymes involved in cellular replication. In the case of proliferative diseases, target enzymes are protein tyrosine kinases (PTKs). PTKs are intimately involved in cellular functions relating to signaling and growth, and enhanced PTK activity has been closely associated with proliferative diseases including cancer.[5,6] Thus, an effective PTK antagonist would be invaluable in the development of new chemotherapeutic agents. Halenaquinone has been identified as

one of only four natural products to effectively inhibit PTK activity[3] and is a potent and irreversible inhibitor of several PTKs. Halenaquinone has been shown to inhibit the oncogenic $pp60^{v\text{-}src}$, a PTK encoded by the *Rous sarcoma* virus,[3b] which has been shown to be associated with the appearance of cancer. Halenaquinone has also shown inhibitory properties toward the epidermal growth factor receptor PTK,[3a] a kinase associated with psoriasis.[6b] Halenaquinone's utility as an enzymatic inhibitor is not restricted to PTKs. It has also been reported[7] to be a potent inhibitor of topoisomerase 1 (Topo 1) purified from the nuclei of mouse leukemic cells L1210. As the Topo 1 enzyme is responsible for the catalytic reproduction of DNA in cells contained within tumerous growths, halenaquinone may be useful for disrupting the replication of these cells and thereby retarding tumor growth. Although Topo 1 inhibition was the primary focus of their investigation, Tsuji and associates also observed cytotoxic properties[7] in their assay against several kinds of leukemic cells. This result is contrary to an earlier report[3a] in which halenaquinone was reported to exhibit no cytotoxic activity when applied to a varied panel of tumor cells. Ohizumi and coworkers have more recently reported[8] that halenaquinone exhibits cytotoxic activity toward nerve growth factor (NGF) treated PC12 cells, inducing apoptosis, or programmed cell death, in a concentration dependent manner. PC12 cells treated with halenaquinone suffered shrinkage of cell soma, fragmentation of neurites and chromatin condensation, characteristic features of an apoptotic mechanism. NGFs suppress apoptosis through a series of reactions that ultimately lead to the activation of PTK receptors in several types of neurons and neuronal cells. By activating these receptors, messenger molecules are generated which activate intracellular signaling molecules and suppress programmed cell death. Therefore, it was concluded[8] that halenaquinone caused the death of P12 cells by inhibiting PTK activity.

Halenaquinone (**1**) and xestoquinone (**2**) are structurally very similar differing only in the functionality at the C3 position (Figure 1.3). While xestoquinone has a methylene group at this site, halenaquinone has a carbonyl group. Surprisingly, despite this strong structural similarity, the two compounds exhibit distinct biological properties.

Figure 1.3 Numbered Framework of Halenaquinone (1) and Xestoquinone (2)



1 **2**

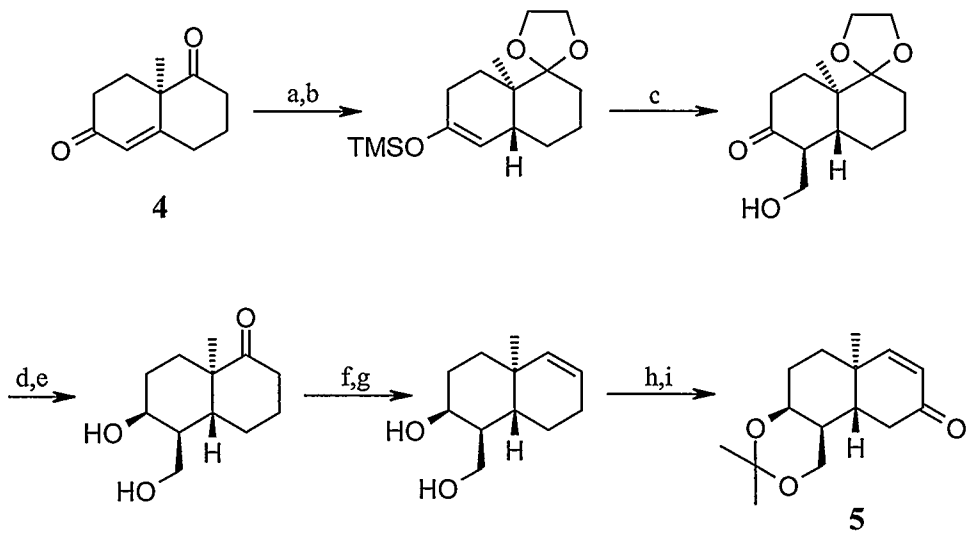
While halenaquinone is a potent inhibitor of PTKs and Topo 1, xestoquinone exhibits only weak inhibition of these enzymes.[3,7] Crews and coworkers attempted to understand the relative inactivity of **2** by examining the role of the keto-furan region of **1** in the inhibition of PTKs.[3a] They suggested that the simplest rationale for the inhibitory activity was irreversible binding of PTKs *via* Michael addition of the enzyme at C1, C14 or C15 of **1**. This would imply that the absence of a Michael acceptor site at C1 in **2** was at least partially responsible for its relative inactivity. When several halenaquinone analogs were examined in an effort to determine which structure features were necessary for enzyme inhibition,[3] it was noted that in addition to electrophilic sites at each end of a pentacyclic framework, strong PTK antagonists tended to have polyunsaturated planar skeletons with quinone end rings. This suggested that the mechanism of PTK inhibition is likely dependent upon several structural factors in addition to the presence of an electrophilic keto-furan moiety.

1.2 Previous Syntheses of Halenaquinone

To date, three syntheses of halenaquinone have been reported. The first total synthesis of (+)-halenaquinone was reported in 1988 by Harada and co-workers.[9] They devised a convergent route to **1** using a Diels-Alder reaction to form the tetracyclic skeleton followed by formation of the furan ring in the late stages of the synthesis. Their synthetic strategy also involved the use of an optically active starting material with the required angular methyl group already installed and retained throughout the synthesis. The optically pure Wieland-Miescher ketone **4**[10] was prepared asymmetrically using (*R*)-

D-(+)-proline as a chiral catalyst and converted to the Diels-Alder precursor **5** in nine steps (Scheme 1.1).

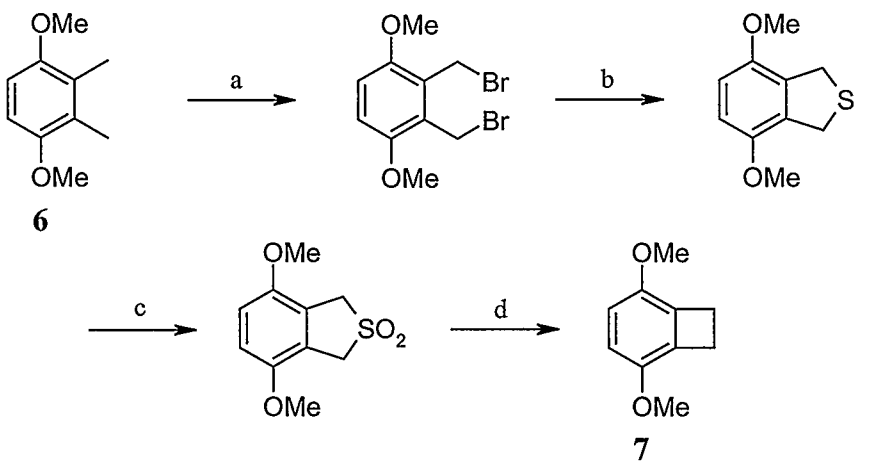
Scheme 1.1



Conditions: a) 2-ethyl-2-methyl-1,3-dioxolane, *p*TsOH (90%); b) Li, NH_3, THF; TMSCl, Et_3N; c) MeLi, THF; CH_2O (82% over two steps); d) Li(*s*Bu)$_3$BH, THF (92%); e) water, *p*TsOH (98%); f) *p*tosylhydrazine, EtOH; g) MeLi, THF (100% over two steps); h) acetone, *p*TsOH (86%); i) CrO_3, 3,5-dimethylpyrazole, DCM (63%).

The second Diels-Alder precursor, 3,6-dimethoxybenzocyclobutene (**7**), was prepared in four steps from 2,3-dimethyl-1,4-dimethoxybenzene (**6**) using the thermal elimination of sulfur dioxide to form the desired bicycle (Scheme 1.2).

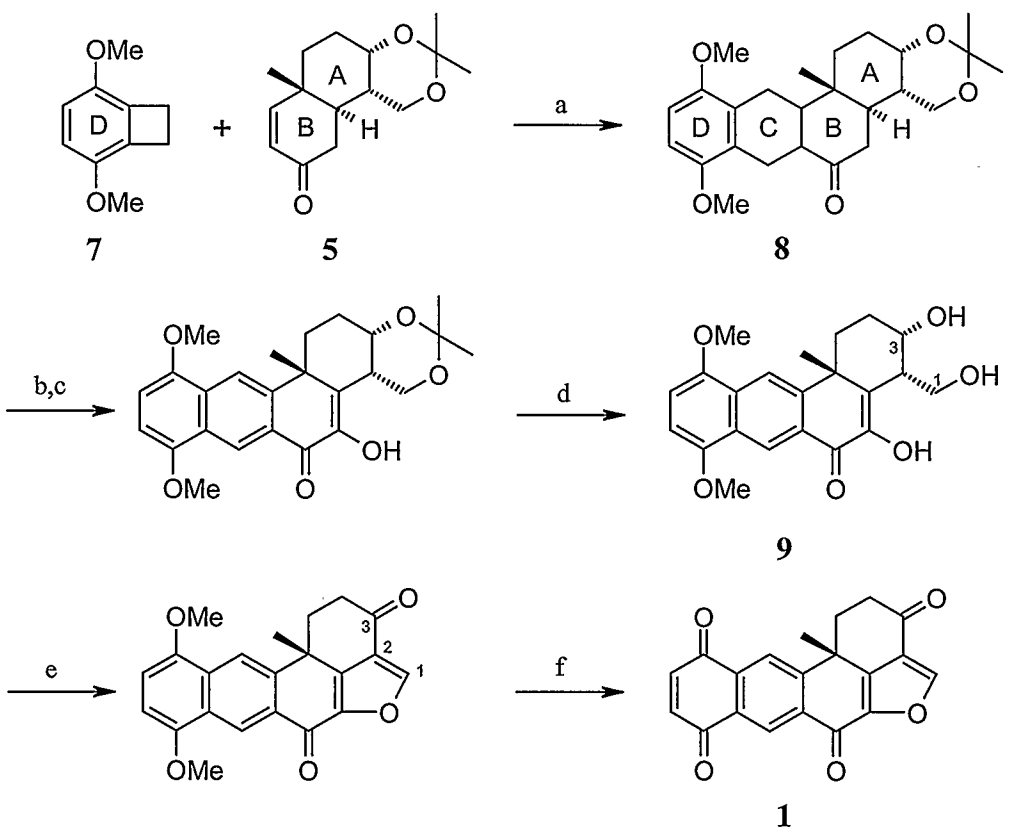
Scheme 1.2



Conditions: a) NBS, AIBN, CCl_4; b) Na_2S, EtOH (70% over two steps); c) MCPBA, DCM (89%); d) 305-310 °C (48%).

The Diels-Alder reaction between dieneophile **5** and the diene, generated by the opening of the four membered ring of **7**, gave the desired tetracyclic adduct **8** (Scheme 1.3). Tetracycle **8** was converted to triol **9** in three steps. This was followed by oxidation of the C1 primary and C3 secondary alcohols. Cyclization then ensued which generated the required furan ring and C3 ring ketone moiety and completed the pentacyclic framework of halenaquinone (Scheme 1.3). Oxidative cleavage of the hydroquinone dimethyl ether moiety with CAN completed the total synthesis of (+)-halenaquinone. Although this synthetic route was convergent in nature and had many high yielding steps, it used an optically pure starting material in order to obtain the chiral product. Thus, it does not satisfy the requirements of a true asymmetric synthesis.

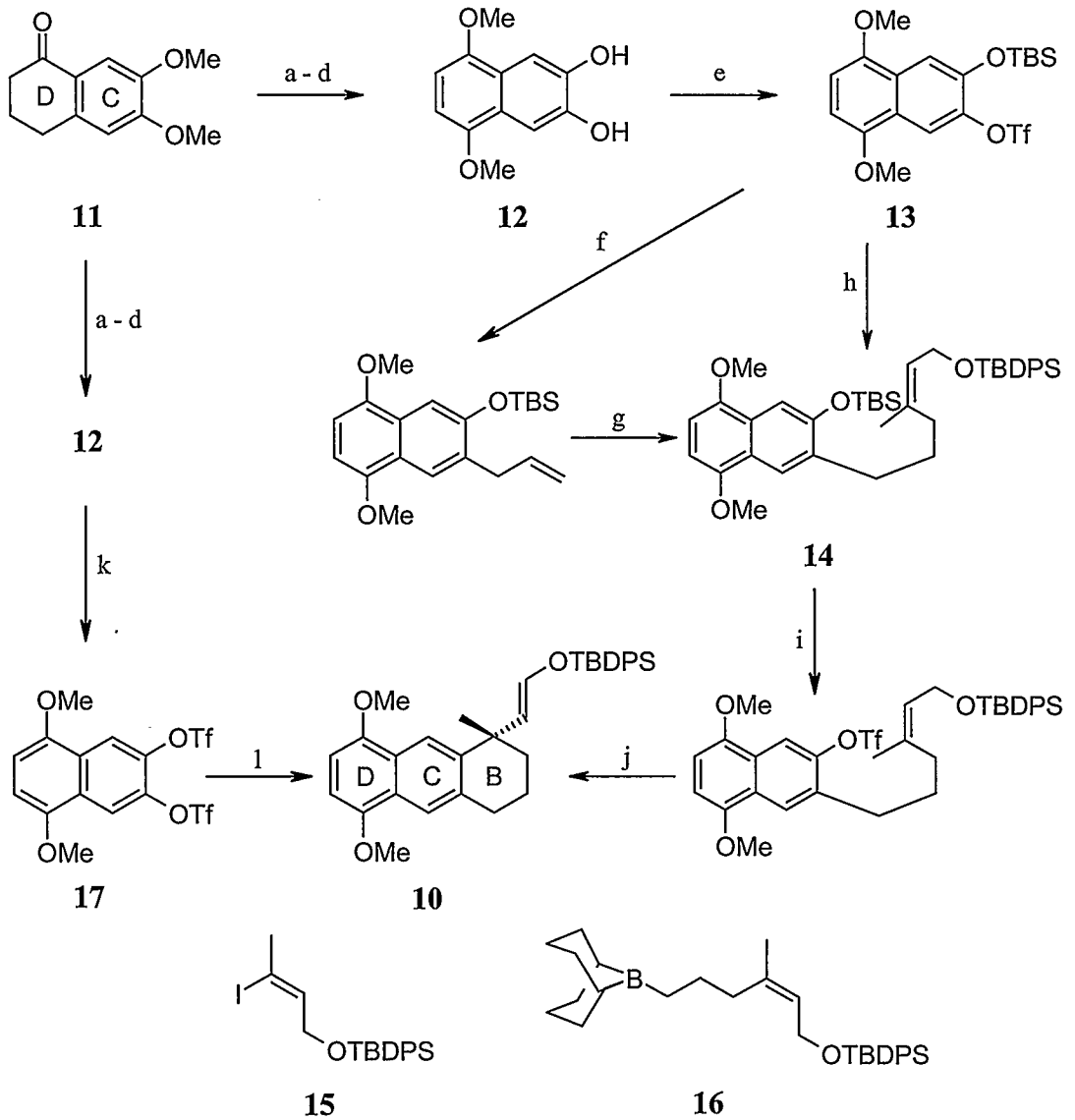
Scheme 1.3



Conditions: a) benzene, 210-215 °C, 20 h (33%); b) DDQ, benzene (89%); c) *t*BuOK, *t*BuOH, O_2; d) 60% aq. HOAc; e) DMSO, DCC, benzene, TFA, pyridine (44% over three steps); f) CAN, aqueous MeOH (45%).

The first truly asymmetric synthesis of (+)-halenaquinone was reported in 1996 by Shibasaki and co-workers.[11] They proposed and executed two routes to a single tricyclic intermediate **10** (Scheme 1.4). The first involved an asymmetric Heck reaction, and the second involved a cascading Suzuki cross-coupling followed by an asymmetric Heck reaction (Scheme 1.4).

Scheme 1.4



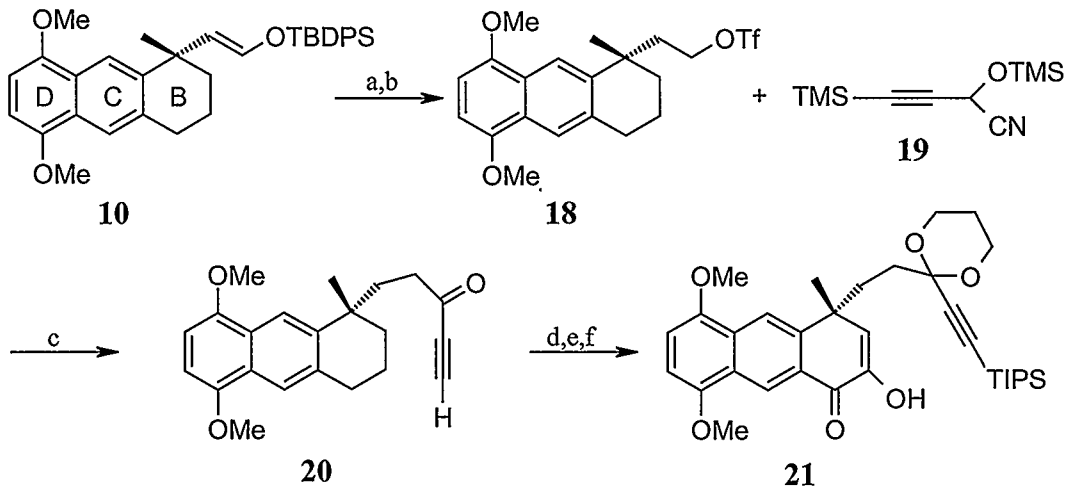
Conditions: a) (1) BBr_3 (2.1 equiv.), DCM , -78 °C - rt, (2) BnBr (2.0 equiv.), K_2CO_3, Bu_4NI, DMF, 60 °C (92% over two steps); b) CrO_3 (5 equiv), HOAc, H_2O, 0 °C - rt; c) KHMDS (3 equiv.), THF, -78 °C, then MeI (6 equiv.), -78 °C - rt (63%); d) H_2 (1 atm), Pd/C, EtOAc, rt (100%); e) (1) TBSCl (1.1 equiv), Et_3N, DCM, 0 °C, (2) Tf_2O (1.3 equiv.), Et_3N, DCM, -78 °C - rt (85% over two steps); f) CH_2CHCH_2MgBr (5 equiv.), $PdCl_2$ (dppf)·CH_2Cl_2 (9 mol %), Et_2O, -78 °C - rt. (100%); g) (1) 9-BBN (2.1 equiv.), THF, 0 °C - rt, (2) **15** (1.5 equiv.), $PdCl_2$(dppf)·CH_2Cl_2 (5 mol %), K_3PO_4·nH_2O, THF, 50 °C (90% over two steps); h) **16** (1.3 equiv.), $PdCl_2$(dppf)·CH_2Cl_2 (10 mol %), K_2CO_3, THF, 50 °C (69%); i) (1) TBAF (1.0 equiv.), THF, 0 °C, (2) Tf_2O (1.3 equiv.), Et_3N, DCM, -78 °C - rt (69% over two steps) j) Pd $(OAc)_2$ (10 mol %), (*S*)-BINAP (20 mol %), K_2CO_3, THF, 60 °C (78%, 87% ee); k) Tf_2O (3 equiv.), pyridine, DCM, -78 °C - rt (99%); l)**16** (1.1 equiv.), Pd $(OAc)_2$ (20 mol %), (*S*)-BINAP (40 mol %), K_2CO_3, THF, 60 °C (85%, 20% *ee*).

Both routes to **10** began by converting 6,7-dimethoxy-1-tetralone (**11**), the DC ring framework, to catechol derivative **12**. The first route then proceeded with monosilylation followed by trifluoromethanesulfonylation to generate **13** which was then converted into Heck reaction precursor **14**. This was either done in a single step with alkylborane **16**, or *via* a two step sequence of cross-coupling with allylmagnesium bromide followed by Suzuki cross coupling with alkenyl iodide **15**. Unfortunately, the one step process gave a yield of 69% whereas the two-step process gave an overall yield of 90%. After conversion to the triflate, an intramolecular Heck reaction was employed to complete the DCB ring system. The Pd-catalyzed asymmetric cyclization gave **10** in 78% yield with 87% *ee*.

The second route to the asymmetric DCB system involved conversion of catechol derivative **12** to ditriflate **17**, which was then subjected to a cascade Suzuki cross-coupling with **16** followed by an asymmetric Heck reaction giving **10** in 20% yield and 87% *ee*. Although the alternative routes for preparation of the DCB system were anticipated to vary in both yield and selectivity, the only difference between the strategies was a moderate increase in yield for intermediate **10** from 11% for the shorter more elegant cascading preparation to 24% for the longer route. Selectivity for both remained essentially the same.

Key intermediate **10** was then converted to the corresponding triflate **18** which was treated with the acyl anion equivalent of **19** to yield ketone **20** in 63% yield (Scheme 1.5). Protection of the carbonyl as an acetal and the ethynyl functionality with a TIPS group followed by benzylic oxidation and exposure to O_2 (1 atm) and *t*BuOK in *t*BuOH completed intermediate **21**.

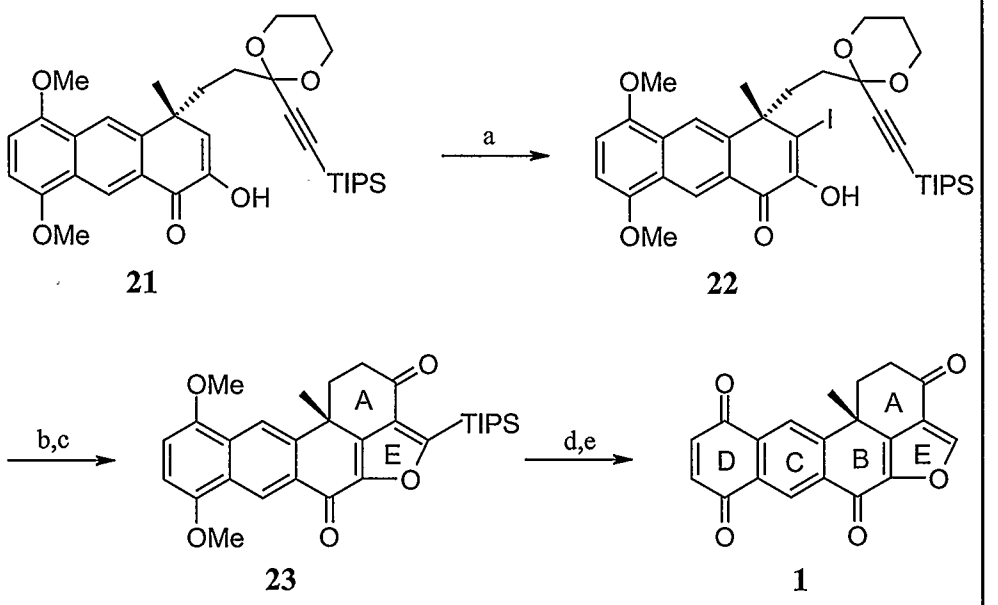
Scheme 1.5



Conditions: a) (1) TBAF (2 equiv.), HOAc (3 equiv.), THF, 0 °C - rt, (2) $NaBH_4$ (5 equiv.), MeOH, 0 °C - rt (93% over two steps); b) Tf_2O (1.2 equiv), pyridine, DCM, -78 °C - rt; c) LDA/**19** (1.5 equiv.), THF, -78 °C, then H^+, then ^-OH, then TBAF, HOAc (82% over two steps); d) (1) $HO(CH_2)_3OH$ (10 equiv.), $TsOH{\cdot}H_2O$, benzene, reflux (98%); (2) BuLi (2 equiv.), THF, -78 to -50 °C, then TIPSCl (2 equiv), -78 °C - rt (98%); e) DDQ (3 equiv.), DCM, H_2O, rt (96%); f) O_2 (1atm), *t*BuOK (5 equiv.), *t*BuOH, 35 °C (79%).

Tricyclic intermediate **21** underwent further elaboration to precursor **22**, with the addition of the alkynyl and iodo substituents necessary for the one-pot construction of the A and E rings (Scheme 1.6). Subjecting intermediate **22** to mildly acidic conditions followed by 0.28 equiv. of $Pd_2(dba)_3{\cdot}CHCl_3$ and 5 equiv. of K_2CO_3 in DMF at rt gave key pentacyclic intermediate **23** in 72% yield (Scheme 1.6). Cleavage of the TIPS groups followed by oxidation of the D ring to the quinone completed this synthesis of (+)-halenaquinone.

Scheme 1.6

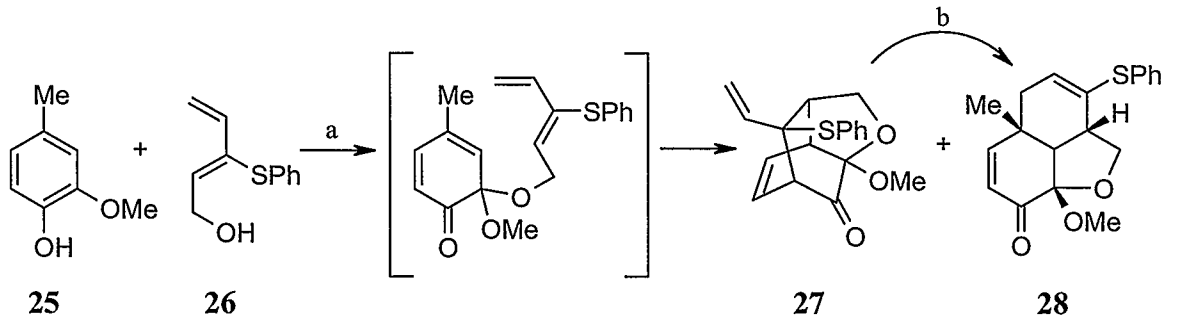


Conditions: a) NaI (10 equiv.), $CuSO_4$, MeOH, H_2O_2, rt (97%); b) $TsOH{\cdot}H_2O$, acetone, H_2O, 60 °C (98%); c) $Pd_2(dba)_3{\cdot}CHCl_3$ (0.28 equiv.), K_2CO_3 (5 equiv.), DMF, rt (72%); d) TBAF (16 equiv.) HOAc (24 equiv.), MeCN, THF, 60 °C (83%); e) CAN (6.7 equiv.), MeCN, H_2O, rt (99%).

Shibasaki's asymmetric synthesis of halenaquinone offered both good selectivity and an elegant approach to the asymmetric construction of the pentacyclic framework. Unfortunately, the lengthy linear nature of this strategy ultimately limited the overall yield despite several high yielding steps. Thus, a convergent asymmetric approach still remained desirable.

Rodrigo and associates reported the most recent synthesis of halenaquinone in 2001.[12] They employed a racemic strategy analogous to that used in their 1994 synthesis of xestoquinone.[13] 3-Phenylthiopenta-2,4-dien-1-ol (**26**) was prepared in four steps and 63% overall yield from propargylic alcohol using known procedures.[14] Dienol **26** was subsequently reacted with methylguaiacol **25** and [bis(trifluoroacetoxy)iodo]benzene, exploiting Rodrigo's *o*-benzoquinone monoketal Diels-Alder protocol[15] to give a mixture of adducts **27** and **28** (Scheme 1.7). The mixture was then refluxed in 1,2,4-trimethylbenzene converting the undesired component (**27**) to the desired naphthofuranone **28** by means of a Cope rearrangement.

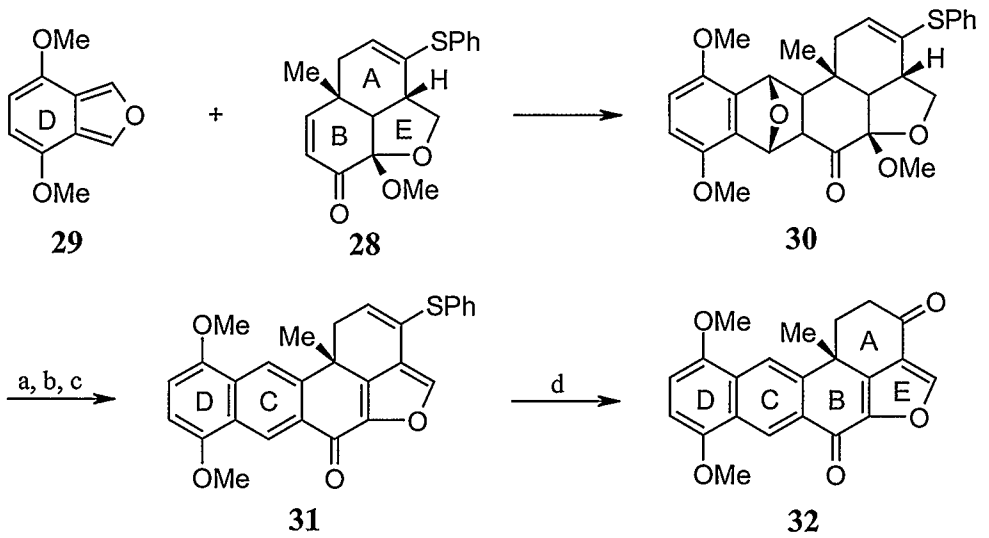
Scheme 1.7



Conditions: a) $PhI(O_2CCF_3)_2$, BHT (2 mol %), $NaHCO_3$, THF; b) 1,2,4-trimethylbenzene , reflux (36% over two steps).

Naphthofuranone **28** was then subjected to a second Diels-Alder reaction with 4,7-dimethoxyisobenzofuran (**29**) to give bridged addition product **30** (Scheme 1.8). Aromatization of the C ring followed by aromatization of the dihydrofuran with *p*-chloranil gave thiophenol **31**. Hydrolysis of the thiophenyl group then gave **32**, which is a known[9] synthetic precursor of halenaquinone. Isolation of **32** effectively completed Rodrigo's racemic synthesis.

Scheme 1.8



Conditions: a) NaOMe, MeOH (93%); b) TFA, DCM (97%); c) *p*-chloranil, *p*-xylene (46%); d) AcOH, $TiCl_4$, H_2O (63%).

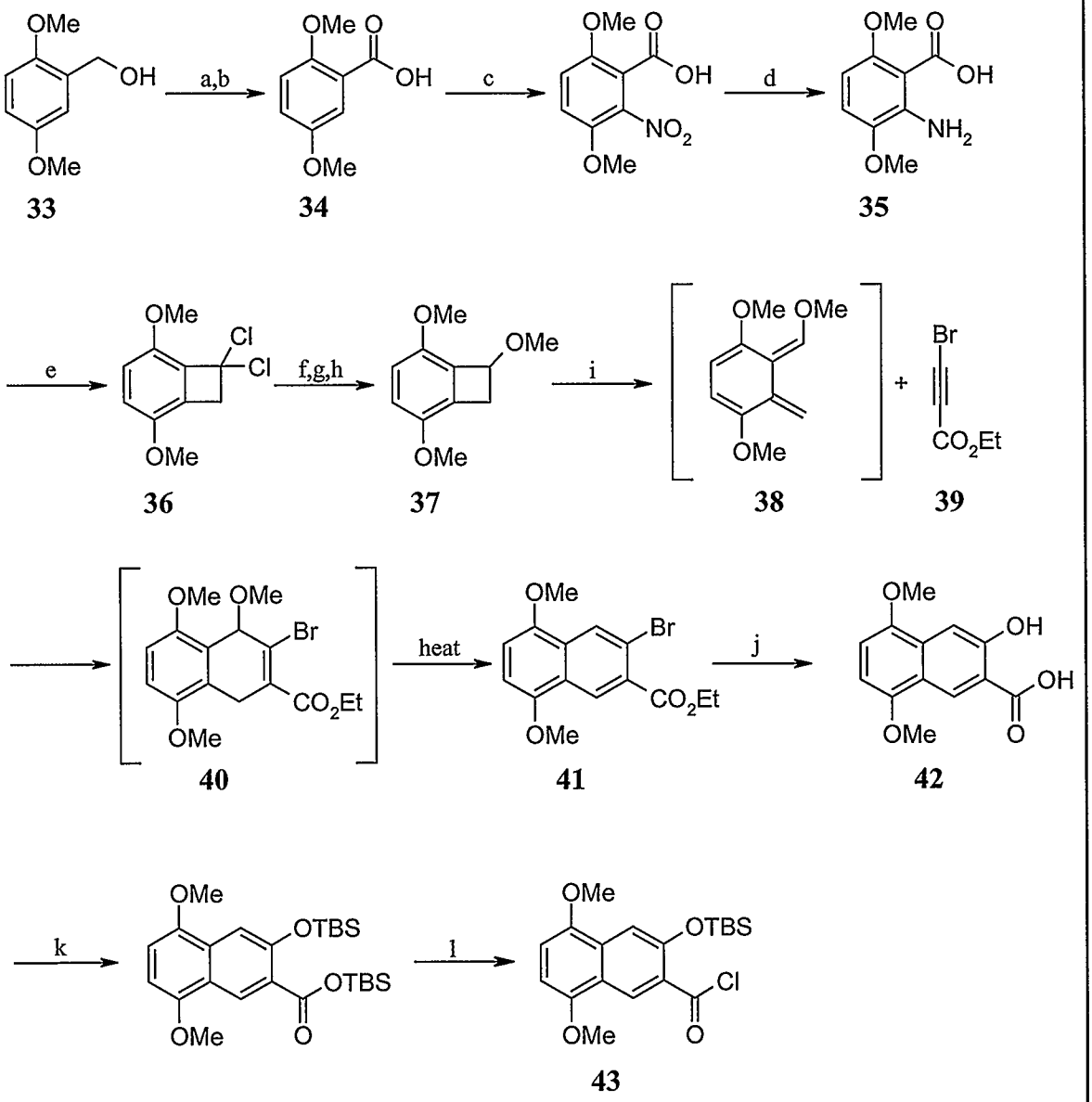
Although the current preparations of halenaquinone are not without merit, Harada's use of an optically active starting material to obtain a chiral product, Shibasaki's lengthy linear approach and Rodrigo's racemic synthesis leave room for the development of a convergent asymmetric route to halenaquinone.

1.3 Previous Synthesis of Xestoquinone

The Keay group has also maintained an active interest in the synthesis of pentacyclic marine metabolites culminating in the publication of an elegant asymmetric route to xestoquinone.[16] This convergent approach featured a one pot Pd-catalyzed polyene cyclization which established the stereogenic centre while concurrently closing the A and B rings to complete the pentacyclic framework. This strategy required the preparation of two subunits, naphthalene derivative **43**[16,17] (Scheme 1.9) and furan derivative **48**[18] (Scheme 1.10).

The preparation of the naphthoic subunit **43** began with the oxidation of 2,5-dimethoxy benzyl alcohol (**33**) to the corresponding benzoic acid **34** (Scheme 1.9).

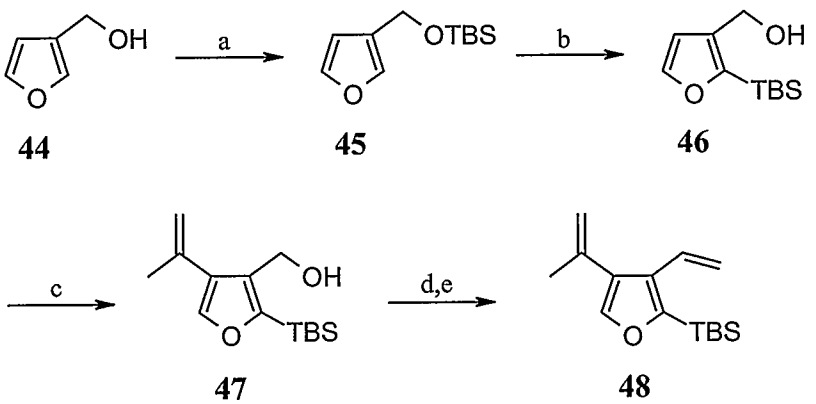
Scheme 1.9



Conditions: a) Swern; b) $KMnO_4$ (1.4 equiv); c) conc. HNO_3; d) H_2, 10% Pd/C; e) isoamyl nitrite, HCl, then 1,1-dichloroethylene, propylene oxide; f) dil. H_2SO_4, MeOH; g) $NaBH_4$, EtOH h) MeI, Ag_2O; i) **39** toluene, reflux, 4Å molecular sieves, 24h (65%); j) *n*BuLi (1.05 equiv) -95 °C; then add $B(OMe)_3$ (3 equiv.); then add H_2O_2 (4 equiv.), NaOH (4 equiv.); then 10% HCl (87%); k) TBSOTf (2.1 equiv.) NEt_3 (3 equiv.) 21h; l) $(COCl)_2$ (2.5 equiv.), hexanes, 19h (79% over two steps).

The resultant acid was then subjected to nitration and subsequent reduction to afford *o*-aminobenzoic acid **35**. Diazotization of amino acid **35** formed the corresponding benzyne, which reacted *in situ* with 1,1-dichloroethylene generating adduct **36**. The dichloride was then hydrolyzed to the keto-group, reduced, and subjected to O-methylation to yield 1,3,6-trimethoxybenzocyclobutene (**37**). Reaction of **37** with ethyl 3-bromopropynoate (**39**) in refluxing toluene over 4Å molecular sieves resulted in the formation of naphthalene **41** in good yield. The reaction proceeded *via* thermolysis of **37** to intermediate *o*-quinone dimethide **38** which underwent a Diels-Alder addition with acetylenic dienophile **39**. This generated adduct **40**, which rapidly aromatized to naphthyl **41**. Halogen-metal exchange of bromonaphthalene **41** with *n*BuLi followed by trapping with $B(OMe)_3$, *in situ* oxidation and hydrolysis gave naphthol acid **42**. Finally, generation of the disilane with TBSOTf and subsequent treatment with oxalyl chloride afforded naphthol chloride **43**.

Scheme 1.10

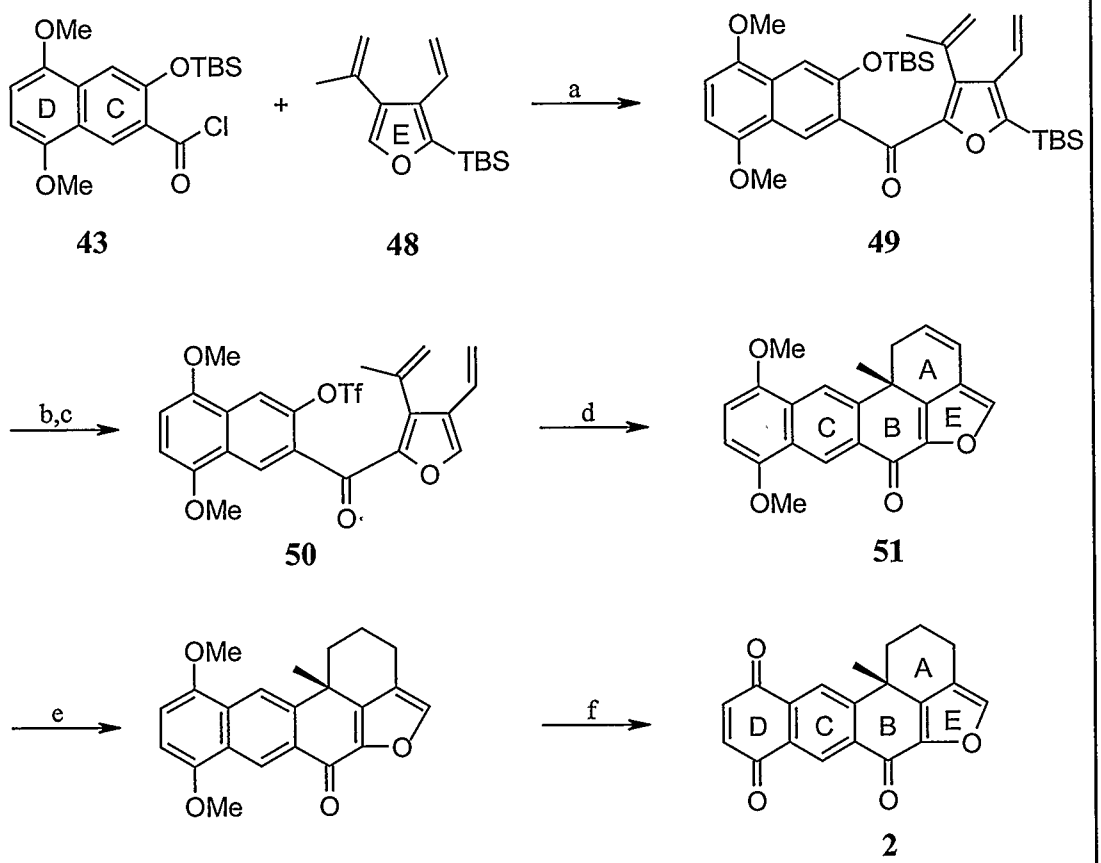


Conditions: a) TBSCl, imidazole, DMF (96%); b) *n*BuLi, THF, HMPA, 0 °C (87%) c) *n*BuLi (2.2 equiv.), DME, 0 °C, 1h; then add $B(MeO)_3$, 0° C, 1h; then add $Pd(PPh_3)_4$, H_2O, 2-bromopropene, 80 °C, 4h (85%); d) Swern (75%) e) $Ph_3P{=}CH_2$, THF (87%).

Furan derivative **48** was prepared in 6 steps from 3-furanmethanol (**44**) (Scheme 1.10).[18] Treatment of **44** with TBSCl and imidazole in DMF gave silylated furan **45** in good yield. Subsequent treatment with a mixture of *n*BuLi and HMPA in THF at 0 °C effected the desired [1,4] O → C silyl migration generating 2,3-disubstituted furan **46**.

Furan **46** was then subjected to Keay's modified Suzuki reaction conditions[19] in which the furyl-boronic acid is generated *in situ* and coupled to 2-bromopropene yielding selectively C4 alkylated product **47**. Swern oxidation followed by a Wittig reaction provided the required dienyl furan **48**.

Scheme 1.11



Conditions: a) *s*BuLi/**43** (1.3 equiv.), THF -78 °C (33%); b) TBAF (2.05 equiv.), THF 0 °C (99%) c) NaH (4 equiv.), $PhNTf_2$ (4 equiv.), DMF; d) $Pd_2(dba)_3$ (2.5 mol %), (S)-BINAP (10 mol %), PMP (8 equiv.), toluene, reflux, 22 h (82%, 68% ee); e) H_2 (1 atm), 5% Pd/C (99%); f) CAN, $MeCN/H_2O$, 0 °C.

Coupling the anion of furan **48** to naphthoyl chloride **43** at -78 °C resulted in the formation of desired ketone **49** (Scheme 1.11). Subsequent desilylation followed by conversion of the resultant alcohol to the corresponding phenolic triflate completed the formation of cyclization precursor **50**. Triflate **50** was then treated with $Pd_2(dba)_3$ and

(*S*)-BINAP in the presence of excess of PMP in refluxing toluene for 22 h which generated pentacycle **51** in 68% *ee* (82% yield). This key transformation proceeded by closure of the B ring *via* the initial 6-*exo*-trig cyclization with concurrent generation of the angular methyl group followed by a second 6-*endo*-trig closure to form the A ring completing the pentacyclic framework of (+)-xestoquinone. Catalytic hydrogenation of **51** over 5% Pd/C followed by oxidative cleavage of the hydroquinone dimethyl ether moiety completed the synthesis of (+)-xestoquinone (**2**).

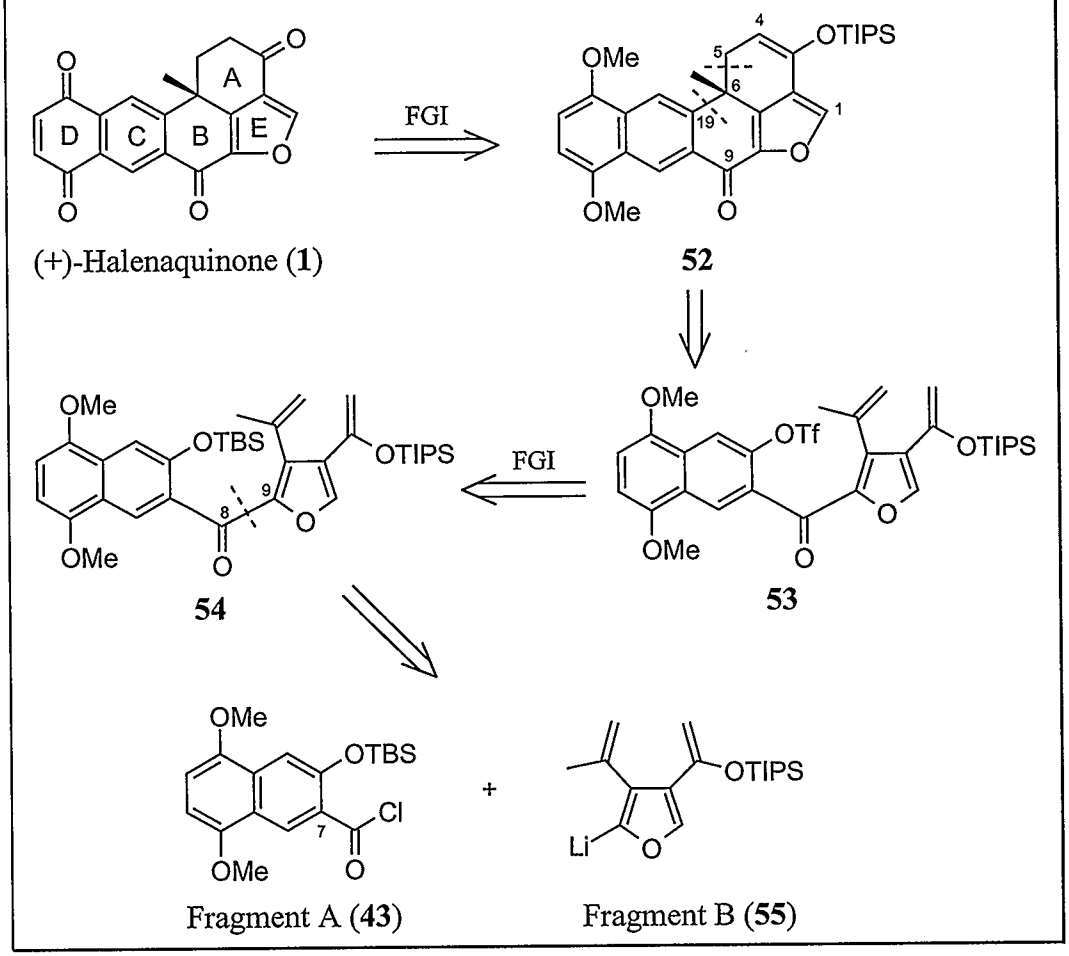
1.4 Conclusion

To date the three total syntheses of halenaquinone have been reported, however none provide a convergent asymmetric path to the natural product. Harada[9] and Rodrigo[12] published synthetic routes to the natural product that were convergent but were not asymmetric. In contrast, Shibasaki[11] reported an elegant asymmetric route that lacked efficiency due to its lengthy linear nature. Thus, the development of a synthetic route to halenaquinone that is both asymmetric and convergent presented a worthy target, which, as such, was of great interest to the Keay group.

1.5 Retrosynthesis

Retrosynthetic analysis of **1** illustrates the transformations required in order to design a synthetic route toward halenaquinone that is both asymmetric and convergent (Scheme 1.12).

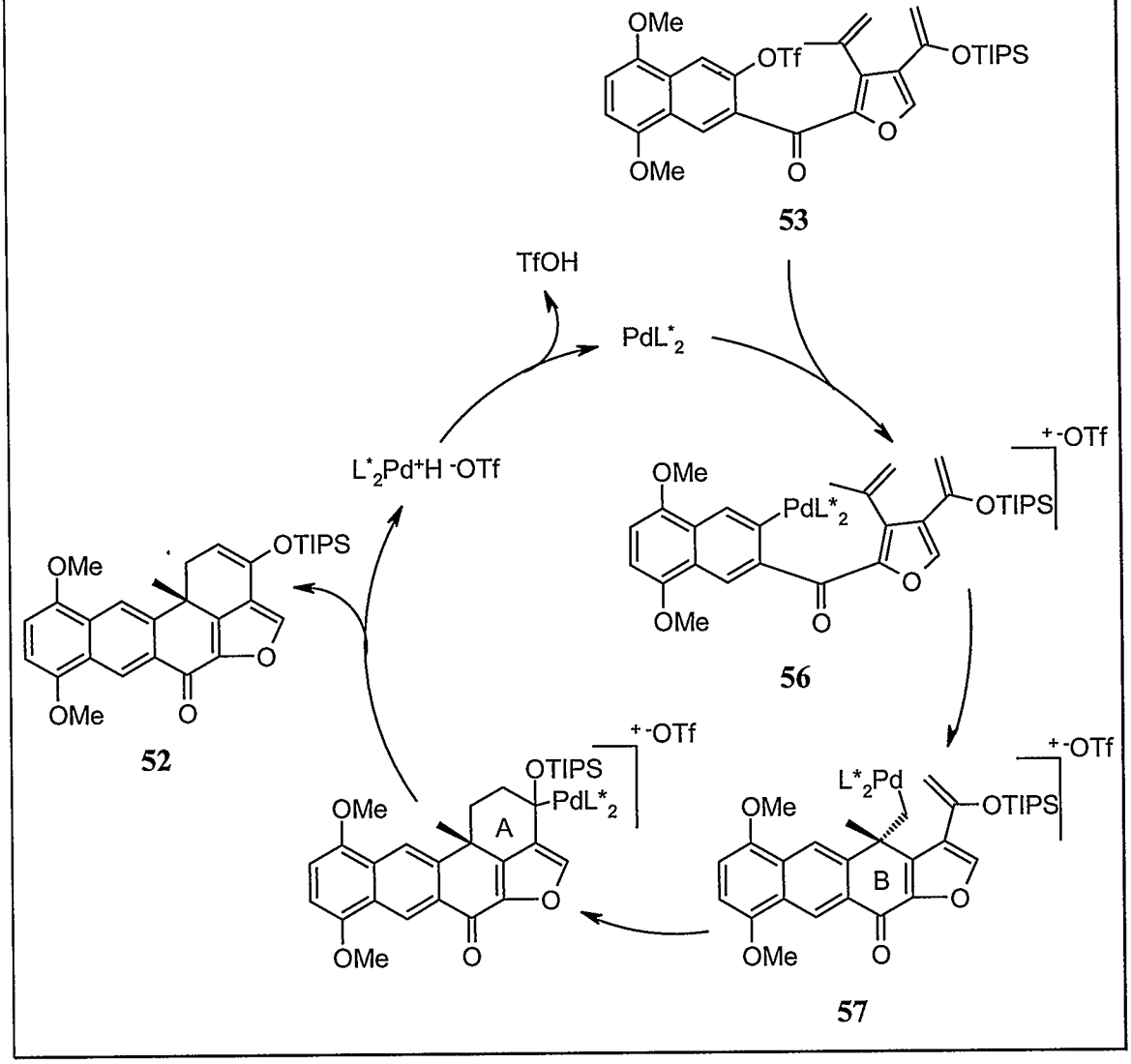
Scheme 1.12



Precursor **52** can be derived from halenaquinone (**1**) in two steps. First, a functional group interconversion transforms the A ring carbonyl function into a silyl enol ether. The forward reaction, the final step in the synthesis, is therefore cleavage of this silyl protecting group. The second transformation is the conversion of the of the quinone D ring into the corresponding dimethyl ether. The forward reaction here is oxidative cleavage of the hydroquinone dimethyl ether moiety of **52** with CAN, the same

conditions used by Harada,[9] Shibasaki,[11] and Keay[16] to establish the quinone rings of both halenaquinone and xestoqinone from analogous precursors. Disconnection of the C6 - C19 bond in the B ring and the C4 - C5 bond in the A ring of **52** leaves a system of alkenes in **53** well suited to an asymmetric Pd-catalyzed polyene cyclization. In one step, this key transformation should effect the closure of both the A and B rings while establishing the required stereogenic centre (Scheme 1.13).

Scheme 1.13



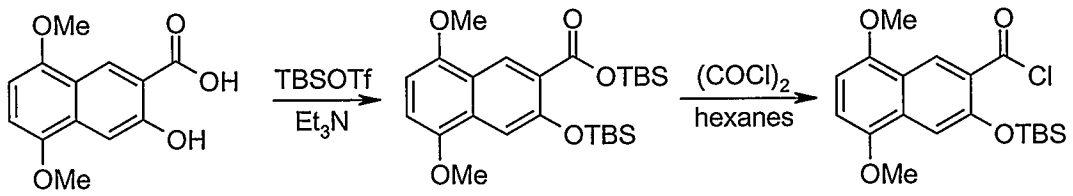
The relevant catalytic cycle begins with insertion of the asymmetric Pd species into the carbon triflate bond of **53**. This is followed by formation of intermediate **57** *via* a

6-*exo-trig* cyclization with closure of the B ring and establishment of the stereogenic centre. At this stage, the Pd species is unable to undergo elimination as the adjacent carbon atom is tertiary, and a β-hydrogen atom is required for this process. Therefore, a subsequent 6-*endo-trig* cyclization occurs, closing the A ring and completing the pentacyclic framework. At this stage β-hydride elimination can occur, generating halenaquinone precursor **52** and returning the asymmetric Pd species to the catalytic cycle.

Cyclization precursor **53** can in turn be prepared from **54** (Scheme 1.12). Cleavage of the triflate leaves a phenyl hydroxy group that is accessible from the corresponding phenolic TBS ether of compound **54**. A disconnection can be made between C8 and C9 of **54** to generate two subunits of approximately equal complexity. Fragment A is thus a naphthoic acid chloride which reacts with lithiated furan **55** *via* the C7 acid function, which in the forward direction yields **54**.

Although key intermediate **43** is a known compound[17] prepared in 13 steps from 2,5-dimethoxy-benzyl alcohol (Scheme 1.9), it was felt that a more efficient route to this naphthalene derivative could be developed. The final two steps in this earlier route, were both efficient and relevant to our strategy toward halenaquinone so the target of the new route would in fact be hydroxynaphthoic acid **42** (Scheme 1.14).

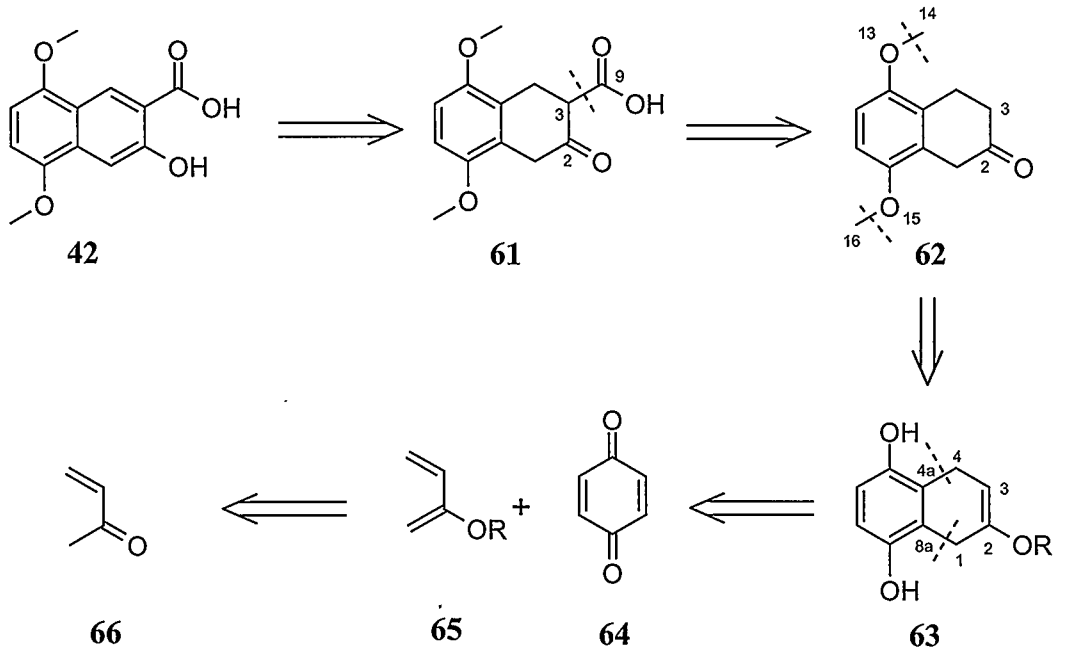
Scheme 1.14



42 **58** **43**

Retrosynthetic analysis of 3-hydroxy-5,8-dimethoxy-2-naphthoic acid (**42**) illustrates how Fragment B can be prepared in far fewer steps by constructing the bicyclic skeleton *via* a Diels-Alder addition with *p*-quinone (**64**) and 2-substituted diene **65** (Scheme 1.15).

Scheme 1.15

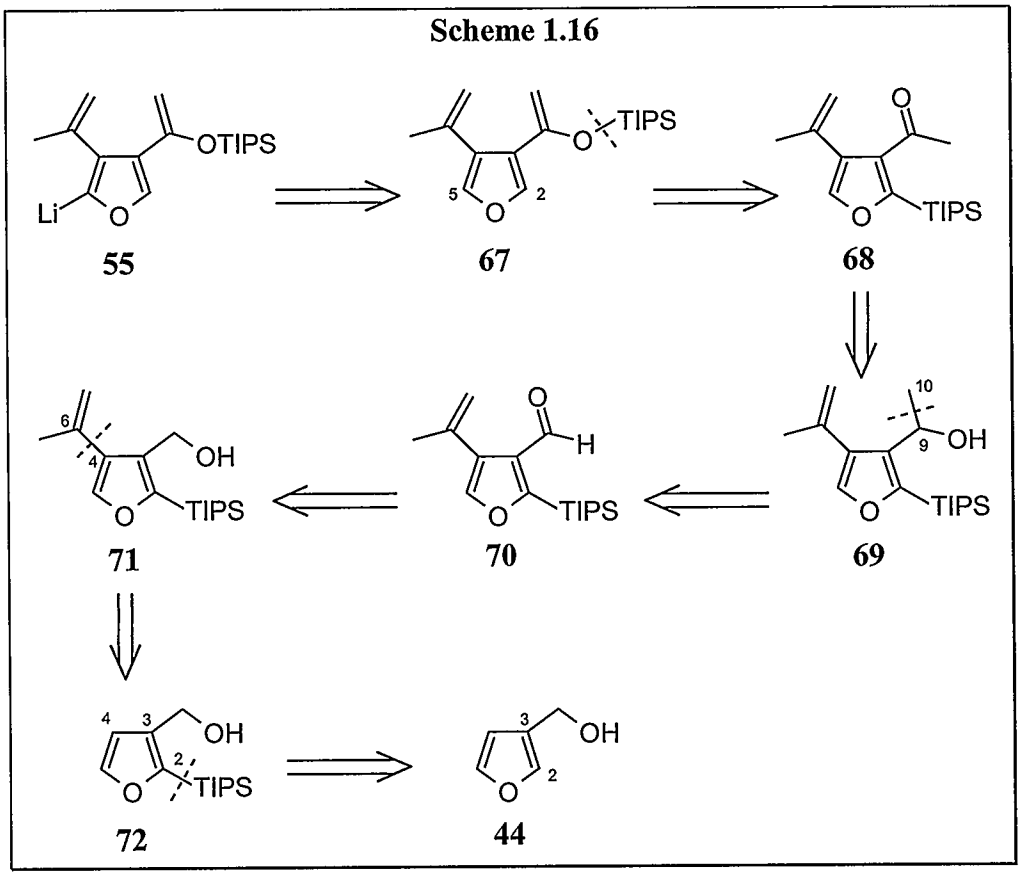


Aromatized naphthoic acid **42** can be dearomatized in one step to β-keto acid **61**, in the forward direction this corresponds to an oxidation. Disconnection of the bond connecting C3 to C9 of **61** effectively decarboxylates the β-keto acid generating tetralone **62**, a system well suited for the forward reaction; a regioselective carboxylation.[20] Two transformations are required to form tetralone **62** from precursor **63**. First, disconnection of both the C14 and C16 methyl groups of **62**, followed by protonation, results in the generation of *p*-hydroxyl units of diphenol **63**. The forward reaction is thus O-methylation of diphenol **63**. Second, tautomerization of the C2 ketone of **62** into a C2 – C3 enol function and trapping of the enolate generated by deprotonation with some group R, completes the transformation to diol **63**. The forward reaction is thus cleavage of the R group, which regenerates the C2 carbonyl function. Tautomerization of the 5,8-diol **63** to the 5,8-dione system followed by disconnection of the C4 – C4a and C1 – C8a bonds of the adduct gives *p*-quinone (**64**), a readily available starting material, and diene **65**. Compounds **64** and **65** are well suited for the forward reaction, a Diels-Alder cycloaddition, as diene **65** can be made to be electron rich by the nature of the R group employed and dienophile **64** is electron poor. Disconnection of the R group from **65**

leaves methyl vinyl ketone (**66**) another simple and readily available starting material.

Retrosynthetic analysis of lithiated furan derivative **55** illustrates how Fragment B can be constructed from 3-furanmethanol (**44**) through a sequence analogous to that performed in the preparation of dienyl furan **48** (Scheme 1.10).

Scheme 1.16



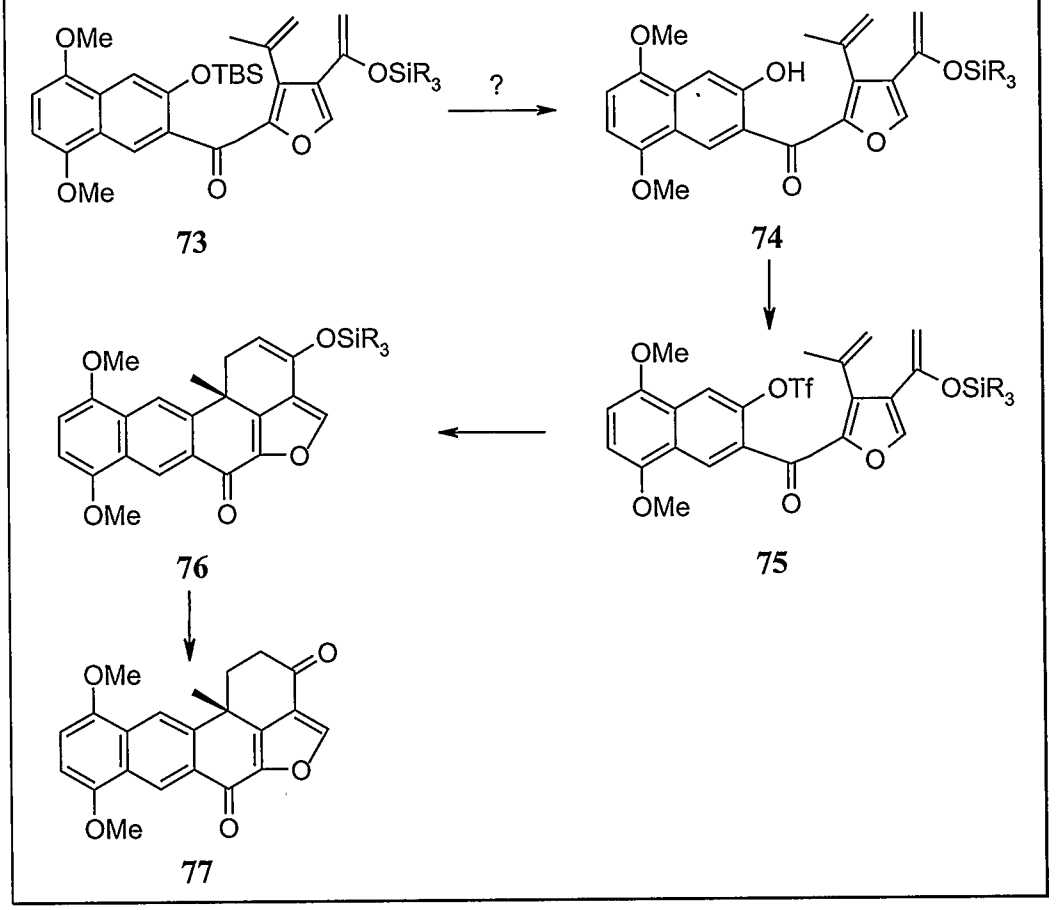
Silyl enol ether **55** can be prepared *via* the selective lithiation of enol ether **67** (Scheme 1.16). A disconnection between the silyl group and the enol oxygen of TIPS enol ether **67** leads to methyl ketone **68** when accompanied by the migration of the TIPS group to the C2 position of the furyl ring. The forward reaction therefore is simply the corresponding [1,4] C → O silyl migration. Methyl ketone **68**, in turn, can be reduced to secondary alcohol **69** thus, the forward transformation requires an oxidative procedure. Removal of the C10 methyl group of **69** by disconnection of the bond connecting C9 to C10 gives the corresponding aldehyde (**70**), which can be further reduced to primary alcohol **71**. The forward reaction would thus require the oxidation of primary alcohol **71**

to aldehyde **70** followed by the attack of a nucleophilic methyl group at the carbonyl carbon of **70**. A disconnection through the bond connecting C4 to C6 in **71** generates two subunits, an electrophilic propene component and a C4 furyl anion. This disconnection is the reverse of a Suzuki reaction between 2-bromopropene and 2,3-substituted **72**. Compound **72** is a known species,[21] which was prepared by protection of 3-furanmethanol (**44**) as the TIPS ether followed by [1,4] O → C silyl migration.

1.6 The Role of Silyl Substituents in the Synthetic Strategy

The decision to incorporate a TBS phenol ether into Fragment A and TIPS groups into Fragment B was carefully evaluated since both play important roles in the synthetic strategy. In the final steps of the synthesis the TIPS silyl enol ether serves several functions. Thus, in order for the TIPS protecting group to be a satisfactory SiR_3 group, it had to meet several requirements. First, it had to be stable to some set of conditions that could be used to cleave the phenolic TBS group of **73** (Scheme 1.17).

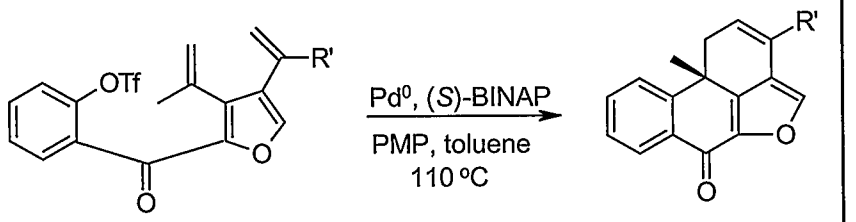
Scheme 1.17



Selective cleavage of the TBS group to obtain triflate **75** *via* naphthol **74** is crucial to the synthesis as closure of the A ring occurs through the terminal alkene of the SiR_3 enol ether. Although an explicit example of selective cleavage of a phenolic TBS in the presence of a TIPS enol ether could not be found in the literature, it is known that TIPS ethers are generally more robust than TBS ethers.[22] The second requirement is that the R group be easily cleaved in the final steps of the synthesis, allowing for transformation of silyl enol ether **76** into ketone **77** under mild conditions. The TIPS group is again suitable since, typically, TIPS enol ethers can be cleaved under mild acidic conditions.[22b] The final requirement for an effective R group is that it must have substantial steric bulk. Previous work[23] performed by Steve Lau using model systems designed to study asymmetric polyene cyclizations using Pd^0, (*S*)-BINAP and PMP in toluene at 110 °C revealed an interesting trend. As the size of the group in the R' position of **78** was

increased, a corresponding increase in the enantioselectivity of the Pd-catalyzed cyclization was also observed (Scheme 1.18). When R' = H, **78a**, an *ee* of 68% was observed for desired *S*-isomer **79a**. In contrast, when R' = Me, **78b**, the *ee* jumped to 90%. PM3 calculations performed by Lau and Keay suggest that a further increase in the size of the R group may result in even greater enantioselectivity.[24] In accordance with these findings, the three isopropyl substituents of the TIPS group should provide enough steric bulk to further enhance the selectivity of this key step.

Scheme 1.18

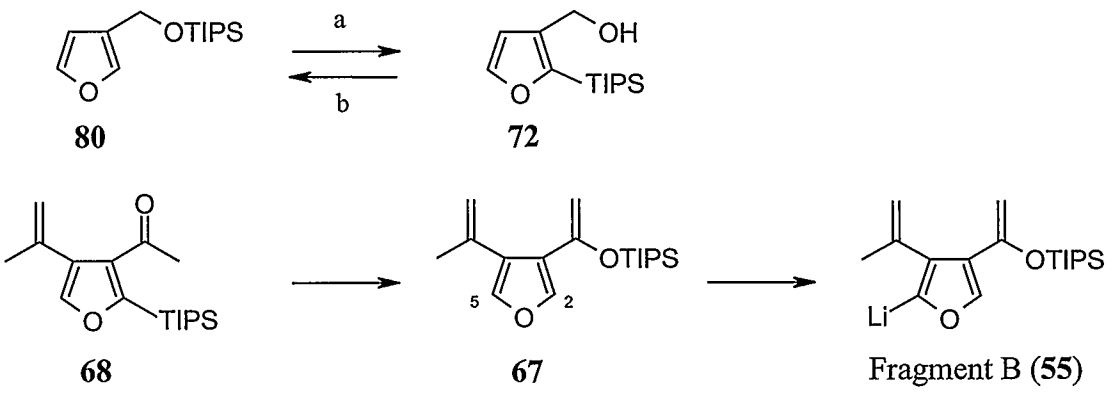


78a R' = H
78b R' = Me

79a 68%
79b 90%

The TIPS group also plays several roles in the final and critical steps in the preparation of Fragment B. Previous work in the Keay lab performed by Bures and others[21] examined [1,4] O → C and [1,4] C → O silyl migrations of 2,3-substituted furan rings. They found that under one set of conditions, the silyl group of **80** could be transferred to the C2 position *via* [1,4] O → C silyl migration, to generate **72** in high yield (Scheme 1.19). Under a separate set of conditions, a [1,4] C → O migration could be induced, effectively reversing the previous reaction and converting **72** into **80**. It was therefore hoped that some related set of conditions could be applied to the more complex 2,3,4-trisubstituted furan compound **68** in order to effect the analogous C → O migration and generate silyl enol ether **67**. Although the functionality generated by the migration differs between the cases, a silyl ether in **72** and a silyl enol ether in **67**, it was anticipated that the process would be similar and critical intermediate **67** could be obtained from methyl ketone **68**.

Scheme 1.19



Conditions: a) *n*BuLi (1.2 equiv.), HMPA, THF, 0 °C - rt (89%); b) NaH, DMF, 0 °C - rt (86%).

The TIPS group was also anticipated to aid in the subsequent selective lithiation of **67** to yield Fragment B (**55**, Scheme 1.19). The silyl group should aid in selective lithiation at the C5 position of the furan ring in three ways. First, the steric bulk of the TIPS substituent may physically block lithiation at the C2 position. Second, use of a sterically bulky base would interact negatively with the large silyl group, further restricting anion formation at the C2 position. Third, decreased basicity of the silyl enol ether oxygen makes it less able to direct lithiation toward the C2 position.

The chosen silyl group has the potential to significantly impact several key steps in the synthetic strategy and was therefore carefully considered. With the above information in hand, it was felt that the TIPS group could be safely incorporated into Fragment B early in the preparation. Further discussion is included in relevant sections throughout.

Chapter 2

2. Synthesis of Fragment A *via* Naphthoic Acid 58

2.1 Introduction

This chapter begins with an examination and discussion of the three methods used in the construction of the bicyclic framework of Fragment A. This is followed by an examination of the methods used in the functionalization of the core structure and ultimately the preparation of naphthoic acid **42**, which effectively completes the synthesis of this fragment. The remainder of the chapter will focus on the preparation of Fragment A', an alternative naphthoic subunit that if substituted for Fragment A, reduces the number of steps in the synthesis of halenaquinone (**1**) .

2.1.1 Synthetic Strategy Toward the Construction of Fragment A

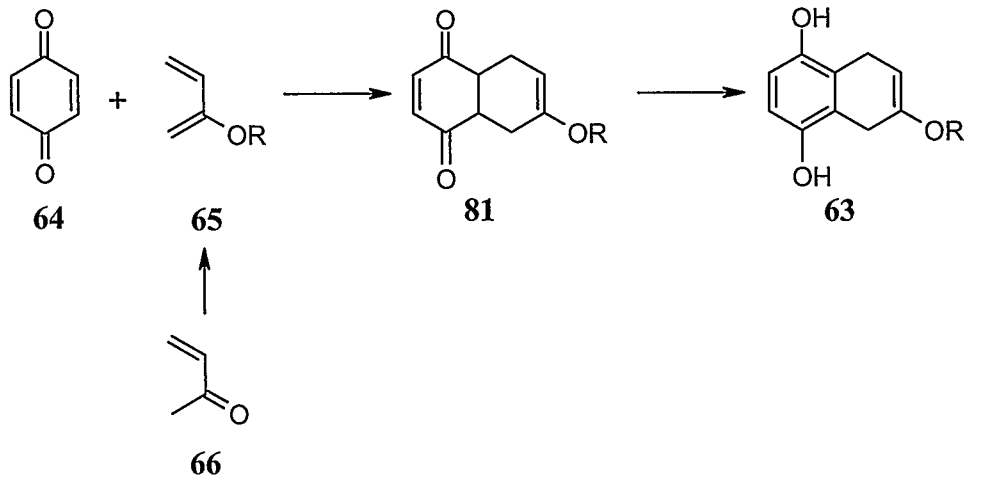
Fragment A is a known compound and has been successfully prepared in 14 steps from 2,5-dimethoxybenzyl alcohol (**33**, Scheme 1.9).[16,17] Since the existing synthesis of Fragment A was somewhat lengthy a new approach to this key intermediate was devised. This new route would utilize the same two final steps as the previous route (Scheme 1.14); thus, attention was focused on developing a more efficient synthesis of 3-hydroxy-5,8-dimethoxy-2-naphthoic acid (**42**, Scheme 2.1).

Scheme 2.1

42 Fragment A (**43**)

In accordance with the synthetic strategy proposed in the previous section (Scheme 1.15) a suitable diene **65** was required. R groups were chosen based on their ability to easily trap the enolate generated by deprotonation of ketone **66** and form the corresponding diene in good yield. Once formed, that diene had to react readily in a Diels-Alder addition with *p*-quinone (**64**) to generate adduct **81,** which would likely tautomerize to **63** (Scheme 2.2). The carbon skeleton thus constructed could then subjected to a series of transformations to form naphthoic acid **42,** a known precursor in the preparation of Fragment A.

Scheme 2.2

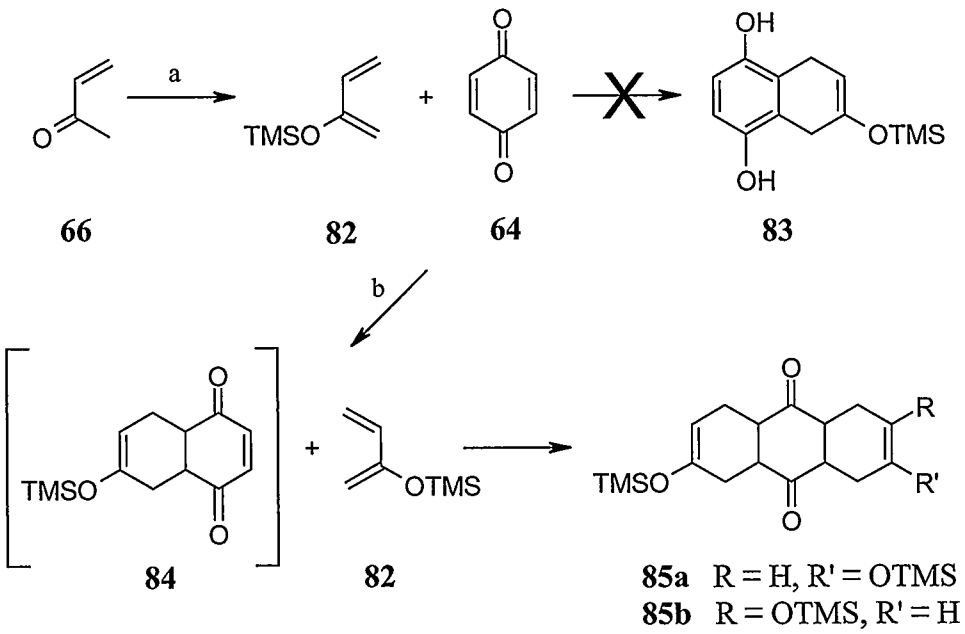


2.2 Construction of Bicyclic Skeleton 63 *via* the Diels-Alder Reaction

2.2.1 Synthesis and Diels-Alder Reaction of TMS Enol Ether 82

The first diene considered was 2-(trimethylsiloxy)-1,3-butadiene (**82**) in which R = TMS (Scheme 2.3).

Scheme 2.3



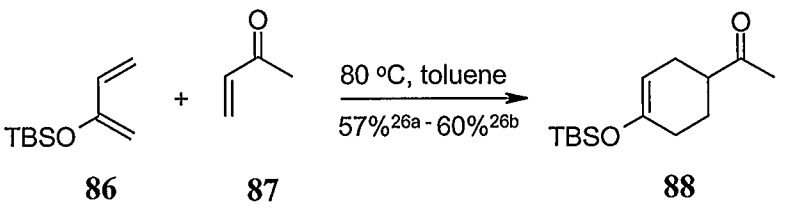
66 **82** **64** **83**

84 **82** **85a** R = H, R' = OTMS
85b R = OTMS, R' = H

Conditions: a) TMSCl (1.2 equiv.), Et_3N (2.3 equiv.), DMF, 90 °C (60%). b) **82** (1.0 equiv.) toluene, 90 °C.

Following the procedure of House *et al*,[25] methyl vinyl ketone (**66**) was slowly added to a solution of Et_3N (2.3 equiv.) and TMSCl (1.2 equiv.) in DMF. Heating the reaction mixture for 48 h at 90 °C resulted in successful formation of TMS diene **82** (60%). With **82** in hand, the requisite bicyclic skeleton could be constructed *via* a Diels-Alder reaction with *p*-quinone. Since a successful Diels-Alder addition had been reported[26] between 2-siloxy diene **86** and unsymmetrical dienophile **87** to give adduct **88** in good yield (Scheme 2.4) it was hoped that applying the same conditions to the addition of **82** and **64** would give adduct **83**.

Scheme 2.4



86 **87** **88**

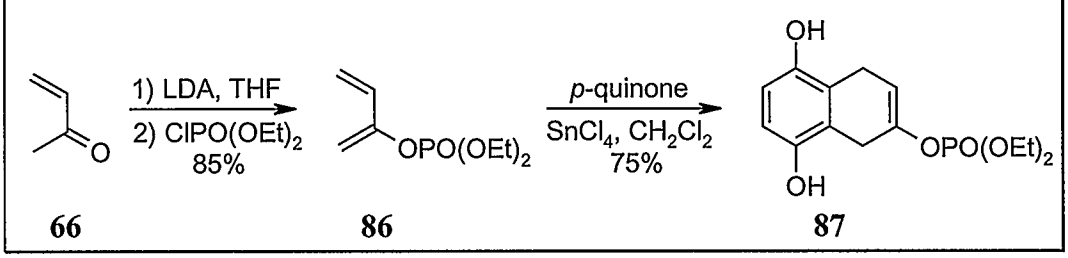
Diene **82** and *p*-quinone (**64**) (1 equiv.) were therefore dissolved in toluene and heated to 90 °C for 48 h. TLC analysis of the reaction mixture over time showed formation of several products. Unfortunately, ^{1}H NMR analysis confirmed that the major components of the crude product mixture were not desired adduct **83**. Disappointingly, attempts to separate the complex mixture using flash column chromatography failed to give clean separation. Further, unless 1% Et_3N was added to the solvent system, column chromatography resulted in an additional change in the composition of the mixture, likely the result of desilation due to the acidic silica gel used. Although not specifically identified, the primary products of the reaction appeared to be isomers of double addition products **85a** and **85b** in which a second equivalent of diene **82** reacted with the unsubstituted double bond of adduct **84** (Scheme 2.3). These results implied that adduct **84** was at least as reactive as quinone **64** under these conditions. Isolation of the single addition product was therefore not practical as adduct **84** represented only a small component of the complex mixture. Thus, diene **82** appeared unsuitable for the addition reaction as yields were detrimentally affected by the facile formation of double addition products.

Although several strategies could have been employed to minimize the formation of the double Diels-Alder addition products, attention was instead turned to a promising alternative diene.

2.2.2 Synthesis and Diels-Alder Reactions of Enol Phosphate 86

A search of the literature uncovered a procedure in which a dienyl phosphate was prepared[27,28] and reacted with *p*-quinone in a Diels-Alder reaction to give **87**, the desired monoadduct[28b] (Scheme 2.5).

Scheme 2.5

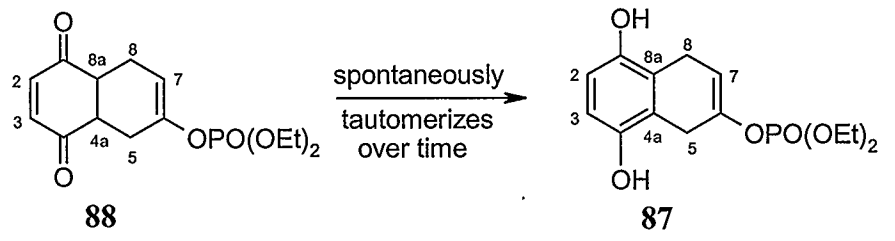


66 **86** **87**

Use of dienyl phosphate **86** rather than the analogous siloxy diene offered two important benefits. First, dienyl phosphates are more robust, particularly under acidic conditions that often decompose their siloxy analogues.[28] Second, when reacted with *p*-quinone in the presence of a Lewis acid catalyst, exclusive formation of the Diels-Alder monoadduct **87** was observed.[28b] Therefore, the two major sources of loss that had resulted from using siloxy diene **82** could be avoided.

Treatment of methyl vinyl ketone (**66**) with LDA in THF generated the required enolate that was trapped with diethyl chlorophosphate (2 equiv.) to form dienyl phosphate **86** in 85% yield.[27,28] In contrast to TMS diene **82**, **86** was stable to flash column chromatography over silica gel. Following distillation, diene **86** (1.2 equiv.) was dissolved in DCM and reacted with *p*-quinone (**64**, 1 equiv.) at 0 °C in the presence of $SnCl_4$ (1.2 equiv.) to construct the bicyclic skeleton.[28b] After 5 h, TLC analysis showed complete consumption of quinone **64** concurrent with the appearance of two new spots alongside a spot corresponding to unreacted diene **86**. Flash column chromatography of the crude tar-like material allowed recovery of unreacted diene and isolation of two products. The more polar product was concentrated under reduced pressure to give a white solid that was identified by ^{1}H NMR[28b] as diphenol **87** (Scheme 2.6).

Scheme 2.6



88 **87**

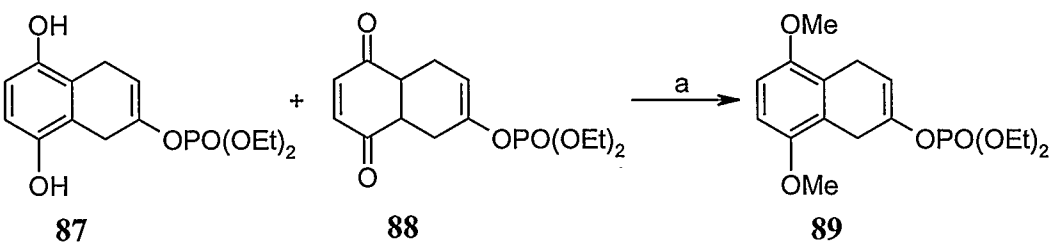
The less polar compound was isolated as a viscous brown material. ^{1}H NMR analysis generated several diagnostic peaks: a multiplet between 3.11-3.47 ppm corresponded to the protons on C4a and C8a (Scheme 2.6), and a second broad multiplet between 2.24-2.83 ppm corresponded to the pairs of protons on C5 and C8. This less polar product was therefore identified as naphthoquinone **88**, a tautomer of diol **87**. Oddly, Liu *et al*[28b] did not report the formation of this tautomer. Additional peaks corresponding to the ethyl

group of the diethyl phosphate, the vinyl proton (C7) and the two protons of the quinone ring (C2 and C3) were also observed. These peaks were very similar to those generated by the analogous protons of diphenol **87**. Since these protons were not involved in the tautomerization, their similar shifts and splitting patterns lent further support to the identification of the less polar compound as **88**. Fortunately, in accordance with the initial synthetic strategy the next transformation was to be O-methylation and since this conversion could be effectively applied to either **87** or **88**, the appearance of the naphthoquinone isomer did not affect the efficiency of this step.

2.3 O-Methylation of Enol Phosphate Adducts 87 and 88

With phosphorylated adducts **87** and **88** in hand the next transformation required was O-methylation of the adducts to form the corresponding 5,8-dimethoxy species **89** (Scheme 2.7).

Scheme 2.7



87 **88** **89**

Conditions: a) NaH (4 equiv.), **87** and/or **88**, DMF, rt then MeI (4 equiv.), 3h (>99%).

The formation of the dimethoxy species was critical to the synthetic strategy in order to protect the diphenol (or quinone) from side reactions throughout the remaining steps. In addition, the resultant aryl 1,4-dimethoxy system could be oxidized to give the quinone ring of halenaquinone in the late stages of the synthesis.[9,16]

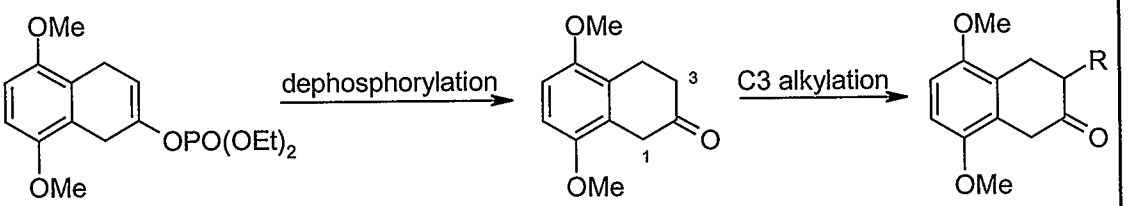
Initial attempts at O-methylation used conditions derived from a literature procedure.[29] Adduct(s) **87** and/or **88** were deprotonated with NaH (3 equiv.) at rt in DMSO. The resulting anion was treated with an excess of MeI and stirred for 2 h. Following workup, the yellow oil isolated was identified by ^{1}H NMR analysis as 5,8-dimethoxy derivative **89**. A new singlet at 3.78 ppm, integrating to 6 H appeared in a spectrum otherwise similar to that of adduct **87**. This new peak, together with ^{13}C NMR

data identifying 2 new methyl carbon atoms, pointed to the successful incorporation of the two methyl groups. Further analysis by HRMS gave a value of 342.1225 amu, which coincided with a calculated value of 342.1232 amu for $C_{16}H_{23}O_6P$, further supporting the identification of the oil as 5,8-dimethoxy compound **89**. Disappointingly, despite the successful preparation of the O-methylated product, yields were consistently low using the unmodified literature procedure. Gratifyingly, substituting DMF as the solvent gave smooth and nearly quantitative conversion of adducts **87** and **88** to methylated compound **89** (>99%).

2.4 Dephosphorylation of Enol Phosphate 89

The next step in the synthesis of Fragment A was anticipated to be a relatively simple dephosphorylation that would convert enol phosphate **89** into ketone **62** (Scheme 2.8). Once deprotected, ketone **62** could be alkylated at C3 with some group R that was suitable for conversion to an acid chloride.

Scheme 2.8

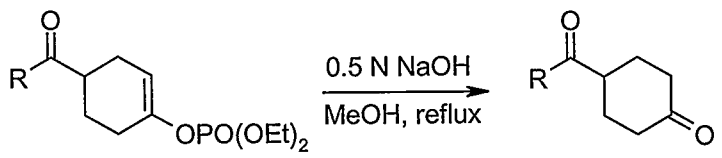


89 **62** **90**

2.4.1 Dephosphorylation Under Basic Conditions

Initial attempts at dephosphorylation focused on the methods used by Liu and associates[28] in the deprotection of related enol phosphorylated compounds (Scheme 2.9).

Scheme 2.9

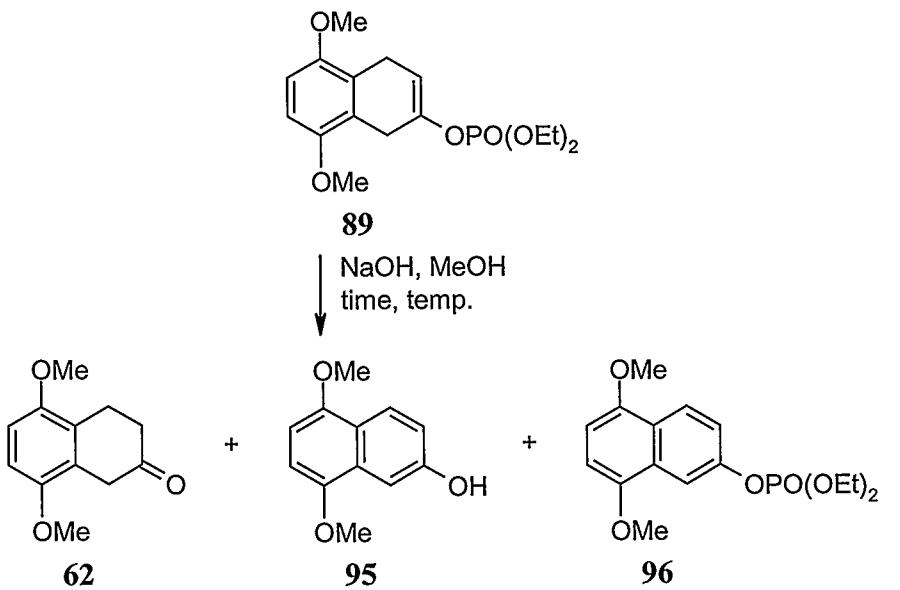


R = Me **91**
R = Et **93**

92 (12%)
94 (27%)

When enol phosphates **91** and **93** (Scheme 2.9) were treated with 0.5 N NaOH in MeOH at reflux for 3.5 to 5 h respective yields of 12% and 27% were obtained.[28b] Subjecting **89** to treatment with 0.5 N NaOH in MeOH at rt showed only SM after 48 h (Entry 1, Table 2.1).

Table 2.1: Attempts to Dephosphorylate 89 Using NaOH in MeOH



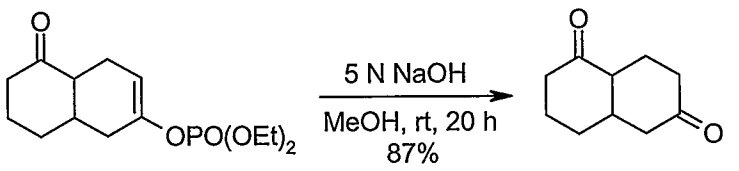
Entry	NaOH Concentration	Time	Temperature	Result
1	0.5 N NaOH	48 h	rt	NR
2	0.5 N NaOH	48 h 12 h	rt Reflux	NR **95** and **96**
3	5 N NaOH	20 h	rt	NR
4	5 N NaOH	18 h	Reflux	NR
5	4 N NaOH	1.5 h	Reflux	SM, **62** (trace)
6	4 N NaOH	4 h	Reflux	SM, **62** (trace)
7	4 N NaOH	23 h	Reflux	CM and **95**
8	4 N NaOH	1 h	Reflux	64%
9	4 N NaOH	1 h	Reflux	0 – 17%

When this same mixture was heated to reflux (Entry 2, Table 2.1), complete consumption of starting material was observed in 12 h. Unfortunately, the products of this reaction were identified as **95** and **96** the aromatized analogs of desired product **62** and starting material **89**. Analysis of the first product by GC-MS generated a spectrum with a

molecular ion peak of 340 amu corresponding to a molecular formula of $C_{16}H_{21}O_6P$, which indicated the formation of phosphorylated naphthol **96**. The mass spectrum for the second product exhibited a molecular ion peak of 204 amu corresponding to a molecular formula of $C_{12}H_{14}O_3$, consistent with naphthol **95**.

The isolation of **95** suggested that increasing the temperature at which the reaction was performed had aided in the cleavage of the phosphate group. Unfortunately, the elevated temperature also appeared to facilitate the undesirable oxidation of the starting material and likely **62**, the desired product of dephosphorylation, as it was generated. The second method used by Liu for the preparation of ketones from their parent enol phosphates was treatment with 5 N NaOH in methanol at rt for 20 h. These conditions were used to generate the desired ketone from bicyclic phosphorylated species **97** (Scheme 2.10).[28b]

Scheme 2.10



97 **98**

Despite reported[28b] yields of up to 87% of ketone **98** from **97**, direct application of these conditions to enol phosphate **89** (Entry 3, Table 2.1) gave no reaction after 20 h. Since performing the reaction at rt proved unsuccessful, it was hoped that repeating the procedure but heating to reflux would effect the desired transformation. Regrettably, this was not the case, and only SM was observed after refluxing for 18 h (Entry 4, Table 2.1). Decreasing the concentration of NaOH to 4 N, but doubling the ratio of base to substrate and refluxing for 1.5 h gratifyingly generated detectable amounts of **62** (Entry 5, Table 2.1). Increasing the base to substrate ratio further, tripling the equivalents of NaOH with respect to the initial reaction, failed to give a significant improvement and again, only trace amounts of **62** were detected after 4 h (Entry 6, Table 2.1). It was thought that perhaps the reaction time was too short and that increasing that time would lead to the formation of **62** in useful quantities. After 23 h of refluxing **89** with 4 N NaOH, however

(Entry 7, Table 2.1), no ketone could be detected, and instead, a complex mixture was obtained. Amid this mixture, ^{1}H NMR analysis revealed the unmistakable aromatic peaks of naphthol **95**. The detection of **95** but not **96** as a component of the crude mixture implied that one of two processes was occurring; either dephosphorylation was effected as anticipated, but the ketone obtained was unstable to the reaction conditions and was immediately oxidized *in situ* to **95** or cleavage of the phosphate group occurred following the aromatization of **89** to naphthyl phosphate **96**.

The reaction conditions were again modified, increasing the amount of NaOH in an attempt to force the reaction to proceed quickly and hopefully circumvent the formation of aromatized species **95**. When the molar ratio of NaOH to substrate was again tripled (with respect to the preceding reaction) and the reaction mixture brought to reflux, the starting material appeared to be consumed within 1 h by TLC analysis (Entry 8, Table 2.1). After purification *via* flash column chromatography, a white flocculent material was isolated that was subsequently identified by ^{1}H NMR analysis[30] as ketone **62** (64%). Frustratingly, despite the moderate yield obtained when these conditions were applied to **89** on a small scale (26 mg), they consistently failed to give good conversion when applied on larger scale (Entry 9, Table 2.1).

It therefore appeared that the dephosphorylation of **89** could not be successfully affected by NaOH hydrolysis. Attempts to optimize these conditions resulted in complex mixtures, low yields and aromatization of both phosphate **89** and ketone **62**. These results, coupled with poor reproducibility upon scale up made these conditions impractical for use in the early stages of a total synthesis. Therefore work toward optimization of these conditions ceased.

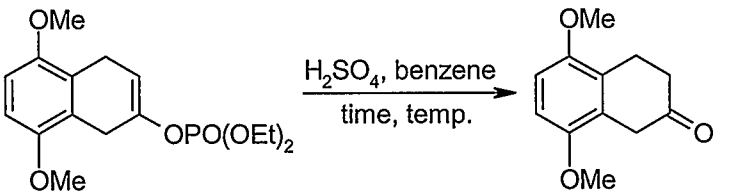
2.4.2 Dephosphorylation Under Acidic Conditions.

A second search of the literature uncovered several methods by which dephosphorylation could be effected. By far, the simplest of these appeared to be cleavage of the phosphate group under acidic conditions.[31,32]

The general procedure employed in this series of reactions was to dissolve enol phosphate **89** in benzene and then add aqueous sulfuric acid. Since the solvent employed was not one in which the acid was miscible, the reaction required vigorous stirring to

bring enol phosphate **89** into contact with the acid. In this way, both the substrate and product spent less time in direct contact with the acid, and this was anticipated to minimize the *in situ* decomposition of these materials. Compound **89** was first treated with 15% H_2SO_4 (Entry 1, Table 2.2) at rt. Disappointingly, this resulted in no reaction after 21 h.

Table 2.2: Attempts to Dephosphorylate 89 Using H_2SO_4 in Benzene



89 **62**

Entry	H_2SO_4 Concentration	Temperature	Time	Result
1	15%	rt	21 h	NR
2	15% conc.	60 °C rt	4 h 16 h	NR SM, **62** (trace)
3	25%	reflux	4 h	NR
4	50%	rt	24 h	SM, **62** (trace)
5	50%	60 – 70 °C rt	2 h to 8 h 16 h to 20 h	SM, **62** (0 – 74%), CM
6	conc.	0 °C → rt	2 h	**62** (15%)
7	conc.	0 °C → rt	17 h	CM

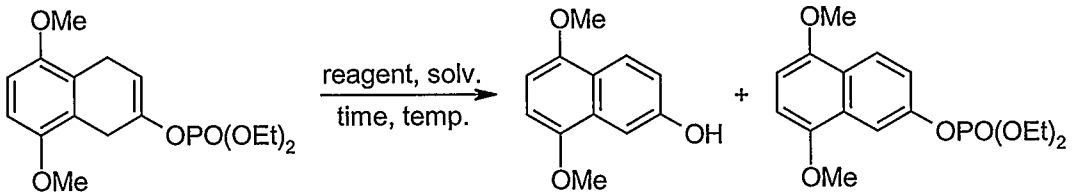
Repeating the previous reaction at 60 °C (Entry 2, Table 2.2) again resulted in the recovery of unreacted starting material after 4 h. The solution was then cooled to 0 °C and a few drops of conc. H_2SO_4 were added before the mixture was allowed to warm to rt. After an additional 16 h, the reaction mixture still appeared to contain only **89** by TLC. Surprisingly, ^{1}H NMR analysis of the crude product showed the formation of trace amounts of **62**. Since the dephosphorylation appeared to be occurring slowly in the presence of a higher concentration of acid, **89** was treated with 25% H_2SO_4 (Entry 3, Table 2.2) and the reaction mixture brought to reflux. Unfortunately, no reaction was observed after 4 h. A further increase in the concentration of acid to 50% H_2SO_4 (Entry 4, Table 2.2) gave a small but observable conversion to product. Several reactions were

then performed using 50% H_2SO_4 (Entry 5, Table 2.2) at elevated temperature (60 – 70 °C, 2 – 8 h). The reactions were monitored by TLC analysis, and if decomposition products were detected, the reactions were cooled to rt and allowed to continue until the SM appeared consumed (0 – 20 h). These conditions gave the best conversion thus far, forming **62** in up to 74% yield. Unfortunately, this method of dephosphorylation proved unreliable; despite several attempts, the isolated yield of 74% could not be duplicated, and typical yields ranged from 10 – 15%. Since the use of 50% H_2SO_4 required a relatively lengthy reaction period, it was anticipated that using a higher concentration of acid may effect a faster and more reliable dephosphorylation, noting that some success had already been observed with conc. H_2SO_4 (Entry 2, Table 2.2). Although treatment of **89** with conc. H_2SO_4 at rt (Entry 6, Table 2.2) resulted in the complete consumption of starting material within 2 h, ketone **62** was isolated in a disappointing 15% yield with the balance of the material suffering decomposition. Allowing the reaction to proceed for an additional 15 h (Entry 7, Table 2.2) resulted in the complete decomposition of all of the product generated in the early stages of the reaction. Thus, there appeared to be an inherent problem with the use of acidic conditions for the dephosphorylation of intermediate **89**. In order to effect the cleavage, relatively harsh conditions were required; however, employing such conditions facilitated the decomposition of both the substrate and the desired product.

2.4.3 Dephosphorylation Using Other Methods

With relatively few methods available for efficient dephosphorylation,[31b] any applicable literature examples for the cleavage of phosphate groups that could be found were tested. The first of these appeared in the total synthesis of (±)-9-pupukeanone[33] in which an enol phosphate was converted to the corresponding ketone (97%) using sodium ethoxide in EtOH. Treating compound **89** with 2 M NaOEt (20 equiv.) in EtOH at rt however, showed SM and naphthyl phosphate **96** after 24h and naphthol **95** after 48 h (Entry 1, Table 2.3). These results suggested that aromatization of **89** to **96** was occurring prior to dephosphorylation and therefore NaOEt was not a suitable reagent for this transformation.

Table 2.3: Attempts to Dephosphorylate 89 Using NaOEt or NH_4F



89 **95** **96**

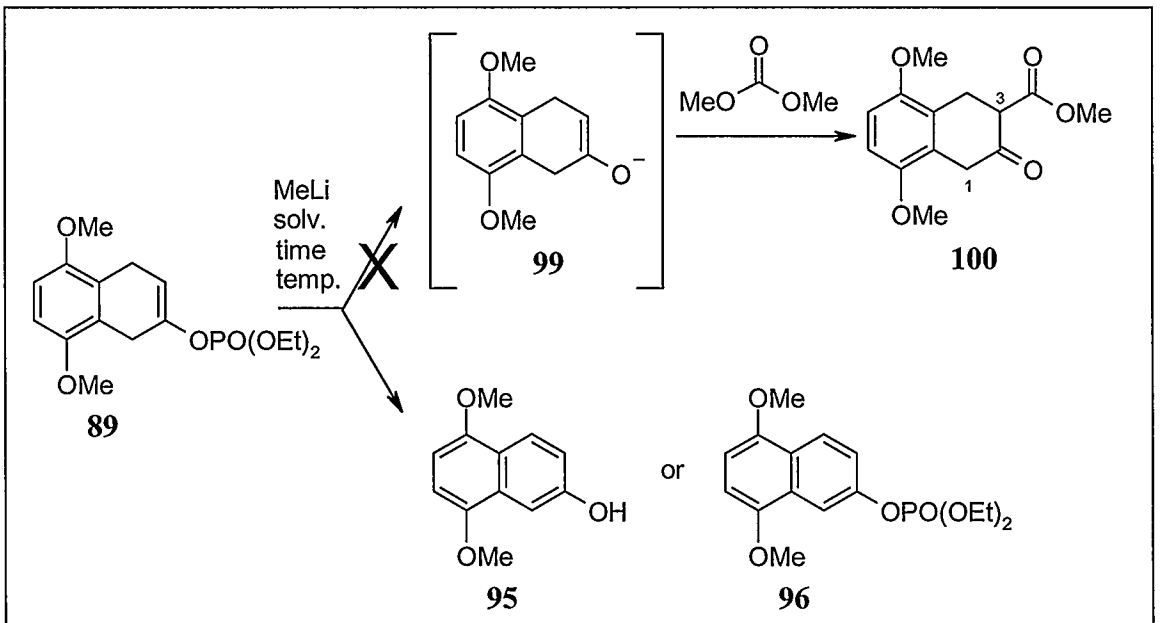
Entry	Reagent	Solvent	Temperature	Time	Result
1	NaOEt (20 equiv.)	EtOH	rt rt	24 h 48 h	SM, **96** **95**
2	NH_4F (10 equiv.)	MeOH	rt rt	24 h 48 h	NR SM, **95** (trace)

Krawczyk *et al*[31] used ammonium fluoride to effect the cleavage of an enol phosphate and obtained the desired ketone in 52% yield. Unfortunately, treatment of **89** with NH_4F (10 equiv., Entry 2, Table 2.3) in MeOH at rt gave no conversion to product after 48 h. Adding an additional portion of NH_4F (10 equiv.) and allowing the reaction to stir a further 24 h showed primarily unreacted SM and a trace amount of oxidized species **95**.

The next method of dephosphorylation tested was treatment with MeLi which had been reported to generate the corresponding ketones in 17% – 76% yield.[34] It had also been shown that successful alkylation of lithium enolates derived from enol phosphorylated species could be effected on simple systems in one pot reactions.[35] This offered the intriguing possibility of combining dephosphorylation and the required C3 alkylation into a single step (Table 2.4). Dimethyl carbonate was selected as an appropriate alkylating agent[27,36] as the methyl ester (**100**) thus generated should be both stable and easily transformed into the requisite acid chloride of Fragment A. Phosphate **89** was dissolved in DME at rt along with a few crystals of Ph_3CH[37] to indicate the point at which complete anion formation occurred (Entry 1, Table 2.4). To this solution was added MeLi dropwise until a deep red colour persisted (5 min). An excess of dimethyl carbonate was then slowly added and the clear yellow reaction mixture was stirred for 3.5 h. The mixture was then cooled to 0 °C and acidified using ice cold 10% HCl. Following work-up, the reaction mixture yielded an orange oil which, when analyzed by ^1H NMR,

was identified as a complex mixture. Although aromatized ketone **95** could be identified as a component of the mixture, the spectrum lacked peaks indicative of unreacted **89** or ketone **62**.

Table 2.4: Attempts to Dephosphorylate 89 with MeLi and Alkylate the Resulting Enolate with Dimethyl Carbonate



Entry	Alkylating Agent	Equiv. MeLi	Solvent	Temp	Time	Result
1	$CO(OMe)_2$	2.1	DME	rt	3.5 h	CM containing **95**
2	$CO(OMe)_2$	2.1	THF	0 °C → rt reflux	25 min 4.5 h	NR CM containing **95**
3	-	1.1	THF	-78 °C -40 °C 0 °C rt rt	1.5 h 1.5 h 40 min 20 min 17 h	NR NR NR NR SM and **95** (~10%)
4	-	1.2	DME	rt	15 min	**95** and **96**
5	-	2.1	DME	-60 °C	1 h	**95** and **96**

The reaction then repeated, this time using THF at 0 °C in place of DME at rt (Entry 2, Table 2.4). MeLi was added to the solution until complete anion formation was indicated (10 min), and an excess of $CO(OMe)_2$ was slowly added. The reaction mixture was allowed to warm to rt; however, no colour change indicating consumption of the anion was seen after 25 min. The mixture was then brought to reflux and heated until a colour

change was observed (4.5 h). Unfortunately, the material isolated was again identified as a complex mixture containing **95**. With respect to these results, it was unclear as to exactly where the reaction was failing and whether or not enolate **99** was being formed *in situ*. Since **95** was observed as a component of the material obtained from both reactions, some dephosphorylation must have occurred; however, in the presence of the alkylating agent, the fate of any ketone that may have formed remained unclear. A third experiment was thus devised in which **89** underwent treatment with MeLi and the anion thus generated was quenched with H_2O in lieu of reaction with dimethyl carbonate. Isolation of **62** would then indicate successful dephosphorylation. Thus, compound **89** and a small amount of Ph_3CH were dissolved in THF at -78 °C and treated with MeLi until a red colour persisted (Entry 3, Table 2.4). After 1.5 h, an aliquot was analyzed which indicated that no reaction had occurred and so the reaction temperature was raised. Analysis after an additional 1.5 h at -40 °C (teal solution) and then after 40 min at 0 °C (yellow solution) showed only unreacted SM. The reaction mixture was then warmed to rt, and after 20 min a colour change to amber/brown was observed but again only SM was observed by ^1H NMR analysis. After an additional 17 h at rt, another aliquot was analyzed and showed approximately 10% naphthol **95** with the balance remaining as unreacted **89**. From these results, it appeared that Ph_3CH was not working as intended and the deep red colour did not necessarily indicate complete formation of anion **99**, and therefore did not indicate complete dephosphorylation. It was clear that complete dephosphorylation could not be occurring since this would be inconsistent with the phosphorylated SM isolated from the quenched reaction mixture. The reaction was therefore repeated in DME without the Ph_3CH indicator. Treatment of **89** with MeLi (1.2 equiv.) at rt showed the complete consumption of starting material within 15 min when analyzed by TLC (Entry 4, Table 2.4). The products of the reaction however were not identified as ketone **62** but instead as a mixture of aromatized products **95** and **96**. The reaction was then repeated at -60 °C (Entry 5, Table 2.4) in an attempt to slow the reaction. Disappointingly, the result was similar to that of the previous reaction. Although MeLi was marginally successful at effecting cleavage of the phosphate group, ketone **62** was apparently being aromatized to **95** as it was being formed. The

incompatibility of ketone **62** with MeLi thus limited the potential of this method, which was subsequently abandoned.

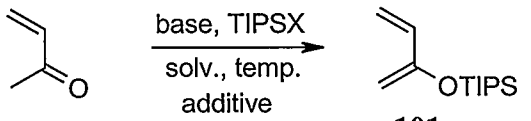
Reliable yields for the dephosphorylation of **89** were thus limited to a disappointing 10 - 15% under acidic conditions. Despite the ease with which dienyl phosphate **86**, adduct **87** and O-methylated species **89** could be prepared, the conditions typically used too convert **89** to ketone **62** were ineffective. Since poor conversion to ketone **62** severely limited the overall efficiency by which Fragment A could be prepared, a new strategy for the construction of this precursor was examined. Because the difficulty in isolating ketone **62** in usable quantities hinged directly on an inability to successfully cleave the phosphate protecting group, it seemed logical that this problematic step should be removed from the synthesis. This could be most easily done by replacing the phosphate with a more labile protecting group while otherwise maintaining the initial strategy for the construction of Fragment A. Upon examination of the literature, replacing the phosphate with one of the more robust silyl groups seemed to be a viable option. The replacement of the phosphate with a silyl group, specifically the triisopropyl silyl (TIPS) group, appeared to offer an effective alternative to the use of TMS diene **82** for which prelminary results had been poor. One benefit of returning to the use of an enol silyl ether was that in contrast to the phosphate group, cleavage of the silyl group was anticipated to relatively straightforward. Several effective procedures for desilation were known including cleavage of the TIPS group under mildly acidic conditions.[22,38] Additionally, by using a siloxy group as a substituent in the C2 position, the diene becomes electron rich[22b] and should undergo a facile cycoladdition with *p*-quinone (**64**) and eliminate the need for a Lewis acid catalyst.

2.5 Revisiting the Diels-Alder Reaction: Synthesis and Reaction of TIPS Enol Ether 101

In order for this strategy to be useful, it was necessary to prepare TIPS diene **101** in good yield (Table 2.5). Although the use of **101** as a diene in studies of unsymmetrical Diels-Alder reactions was common in the literature[39] an explicit, high yielding procedure for its preparation could not be located.

Several conditions for the preparation of diene **101** from methyl vinyl ketone (**66**) by either nucleophilic catalysis or by generation of the enolate followed by trapping with a triisopropyl silyl reagent were therefore applied (Table 2.5).

Table 2.5: Conditions for the Preparation of 2-Triisopropyloxy-1,3-butadiene (101)



66 **101**

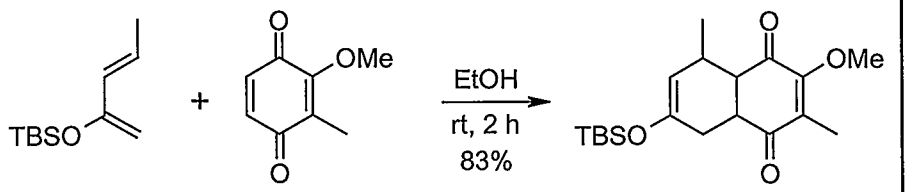
Base	Silylating Agent	Additive	Solvent	Temperature	Yield
Et_3N	TIPSCl	-	DMF	rt	NR
Et_3N	TIPSOTf	-	DCM	-0 °C - rt	42%
Et_3N	TIPSOTf	-	benzene	-0 °C - rt	22%
LDA	TIPSCl	-	THF	-78 °C - rt	NR
LDA	TIPSCl	HMPA	THF	-78 °C - rt	20% - 50%
LDA	TIPSOTf	-	THF	-78 °C - rt	98%

Initial attempts to prepare diene **101** *via* nucleophilic catalysis using Et_3N and TIPSCl in DMF gave no conversion to product. Replacing TIPSCl with the more reactive TIPSOTf and performing the reaction in DCM[40] generated the desired product; however, the isolated yield was only 42%. Performing this reaction in benzene[41] further reduced the yield to 22%. Attempts to increase the isolated yield initially focused on the use of a stronger base, LDA, to generate the enolate which could then be trapped as a silyl enol ether. Treatment of MVK (**66**) with LDA followed by the addition of 2 equiv. TIPSCl, however, failed to generate the desired product. It was supposed that although the enolate had likely been formed, it may have been unreactive toward TIPSCl. Repeating the reaction, with the addition of 1.5 equiv. HMPA[42] to increase the reactivity of the anion gave desired diene **101** in yields of up to 50%. Unfortunately, these conditions offered only a slight increase in yield over the use of Et_3N and required the use of the highly carcinogenic additive, HMPA. Using LDA as the base but replacing TIPSCl with TIPSOTf gratifyingly gave diene **101** in 98% yield[43] without the need for HMPA.

With diene **101** in hand, the bicyclic skeleton of Fragment A could be constructed *via* Diels-Alder addition of **101** to p-quinone (**64**) in a reaction analogous to the formation of phosphate adduct **88** (Scheme 2.5). Altering the substituent on the diene, however, had also altered the electronics of the system. Siloxy diene **101** was electron rich whereas phosphate diene **86** had been electron poor. Since electron rich dienes are more reactive in most Diels-Alder additions,[44] a Lewis acid would no longer be needed to catalyze the reaction.

A facile addition of a 2-siloxy diene can be seen in the synthesis of colombiasin A[45] in which TBS diene **102** (1.2 equiv.) was dissolved in EtOH and reacted with unsymmetrical quinone **103** to yield the desired Diels-Alder adduct **104** in only 2 h at rt (Scheme 2.10).

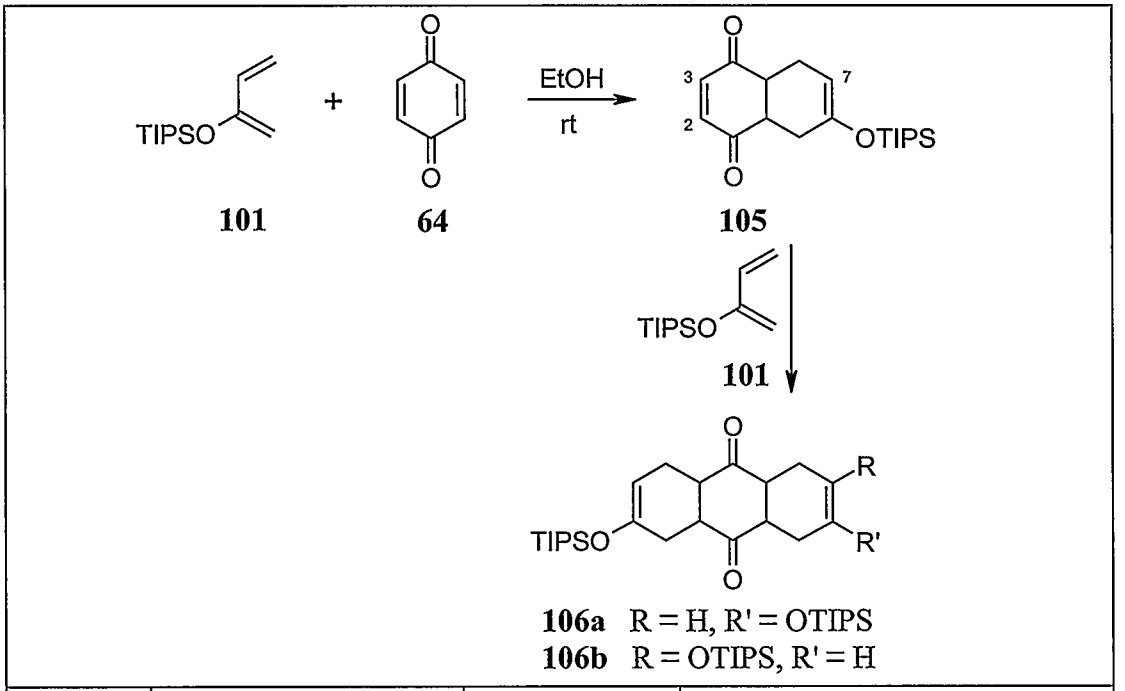
Scheme 2.10



102 **103** **104**

When these conditions were applied to the reaction of diene **101** (1.1 equiv.) with *p*-quinone (**64**, Entry 1, Table 2.6), however, the reaction did not proceed cleanly.

Table 2.6: Diels-Alder Reactions of Diene 101 and *p*-Quinone (64) in EtOH



106a R = H, R' = OTIPS
106b R = OTIPS, R' = H

Entry	Diene : Dienophile	Time	Identified Components of Reaction Mixture
1	1.1 : 1.0	30 min 1 h 2 h	SM **64, 101, 105** **64, 101, 105, 106a, 106b**
2	1.1 : 1.0	4.5 h	**64, 101, 105, 106a, 106b, 109**[a]
3	1.1 : 1.0	48 h	**64, 105, 106a, 106b**
4	1.0 : 1.2	24 h	**64, 101, 105, 106a, 106b**
5	1.0 : 1.1	20 h	**64, 101, 106a, 106b, 110**[b]
6	2.0 : 1.0	30 min 1.5 h 3 h	**64, 101, 105** **64, 101, 105, 106a, 106b** **64, 101, 105, 106a, 106b**

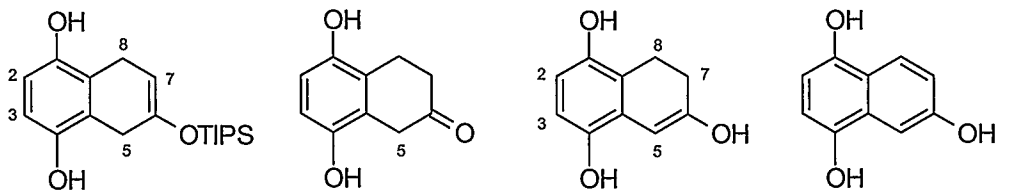
[a]**109** appears after fcc over silica gel (see Figure 2.1). [b]**110** appears after fcc over basic alumina (see Figure 2.1).

After 30 min, TLC analysis showed only SM and after 1 h a single new spot appeared that was later identified as **105** (Table 2.6). After 2 h, TLC analysis showed three additional spots, indicating the formation of additional products. ^{1}H NMR analysis confirmed the presence of both starting materials **64** and **101** and the spectrum also contained several new and unidentified peaks. Although some of the peaks were consistent with the shift and splitting patterns expected for **105**, the low field singlet at 6.80 ppm likely corresponding to the protons at C2 and C3 integrated to far less than 2 H

with respect to any of the vinyl peaks, one of which was presumably generated by the C7 proton. The absence of these protons was consistent with the formation of double Diels-Alder adducts **106a** and **106b** (Table 2.6). Column chromatography of the crude material over silica gel gave **105** as a yellow oil in 8% yield. ^{1}H NMR analysis of the oil yielded a spectrum consistent with dione **105**. Diagnostic peaks included a singlet at 6.80 ppm corresponding to the pair of protons on C2 and C3, a singlet at 4.85 ppm indicating the C7 vinyl proton and a multiplet between 0.48 ppm and 1.52 ppm indicative of the protons in the TIPS group. Multiplets corresponding to the remaining 6 protons were also observed between 2.18 – 3.35 ppm. Further analysis *via* LRMS gave a molecular ion peak of 334 amu consistent with a molecular formula of $C_{19}H_{30}O_3Si$, fragmentation of which corresponded to the loss of an iPr unit (43 amu) offering further confirmation that the preparation of adduct **105** had been successful.[46] The double Diels-Alder adducts **106a** and **106b** were isolated together as a viscous yellow oil that rapidly crystallized to from long yellow needles upon exposure to air. ^{1}H NMR analysis of the crystalline product gave a spectrum similar to that generated by adduct **105** with two exceptions: the low field quinone peak at 6.80 ppm was absent and the C7 vinyl had shifted slightly downfield.

Since the starting material had not been fully consumed in the previous experiment, a second experiment was undertaken in which the reaction stirred for 4.5 h at rt. Ideally, an extended reaction time would lead to higher conversion to product (Entry 2, Table 2.6). After 4.5 h, the solvent was removed under reduced pressure, and the crude products were separated by column chromatography over silica gel. Interestingly, although the same products were observed, several additional products were also isolated. The first new product was readily identified as **107**, a tautomer of adduct **105** (Figure 2.1).

Figure 2.1 TIPS Adduct 107, Ketone 108, Enol 109 and Naphthol 110



107 **108** **109** **110**

^{1}H NMR analysis of **107** gave a spectrum somewhat similar to that generated by **105** with the aromatic protons at the C2 and C3 positions appearing as a singlet at 6.74 ppm and the vinyl proton at C7 appearing at 4.92 ppm. The protons in the TIPS group were observed as a multiplet between 0.48 and 1.52 ppm and in contrast to adduct **105**, the remaining protons now appeared as a single multiplet spanning 2.96 – 3.34 ppm. The splitting and shift pattern generated by TIPS adduct **105** and its tautomer, TIPS diphenol **107** closely paralleled that observed in the ^{1}H NMR spectra obtained for phosphorylated adduct **88** and phosphate diphenol **87** (Scheme 2.6) lending further support to the identification of **107**. The second new product observed was tentatively identified as enol **109**, resulting from the desilation of diphenol **107** (Figure 2.1). The ^{1}H NMR spectrum generated by compound **109** exhibited an AB-quartet spanning 6.31 – 6.50 ppm corresponding to the aromatic protons bound to C2 and C3 along with a pair of triplets at 2.38 and 2.85 ppm corresponding to the C7 and C8 protons. Although keto tautomer **108** (Figure 2.1) was initially expected, a singlet integrating to 2 H between 3.00 ppm and 4.00 ppm corresponding to the C5 protons was conspicuously absent. However, a new low field singlet at 5.91 ppm appeared that integrated to 1 H which was consistent with the vinyl C5 proton of enol **109**. The observation of enol tautomer **109** as the exclusive isomer was likely the result of its enhanced stability as a result of conjugation of the double bond in **109** with the adjacent aromatic ring. The carbonyl group in keto tautomer **108** however, offered no such stabilization, as it was isolated from the aromatic portion of the molecule.[47] Although other products were observed by TLC and ^{1}H NMR, they appeared to form in small amounts and could not be easily isolated or identified. Although an improvement over the previous method, these conditions again led to the formation of several by-products while desired adducts **105** and **107** were isolated in only

22% combined yield. It was surmised that the tautomerization of hydroquinone **105** to diphenol **107** and the desilation of **105** could be attributed to the silica gel used in the separation of the components of the crude reaction. Unfortunately, the acidity of the silica gel was likely responsible for the cleavage of the labile and acid sensitive[48] TIPS enol ether. Additionally, the purification process appeared to facilitate the tautomerization of adduct **105** to diphenol **107** since the diphenol was only observed following chromatography. The reason these products were not observed as components of the previous reaction, having also been purified in this way (Entry 1, Table 2.6), was likely related to scale. The initial reaction was performed on a scale 1/12 that of the second reaction; thus chromatography could be performed rapidly. The greater mass of material used in the second reaction was more susceptible to decomposition as it was in contact with the silica gel for a longer period of time.

Since greater conversion to product was observed after a longer reaction period, a new experiment was undertaken to determine if yields for the addition reaction could be improved in this manner. After 48 h at rt (Entry 3, Table 2.6), TLC analysis showed the complete consumption of diene **101**. Unfortunately, the double Diels-Alder adducts **106a** and **106b** dominated the crude reaction mixture.

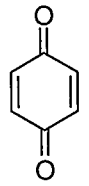
Up to this point, diene **101** had been used in slight excess of the dienophile. It seemed logical that if the reaction was performed with an excess of the dienophile then the single addition product would be favoured. Reversing this ratio by using 1.2 equiv. *p*-quinone (**64**, Entry 4, Table 2.6) gave only a slight increase in conversion to monoadduct (24% of **105**) with continued formation of double Diels-Alder addition products. Column chromatography of the crude material over silica gel using a solvent system containing 2% Et_3N again appeared to result in cleavage of the silyl group from both unreacted diene **101** and adduct **105**. Repeating the reaction with 1.1 equiv. of *p*-quinone (**64**, Entry 5, Table 2.6) gave little improvement and resulted in similar conversion to product after 20 h. Column chromatography of the crude mixture, this time over basic alumina, appeared to result in both desilation of adduct **107**, observed by TLC as a component of the crude material, to **109** and then oxidation of **109** to naphthol **110** (Figure 2.1). Finally, an experiment was performed in which 2.0 equiv. dienophile **64** were used (Entry 6, Table 2.6). An aliquot taken after 30 min gave a ^1H NMR spectrum that showed a 10 : 1 ratio

of diene **101** to adduct **105**. After 1.5 h, a ratio of 10 : 10 : 1 of SM (**101**) to product (**105**) to double Diels-Alder addition product (**106**) was observed. An aliquot taken after 3 h at rt showed a 7 : 5 : 1 ratio which indicated the preferential reaction of diene **101** with monoadduct **105** over quinone **64**. Clearly, there were two serious problems in the preparation of adducts **105** and **107**. First, the compounds were difficult to prepare in respectable yields due to the facile formation of the double Diels-Alder addition products. Second, the adducts lacked the stability required for efficient purification. Two approaches were considered for circumventing these issues: the reaction conditions could be manipulated to minimize side reactions and allow enough product to be generated to be used in the subsequent reaction without further purification, or an efficient method could be developed for the separation of the desired monoadducts from the undesired double addition products. Since good conversion to product is always desirable in the early stages of a total synthesis, the first option was investigated further.

Since the use of a Lewis acid catalyst had been shown to form monoadduct exclusively in the analogous phosphorylated system,[28] these conditions were applied to the silated system. Disappointingly, combining diene **101** (1.3 equiv.), $SnCl_4$ (1.1 equiv.) and quinone **64** in CH_2Cl_2 at 0 °C resulted in the complete desilation of diene **101** within 3.5 h. No addition products were detected, and unreacted *p*-quinone was isolated following the reaction. The methyl vinyl ketone generated *via* decomposition of diene **101** was presumably lost upon concentration of the crude material under reduced pressure. Since, these conditions were incompatible with the silyl enol ether group, attention returned to the optimization of conditions for an uncatalyzed Diels-Alder reaction.

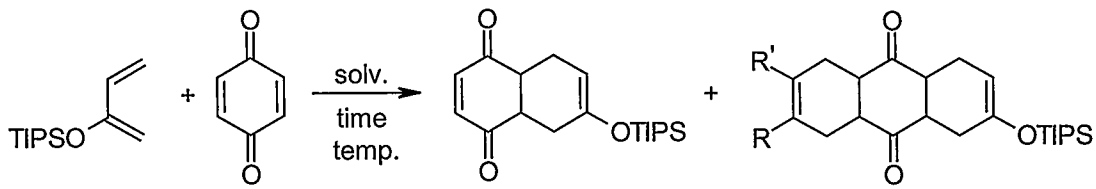
While performing the Diels-Alder reactions using the original conditions, it was observed that although diene **101** and both adducts **105** and **107** were readily soluble in EtOH quinone **64** was not. This, combined with the results of the reactions performed previously in EtOH, appeared to suggest that the facile reaction of adduct **105** with diene **101** may be due to its greater solubility in EtOH. A simple comparison of the solubility of *p*-quinone in several solvents was therefore performed (Table 2.7).

Table 2.7: Solubility of *p*-Quinone (64) in Several Solvents at rt

	MeOH	iPrOH	95% EtOH	DCM	THF	CH_3CN
	Soluble	Sparingly Soluble	Sparingly Soluble	Soluble	Soluble	Soluble

The results indicated that *p*-quinone was particularly soluble in MeOH, DCM, THF and CH_3CN, so, these solvents were employed in test reactions with diene **101**. Quinone **64** and diene **101** (1.1 equiv.) were dissolved in each solvent and stirred at rt (Table 2.8). In THF, approximately 50% conversion to adduct **105** was observed after 2 d, and no other addition products could be seen in the crude reaction mixture until the reaction had progressed for 5 d (Entry 1, Table 2.8). Even then, double addition products **106a** and **106b** represented only a very small portion of the reaction mixture.

Table 2.8: Diels-Alder Reactions of Diene 101 and *p*-Quinone (64) in Various Solvents at rt



101 **64** **105** **106a** R = H, R' = OTIPS
106b R = OTIPS, R' = H

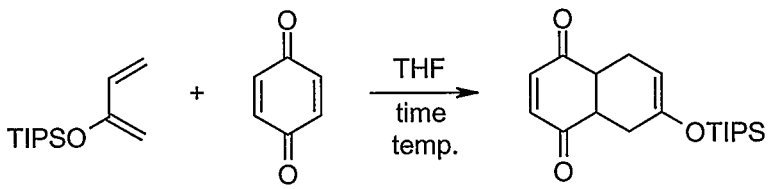
Entry	Solvent	Time	Products
1	THF	2 d	**105**
		5 d	**105, 106a, 106b**
2	DCM	2 d	**105**
		3 d	**105**
		6 d	**105**
3	CH_3CN	4 d	**105** (trace)
		5 d	**105**
4	MeOH	3 h	**105, 106a, 106b**
		20 h	**105, 106a, 106b**
		2 d	CM

Similar results were observed for reaction in DCM (Entry 2, Table 2.8) however after 2 d **106a** and **106b** were not detected and only about 50% conversion to product was observed after 6 d. Performing the analogous reaction in CH_3CN (Entry 3, Table 2.8) gave less promising results. The desired adduct was not seen until the reaction had stirred for 4 d and, even then, in amounts barely observable over the baseline of the ^1H NMR spectrum. After 5 d the reaction was stopped because although adducts **106a** and **106b** were not detected, conversion to product had slowed to a degree that made this set of conditions impractical for the preparation of **105**. Repeating the reaction in MeOH (Entry 4, Table 2.8) gave rapid but poor results with formation of **106a** and **106b** as well as desired adduct **105** within 3 h. After 2 d in MeOH, a complex mixture was generated. Since the use of THF and DCM appeared to be the most promising, reaction in these solvents was investigated further.

Unfortunately, further attempts to prepare adduct **105** in DCM gave disappointing results. Using *p*-quinone in excess of the diene failed to generate **105** exclusively, and DCM was abandoned as a solvent since results in THF were more promising.

In contrast to the reactions performed in EtOH (Table 2.6), increasing the ratio of quinone **64** to diene **101** resulted in the preferential formation of monoadduct **105** when the reaction was performed in THF (Table 2.9).

Table 2.9: Diels-Alder Reactions of Diene 88 and *p*-Quinone (64) in THF



101 **64** **105**

Entry	Diene : Dienophile	Temperature	Time	Products (Yield)[a]
1	1.0 : 1.1	rt	4 d	**105** (50%)
2	1.0 : 2.0	50 °C	2 d	**105** (50%)
3	1.0 : 2.5	rt	6 d	**105** (98%)

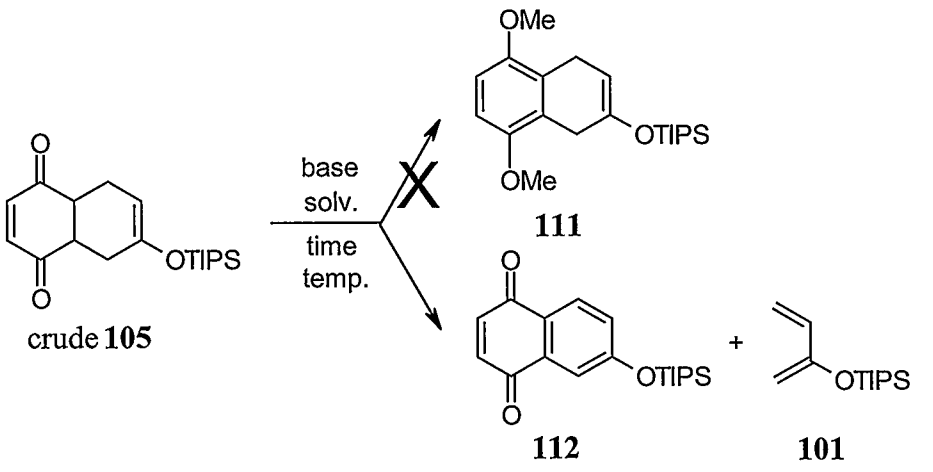
[a]Percent conversion by ^1H NMR.

When the diene was used in excess of the dienophile (Entry 1, Table 2.8) double addition products **106a** and **106b** were observed; however, when 1.1 equiv. quinone was used (Entry 1, Table 2.9), the reaction proceeded to give 50% conversion to monoadduct **105** after 4 d at rt. A further increase of *p*-quinone to 2.0 equiv. and heating to 50 °C resulted in the same conversion to product in 2 d, reducing the reaction time by one half. Again, the formation of double addition products **106a** and **106b** were not observed. Thus, it appeared that performing the reaction in THF could give exclusive formation of the desired product **105**. The reaction was then performed with 2.5 equiv. dienophile at rt (Entry 3, Table 2.9). Gratifyingly, after 6 d, conversion to monoadduct **105** was determined to be 98% by ^{1}H NMR analysis. Thus, further optimization of the Diels-Alder reaction was discontinued as a satisfactory method for the preparation of the framework of Fragment A had been determined.

2.6 O-Methylation of TIPS Enol Ether Adduct 105

With an efficient method for the formation of adduct **105** in hand attention could be focused on the subsequent O-methylation reaction for the formation of dimethoxy derivative **111** (Table 2.10). Purification of adduct **105** had thus far proven difficult by column chromatography, often resulting in oxidation, desilation and occasionally both. Since conversion to **105** was high in the preceding Diels-Alder reaction it was hoped that the reaction mixture obtained from the addition reaction could be used in the subsequent methylation step without purification. It was anticipated that applying the same conditions which were employed in the O-methylation of enol phosphorylated species **87** and **88** (Scheme 2.7) would be equally successful when applied to the methylation of crude TIPS adduct **105**. Unfortunately, when the crude mixture was treated with NaH (3 equiv.) followed by an excess of MeI, a complex mixture was observed after 1.5 h (Entry 1, Table 2.10).

Table 2.10: Attempts to Methylate Crude Silyl Enol Ether 105



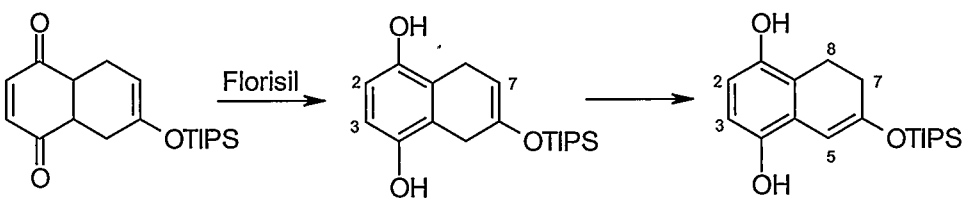
Entry	Base	Solvent	Temperature	Time	Products
1	NaH (3 equiv.)	DMF	rt	1.5 h	CM
2	K_2CO_3 (5 equiv.)	acetone	55 °C	48 h	CM
3	NaH (3 equiv.)	THF	-10 °C - 0 °C	16 h	**101, 112**

Since a related system had been reported[45] to undergo methylation by refluxing the substrate and K_2CO_3 for 48 h in acetone with an excess of MeI, it was hoped that these conditions would be more compatible with substrate **105** (Entry 2, Table 2.10). Unfortunately, under these conditions, a complex mixture was again observed. In an effort to eliminate the need to concentrate crude adduct **105** and then redissolve it in a different solvent for the subsequent reaction, conditions for O-methylation in THF were searched. A precedent was found[49] in which an O-methylation was performed in THF, and these conditions were applied to adduct **105** (Entry 3, Table 2.10). Deprotonation of **105** with NaH (3 equiv.) was performed by warming the reaction mixture from -10 °C to 0 °C. To this anion solution was added an excess of MeI, and the reaction was allowed to warm slowly to rt overnight (16 h). The crude product, however, was identified as a mixture dominated by diene **101**, the product of a retro Diels-Alder reaction, and a second compound that was later identified as oxidized adduct **112**. Several other products appeared as small components of the mixture and although they were not rigorously identified they did not correspond to desired product **111**.

In summary, the conditions employed in the methylation of crude adduct **105** failed to generate the desired product. This result was discouraging, as purification of Diels-Alder product **105** had previously proven problematic.

Since purification of **105** appeared to be necessary for success in the subsequent step, additional methods toward this end were considered. Initial attempts at modifying the method of purification focused on the stationary phase used for column chromatography. Silica gel appeared too acidic to be used as it gave decomposition of silyl enol ether **105**. Basic conditions also resulted in the decomposition of the target compound. Thus, since both acidic and basic conditions appeared to facilitate decomposition, performing the purification under more neutral conditions appeared to be a logical alternative. Pleasingly, column chromatography over Florisil®, a mildly basic sorbant, did not result in cleavage of the sensitive silyl enol ether function or in oxidation of the substrate. Disappointingly, although nearly complete conversion to product was observed in solution, the yield of the isolated adduct decreased upon purification. Fortunately, despite the apparent retro Diels-Alder addition occurring on the column, nearly all of the intact diene **101** could be recovered. For example, purification of the dark brown paste obtained by concentration of the crude reaction mixture resulted in the isolation of 60.2% of the adduct and 37.9% of diene **101**, accounting for 98.1% of diene **101** initially used in the reaction. Interestingly, purification over Florisil® also resulted in the complete tautomerization of dione **105** to diphenol **107** (Scheme 2.11).

Scheme 2.11

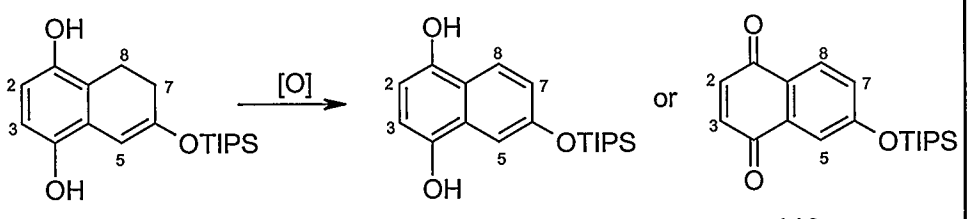


105 **107** **113**

Compound **107** was isolated as a bright yellow oil and was used quickly in the subsequent reaction as, like **105**, it also proved to be relatively unstable.[50] Migration of the double bond to yield **113** (Scheme 2.11) as a mustard yellow solid was facile at rt

after the solvent had been removed and some exposure to air had occurred. Analysis by ^{1}H NMR confirmed the double bond migration with the appearance of two triplets at 2.43 ppm and 2.77 ppm indicative of the C7 and C8 protons of **113**. Additionally, the singlet indicative of the vinyl proton at C5, now conjugated with the adjacent aromatic system, was shifted downfield to 5.77 ppm from 4.92 ppm for the C7 vinyl proton of the isolated double bond of **107**. Furthermore, the signal observed for the C2 and C3 aromatic protons of **107** appeared as a singlet whereas a pair of doublets was observed for the analogous C2 and C3 protons of **113**. Taken together, the spectral data confirmed the identity of the solid as silyl enol ether **113**. Fortunately, since the O-methylation would be unaffected by the double bond migration and cleavage of the silyl group from either methylated isomer would generate the same product, the appearance of double bond isomer **113** had no deleterious effect the course of the synthesis. However, once migrated, care had to be taken to avoid exposure of compound **113** to air, as a subsequent oxidation was found to occur readily. Upon such exposure, the dark yellow crystalline material identified as **113** would turn a blood red/black colour. The dark crystalline product was originally thought to be naphthol **114**; however, the ^{1}H NMR spectrum generated by this material could not rule out quinone **112** as the oxidized product (Scheme 2.12).

Scheme 2.12



113 **114** **112**

The spectrum generated by the crystals contained a singlet at 6.92 ppm corresponding to the protons at C2 and C3. In contrast to diphenol **107**, the region between this singlet and the signals indicative of the intact TIPS group (1.11 – 1.38 ppm) was devoid of peaks. New peaks, however, appeared farther downfield: two doublets at 7.48 and 8.00 ppm and a doublet of doublets at 7.19 ppm that were consistent with the protons corresponding to

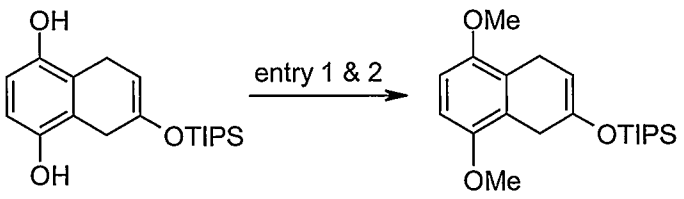
C5, C7 and C8 of either naphthol **114** or quinone **112**. Since hydroxyl protons had not been observed in the ^{1}H NMR spectra for either enol phosphorylated diphenol **87** or enol silyl ether **107**, the absence of these protons in the spectrum was not necessarily indicative of the presence of dione **112**. Although it seemed unlikely that oxidation of naphthol **114** to quinone **112** had occurred the unidentified compound was subjected to further analysis. The IR spectrum contained a strong absorption at 1673 cm^{-1} characteristic of the C=O stretch for quinones,[51] indicating the formation of **112**. Analysis by GC-MS generated a molecular ion peak of 330 amu, consistent with a molecular formula of $C_{19}H_{26}O_3Si$ for quinone **112**. Finally, ^{13}C NMR analysis showed two peaks at 185.3 and 184.3 ppm, consistent with two carbonyl carbons and confirming the identity of the crystalline product as quinone **112**.

Attempts to further purify diphenol **107** by distillation under reduced pressure (85 °C at 0.91 x 10^{-1} torr) resulted in the isolation of a dark red/brown paste that, when analyzed by ^{1}H NMR, appeared identical to **112**.

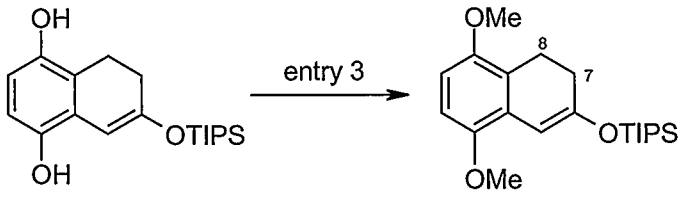
Conditions for the purification of adduct **105** had thus been determined which, when applied, resulted in the tautomerization of **105** to diphenol **107**. It was also apparent that due to the relative instability of both **105** and **107** toward oxidation, the compounds needed to be used immediately upon isolation by column chromatography.

With pure samples of silyl enol ethers **107** and **113** in hand, attempts to prepare dimethoxy compound **111** could resume. The conditions that had proven effective in the nearly quantitative methylation of enol phosphorylated species **89** were no longer quantitative when applied to silyl derivative **107** (Entry 1, Table 2.11), generating **111** in at most 76% yield.

Table 2.11: Attempts to O-Methylate Silyl enol Ethers 107 and 113



107 **111**



113 **115**

Entry	Adduct	Base	Solvent	Temperature	Time	Yield
1	**107**	NaH (3 equiv.)	DMF	rt	1.5 h	76%
2	**107**	NaH (3 equiv.)	THF	-10 °C - 0 °C	16 h	94%
3	**113**	NaH (3 equiv.)	THF	-10 °C - 0 °C	16 h	69%

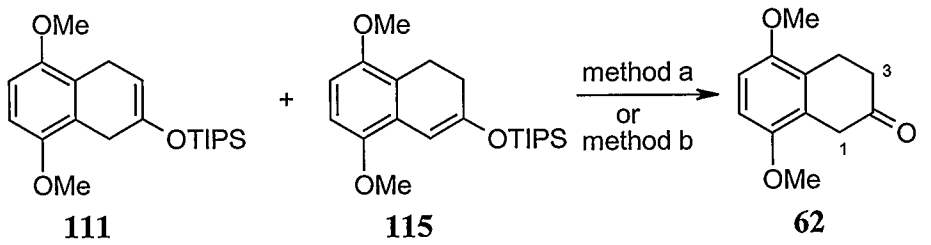
Pleasingly, performing the reaction in THF and forming the anion at 0 °C gave clean formation of dimethoxy derivative **111** in 94% yield (Entry 2, Table 2.11). ^{1}H NMR analysis of the product gave a spectrum similar to that of diphenol **107** except for the appearance of two new singlets at 3.78 and 3.80 ppm indicating successful methylation. Adduct **113** could also be treated under these reaction conditions (Entry 3, Table 2.11) to give O-methylated adduct **115** in 69% yield. Analysis of the product obtained by ^{1}H NMR once again showed two triplets at 2.37 and 2.90 ppm corresponding the protons at C7 and C8. The presence of these triplets indicated that neither oxidation nor migration of the double bond had occurred. Again, successful methylation was indicated by the generation of two singlets at 3.50 and 3.53 ppm in a spectrum otherwise appearing much like that generated by diphenol **113**. Dimethoxy systems **111** and **115** were subsequently purified *via* column chromatography using Florisil®. Fortunately, minimal oxidation was observed after isolation, and compounds **111** and **115** could be stored for short periods of time at low temperature under an atmosphere of N_2. With a method for the preparation of

O-methylated adducts **111** and **115** now developed, work could continue toward Fragment A.

2.7 Desilation of TIPS Enol Ethers 111 and 115

The next step in the synthesis of Fragment A was the desilation of compounds **111** and **115** to generate tetralone **62** (Scheme 2.13).

Scheme 2.13



Conditions: a) TBAF (1.0 - 4.0 equiv.), THF, -78 °C, 15 min - 2 h (0 - 45%); b) 6 M HCl, DMF, 0 °C - rt, 2 h (88%).

Initially, the sensitivity of the TIPS enol ether was anticipated to allow for cleavage of the silyl group by simply passing the adducts through a silica gel column which would save a step in the synthesis. Although the desired ketone was observed using this method, problems with oxidation were again detrimental to overall yields. In order to prevent the undesired oxidation, it was proposed that the desilation be performed quickly and at low temperature. Several examples were found that suggested that a TIPS enol ether could be efficiently cleaved using TBAF in THF.[52] Thus, O-methylated adducts **111** and **115** were treated with TBAF (1.1- 4.0 equiv.) in THF at –78 °C. Although ketone **62** was observed as the exclusive product of these reactions, it required purification before it could be used in the subsequent step. Consistent with previous problems of substrate oxidation, ketone **62** was difficult to purify and yields were detrimentally affected. As a result, the desired product could be isolated in up to only 45% yield.

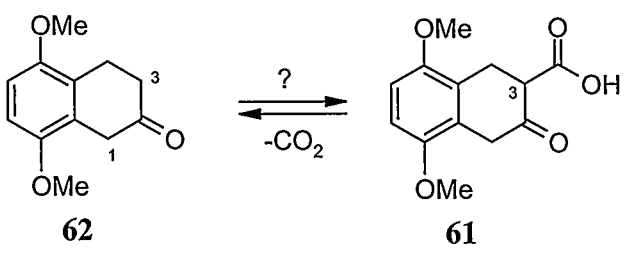
A method of desilation was therefore required that would eliminate the need for additional purification. Since the TIPS group had shown substantial acid sensitivity in the synthesis so far, it was hoped that this sensitivity could be exploited in the

deprotection procedure. Because mild acid at rt promoted a slow deprotection, it was anticipated that a higher concentration of acid would effect a clean and rapid desilation without requiring increased temperatures. Silyl enol ether **115** dissolved in DMF at 0 °C was therefore treated with a few drops of 6 M HCl. The reaction mixture was then allowed to warm slowly to rt until all the SM appeared consumed according to TLC analysis (2 h). Pleasingly, after workup, clean conversion to product was observed, and removing excess DMF under reduced pressure gave ketone **62** (88%) cleanly as a white fluffy solid.

2.8 Regioselective Carboxylation of Tetralone 62

The next step in the preparation of Fragment A was selective carboxylation at the C3 position of ketone **62** (Scheme 2.14).

Scheme 2.14

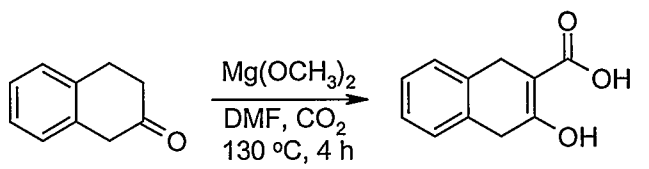


62 **61**

Resulting acid **61** would have a handle at C3, which could easily be converted to an acid chloride for coupling with Fragment B (Scheme 1.11). Installation of an acid function in the C3 position of ketone **62** initially appeared somewhat risky as decarboxylation of β-keto acids is typically facile.[53] Suprisingly however, a search of the literature provided several examples in which carboxylation could be selectively performed on analogous substrates using Mg salts and the resultant β-keto acids successfully isolated.[20,54] The carboxylation was first attempted using β-tetralone (**116**) as a model to test the efficiency and selectivity of reaction prior to carboxylation of the elaborated system. The reaction was performed by preparing a suspension of $Mg(OCH_3)_2$ in DMF then saturating the solution with CO_2 by bubbling CO_2 through the mixture for 1 h. β-Tetralone (**116**) was dissolved in DMF and then slowly added to the Mg reagent after which the reaction

mixture was brought to 130 °C for 4 h (Scheme 2.15). Following careful acidification, the crude material was isolated and analyzed by ^{1}H NMR which showed both unreacted **116** and another product tentatively identified as enol acid **117** as two components of the crude mixture.

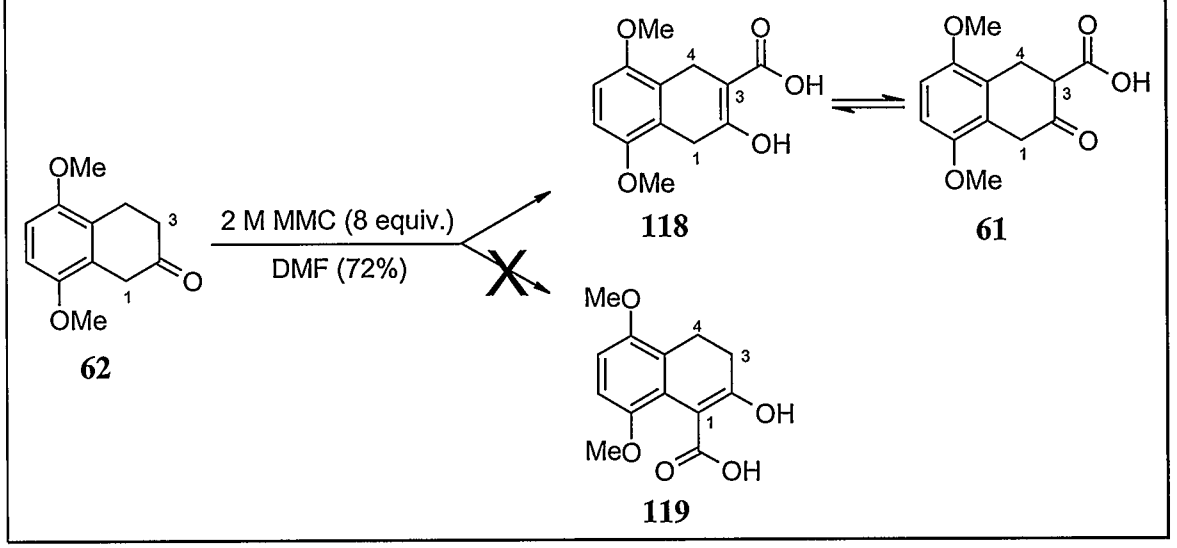
Scheme 2.15



116 **117**

Repeating this procedure with ketone **62** in place of β-tetralone, however, consistently failed to give incorporation of the acid at either the C1 or C3 position. Since it was not know whether the CO_2-saturated Mg reagent had been successfully prepared *in situ* prior to the addition of the substrate, and methyl magnesium carbonate (MMC) was available commercially as a 2 M solution, the reaction was repeated using this molar solution of MMC. Heating ketone **62** in the presence of MMC (8 equiv.) at 130 °C for 4 h followed by careful acidification yielded the carboxylated material (72%) as a fine white powder (Scheme 2.16).

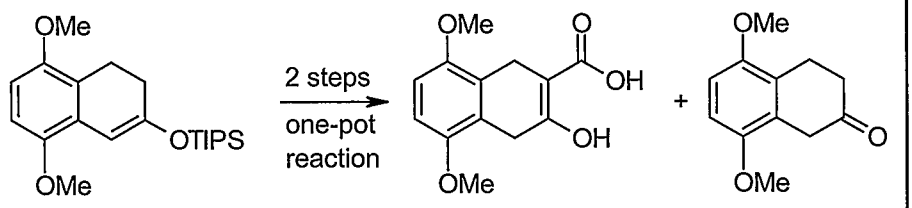
Scheme 2.16



^{1}H NMR analysis of the solid produced a spectrum with a new singlet at 12.73 ppm consistent with a carboxylic acid proton. Additionally, the pair of triplets that would indicate the CH_2 units at C3 and C4 of compound **119** if carboxylation had occurred at the C1 position were absent. Interestingly, no peak was observed for the C3 proton of β-keto acid **61**, suggesting that the observed product was actually enol **118**, a tautomer of **61** (Scheme 2.16). Although problems with aromatization had been previously encountered, the appearance of a multiplet between 3.42 and 3.55 ppm corresponding to the four protons bound to C1 and C4 indicated that under these conditions, no aromatization of the SM or product had occurred. GC-MS analysis of the material showed a molecular ion peak at 250 amu, and HRMS gave an exact mass of 250.0835 amu; both values were consistent with a molecular formula of $C_{13}H_{14}O_5$ and thus offered further evidence of the successful formation of acid **118**.

Attempts to combine the desilation (6 M HCl in DMF) and carboxylation (MMC) procedures into a one-pot reaction were briefly explored (Scheme 2.17). This combination offered the advantages of reducing the length of the synthesis and eliminating the need to isolate and purify ketone **62** which had proven prone to oxidation.

Scheme 2.17



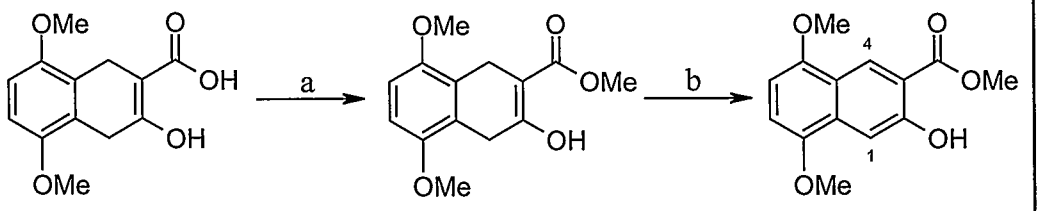
115 **118** **62**

When **115** was combined with 6 M HCl in DMF, the SM appeared consumed after 2 h, by TLC analysis. The acidic reaction mixture was then treated with 2 M MMC until litmus paper indicated a neutral solution. An additional 8 equiv. MMC solution were added, and the reaction mixture was heated to 130 °C for 4 h. Following acidification, a solid material was isolated. When analyzed by ^{1}H NMR, this solid gave a spectrum identical to that of ketone **62** not acid **118** (Scheme 2.17). Treating O-methylated adduct **115** directly with MMC was also considered as route that would circumvent the desilation step in the preparation of enol acid **118**. Following the same procedure for carboxylation of the isolated ketone (Scheme 2.16) disappointingly gave a 3 : 1 mixture of ketone **62** to unreacted **115** by ^{1}H NMR analysis. Although trace amounts of acid **118** were observed, the peaks were barely detectable in the baseline of the ^{1}H NMR spectrum of the crude material. The poor results obtained in these one-pot reactions led to this strategy being abandoned and the desilation and carboxylation were kept as discrete steps. However, with a successful method for the preparation of **118** in hand and the one-pot reaction strategy abandoned, work toward Fragment A could continue.

2.9 Final Steps in the Synthesis of Target Naphthoic Acid 42

It was initially anticipated that acid **118** would be prone to decarboxylation, and it was therefore converted immediately to the corresponding methyl ester **120**. Applying a procedure employed by Nozulak *et al*[20] to effect the same transformation on a similar system, **118** was treated with Et_3N and methyl chloroformate in DCM at 0 °C. Pleasingly, after 2 h, ester **120** (98%) was isolated as a fine yellow powder (Scheme 2.18).

Scheme 2.18



118 **120** **121**

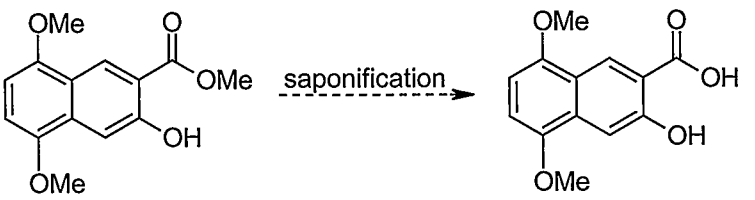
Conditions: a) Et_3N (1.2 equiv.), methyl chloroformate (2.1equiv.), DCM, 0 °C, 2 h (98%); b) DDQ (1.3 equiv.), DCM, rt , 15 min (64%).

^{1}H NMR analysis of **120** showed three singlets between 3.80 and 3.84 ppm indicative of the three methoxy groups. Additionally, only one peak was observed above 6.68 ppm, a singlet at 12.26 ppm corresponding to the hydroxyl group, which indicated the absence of an acid proton. IR analysis gave a spectrum with a carbonyl stretching frequency of 1680 cm^{-1}, an absorption indicative of the newly formed conjugated ester.[51] Furthermore, LRMS of **120** generated a molecular ion peak of 264 amu and analysis by HRMS gave an exact mass of 264.1004 amu, two values consistent with a molecular formula of $C_{14}H_{16}O_5$ and the successful formation of the desired methyl ester.

The next step in the synthesis required the aromatization of the functionalized system to generate hydroxyl naphthyl ester **121** (Scheme 2.18). Given the earlier problems with oxidation it was anticipated that the system would readily aromatize and easily form compounds that were stable and easy to handle. Combining ester **120** and DDQ (1.3 equiv.) in DCM for 15 min at rt upon work-up gave **121** (64%) as bright yellow needles. Analysis of the solid by ^{1}H NMR showed two new singlets at 7.66 and 8.85 ppm, corresponding to the protons on C1 and C4. This coincided with the loss of the broad peak at 3.53 ppm associated with the -CH_2 protons at C1 and C4 in **120**. Additional analysis by HRMS gave an exact mass of 262.0844 amu, corresponding to a molecular formula of $C_{14}H_{14}O_5$ for naphthol **121**.

In accordance with the initial synthetic strategy, the next step was to be saponification of the ester (Scheme 2.19). Subsequent protection of the naphthol hydroxyl group as a TBS ether and then conversion of the acid to the acid chloride would effectively complete Fragment A (Scheme 1.14).

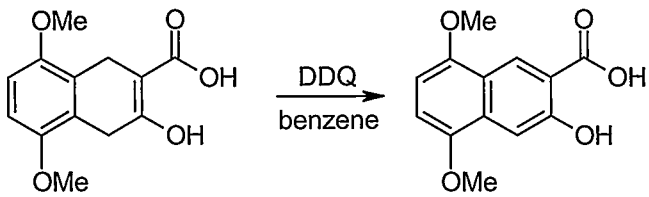
Scheme 2.19



121 **42**

Alternatively, if enol acid **118** could be aromatized directly to naphthol acid (**42**, Scheme 2.20) two steps in the preparation of Fragment A could be eliminated: the esterification of acid **118** and following aromatization, the saponification of methyl ester **121**.

Scheme 2.20



118 **42**

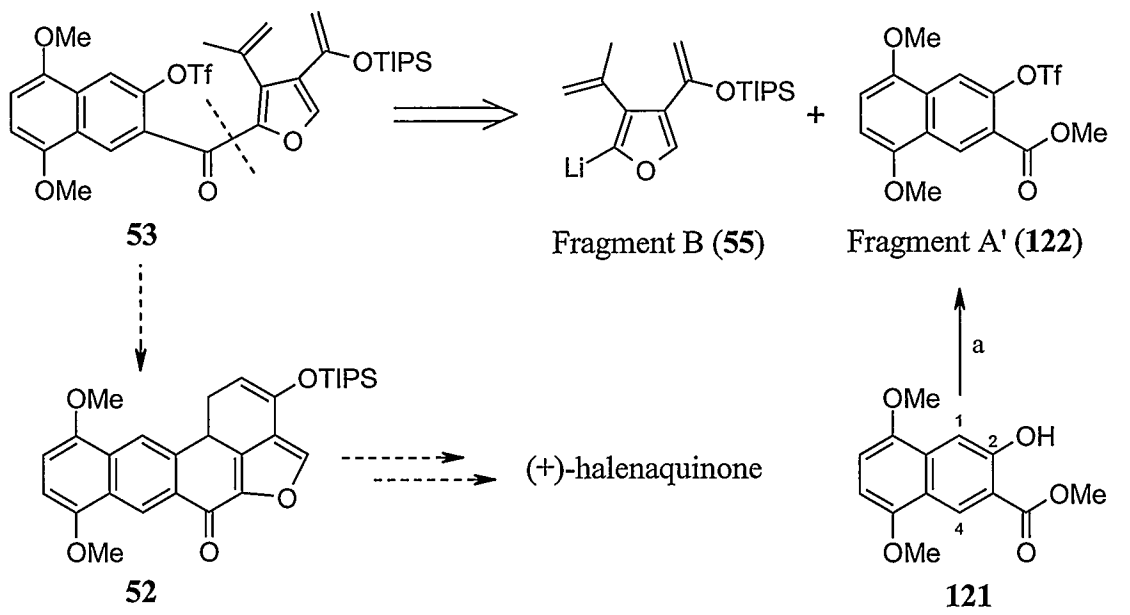
Since oxidation of **118** to **42** would improve the efficiency by which Fragment A could be prepared, this transformation was investigated further. Disappointingly, applying the procedure used to oxidize methyl ester **120** to naphthol ester **121** failed when applied to enol acid **118**, which instead resulted in the formation of a complex mixture. Since benzene was found to be an appropriate solvent when DDQ was used to aromatize a related system,[55] the reaction was repeated in this solvent. Acid **118** was ground to a fine powder, suspended in benzene at rt to which a large excess of DDQ was added. After 20 h, TLC analysis indicated complete consumption of the SM along with the appearance of a new spot. The solvent was then evaporated from the crude reaction mixture to yield a white and yellow solid. ^{1}H NMR analysis of the solid yielded a spectrum consistent with the known compound[17] and thus indicated successful formation of naphthol acid **42**.

Unfortunately, separating the naphthol acid from the oxidizing agent proved to be somewhat challenging. Naphthol acid **42** would therefore be used crude in the subsequent step or additional work toward its purification could be performed; however, its successful preparation effectively completed the synthesis of Fragment A.

2.10 Synthesis of Coupling Precursor 122 (Fragment A')

At this point, the possibility of coupling Fragment B directly to aromatized ester **121** offered an intriguing alternative to the direct aromatization of enol acid **118**. The C2 hydroxyl group of **121** could be converted to the triflate prior to the cyclization, thus eliminating the need to protect the C2 hydroxyl group of naphthol acid **42** as the TBS ether. Although no steps would be saved in the preparation of this fragment, the total number of steps in the synthesis would be reduced as the triflate would be in place prior to the coupling of Fragments A' and B (Scheme 2.21).

Scheme 2.21



Conditions: a) Tf_2O (1.1 equiv.), Et_3N (2.6 equiv.), DCM, 0 °C (50%).

After coupling Fragment B to triflate **122** (Fragment A') to yield **53**, only cyclization, cleavage of the TIPS group and a known oxidative step would remain in the synthesis of

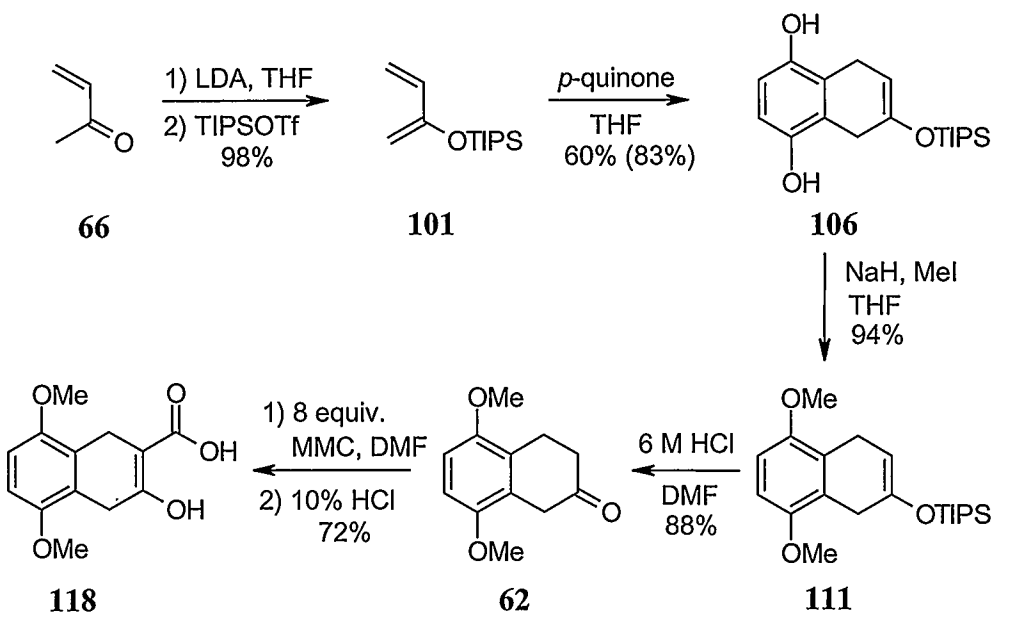
halenaquinone. With this new strategy and naphthol ester **121** in hand, work could begin toward the preparation of Fragment A' (**122**).

Treatment of naphthol derivative **121** with Et_3N and triflic anhydride in DCM at –45 °C for 15 min yielded naphthyl triflate **122** as a yellow crystalline solid. ^1H NMR analysis of the material generated a spectrum similar to that of naphthol **121** but with a substantial downfield shift for the singlets which corresponded the protons bound to C1 and C4. This shift from 7.66 and 8.85 ppm to 8.08 and 9.00 ppm was consistent with the electron withdrawing properties of the newly introduced triflate group. Further analysis by GC-MS gave a molecular ion peak at 394 amu corresponding to a molecular formula of $C_{15}H_{13}O_7SF_3$ with a peak at 261 amu implying fragmentation of the SO_2CF_3 group and therefore successful incorporation of the triflate.

2.11 Conclusion

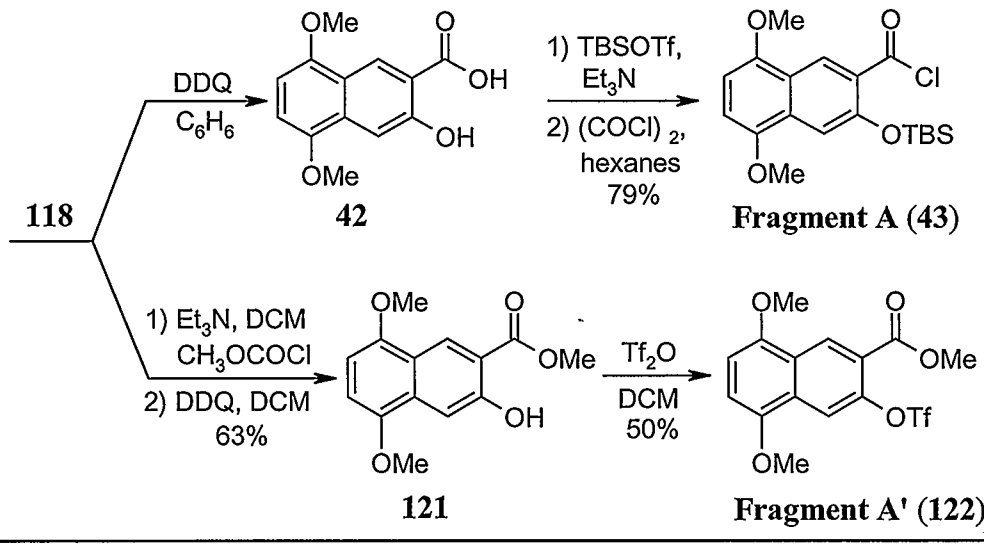
An efficient route for the preparation of 3-hydroxy-5,8-dimethoxy-1,4-dihydro-naphthalene-2-carboxylic acid (**118**) was successfully developed in 5 steps from methyl vinyl ketone (**66**, Scheme 2.22).

Scheme 2.22



Although several dienes were used as starting materials, TIPS enol ether **101** proved most effective over the course of the synthesis as the TIPS group was readily attached and cleaved as necessary. From enol acid **118** aromatization to 3-hydroxy-5,8-dimethoxy-2-naphthoic acid (**42**) formally completed the synthesis of Fragment A (**43**) in 8 steps from **66** (Scheme 2.23). This synthetic route was a significant improvement in efficiency over the previous synthesis in which **43** was constructed in 13 steps from 2,5-dimethoxy benzyl alcohol (**33**, Scheme 1.9).[16,17]

Scheme 2.23



Additionally, an alternative subunit, Fragment A' (**122**) was prepared in 8 steps from **66**. Applying the same 5 steps in the preparation of β-keto acid **118** (Scheme 2.22) but altering the final 3 steps completes the synthesis of Fragment A' (Scheme 2.23). The replacement of Fragment A with Fragment A' as a subunit in the total synthesis offered two important benefits; first, Fragment A' could be efficiently prepared in the same number of step as employed in the construction of Fragment A and second, the use of Fragment A' represented a substantial reduction in the total number of steps which were required in the preparation of halenaquinone (**1**).

Chapter 3

3. Synthesis of Fragment B and Model System Study

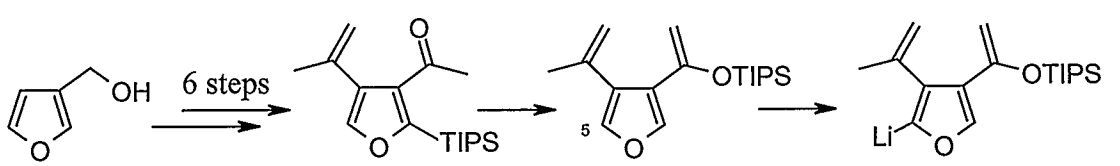
3.1 Introduction

This chapter begins with an examination of the methods used in the construction of the second subunit of halenaquinone, Fragment B. This is followed by a section dealing with the preparation of a model system used to determine appropriate conditions for coupling, selective deprotection, triflate formation and cyclization which could be applied to the fully elaborated system.

3.1.1 Synthetic Strategy for Construction of Fragment B

In accordance with the retrosynthesis of Fragment B (Scheme 1.16), this subunit was to be derived by functionalizing 3-furanmethanol (**44**, Scheme 3.1). A series of transformations would allow construction of methyl ketone **68** which would then be subjected to two key steps: a C → O silyl migration to give silyl enol ether **67** followed by selective lithiation at C5 of furan **67** to give **55**. In this way, the synthesis of Fragment B would be completed in 8 steps from **44**.

Scheme 3.1

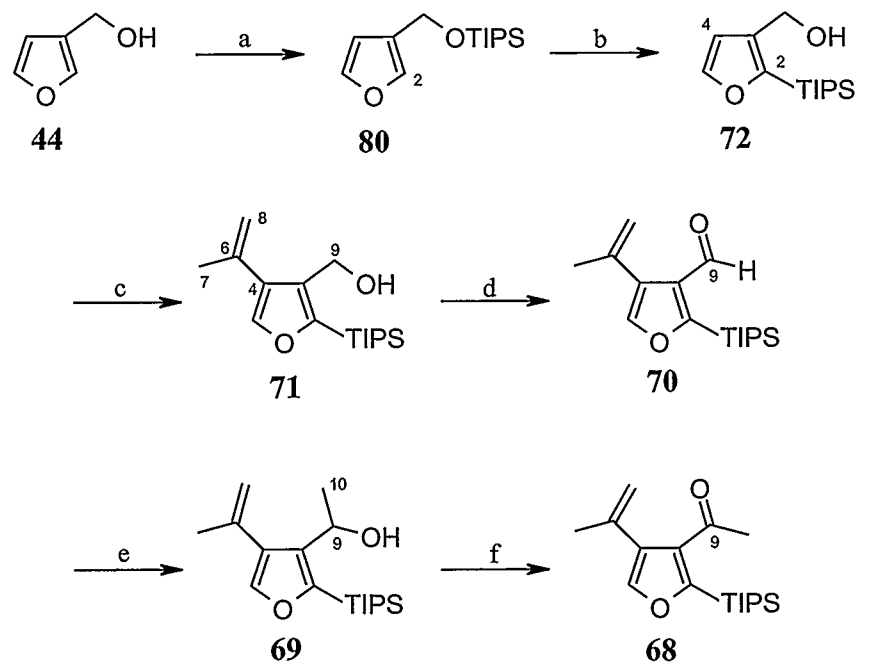


44 **68** **67** Fragment B (**55**)

3.2 Construction of Fragment B Precursor, Methyl Ketone 68

The construction of Fragment B began with protection of the hydroxyl group of 3-furanmethanol (**44**) as the corresponding TIPS ether **80**. Once obtained, **80** was then subjected to a [1,4] O → C silyl migration to yield C2-functionalized furan **72** (Scheme 3.2).

Scheme 3.2



Conditions: a) TIPSCl (1.5 equiv.), imidazole (2.0 equiv.), DMF (99%); b) *n*BuLi (1.4 equiv.), THF, HMPA (1.5 equiv.), 0 °C (99%) c) *n*BuLi (2.2 equiv.), DME, 0°C, 1h; then add $B(MeO)_3$ (2.2 equiv.), 0° C, 1h; then add $Pd(PPh_3)_4$ (5 mol %) H_2O, 2-bromopropene (2.2 equiv.), 50 °C, 24 h (80%); d) TPAP (5 mol %), NMO (1.5 equiv.), DCM (91%) e) MeLi (1.5 equiv.), THF, 0 °C (99%) f) PDC (1.5 equiv.), DCM (86%).

Previous work performed in the Keay laboratory by Bures *et al*[21] examined [1,4] O → C and C → O silyl migrations of several substrates including the conversion of silyl ether **80** into migration product **72**. Following the procedure of Bures *et al*,[21] 3-furanmethanol (**44**) was dissolved in DMF and treated with imidazole (2.0 equiv.) followed by TIPSCl (1.5 equiv.) which, following work-up, gave silyl ether **80** in nearly

quantitative yield (Scheme 3.2). Following distillation, **80** was dissolved in THF and mixed with HMPA (1.5 equiv.) at rt. The reaction mixture was then cooled to 0 °C and treated with *n*BuLi (1.4 equiv.) to deprotonate the furan at C2. After 3 h, C2 substituted furan **72** was isolated in 99% yield.

The next step toward the preparation of Fragment B required the regioselective installation of a propene unit at the C4 position of furan **72**. Incorporation of this olefin was required for the formation of the B ring of halenaquinone (**1**) in the key Pd-catalyzed cyclization step in the late stages of the synthesis (Scheme 1.13). Previously in the Keay laboratory, conditions had been developed for the C4-selective alkylation of 2,3-disubstituted furan rings using a modified Suzuki protocol.[19] Keay's modified Suzuki conditions required the *in situ* generation of the corresponding furyl-boronic acid. This was accomplished by dissolving **72** in DME at 0 °C and treating the resultant solution with *n*BuLi (2.2 equiv.). The reaction mixture was then warmed to rt, and trimethyl borate (2.2 equiv.) was added. After 20 h, the reaction was quenched with 2 M Na_2CO_3, then treated with 2-bromopropene (2.2 equiv.) and $Pd(PPh_3)_4$ (5 mol %) and then warmed to 50 °C for 24 h or until TLC analysis showed the complete consumption of SM. Following work-up, the semisolid material obtained was purified by column chromatography to yield **71**, as a waxy beige solid (82%). ^{1}H NMR analysis of the material generated a spectrum with three new peaks; two signals appeared at 5.08 and 5.40 ppm and corresponded to the C8 methylene protons of **71** and a third peak at 2.08 ppm corresponded to the protons of the C7 methyl group (Scheme 3.2). Furthermore, concurrent disappearance of the doublet at 6.50 ppm, which corresponded to the C4 furan proton of furan **72**, indicated the regioselective incorporation of the alkyl group. Further analysis by ^{13}C NMR showed 10 distinct carbon atoms, consistent with the alkylated furan. Additionally, HRMS analysis gave an exact mass of 251.1467 amu, corresponding to a molecular formula of $C_{14}H_{23}O_2Si$ and thus indicated the successful preparation of furan **71**.

With C4-functionalized furan **71** in hand, attention could be turned to the conversion of the primary alcohol into the desired methyl ketone. This was done by first oxidizing alcohol **71** to aldehyde **70** (Scheme 3.2). Treatment of **71** with catalytic TPAP (5 mol %) dissolved in DCM in the presence of stoichiometric reoxidant NMO (1.5

equiv.) showed the complete consumption of SM by TLC analysis within 2 h at rt. Distillation of the crude product yielded aldehyde **70** (91%) as a pale yellow oil. ^{1}H NMR analysis of the oil gave a spectrum with a new singlet at 10.28 ppm indicative of an aldehyde concurrent with the disappearance of the singlet at 4.60 ppm corresponding to the C9 protons of alcohol **71**. Further analysis by ^{13}C NMR indicated a peak at 186.6 ppm, a downfield absorption characteristic of an aryl aldehyde,[51] while HRMS gave an exact mass of 249.1311 amu corresponding to a molecular formula of $C_{14}H_{21}O_2Si$, further confirming the successful preparation of aldehyde **70**.

In order to convert the C3 substituent into the desired methyl ketone, aldehyde **70** was required to undergo a one-carbon homologation. The addition of one carbon was to be performed *via* nucleophilic attack of MeLi to yield the corresponding secondary alcohol. Treatment of **70** with MeLi (1.5 equiv.) in THF at 0 °C showed complete consumption of starting material by TLC analysis after 2 h. Following work-up, the crude yellow oil isolated was purified by column chromatography yielding a waxy white solid that was subsequently identified as alcohol **69** (99%, Scheme 3.2). ^{1}H NMR analysis of the solid yielded a spectrum in which a new quartet had appeared at 5.40 ppm indicative of the proton bound to C9. The appearance of the quartet was concurrent with the disappearance of the lowfield aldehydic proton of **70**. ^{13}C NMR analysis confirmed the incorporation of the methyl group with 11 distinct carbon atoms appearing in the spectrum, 3 of which were identified as methyl carbons by subsequent DEPT experiments. The exact mass obtained *via* HRMS was 265.1624 amu corresponding to a molecular formula of $C_{15}H_{25}O_2Si$ and therefore indicating the successful preparation of secondary alcohol **69**.

With the C3 substituent successfully homologated, oxidation of the secondary alcohol was the final step required for the construction of methyl ketone **68** (Scheme 3.2). Treatment of alcohol **69**, dissolved in DCM at rt, with an excess of PDC yielded the crude product as a yellow oil after work-up. Column chromatography of the crude product followed by distillation gave methyl ketone **68** as a clear colourless oil (92%). ^{1}H NMR analysis showed the disappearance of the quartet indicative of the C9 proton in SM **69**. ^{13}C NMR analysis confirmed regeneration of the carbonyl moiety by the appearance of a distinctive absorption at 189.9 ppm characteristic of an aryl ketone[51] and

thereby indicated the successful preparation of methyl ketone **68**. With a reliable 6 step route to migration precursor **68** having been successfully developed, work could proceed on the critical silyl migration.

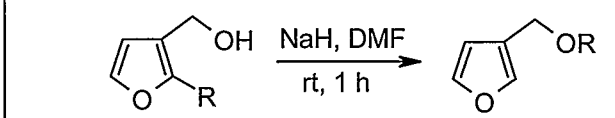
3.3 Preparation of TIPS Enol Ether 67 *via* Silyl Migration

With migration precursor **68** in hand, TIPS enol ether **67** could then be prepared from the methyl ketone *via* a [1,4] C → O migration. The silyl enol ether, once installed, was required to serve a dual purpose: to provide the second olefin for the formation of the A ring in the key Pd-catalyzed cyclization and to mask the requisite A ring carbonyl function that would be revealed in the final steps of the synthesis (Scheme 1.12).

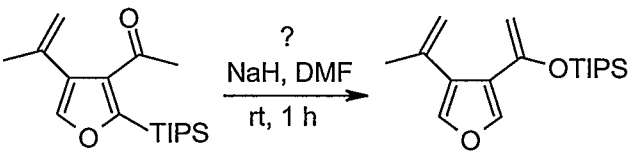
3.3.1 Migration Studies Using NaH (Part 1)

Previous work performed in the Keay laboratory showed that [1,4] C → O silyl migrations could be effected on simpler systems using NaH in DMF at rt (Scheme 3.3).[21]

Scheme 3.3



123a R = TMS **124a** (88%)
123b R = TIPS **124b** (89%)
123c R = TBDPS **124c** (89%)



68 **67**

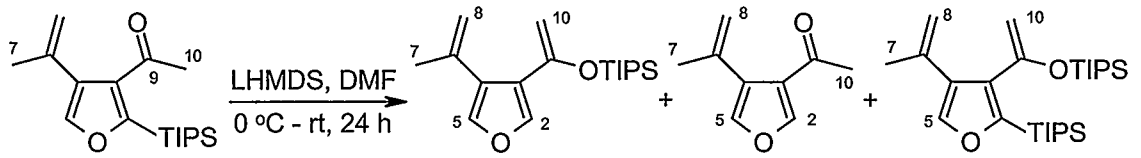
It was therefore hoped that applying these same conditions to the more complex furyl system **68** would result in a similar transformation, generating the desired silyl enol ether **67**. Instead, treating **68** with NaH in DMF (-61 °C - rt) gave a complex mixture of which ^{1}H NMR analysis showed no peaks that could be assigned to either desired product **67** or

SM **68**. Although somewhat discouraging, it was hoped the reaction conditions could be modified to give a cleaner result.

3.3.2 Migration Studies Using LHMDS

Otherwise maintaining the same reaction conditions but replacing NaH with LHMDS was anticipated to result in a cleaner and slower reaction. Applying these conditions to **68** did appear to slow the reaction; TLC analysis indicated the presence of SM after 24 h at rt. Unfortunately, TLC analysis also showed four new spots suggesting that even if the desired product was formed, the reaction had not proceeded cleanly (Scheme 3.4).

Scheme 3.4



68 **67** **125** **126**

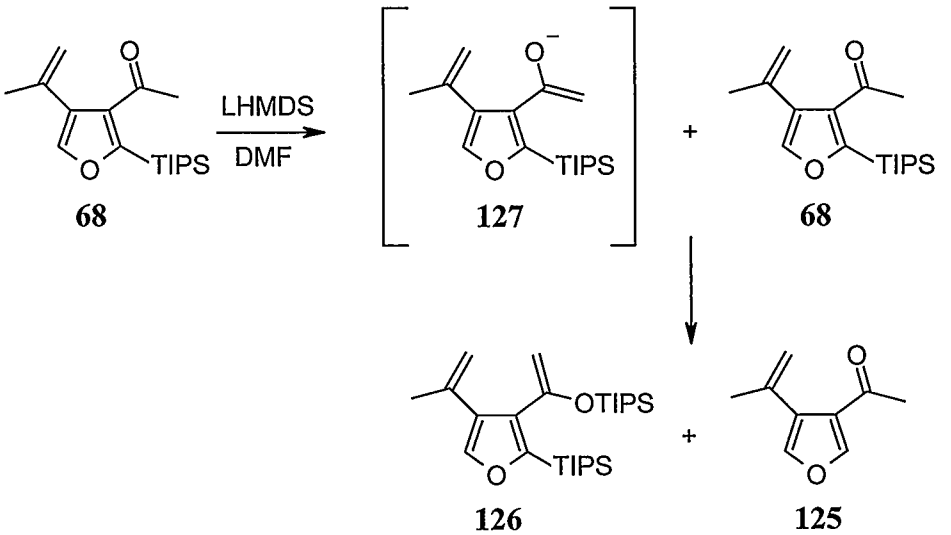
The largest component of the mixture was identified as unreacted SM **68** (60%). Pleasingly, silyl enol ether **67** was also identified as a product of the reaction. ^{1}H NMR analysis of the clear colourless oil gave a spectrum with 2 finely split doublets in the aromatic region at 7.25 and 7.48 ppm. These peaks corresponded to the pair of furyl protons at the C2 and C5 positions of migration product **67**. A peak also appeared at 2.02 ppm indicative of the C7 methyl group of **67**; previously, 2 singlets had been observed at 2.04 and 2.41 ppm corresponding to the C7 and C10 methyl groups of ketone **68**. Successful formation of the enol ether function was further evidenced by the appearance of a new pair of broad signals at 4.38 and 4.54 ppm corresponding to the pair of vinyl protons now at C10. LRMS analysis of the oil gave a spectrum that was different than that generated by ketone **68**. Where a molecular ion peak was not observed for **68**, enol ether **67** yielded a large (100% relative intensity) molecular ion peak accompanied by a fragmentation pattern distinct from that generated by the isomeric SM. Analysis by

HRMS gave an exact mass of 128.2025 amu corresponding to a molecular formula of $C_{18}H_{30}O_2Si$ and lending further support to the identification of the isolated material as silyl enol ether **67**. Unfortunately, **67** represented only about 5% of the product mixture by ^1H NMR integration. Besides unreacted SM, two other compounds were identified as components of the mixture: desilated methyl ketone **125** and disilated material **126**, each of which comprised 18% of the product mixture by integration. Desilated furan **125**, when analyzed by ^1H NMR, generated a spectrum with several distinguishing characteristics. Two finely split doublets appeared at 7.94 and 7.32 ppm corresponding to the furyl C2 and C5 protons, substantially farther downfield than the analogous protons of silyl enol ether **67**. Additionally, a single pair of peaks was observed in the vinyl region, at 5.07 and 5.12 ppm, indicating of the presence of a single olefin and consistent with compound **125**. Two singlets appeared at 2.42 and 2.02 ppm and corresponded to the C10 and C7 methyl groups respectively. The appearance of these peaks taken together with the disappearance of the peaks characteristic of an intact TIPS group appeared to indicate formation of desilated methyl ketone **125**. The second by-product proved difficult to isolate from the crude mixture; however, several diagnostic peaks allowed the tentative identification as disilated material **126**. A singlet at 7.50 ppm could be correlated to the C5 furyl proton. It should be noted that the C2 and C5 furyl protons of **67** and **125** were split into fine doublets due to long range coupling. The absence of this coupling from the furyl peak of **126** suggested that the C1 position was likely substituted. Additionally, four broad signals appeared in the vinyl region, at 4.43, 4.48, 5.13 and 5.29 ppm. These peaks were aligned in a pattern similar to that observed for the C8 and C10 protons of silyl enol ether **67**; the different shifts observed for these protons, however, suggested that although similar in structure to **67**, compound **126** was distinct. Analysis *via* LRMS generated a molecular ion peak of 462 amu, a value consistent with a molecular formula of $C_{27}H_{50}O_2Si_2$ which supported the identification of the second by-product as disilyl furan **126**.

The presence of compounds **125** and **126** as the major products of the migration suggested a fundamental problem with the reaction under these conditions. For disilated furan **126** to have formed, the enolate generated by LHMDS must have reacted with a

second equivalent of SM in an intermolecular process which would also give desilated methyl ketone **125** (Scheme 3.5).

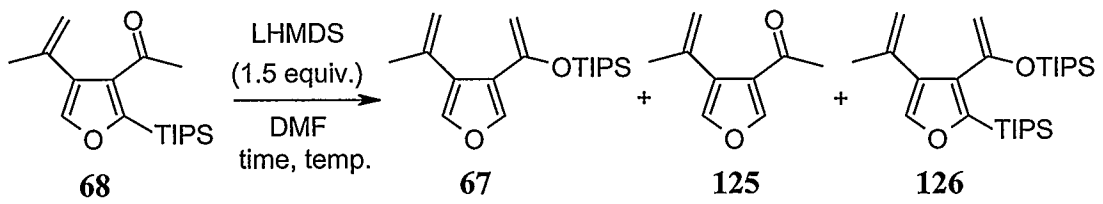
Scheme 3.5



The detection of **125** and **126** in a 1 : 1 ratio further supported the theory that an intermolecular reaction was taking place since 1 mole of **125** would be produced for each mole of **126**. Under the initial LHMDS reaction conditions, the intermolecular reaction was occurring with nearly four-fold preference over the desired intramolecular reaction. These results were initially discouraging since compounds **125** and **126** were not useful synthetic intermediates; however, the appearance of silyl enol ether **67** as a small component of the reaction mixture was encouraging, and it was anticipated that the course of the migration could be skewed in preference of an intramolecular reaction by careful manipulation of the reaction conditions.

The first variable to be changed was the temperature of the reaction, and ketone **68** was treated with LHMDS (1.5 equiv.) in DMF at a variety of temperatures. At -61 °C, no conversion to product was observed by TLC analysis after 3 h (Entry 1, Table 3.1). In an effort to initiate the reaction, the temperature was raised in increments. After 3 h at -42 °C, -20 °C and finally -10 °C, only unreacted SM was observed by TLC (Entries 2 – 4, Table 3.1).

Table 3.1: Attempted Formation of 67 Using LHMDS (1.5 equiv.) in DMF



68 **67** **125** **126**

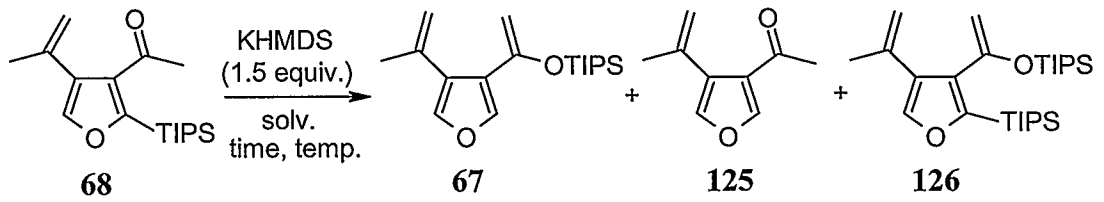
Entry	Temp.	Time	Products
1	-61 °C	3 h	NR
2	-42 °C	3 h	NR
3	-20 °C	3 h	NR
4	-10 °C	3 h	NR
5	0 °C	2 h 2 h 40 min 4 h 30 min 5 h 30 min	NR **67**, **125** and **126** **67**, **125** and **126** **67**, **125** and **126**

Further raising the to 0 °C (Entry 5, Table 3.1) showed no reaction by TLC analysis after 2 h; however, after 2 h 40 min had elapsed, TLC and subsequent ^{1}H NMR analysis indicated formation of both de- and disilated compounds **125** and **126** as well as a small amount of silyl enol ether **67**. After 5 h 30 min at 0 °C, the amount of desired product **67** appeared to remain constant by ^{1}H NMR analysis while **125** and **126** continued to form. Therefore, it appeared that lowering the temperature at which the reaction was performed favoured the intermolecular reaction, not the desired intramolecular process.

3.3.3 Migration Studies Using KHMDS

Since the formation of the desilated and disilated products appeared facile when LHMDS was used in DMF, the conditions for the reaction were again manipulated. Replacing LHMDS with KHMDS and repeating the reaction in DMF and allowing the reaction mixture to warm from -61 °C to rt, resulted in the complete consumption of SM after 20 h (Entry 1, Table 3.2).

Table 3.2: Attempts to Prepare Silyl Enol Ether 67 *via* Silyl Migration Using KHMDS (1.5 equiv.) in Various Solvents at Various Temperatures



68 **67** **125** **126**

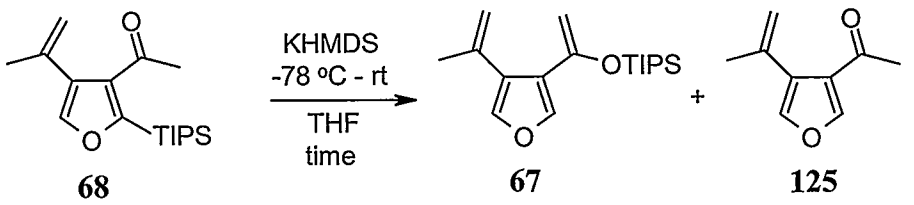
Entry	Solv.	Temp.	Time	67	SM (68)	125	126
1	DMF	-61 °C – rt	18 h	-	-	1.0	-
2	tol.	-78 – 0 °C	1 h	-	1.0	-	-
3	tol.	0 °C	8 h	-	1.0	-	-
4	tol.	rt	6 d	-	1.0	-	-
5	tol.	60 °C	2 h	-	1.0	-	-
6	Et_2O	-15 °C – rt	20 h	trace	~1.0	-	-
7	Et_2O + DMF	rt	24 h	0.25	1.0	-	-
8	Et_2O + DMF	rt	48 h	0.40	1.0	0.16	0.16

When analyzed by ^1H NMR and GC-MS, the crude product was identified as desilated methyl ketone **125**. Interestingly, in this case, **125** was not accompanied by disilated furan **126**. This result implied that the intermolecular reaction observed using LHMDS in DMF (Entry 5, Table 3.1) was likely not occurring. The formation of desilated product **125** was more likely due to the relatively harsh reaction conditions which cleaved the TIPS group from either SM **68** or product **67** before it could be detected. In an effort to decrease the activity of the KHMDS, the reaction was repeated at low temperatures in a less polar solvent, toluene (Entry 2, Table 3.2). Warming the reaction from -78 to 0 °C gave no reaction after 1 h. After an additional 8 h at 0 °C, still no reaction was observed and the reaction was therefore warmed to rt (Entries 3 & 4, Table 3.2). Disappointingly, after 6 d at rt, no conversion to product was evident. The reaction mixture was then warmed to 60 °C (Entry 5, Table 3.2) but this also failed to effect a reaction. Since the KHMDS had shown high activity in DMF but none in toluene, a solvent of intermediate polarity was tested. Gratifyingly, treating **68** with KHMDS (1.5 equiv.) in Et_2O at -15 °C and warming the mixture slowly to rt showed formation of silyl enol ether **67** after 20 h

(Entry 6, Table 3.2). Unfortunately, ^{1}H NMR analysis of the mixture showed that the primary component of the mixture was SM. Peaks corresponding to silyl enol ether **67** appeared but were barely visible above the baseline. Despite poor conversion to product under these conditions, **67** appeared to be the sole product of this reaction. This was a notable improvement since preventing the formation of compounds **125** and **126** remained desirable. Since adding an excess of DMF had been shown to increase the rate of C $\rightarrow$ O silyl migrations,[21] the reaction was repeated with the addition of DMF (Entry 7, Table 3.2). Gratifyingly, after 24 h at rt, in the presence of DMF, silyl enol ether **67** was observed in a 0.25 : 1.0 ratio wrt unreacted SM. After 48 h at rt (Entry 8, Table 3.2) the relative amount of **67** to **68** had increased further, exhibiting a ratio of 0.40 : 1.0. Disappointingly, the increase in silyl enol ether **67** was accompanied by the formation of desilated furan **125** and disilated furan **126**. The formation of silyl enol ether **67** was thus found to be slow in Et_2O and, although the DMF additive appeared to accelerate the reaction, it also appeared to promote the undesirable intermolecular reaction. Despite this, these results were promising, since using a moderately polar solvent such as Et_2O with no additive did result in generation of silyl enol ether **67** as the sole product, albeit in small amounts. Expanding on this idea, it was thought that the use of another solvent, slightly more polar than Et_2O, may result in greater conversion to product. THF was a readily available solvent with a polarity between that of DMF and Et_2O and was therefore selected for use in the silyl migration.

Methyl ketone **68** was treated with KHMDS (1.5 equiv.) in THF at –78 °C and the reaction mixture allowed to warm slowly to rt (Entry 1, Table 3.3). After 24 h, ^{1}H NMR analysis of the crude product gave a product to SM ratio of 0.50 : 1.0. Pleasingly, silyl enol ether **67** appeared as the exclusive product, suggesting that these conditions favoured the intramolecular reaction while not being harsh enough to result in direct desilation.

Table 3.3: Attempts to Prepare Silyl Enol Ether 67 *via* Silyl Migration Using KHMDS in THF -78 °C - rt



68 **67** **125**

Entry	Equivalents KHMDS	Time	67	SM (68)	125
1	1.5	24 h	0.50	1.0	-
2	1.5	48 h	1.0	1.0	-
3	1.5	72 h	0.70	1.0	0.35
4	1.0	24 h	0.31	1.0	-
5	1.0	48 h	0.77	1.0	-
6	1.0	72 h	0.17	1.0	0.03
7	2.5	24 h	0.22	1.0	-
8	2.5	48 h	0.23	1.0	0.32
9	2.5	72 h	-	1.0	0.72

After 48 h had elapsed, the ratio further improved to a 1.0 : 1.0 mixture of product to SM (Entry 2, Table 3.3). Surprisingly, after 72 h (Entry 3, Table 3.3) the ratio decreased to 0.70 : 1.0 : 0.35 (**67** to SM to **125**). The appearance of compound **125** was presumably the result of the desilation of **67**, thereby offering an explanation for the disappearance of silyl enol ether **67** wrt SM **68**. In addition to these compounds, a few small unidentified peaks were also observed suggesting that further decomposition was occurring. Although repeated several times, greater than 50% conversion to product could not be achieved under these conditions. It appeared that, after the 1.0 : 1.0 ratio was obtained, typically after 48 h to 72 h, the formation of **67** effectively ceased. At this point, the only further reaction observed was the apparent decomposition of **67** to **125**. Fortunately, if the reaction was closely monitored and quenched after 50% conversion was reached, purification of the crude product mixture by flash column chromatography, allowed for the isolation of **67** in up to 48% yield. Additionally, unreacted SM was easily recovered and could be resubjected to the migration conditions with minimal loss of material.

At this stage it was unclear if the decomposition in the late stages of the migration was the result of using excess KHMDS. In order to determine if this was indeed the case,

the reaction was repeated using 1.0 equiv. KHMDS. After 24 h (Entry 4, Table 3.3), a 0.31 : 1.0 ratio of **67** to SM was observed and, after 48 h, the ratio had increased to 0.77 : 1.0 (Entry 5, Table 3.4). After 72 h, the ratio again dropped, this time to 0.17 : 1.0, representing a substantial loss of product (Entry 6, Table 3.3). The disappearance of silyl enol ether **67** was concurrent with the appearance of desilated furan **125** as well as several small new peaks indicating continued decomposition. In general, the behaviour of this reaction appeared to parallel that observed when 1.5 equiv. of KHMDS was used; however, with less KHMDS, conversion to product had apparently slowed and resulted in no useful improvement.

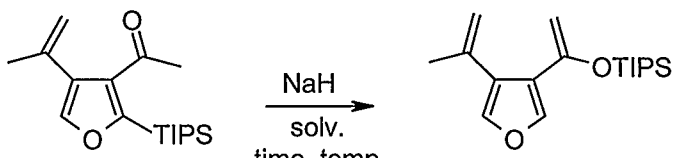
The rate of reaction thus appeared to be dependent on the concentration of KHMDS employed, and a lengthy reaction time appeared to coincide with decomposition of the desired product. It was therefore hoped that treatment of **68** with a greater excess of KHMDS would result in a rapid reaction and thus limit decomposition. The reaction was repeated with 2.5 equiv. KHMDS. After 24 h, the ratio of **67** to SM was only 0.22 to 1.0 (Entry 7, Table 3.3). After 48 h, the ratio of product to SM remained essentially the same; however, desilated furyl system **125** became apparent in the ^{1}H NMR spectrum (Entry 8, Table 3.4). After 72 h at rt, all of the silyl enol ether **67** had disappeared, and only SM and desilated compound **125** were observed (Entry 9, Table 3.4). It therefore appeared that the use of such a large excess of KHMDS had only a detrimental effect, promoting the desilation of desired product **67**.

Encouragingly, by using KHMDS (1.5 equiv.) as a base and performing the reaction in THF, it was possible to generate desired migration product **67** in moderate yields and entirely eliminate the competing intermolecular reaction. It could also be concluded that, to some degree, KHMDS was incompatible with the sensitive silyl enol ether functionality. Even the 1.5 equiv. KHMDS that had led to the highest conversion of **68** to silyl enol ether **67** eventually resulted in desilation. Although these conditions were moderately successful, the reaction itself proved to be surprisingly sensitive and careful monitoring was required to eliminate or minimize desilation of **67**. It was thought that using a base other than KHMDS might offer a solution to the problem of decomposition especially if the alternate base was unable to react with the sensitive silyl enol ether.

3.3.4 Migration Studies Using NaH (Part 2)

Since work performed previously in the Keay laboratory to effect C → O silyl migrations on simpler furyl substrates[21] used NaH in DMF, and NaH was not expected to react with silyl enol ether **67**, attention was returned to optimizing these conditions. Although initial results had been poor using NaH in DMF it was hoped that cooling the reaction mixture and careful monitoring of the reaction as it warmed to rt would result in a cleaner reaction, as it could be stopped once a significant amount of product was observed. Methyl ketone **68** was thus treated with an excess of NaH in DMF at 0 °C, and the reaction was allowed to warm slowly to rt (Entry 1, Table 3.4).

Table 3.4: Attempts to Prepare Silyl Enol Ether 67 *via* Silyl Migration Using NaH in Various Solvents at Various Temperatures



68 **67**

Entry	Solvent	Temperature	Time	67	SM (68)
1	DMF	0 °C – rt	24 h	CM	
2	THF	0 °C – rt	24 h	-	1.0
3	THF	50 °C	2 h	-	1.0
4	THF	reflux	24 h	1.0	1.0
5	THF	reflux	48 h	0.74	1.0
6	THF + DMF	reflux	5 h	0.64	1.0
7	THF + DMF	reflux	48 h	CM	
8	DME	0 °C – rt	48 h	trace	1.0
9	DME	reflux	5 h	0.28	1.0
10	DME	reflux	21 h	-	1.0
11	Et_2O	0 °C – rt	24 h	-	1.0
12	Et_2O	rt	48 h	-	1.0
13	Et_2O	reflux	2 h	-	1.0
14	Et_2O + DMF	reflux	2 h	0.01	1.0
15	Et_2O + DMF	reflux	4 h	0.07	1.0
16	Et_2O + DMF	rt	14 d	0.10	1.0

Unfortunately, after a total of 24 h, a complex mixture was again obtained, within which, neither SM **68** nor silyl enol ether **67** appeared. Since DMF had given poor results when

used in the LHMDS and KHMDS migrations as well and the more moderately polar solvent THF had proven more effective, the reaction was repeated in THF. After 24 h at rt, no conversion to product was observed by ^{1}H NMR analysis (Entry 2, Table 3.4). In order to accelerate the reaction, the temperature was raised to 50 °C but after 2 h at this temperature, no reaction was observed (Entry 3, Table 3.4). The reaction mixture was therefore heated to reflux and, after 24 h, ^{1}H NMR analysis gratifyingly showed 50% conversion to product (Entry 4, Table 3.4). Pleasingly, desilated compound **125** was not observed; instead, the spectrum showed clean conversion to silyl enol ether **67**. However, after 48 h, the ratio of **67** to SM **68** dropped to 0.74 : 1.0 (Entry 5, Table 3.4). Although desilated furan **125** was not detected, the ^{1}H NMR spectrum no longer appeared clean. Again, conversion to product appeared to cease at a 1.0 : 1.0 ratio of product to SM. In an attempt to push the reaction over this apparent barrier, DMF (1 drop for 150 mg **68**) was added and the reaction mixture brought to reflux (Entry 6, Table 3.4). After 5 h, analysis by ^{1}H NMR showed that the ratio of product to SM again decreased to 0.64 : 1.0. After refluxing for an additional 48 h, a complex mixture of products was obtained (Entry 7, Table 3.4).

Greater than 50% conversion to product could not be obtained using NaH in THF, and the addition of DMF appeared to promote decomposition of the desired product. Since the rate of reaction appeared to have some correlation with the polarity of the solvent and the reaction did not proceed in THF at rt, the reaction was repeated in DME, a solvent more polar than THF. However, after 48 h, only trace amounts of silyl enol ether **67** could be detected by ^{1}H NMR analysis (Entry 8, Table 3.4). The reaction was therefore heated to reflux and gratifyingly, after 5h, a ratio of 0.28 : 1.0 (**67** : **68**) was obtained (Entry 9, Table 3.4). Unfortunately, after 48 h had elapsed, all of the product that had been formed by the reaction apparently decomposed while SM **68** had persisted (Entry 10, Table 3.4). In DME, as in THF, the reaction failed to proceed at rt; however, with heating, loss of product had severely limited the utility of these conditions. Consistent with the apparent trend in polarity, when the reaction was repeated in Et_2O, the results were poorer in this less polar solvent than those observed with THF. After 48 h at rt followed by 2 h at reflux, no conversion to product was observed (Entries 11 - 13, Table 3.4). Adding DMF to the reaction mixture allowed 1% conversion to product after

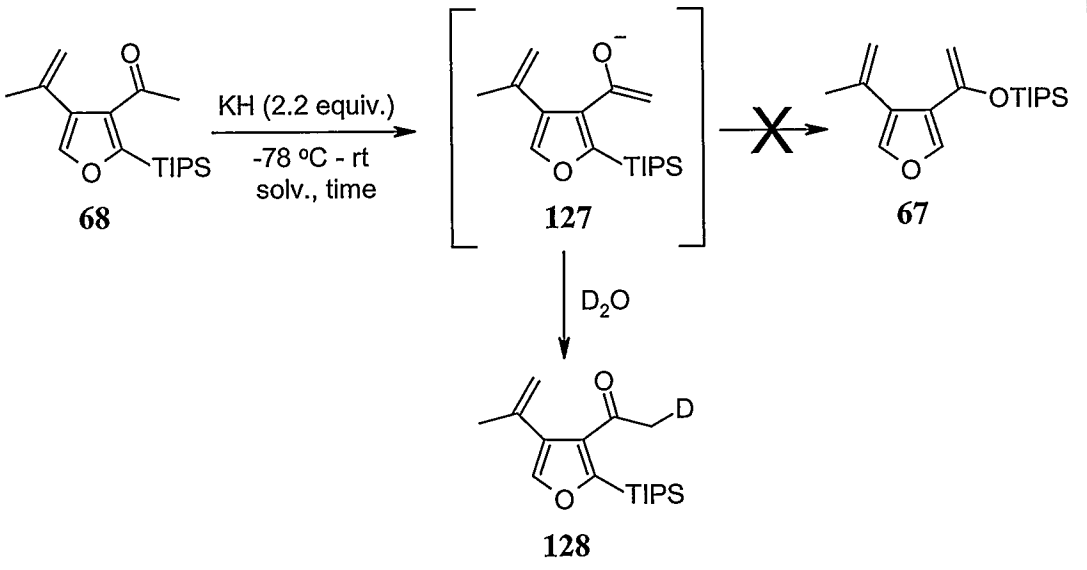
heating to reflux for 2 h (Entry 14, Table 3.4). After 4 h had elapsed, 3.5% conversion to product was observed (Entry 15, Table 3.4). Since no further conversion to product was evident, the reaction was allowed to cool to rt. After 2 weeks, the crude reaction mixture disappointingly showed only 5% conversion to product (Entry 16, Table 3.4). This suggested that even with the addition of DMF use of a solvent less polar than THF was impractical as the rate of reaction was slow. This result is consistent with the initial correlation drawn between solvent polarity and reaction time that had appeared to govern the previous migration reactions.

The use of excess NaH in refluxing THF allowed for up to 50% conversion to product, matching the best migration conditions previously obtained (KHMDS in THF at rt). Use of NaH offered the added bonus that less vigilance was required in monitoring the reaction as decomposition appeared less facile and desilation of **67** to give **125** was not observed. Interestingly, all of the reactions in which the product was consumed, involved heating the reaction mixture. Desilation had not typically been observed under these conditions and the by-products were difficult to isolate and identify. It was therefore proposed that the loss of material may have been the result of addition reactions between 2 or more molecules of silyl enol ether **67**. Since this explanation for the disappearance of SM seemed more likely at higher temperatures, it was hoped that repeating the reaction at lower temperatures using a more reactive base than NaH would result in greater conversion to product. Of course, the new base would have to be unable to react with the product and promote desilation.

3.3.5 Migration Studies Using KH

Since KH was both reactive and unable to react with silyl enol ether **67**, the reaction was repeated using KH in place of NaH. Methyl ketone **68** was dissolved in THF and slowly added to a suspension of KH (2.2 equiv.) in THF cooled to -78 °C. After 1 h, an aliquot was quenched with D_2O and analyzed by ^1H NMR which showed no product or anion formation (Entry 1, Table 3.5).

Table 3.5: Attempts to Prepare Silyl Enol Ether 67 *via* Silyl Migration Using KH in Et_2O or THF



Entry	Solvent	Temperature	Time	Additive	Result
1	THF	-78 °C	1 h	-	NR
2	THF	0 °C	1 h	-	**68, 128**[a]
3	THF	0 °C	2 h	-	**128**[a]
4	THF	0 °C – rt	1 h	-	**128**[a]
5	THF	rt	24 h	-	**128**[a]
6	THF	rt	1 h	18-crown-6	**128**[a]
7	THF	rt	24 h	18-crown-6	CM
8	THF	-78 °C – rt	7 d	-	SM
9	Et_2O	-78 °C – rt	72 h	-	SM

[a]reaction quenched with D_2O.

The temperature was therefore raised to 0 °C and, although no product was observed, partial anion formation was detected (Entry 2, Table 3.5). After 2 h at 0 °C, deuterated species **128** was observed as the exclusive product, indicating complete anion formation (Entry 3, Table 3.5). Since anion formation was complete but the migration was not occurring, the reaction mixture was warmed to rt in the hopes of encouraging migration. After 25 h at rt, no silyl enol ether was detected although all of the SM had been converted to the anion (Entries 4 & 5, Table 3.5). The lack of migration product detected was rationalized as the result of a strong association between the anion and the potassium counterion. In an effort to break up this association, 18-crown-6 (2.2 equiv.) was dissolved in the reaction mixture. An aliquot quenched 1 h after the addition of the 18-

crown-6 additive showed that deuterated product **128** had persisted (Entry 6, Table 3.5). Unfortunately, the desired product was not observed and, after 24 h, the anion appeared consumed. ^{1}H NMR analysis of the crude material isolated indicated a complex mixture (Entry 7, Table 3.5). Since the additive appeared to promote decomposition rather than migration and complete anion formation was observed without it, it was thought that the reaction may occur without an additive, but very slowly. After 1 week however, only SM was observed by ^{1}H NMR analysis (Entry 8, Table 3.5). Since the migration had exhibited some dependence on the solvent employed, the reaction was repeated in Et_2O (Entry 9, Table 3.5). Disappointingly, no improvement was observed, and only unreacted SM was detected after 72 h by ^{1}H NMR analysis.

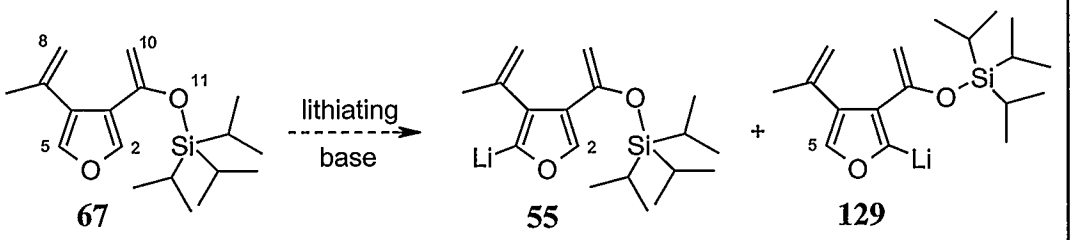
Despite the higher reactivity of KH in THF, with complete anion formation observed even at 0 °C, the failure of the silyl group to migrate resulted in no conversion to product under these conditions. Since several variations of solvent, base, temperature and time failed to offer any significant improvement over the 50% conversion to product obtained with KHMDS (1.5 equiv.) in THF at rt or with NaH (3.8 equiv.) in THF at reflux, optimization of this reaction was stopped. Despite difficulties developing conditions under which high conversion to product could be effected, a method for the preparation of silyl enol ether **67** in useful quantities had been successfully determined. Additionally, several sets of conditions had been found which gave the product of the desired intramolecular reaction exclusively, and unreacted starting material could be easily recovered. Thus, with a method for the preparation of silyl enol ether **67** successfully developed, work toward the completion of Fragment B could continue.

3.4 Selective Lithiation of Silyl Enol Ether 67

Following the successful preparation of TIPS enol ether **67**, the final step in the preparation of Fragment B required the selective lithiation of **67** in the C5 position to give **55** (Scheme 3.6). The selectivity of this lithiation was critical to the success of the synthesis since coupling of this subunit to Fragment A must occur at the C5 position to construct the correct precursor for the cyclization step (Scheme 1.12). There were two characteristics inherent in the system that were anticipated to allow for C5 selective lithiation. First, the steric bulk of the silyl group was predicted to physically block

lithiation at C2. Combining this steric hindrance with the use of a bulky base was anticipated to further enhance the regioselectivity of the reaction. Second, the reduced basicity of the enol ether oxygen atom resulting from the silyl substituent would reduce its capacity to act as a Lewis base[56] making it less likely to draw the lithium into the C2 position. Thus, the TIPS group was anticipated to both sterically and electronically favour the formation of C5-lithiated furan **55** over C2-lithiated **129**.

Scheme 3.6



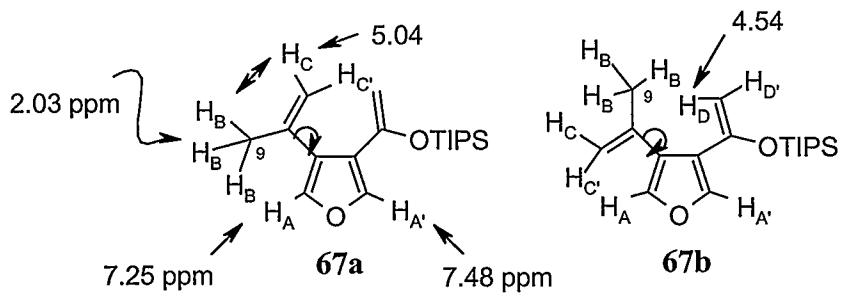
3.4.1 Spectral Assignment of Lithiation Substrate 67

Before selective lithiation experiments could begin, the ^{1}H NMR spectrum of SM **67** had to be unambiguously assigned. This posed a problem because the peaks for the furan bound-protons at C2 and C5 (H_A and $H_{A'}$) were separated by only 0.23 ppm (7.48 and 7.25 ppm) in the ^{1}H NMR spectrum and neither had a neighbouring group that could aid in the assignment of the peaks. Thus, the protons could not be assigned directly. Compounding this problem was the need to assign the signals at 5.19 and 5.04 ppm to the C8 propene hydrogens (H_C and $H_{C'}$) and the signals at 4.54 and 4.38 ppm to the C10 enol hydrogens (H_D and $H_{D'}$). A Nuclear Overhauser Effect Difference Spectrometry (NOE Diff.) experiment was undertaken in order to correlate the observed resonances at 7.48 and 7.25 ppm with their respective furyl protons.

Before the relative shifts of the protons could be assigned, the conformation of the molecule, especially as it related to the proximity of relevant groups, had to be considered (Figure 3.1). Although there was no obvious barrier to rotation about the single bond attaching the propene substituent to the furan ring, it was hoped that the C9 methyl group would spend a sufficient amount of time near the C5 hydrogen (H_A) that, if it was irradiated, there would be a noticeable enhancement in either the signal at 7.48 or at 7.25

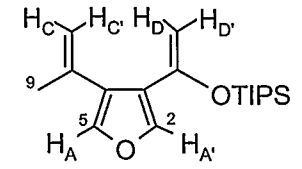
ppm. In this way, the pair of doublets could be differentiated and assigned. If the rotation was rapid at room temperature, the difference in the affected signals could be predicted to be quite small but might still be detectable. Analysis of the results of the semi-empirical AM1 conformer distribution (50 lowest energy conformers up to 1.00 kcal mol^{-1} greater in energy) revealed that the conformers (**67a**) with the C9 methyl group closer to H_A, were nearly equal in abundance to those (**67b**) with vinylic proton H_C closer H_A (Figure 3.1). This suggested that the protons (H_B) to be irradiated would spend at least half of their time near the proton of interest and that the NOE Diff. experiment should be tenable.

Figure 3.1 General Examples of Lowest E Conformers of Furan 67



The NOE Diff. experiment[57] was therefore performed by irradiating the methyl group at 2.03 ppm. Once the initial ^1H NMR spectrum was subtracted from that obtained through selective irradiation, negative peaks appeared at 7.25 ppm (0.82%), 5.04 ppm (1.32%) and 4.54 ppm (0.91%) with no effect observed at 7.48 ppm. These results suggested that the resonance at 7.25 ppm could be tentatively assigned to H_A, the proton at C5 (Figure 3.1).[58] This result was consistent with the results of the semi-empirical AM1 conformer distribution that suggested that the rotation of the propene substituent was facile. This relatively free rotation created the possibility of transfer from H_B to protons other than H_A because the methyl group was nearly equally likely to be close to the enol ether substituent as it was to be close to the proton of interest, H_A. The negative peaks at 5.04 and 4.54 ppm could therefore be assigned to H_C and H_D respectively based on their proximity[59] to the irradiated C9 methyl group (Table 3.6).

Table 3.6: ^{1}H NMR Peak Assignment for 67 as Determined by NOE Diff. Experiment



67

Proton	Assignment
H_A	7.25 ppm[a]
$H_{A'}$	7.48 ppm[b]
H_C	5.04 ppm[a]
$H_{C'}$	5.19 ppm[b]
H_D	4.54 ppm[a]
$H_{D'}$	4.38 ppm[b]

[a]assigned directly by observed enhancement; [b]assigned indirectly by process of elimination.

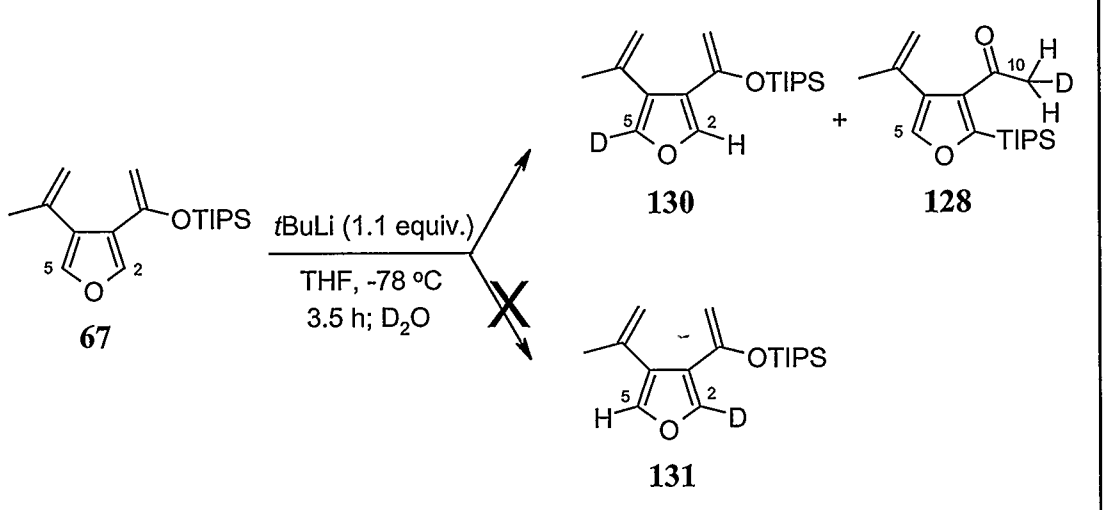
By elimination of the peaks identified by the NOE Diff. experiment, the peaks corresponding to $H_{A'}$, $H_{C'}$ and $H_{D'}$ could also be tentatively[60] assigned to the peaks appearing at 7.48, 5.19 and 4.38 ppm respectively (Table 3.6).

3.4.2 Completion of Fragment B (55)

Having assigned the ^{1}H NMR spectrum of the silyl enol ether, work could begin toward the development of selective lithiation conditions.

It was hoped that using a bulky and reactive base would result in high selectivity by creating steric interference at the C2 position of **67**. Silyl enol ether **67** was therefore treated with *t*BuLi (1.1 equiv.) in THF at –78 °C (Scheme 3.7).

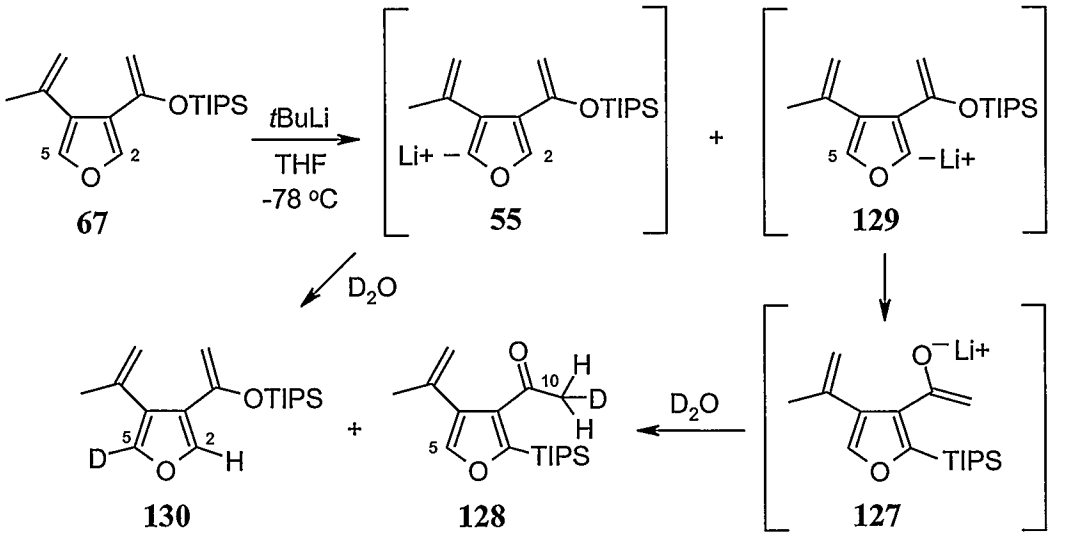
Scheme 3.7



At regular intervals, aliquots from the reaction mixture were quenched with D_2O and analyzed by ^1H NMR to monitor the progress and selectivity of the reaction. If lithiation occurred at the C2 position, reaction with D_2O would result in the formation of deuterated furyl species **131**. Formation of this compound was anticipated to be easily detectable by ^1H NMR, since the absorption at 7.48 ppm generated by H2 would disappear if deuteration were to occur at this site. Additionally, the doublet at 7.25 ppm corresponding to H5 of **67** would be transformed into a singlet in the deuterated species as H2 with which it had previously coupled would have been replaced. In turn, desired C5 deuterated species **130** was predicted to generate a spectrum in which the H2 absorption at 7.48 ppm had become a singlet and the H5 absorption at 7.25 ppm had disappeared. After 1 h, an aliquot was pulled, quenched with D_2O, extracted into ether and the combined organics concentrated under reduced pressure to yield a pale yellow oil. ^1H NMR analysis showed that lithiation was incomplete since the two peaks at 7.48 and 7.25 ppm remained of equal height and split into doublets. After 3 h, ^1H NMR analysis of another deuterated aliquot showed the formation of 2 products. The first component was identified as desired product **130**. The ^1H NMR spectrum exhibited the anticipated pattern of peaks: a singlet at 7.50 ppm corresponding to an uncoupled H2 and disappearance of the doublet at 7.25 ppm, indicative of the successful substitution of H5. The balance of the spectrum remained as expected, virtually unchanged from that of SM **67**. Surprisingly, the second component was not identified as C2-deuterated isomer **131**, as no singlet corresponding to H5 was observed at 7.25 ppm. This result was unexpected because, although there were several factors that had suggested that the lithiation would likely favour the formation of **130** over **131**, it was not anticipated to do so exclusively. The second component of the product mixture generated a ^1H NMR spectrum much like that obtained for migration precursor **68** (Figure 3.8). The only difference between the spectra was that the singlet at 2.41 ppm, indicative of the C10 methyl protons of methyl ketone **68** was replaced by a triplet with peaks of equal height. This spectrum therefore appeared to correspond to furan **128**, an analogue of **68**, with one methyl proton substituted by deuterium. The appearance of **128** and the failure to isolate C2-deuterated species **131** could be explained by a [1,4] O $\rightarrow$ C silyl migration (Scheme 3.8). Isolation of **128** suggested that lithiation occurred at both the C5 and C2 positions to generate **55**

and **129** respectively, however, when lithiation occured at the C2 position, it was followed by the intramolecular migration of the silyl group to generate enolate **127**. When quenched with D_2O, the methyl ketone was regenerated with a deuterium atom incorporated into the C10 methyl group.

Scheme 3.8



With the products identified, the selectivity of the reaction could be determined. Under these conditions a 1 : 1 ratio of **130** to **128** was consistently observed indicating that contrary to predictions, the lithiation was unselective. Although conditions to favour the C5 lithiated species could potentially be found through optimization, testing the validity of subsequent steps, including the cyclization was deemed a higher priority at this stage of the synthesis.

Having determined a reliable method for the preparation of the C5 deuterated species **130** in 8 steps from 3-furanmethanol (**44**), the preparation of Fragment B was complete. Although the final steps were limited to yields of 50%, the material recovered from each reaction, in both cases methyl ketone **68**, could be easily returned to the synthetic route. In this way, despite moderate yields in the late stages of this route, Fragment B could be prepared with minimal loss throughout.

3.5 Synthesis and Application of Model Systems

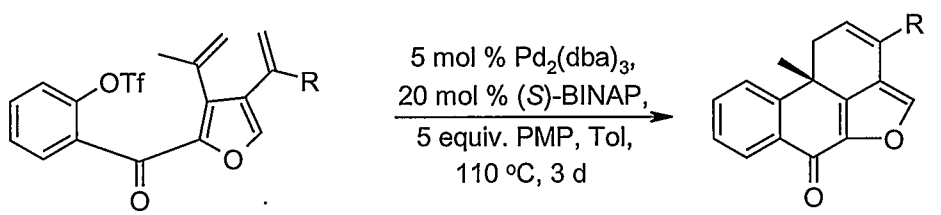
With Fragment B in hand, a relatively simple model system, **132**, was designed (Scheme 3.9). The model was intended to test the validity of the coupling, selective deprotection and Pd-catalyzed cyclization procedures prior to their execution on the fully elaborated system.

Scheme 3.9

54 **132**

The test system had to contain all of the relevant functionalities of the parent system, **54**, including the TIPS enol ether masking the required carbonyl group. The bulky TIPS silyl group was selected in accordance with the previously reported results[24] that had suggested that the steric bulk of a remote substituent in this position would enhance the selectivity of the Pd-catalyzed polyene cyclization (Figure 3.10).

Scheme 3.10



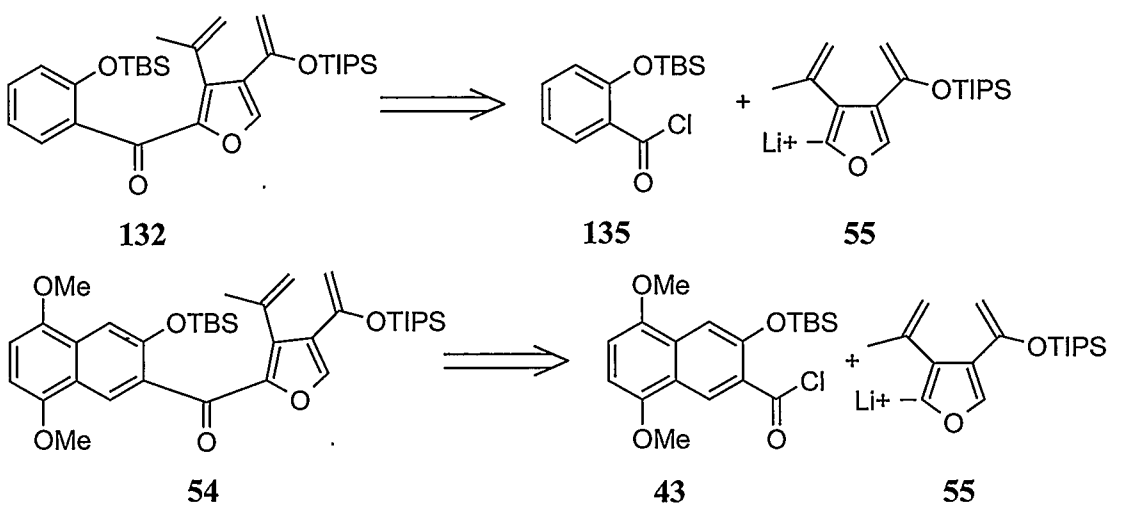
78a R = H
78b R = Me
133 R = OTIPS

79c R = H 68-74% *ee*
79d R = Me 90% *ee*
134 R = OTIPS

In order to fully assess the impact of the silyl group on the selectivity of this key step and retain the olefins required for cyclization, disubstituted furan **55** (Fragment B) was

required in its entirety and could not be replaced by a simplified model (Scheme 3.11). Naphthalene derivative **43**, however, could be greatly reduced in complexity and modeled using a much simpler compound, salicylic acid derivative **135**.

Scheme 3.11

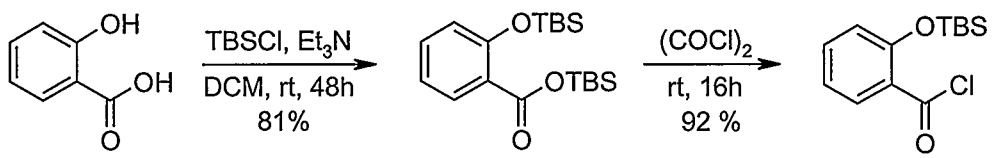


132 **135** **55**

54 **43** **55**

Acid chloride **135** was prepared in two steps from commercially available salicylic acid (**136**) using known procedures (Scheme 3.12).[23,61]

Scheme 3.12

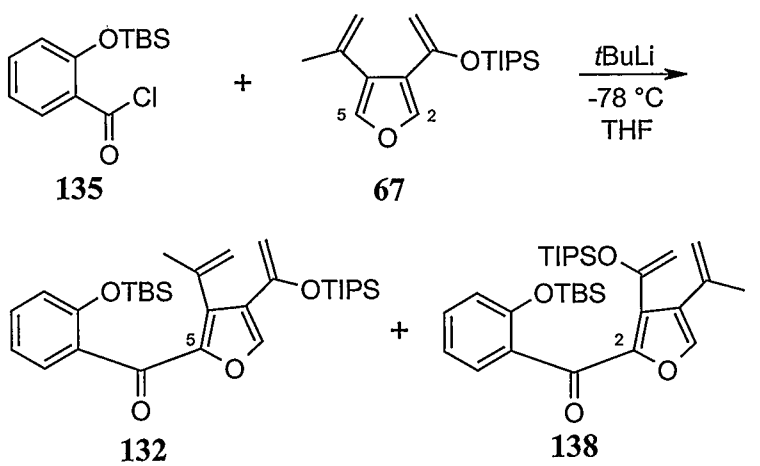


136 **137** **135**

3.5.1 Coupling of the Model System

With furan derivative **67** and a truncated version of Fragment A (**135**) in hand, the construction of the model system was undertaken. The anion of silyl enol ether **67** was generated by treating the furyl subunit with *t*BuLi (1.1 equiv.) in THF for 1 h at –78 °C. The anion was then transferred slowly *via* canula into a stirring solution of acid chloride **135** (1.1 equiv.) likewise dissolved in THF at –78 °C. The reaction mixture was allowed to warm slowly to room temperature (12 h) at which time TLC analysis showed the formation of two products. Pure samples of the two products were obtained by flash column chromatography.[62] It was initially suspected that the pair of compounds were most likely the desired compound **132**, where coupling had occurred at C5 of furan **67**, and isomer **138**, a product in which the coupling had instead occurred at the C2 position (Scheme 3.13).

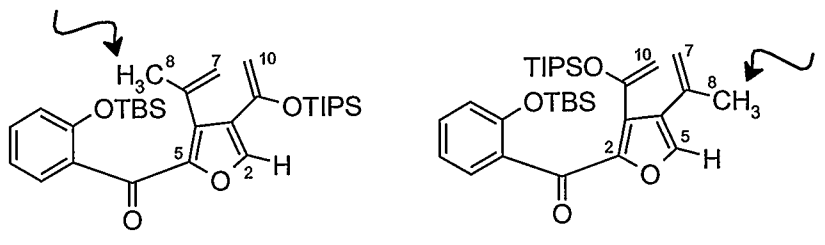
Scheme 3.13



Unfortunately, following separation, conclusive identification of each product as either **132** or **138** was not as straightforward as had been anticipated. When the first component isolated was analyzed by TLC (15 : 1 hexane : EtOAc), the bright yellow oil was found to have an R_f of 0.86; this less polar component will be referred to as compound II. ^1H NMR analysis of compound II gave a spectrum that was strikingly similar to that afforded by the second, more polar component, compound I. Compound I was another

yellow oil with an R_f value of 0.63. Although analogous peaks appeared in the same regions with the same splitting patterns, the chemical shifts were not identical. These differences were most obvious in the region containing the four vinyl protons corresponding to the C7 and C10 methylene units (Figure 3.2). The spectrum for compound I exhibited broadened singlets at 4.35, 4.74, 4.95 and 5.14 ppm whereas compound II exhibited analogous singlets at 4.96, 5.21, 5.38 and 5.56 ppm. When compounds I and II were further analyzed by GC-MS, they generated dissimilar fragmentation patterns and had different retention times, confirming the formation of distinct compounds. Despite the dissimilarity in fragmentation patterns, both compounds exhibited molecular ion peaks of 540 amu. This atomic mass corresponded to the molecular formula of $C_{31}H_{48}O_4Si_2$ expected for either **132** or **138**. Additional analyses were therefore required to conclusively identify compounds I and II, as either data set could easily correspond to **132** or **138**. Since **132** and **138** contained identical numbers and types of carbon atoms, ^{13}C NMR spectra and DEPT experiments were initially predicted to yield spectra too similar for conclusive assignment and, thus, an alternate method to distinguish the pair was thought necessary. For this purpose, an NOE experiment was undertaken. This experiment should have been useful in distinguishing the pair by utilizing the proximity of H5 to the vinylic methyl group in **138** (Figure 3.2).

Figure 3.2 C8 Irradiated Methyl Groups of 132 and 138

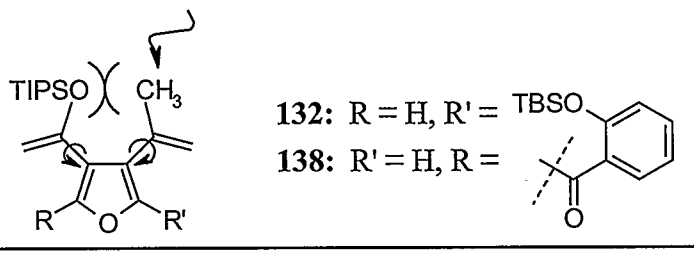


132 **138**

Irradiation of the methyl protons at C8 of **138** was expected to lead to an observable NOE effect on the nearby H5 while irradiation of the analogous methyl protons in **132** should have resulted in no observable enhancement on the distant H2. The NOE experiment was thus performed by irradiating the isolated singlet at approximately 2.0 ppm in each

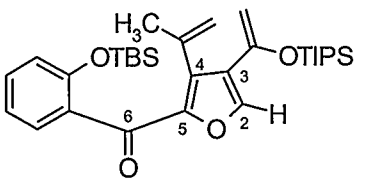
spectrum. Accordingly, an enhancement was anticipated in either the singlet at 7.65 ppm, corresponding to the furyl proton of compound I, or the singlet at 7.57 ppm, corresponding to the furyl proton of compound II. In this way, compound I or II could be identified as **138**, which would allow for the tentative identification of the other compound as **132** by process of elimination. Surprisingly, neither compound I nor II exhibited an NOE effect in the desired region. Instead, the only enhancement observed was at signals corresponding to the TIPS groups in each spectrum. Enhancement of these signals was rationalized by considering that free rotation of the substituents at C3 and C4 of the furan moiety in each system would generate several rotamers of both **132** and **138** in which the C8 methyl and TIPS groups were brought into close proximity (Figure 3.3).

Figure 3.3 Rotamers of Compounds 132 and 138

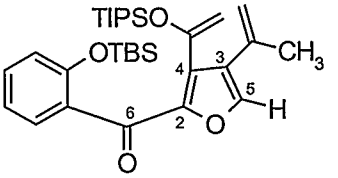


Since a negative NOE experiment could not be relied upon to conclusively eliminate **138** as a component of the product mixture, further spectral analyses were undertaken. Combined ^{13}C NMR analysis and DEPT experiments for the two compounds were performed with the expectation that they would generate very similar spectra. Surprisingly, this was not the case, and the spectra were instead quite dissimilar. The ^{13}C NMR spectrum corresponding to compound I ($R_f = 0.63$) appeared much as anticipated with a peak at 185.5 ppm indicative of a ketone bracketed by two α-aromatic substituents.[51] Peaks at 92.5 and 117.7 ppm, identified as methylene carbons by DEPT experiments, were consistent with the pair of vinyl methylene carbons present in the C3 and C4 substituents of the furyl system of both compounds I and II (Figure 3.4).

Figure 3.4 C2 and C5 Coupled Products 132 and 138



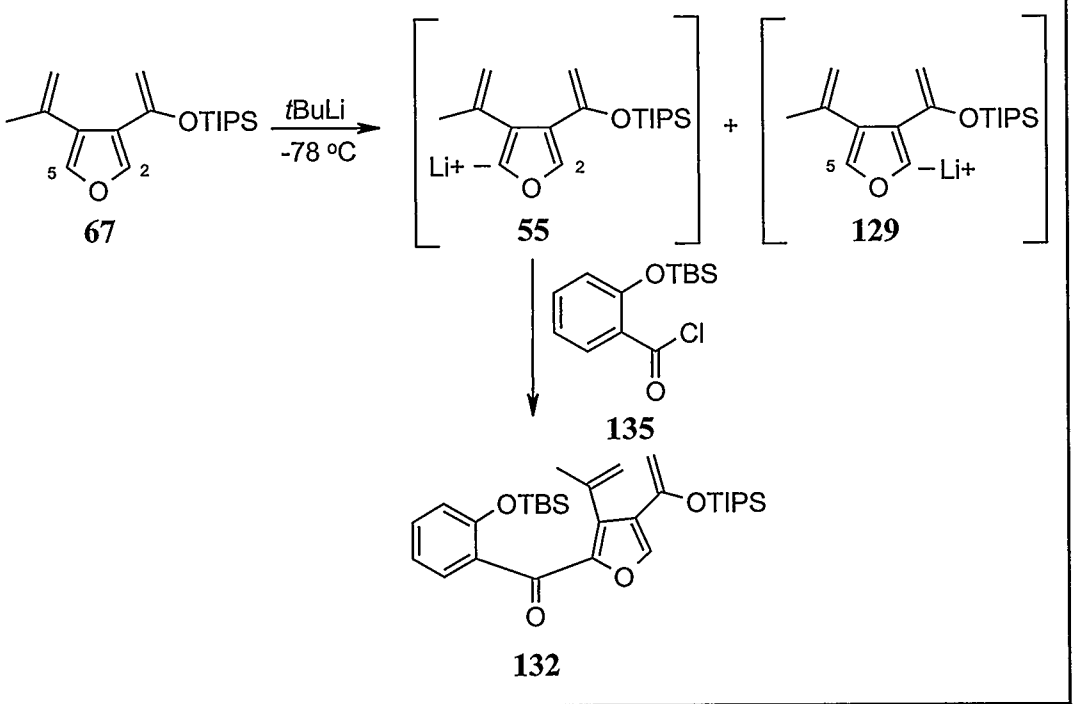
132



138

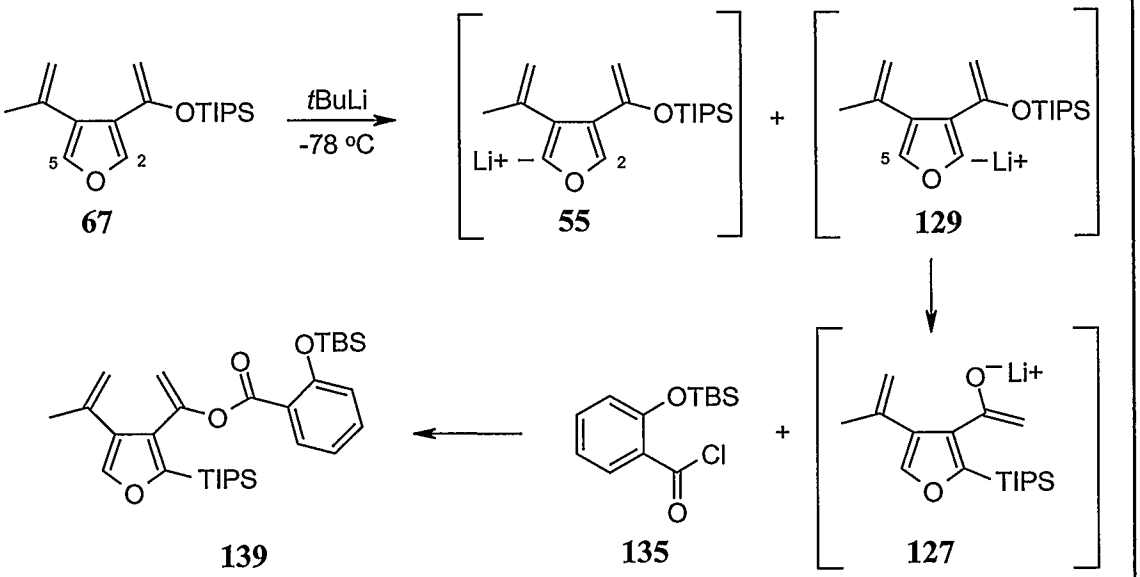
The presence of these diagnostic peaks, in addition to the appearance of the correct number and type of carbon resonances, suggested that compound I ($R_f = 0.63$) likely had connectivity consistent with either **132** or **138**. The ^{13}C NMR spectrum corresponding to compound II ($R_f = 0.82$), however, appeared surprisingly different. Although two methylene peaks appeared at 105.9 and 113.7 ppm, and DEPT experiments were consistent with the required number and type of carbon atoms for a structure such as **132** or **138**, a lowfield peak corresponding to a ketone was not observed. Instead, the lowest field peak appeared at 162.7 ppm, a resonance too far upfield to be consistent with C6 of either **132** or **138**. Resonance in this region is usually associated with the carbonyl groups of carboxylic acids and their derivatives.[51] Re-examination of the lithiation process suggested the possibility of formation of a third product in the addition of furan **55** to acid chloride **135**. Since a 1 : 1 product ratio was consistently observed, it can be presumed that anion formation was equally likely to occur at C2 as at C5 when **135** was treated with *t*BuLi in THF at –78 °C (Scheme 3.8). When lithiation occurred at the desired C5 position (**55**), reaction with salicylic acid chloride **135** generated the desired product **132** (Scheme 3.14).

Scheme 3.14



On the other hand, when lithiation occurred at the C2 position of **67**, anion formation (**129**) could be followed by migration of the TIPS group from the silyl enol ether back to the C2 position of the furan ring to give anion **127** (Scheme 3.15).

Scheme 3.15



When the enolate anion thus generated was reacted with acid chloride **135**, coupling would occur at the enolate to give enol benzoate **139**. For **139** to be observed as a component of the product mixture, O → C migration of the TIPS group must have occurred rapidly once the C2 anion was formed. This facile migration was consistent with earlier attempts to selectively lithiate disubstituted furyl system **67** in the C5 position (Scheme 3.8).

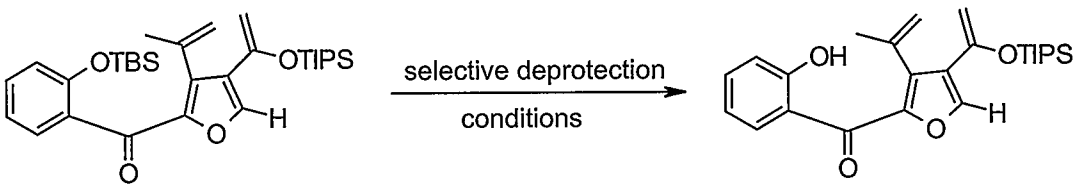
The peak at 162.7 ppm observed in the ^{13}C NMR spectrum was therefore assigned to the carbonyl carbon of enol benzoate **139**, a compound with a molecular formula of $C_{31}H_{48}O_4Si_2$ and a molecular mass of 540 amu, values identical to those of isomers **132** and **138**. IR analysis of compound I (**132**) confirmed the presence of a conjugated ketone exhibiting a strong C=O stretching absorption at 1656 cm^{-1}, a reduced frequency consistent with a carbonyl bracketed by two delocalizing groups. In contrast, IR analysis of compound II (**139**) showed a strong band at 1744 cm^{-1}, a substantially higher frequency than that expected for a ketone[51] and consistent with the carbonyl of a benzyl ester. Together with the balance of the spectral data, compound II (R_f = 0.82), was thus determined to be enol benzoate **139**.

Having determined a method by which the desired coupled system, **132**, could be prepared and isolated from the enol benzoate by-product **139**, the remaining steps in the synthesis of halenaquinone could be attempted using the model system.

3.5.2 Selective Deprotection of a Phenolic TBS Ether in the Presence of a TIPS Enol Ether

With precursor **132** in hand, work toward cyclization of the model system continued. The next transformation to be studied was selective cleavage of the phenolic TBS group in the presence of the TIPS enol ether to give **140** (Table 3.7). In general, it is known that basic conditions favour the cleavage of phenolic TBS groups while acidic conditions favour the cleavage of TIPS enol ethers.[22] Although no precedent for an analogous selective deprotection could be found, a search of the literature was undertaken to establish a variety of conditions under which a TBS ether could be cleaved. These conditions were then compared with literature conditions under which TIPS ethers were unaffected. Several potentially useful sets of deprotection conditions were thus compiled (Table 3.7).

Table 3.7: Summary of Potential Conditions for Selective Deprotection of Phenolic TBS Ether in the Presence of a TIPS Ether.

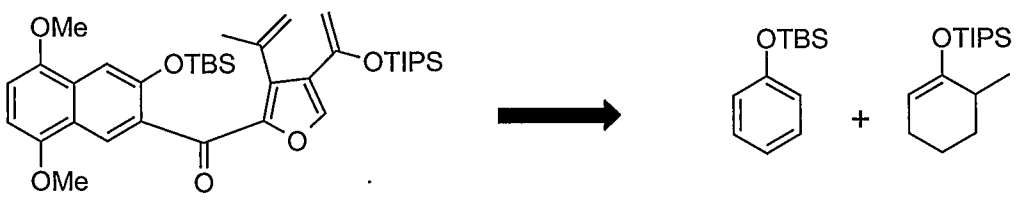


132 **140**

Entry	Conditions	TBS ether	TIPS ether
1	KF/DMF	Phenolic TBS[63]	2° TIPS[63]
2	K_2CO_3, CH_3CN, 55 °C	Phenolic TBS[64]	TIPS enol ether[65]
3	$H_2SiF_{6(cat)}$, CH_3CN a) 10% aq. CH_3CN b) 48% aq. HF	a) Benzyl TBS[66] b) 2° TBS[67]	a) Benzyl TIPS[66] b) 1° TIPS[67]
4	HOAc/THF/H_2O	2° TBS[68]	2° TIPS[68]
5	5% NaOH/95% MeOH	Phenolic TBS[69]	TIPS enol ether[70]

A simpler model system was conceived in order to test and optimize the selective deprotection conditions before applying them to the elaborated system. The relevant functionalities of coupled product **54** were simplified to a 1 : 1 mixture of TBS phenol ether **141** and TIPS enol ether **142** (Scheme 3.16).

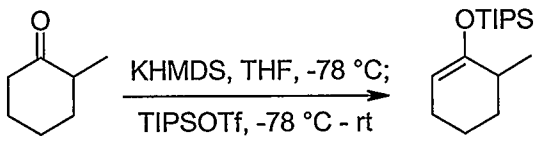
Scheme 3.16



54 **141** **142**

Treatment of 2-methylcyclohexanone (**143**) with KHMDS (2 equiv.) in THF at –78 °C generated the kinetic enolate which was subsequently trapped with TIPSOTf (1.1 equiv.) to generate TIPS enol ether **142** in 68% unoptimized yield (Scheme 3.18).[71]

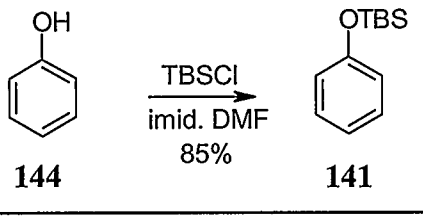
Scheme 3.17



143 **142**

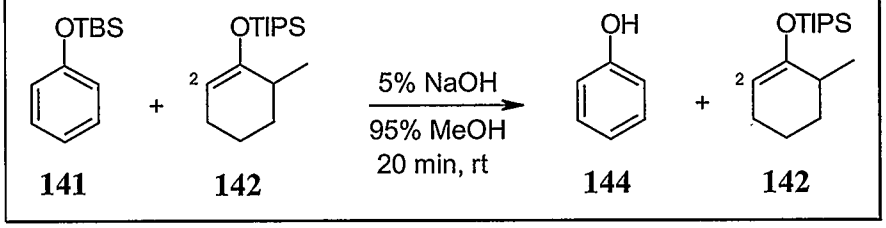
Meanwhile, treatment of phenol (**144**) with TBSCl (1.2 equiv.) and imidazole (2.5 equiv.) in DMF gave TBS phenol ether **141** in 85% unoptimized yield (Scheme 3.18).

Scheme 3.18



The list of deprotection conditions was then re-examined in order to determine which conditions were the simplest and potentially most applicable to elaborated system **54**. Since phenolic TBS ethers had been cleaved[69] by treatment with 5% NaOH in MeOH at rt, and a TIPS enol ether had been reported[70] to be stable to similar conditions, these conditions were applied first. Gratifyingly, treatment of a 1 : 1 molar mixture of **141** and **142** with 5% NaOH in MeOH at rt gave complete cleavage of the TBS ether in less than 20 min leaving the TIPS enol ether **142** intact (Scheme 3.19).

Scheme 3.19

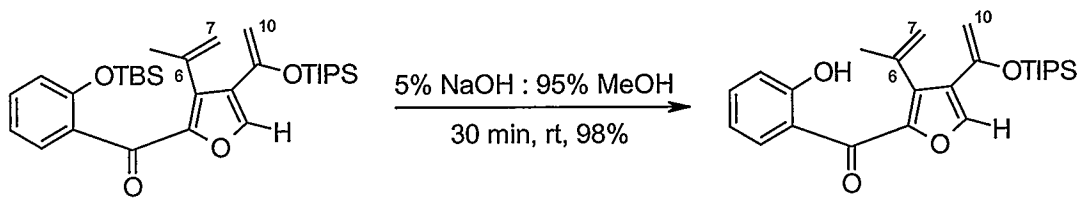


The progress and the selectivity of the cleavage were easily observed by TLC analysis of the crude reaction mixture. Spotting **141** and **142** alongside desilated compounds **143** (2-methylcyclohexanone) and **144** (phenol) gave 4 readily distinguishable spots when run in a 15 : 1 mixture of hexanes to EtOAc and stained with *p*-anisaldehyde. Before the NaOH was added, two spots corresponding to **141** and **142**, appeared at $R_f = 0.85$ and 0.96 respectively. After 10 min, a third spot appeared at $R_f = 0.19$ which matched the spot generated by phenol, the product of TBS deprotection. After 20 min had elapsed, the spot at $R_f = 0.85$ had disappeared, indicating the complete consumption of TBS phenol **141**. Since no spot had appeared corresponding to **143**, and the spot

corresponding to **142** remained unchanged, the reaction appeared to be selective for the cleavage of the phenolic TBS group. The reaction mixture was worked-up and the organic layer reduced and analyzed by ^{1}H NMR. This yielded a spectrum identical to that of TIPS enol ether **142**, the diagnostic peak at 4.78 ppm, indicative of the intact C2 vinyl proton (Scheme 3.19), had been retained, offering further evidence that **142** had been unaffected. The peaks corresponding to **144** were, however, conspicuously absent. This was not surprising as TBS deprotection generated phenol (**144**) which would move to the aqueous layer upon work-up. Careful acidification of the aqueous layer yielded a solid which, when analyzed by ^{1}H NMR, gave a spectrum identical to that of phenol (**144**). The successful isolation of TIPS enol ether **142** and phenol, the product of selective TBS deprotection indicated that these relatively simple conditions should be compatible with the fully elaborated system.

With successful selective desilation of the simple model system, these conditions could be confidently applied to the more complex model system, **132**. Treatment of **132** with a solution of 5% NaOH in MeOH at rt showed complete consumption of starting material in only 30 minutes according to TLC analysis. The crude reaction mixture was then extracted with Et_2O, and the combined organics were dried over $MgSO_4$ and concentrated to give desired product **140** in 98% yield (Scheme 3.20).

Scheme 3.20



132 **140**

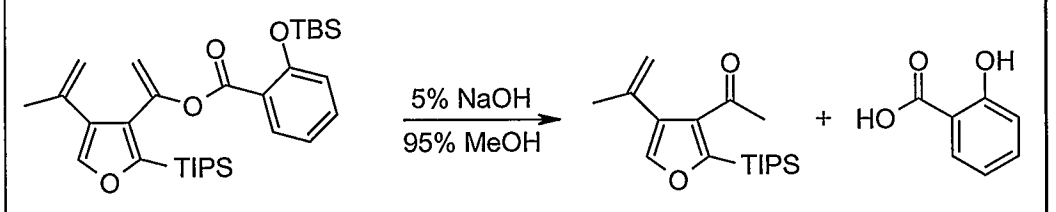
^{1}H NMR analysis this yellow oil showed the formation of a new lowfield singlet at 12.2 ppm, corresponding to a phenolic proton and indicating successful cleavage of the TBS group of **132** to yield **140**. The appearance of the phenolic proton in the spectrum was also accompanied by the disappearance of the singlets at 0.14 and 0.80 ppm

corresponding to the methyl substituents of the TBS group, further confirming the desilation. In order for the deprotection be have been selective, the TIPS enol ether must have remained intact. This was evidenced by the continued presence of a multiplet between 1.09-1.32 ppm corresponding to the three isopropyl substituents. The presence of four signals in the vinyl region at 4.42, 4.86, 5.05 and 5.30 ppm, also indicated preservation of the two vinyl methylene groups at C7 and C10 thereby indicating the retention of the silyl enol ether function and thus the TIPS group. Further analysis of compound **140** by GC-MS generated a spectrum with the expected molecular ion peak of 426 amu consistent with a molecular formula of $C_{25}H_{34}O_4Si$, and analysis by IR showed a broad absorption at 3418 cm^{-1} characteristic of a hydroxyl group. These analyses offered further evidence that the selective deprotection was successful and, with phenol **140** in hand, the investigation of the model system could proceed.

3.5.3 Confirmation of Connectivity and Recovery of Material From Enol Benzoate 139

With development a successful method for the construction of model system **132** and effective conditions for the subsequent selective deprotection step, attention was temporarily returned to enol benzoate **139**. Since **139** was identified as the product of the addition of the oxygen of enolate anion **127** to acid chloride **135**, the two fragments were connected *via* an ester linkage. Thus, treatment with 5% NaOH in MeOH, the previously determined TBS phenol deprotection conditions, was expected to saponify the ester and sever the connection between the two subunits. In this way, successful isolation of methyl ketone **68** and salicylic acid **136** would offer additional confirmation of the connectivity assigned by spectral analysis (Scheme 3.21).

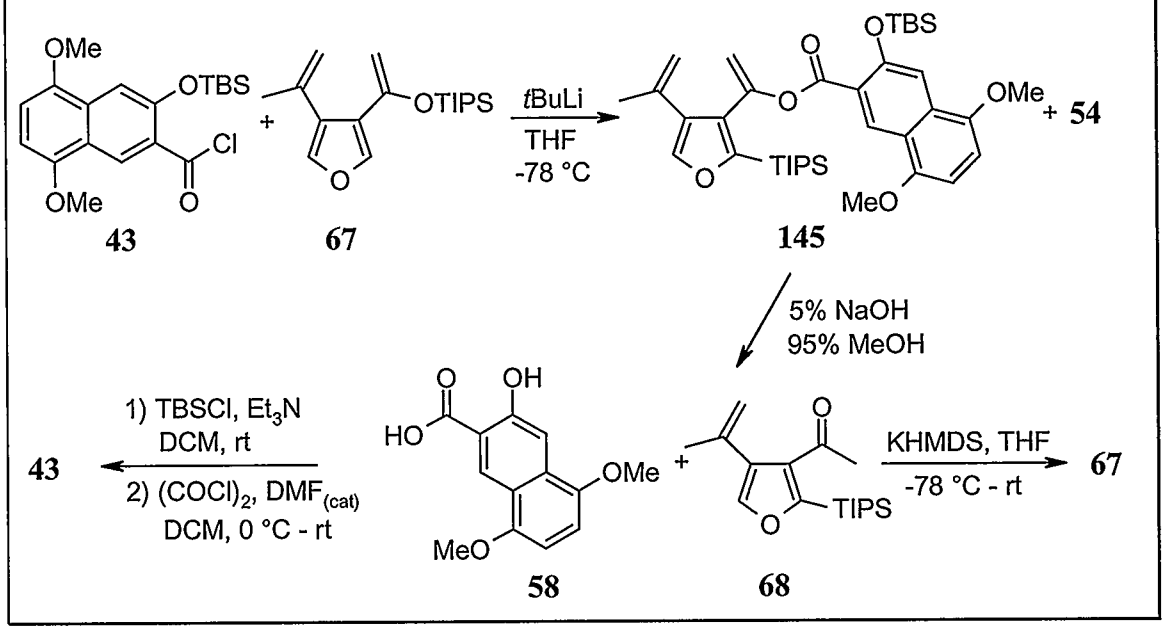
Scheme 3.21



139 **68** **136**

Treatment of coupled product **139** with an excess of the NaOH solution resulted in complete consumption of starting material after stirring for 20 min at rt. The resultant mixture was extracted with Et_2O, and the combined organics were dried over $MgSO_4$ and reduced to a colourless oil which, when analyzed by ^1H NMR, was identical to methyl ketone **68**. The mass spectrum obtained for the oil was also identical to that of **68**. The spectrum exhibited no molecular ion peak and had a base peak of 263 amu which was consistent with the loss of an iPr group (M^+-C_3H_7) from methyl ketone **68**. The combined aqueous layers were acidified with 10% HCl, extracted with Et_2O, dried over $MgSO_4$ and reduced to a white crystalline solid which, when analyzed by ^1H NMR, gave spectra consistent with salicylic acid (**136**). The successful isolation of the expected products of saponification, methyl ketone **68** and acid **136**, confirmed the identity of enol benzoate **139**. The success of this reaction also offered an intriguing possibility when applied to the fully elaborated system. Since lithiation was found to be unselective, the formation of equal amounts of coupled products **145** and **54** were anticipated (Scheme 3.22). Therefore, saponification of enol benzoate **145** offered the possibility for recovery, rather than loss, of valuable material synthesized over several steps.

Scheme 3.22



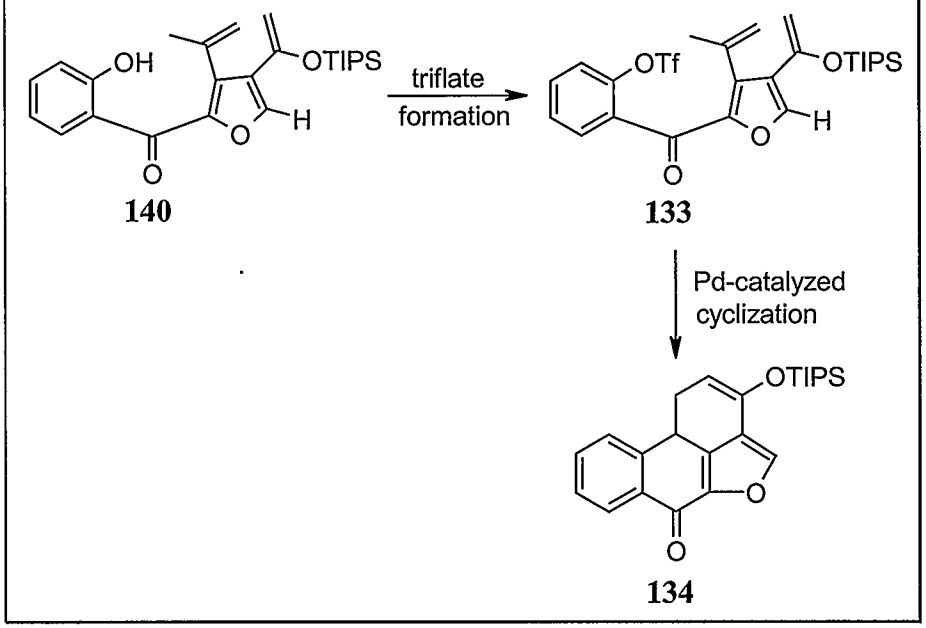
Saponification of **145** was thus predicted to yield two products, naphthol derivative **58** and furan derivative **68**. Naphthol **58** could be easily converted back into starting material for the coupling reaction by protection as the disilylsalicylate followed by formation of acid chloride **43** as described previously. Additionally, furyl methyl ketone **68** could be converted into TIPS enol ether **67** by treatment of **68** with 1.5 equiv. KHMDS in THF as previously described.

Successful saponification of enol benzoate **139** had thus, both confirmed the initial identification of this compound and offered a potentially useful strategy for the recovery of material prepared over several steps.

3.5.4 Formation of the Model Cyclization Precursor, Triflate 133

With phenol **140** in hand, preparation of triflate **133** could be attempted. Once isolated, this triflate could be cyclized to generate tetracycle **134** (Scheme 3.23).

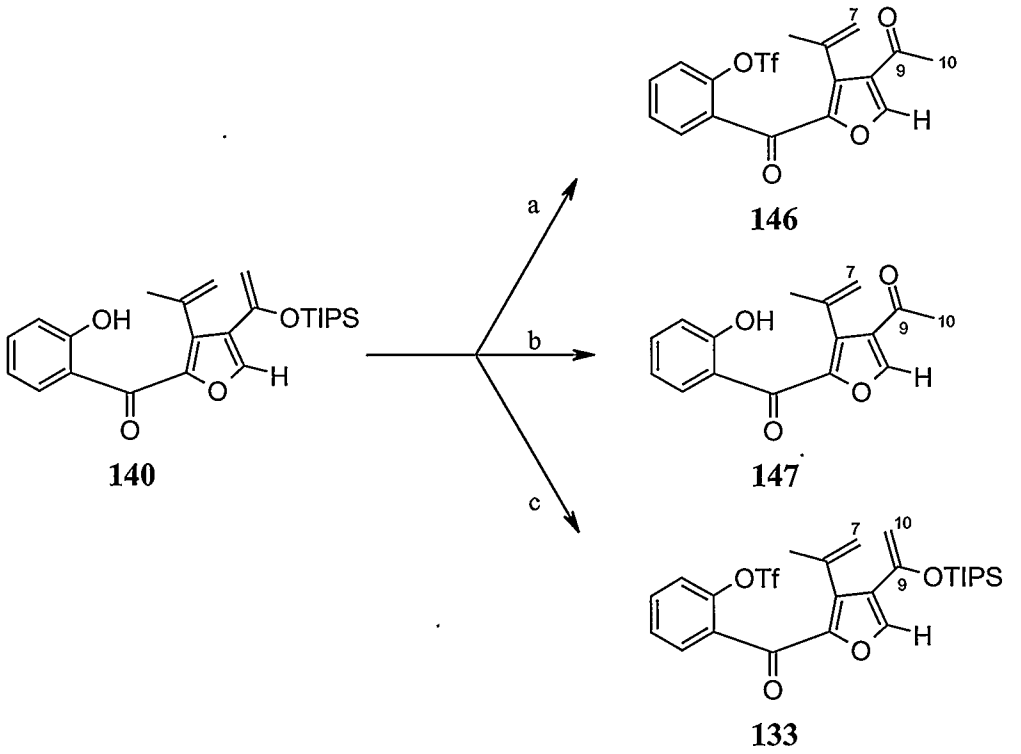
Scheme 3.23



Initially, attempts to form the triflate focused on the use of triflic anhydride with Et_3N as the base. Treatment of phenol **140** under these conditions at -45 °C in DCM gave complete consumption of the starting material within 25 minutes when monitored by

TLC. The disappearance of the starting material coincided with the formation of a new, more polar compound with an R_f of 0.38 (15 : 1 hexane : EtOAc). The reaction mixture was allowed to warm slowly to rt, diluted with DCM and quenched with ice cold water. The organic layer was washed with water and brine, and TLC analysis still showed a spot ($R_f = 0.38$) identical to that generated by the crude reaction mixture. Concentration under reduced pressure yielded a viscous red/brown material which, when analyzed by ^1H NMR, generated a spectrum showing only two peaks in the vinyl region in contrast to the four expected for the two methylene units of triflate **133**. This absence of resonances corresponding to one $=CH_2$ unit was easily explained with reference to the highfield region of the ^1H NMR spectrum which also showed the absence of a multiplet at 1.09-1.32 ppm. Since this multiplet corresponded to the three isopropyl groups on the TIPS substituent, it was concluded that desilation had occurred, resulting in tautomerization of the enol ether and regeneration of the methyl ketone. This conclusion was further supported by the formation of a new singlet at 2.49 ppm integrating to 3 H, which corresponded to the $-CH_3$ group of the methyl ketone. Surprisingly, TLC analysis of both the ^1H NMR sample (dissolved in $CDCl_3$) and the balance of the crude product no longer gave a spot at $R_f = 0.38$. Instead, a new, more polar compound appeared stuck to the baseline. Further analysis by GC-MS gave a molecular ion of 402 amu, a mass consistent with the molecular formula of $C_{17}H_{13}O_6SF_3$. Thus, successful formation of the aryl triflate with concurrent loss of the TIPS group had given **146** (Scheme 3.24). The generation of compound **146** was further evidenced by the presence of a peak at 269 amu corresponding to loss of the SO_2CF_3 group. The loss of the silyl group was confirmed by the presence of the base peak at 43 amu which corresponded to $CH_3C^+=O$, a cation consistent with the fragmentation of a methyl ketone function.[51] Thus, although the triflate was successfully added to the compound, it was accompanied by desilation upon concentration of the crude material to give methyl ketone **146**.

Scheme 3.24



Conditions: a) Tf_2O, E_3N, DCM, -45 °C, 25 min (>99%); b) Tf_2O, DMAP, DCM, -45 °C, 15 min (88%); c) KH, THF, 0 °C, then add $PhNTf_2$, 70 °C, 1 h (97%).

It was proposed that the observed desilation was likely caused by nucleophilic attack upon the silicon atom by excess Et_3N remaining in the crude reaction mixture after the solvent had been removed. If this was indeed the case, replacement of the base with a more sterically hindered, less nucleophilic reagent should eliminate desilation of the product upon work-up. Treatment of phenol **140** under reaction conditions identical to those in the previous experiment but replacing Et_3N with DMAP was expected to result in the formation of desired cyclization precursor **133**. TLC analysis (15 : 1 hex : EtOAc) of the reaction mixture showed complete consumption of the starting material after only 15 minutes with simultaneous formation of a new spot with an R_f value of 0.08. The reaction mixture was worked up as before and reduced to a yellow oil. ^1H NMR analysis of the crude product again showed only two peaks in the vinyl region. A singlet at 2.51 ppm integrating to 3 H (C10, Scheme 3.24) together with the absence of a multiplet at 1.09-1.32 ppm integrating to 21 H confirmed the loss of the silyl group. In addition, a

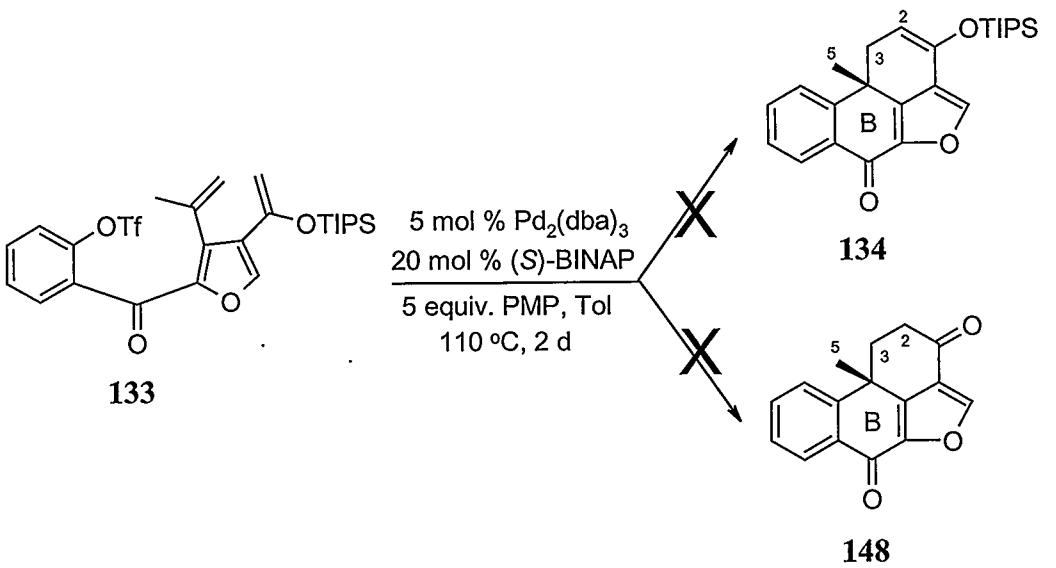
singlet appeared at 11.91 ppm which corresponded to the unprotected phenol and thus confirmed failure to prepare the triflate. The compound isolated was unfortunately desilated starting material **147** (Scheme 3.24).

Since the use of triflic anhydride in the presence of an amine, either Et_3N or DMAP, appeared to be incompatible with the sensitive TIPS enol ether functionality, a third method for triflate formation was considered. This time, deprotonation was effected using a suspension of KH in THF at 0 °C, avoiding the possibility of nucleophilic attack on the silicon atom. After warming to rt, N-phenyl-bis(trifluoromethanesulfonimide) (1.1 equiv.) was added and the reaction mixture heated to reflux. After 1 h TLC analysis (15 : 1 hex : EtOAc) showed complete consumption of the starting material with concurrent formation of a spot with an R_f value of 0.38. The crude reaction was quenched with water, extracted with Et_2O and reduced to give a faintly brown oil. ^1H NMR analysis of the product now indicated the successful formation of triflate **133**. Four peaks in the vinyl region at 4.41, 4.82, 5.06 and 5.27 ppm corresponded to the requisite $=CH_2$ units (C7 and C10, Scheme 3.24), and a 21 H multiplet between 1.07 and 1.26 ppm indicated retention of the TIPS group (Scheme 3.24). Disappearance of the low field peak corresponding to the phenol also pointed to the successful addition of the triflate group. GC-MS analysis further confirmed **133** as the isolated product with a molecular ion peak of 558 amu consistent with a molecular formula of $C_{25}H_{33}O_4SiSF_3$. Thus, effective conditions for the preparation of triflate **133** in the presence of a sensitive TIPS group had been developed and were ready for application to the fully elaborated system.

3.5.5 Attempted Asymmetric Pd-Catalyzed Cyclization of Triflate 133

With triflate **133** in hand, the asymmetric Pd catalyzed cyclization could be attempted. It was anticipated that the same conditions used by Steve Lau[23,24] (Scheme 3.10) to prepare cyclized products **79** from **78** would effect an analogous transformation when applied to triflate **133**. Sealing cyclization precursor **133** in a vial with $Pd_2(dba)_3$ (5 mol %), (*S*)-BINAP (20 mol %), and PMP (5 equiv.) in toluene and heating the reaction mixture to 110 °C for 2 d, however, failed to yield tetracycle **134** (Scheme 3.25).

Scheme 3.25



^{1}H NMR analysis of the crude product indicated that all of the SM had been consumed, and several new peaks appeared in the aromatic region and between 1.00 and 2.50 ppm. Unfortunately, a peak indicative of the C2 vinyl proton of **134** was conspicuously absent. Since the silyl enol ether had proven to be somewhat labile, ketone **148** was identified as a potential product that, if formed, would eliminate the need for a discrete desilation step and further shorten the synthesis. Disappointingly, ketone **148** could also be eliminated as a component of the mixture since the pair of triplets indicative of the C2 and C3 protons were also absent from the spectrum. Additionally, no singlet was observed which would correspond to the protons of angular methyl group C5 indicating that closure of the B ring had failed to occur prior to the decomposition of the SM. Initially, the integrity of the Pd catalyst was suspected as a possible factor in the failure of the cyclization. Unfortunately, repeating the reaction with fresh $Pd_2(dba)_3$ failed to effect the cyclization, and the crude material isolated generated spectra that, when analyzed by NMR, matched those obtained following previous cyclization attempts.

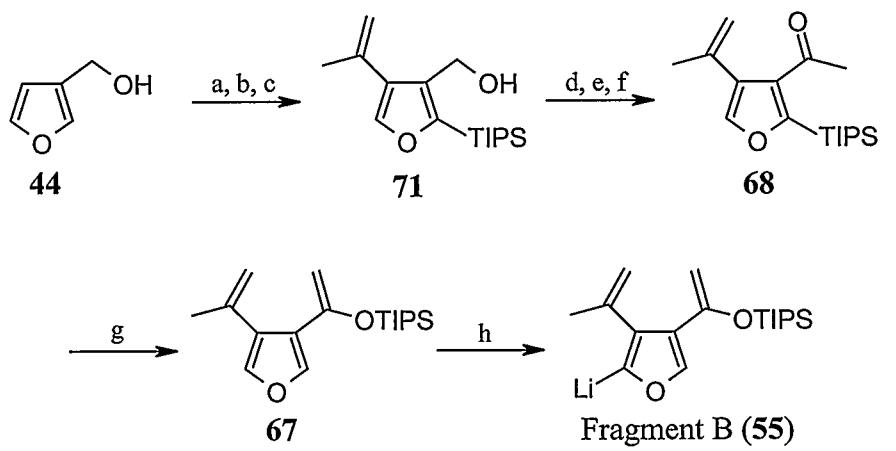
The cyclization step had thus proven to be problematic. Since no obvious flaw in the cyclization process could be detected and since the behaviour of this system could not be paralleled to the results observed when analogous systems had been subjected to similar conditions,[16,23,24] investigations relating to model system **132** ceased. An in-depth

study of the cyclization was clearly required before work could proceed toward the fully elaborated system; unfortunately, this was precluded by time constraints.

3.6 Conclusion

Fragment B (**55**) was successfully prepared in 8 steps from 3-furanmethanol (**44**, Scheme 3.26).

Scheme 3.26

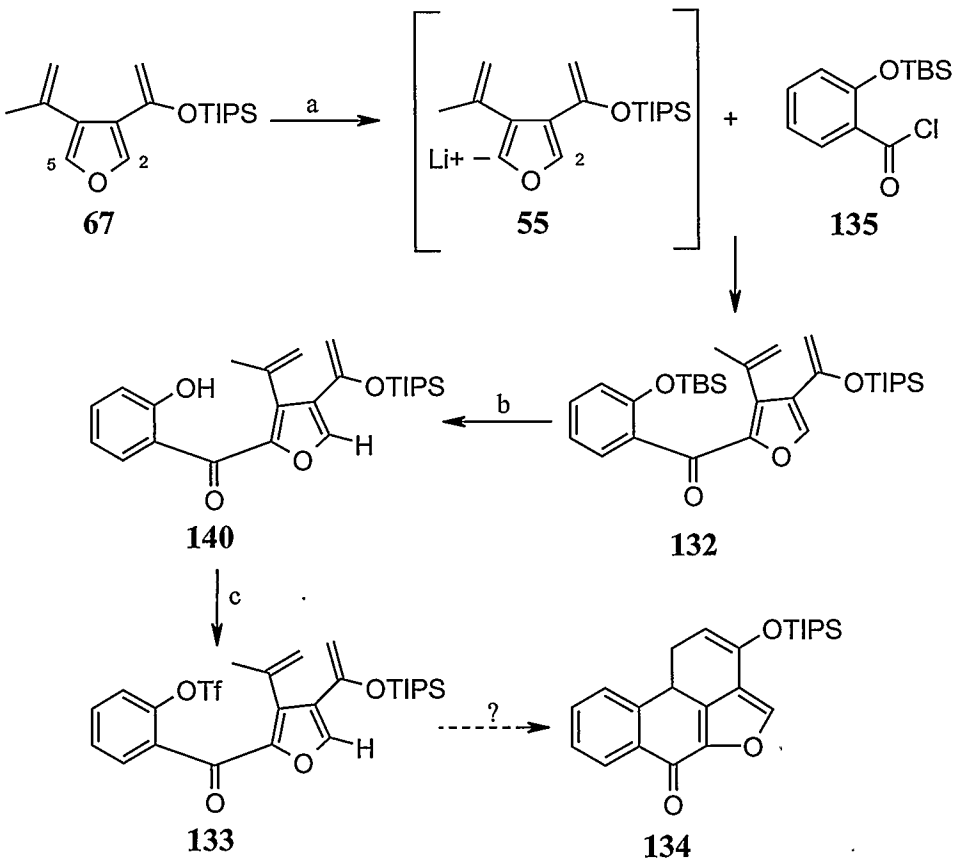


Conditions: a) TIPSCl (1.5 equiv.), imidazole (2.0 equiv.), DMF (99%); b) *n*BuLi (1.4 equiv.), THF, HMPA (1.5 equiv.), 0 °C (99%) c) *n*BuLi (2.2 equiv.), DME, 0°C, 1h; then add $B(MeO)_3$ (2.2 equiv.), 0° C, 1h; then add $Pd(PPh_3)_4$ (5 mol %) H_2O, 2-bromopropene (2.2 equiv.), 50 °C, 24 h (80%); d) TPAP (5 mol %), NMO (1.5 equiv.), DCM (91%) e) MeLi (1.5 equiv.), THF, 0 °C (99%) f) PDC (1.5 equiv.), DCM (86%); g) KHMDS (1.5 equiv.), THF, -78 °C - rt, 72 h (48%); h) *t*BuLi (1.1 equiv.), THF, -78 °C - rt; 16 h (50%).

Methods were successfully developed for the two key transformations: a C → O silyl migration converting methyl ketone **68** into silyl enol ether **67** and lithiation of **67** to yield the completed subunit, **55**.

Additionally, with Fragment B (**55**) in hand, a model system to study the key transformation in the preparation of halenaquinone was constructed (Scheme 3.27).

Scheme 3.27



Conditions: a) *t*BuLi (1.1 equiv.), THF, -78 °C then add **135** warm to rt, 16 h; b) 5% NaOH MeOH, rt, 15 min (98%); c) KH, THF, 0 °C, then add $PhNTf_2$, 70 °C, 1 h (97%).

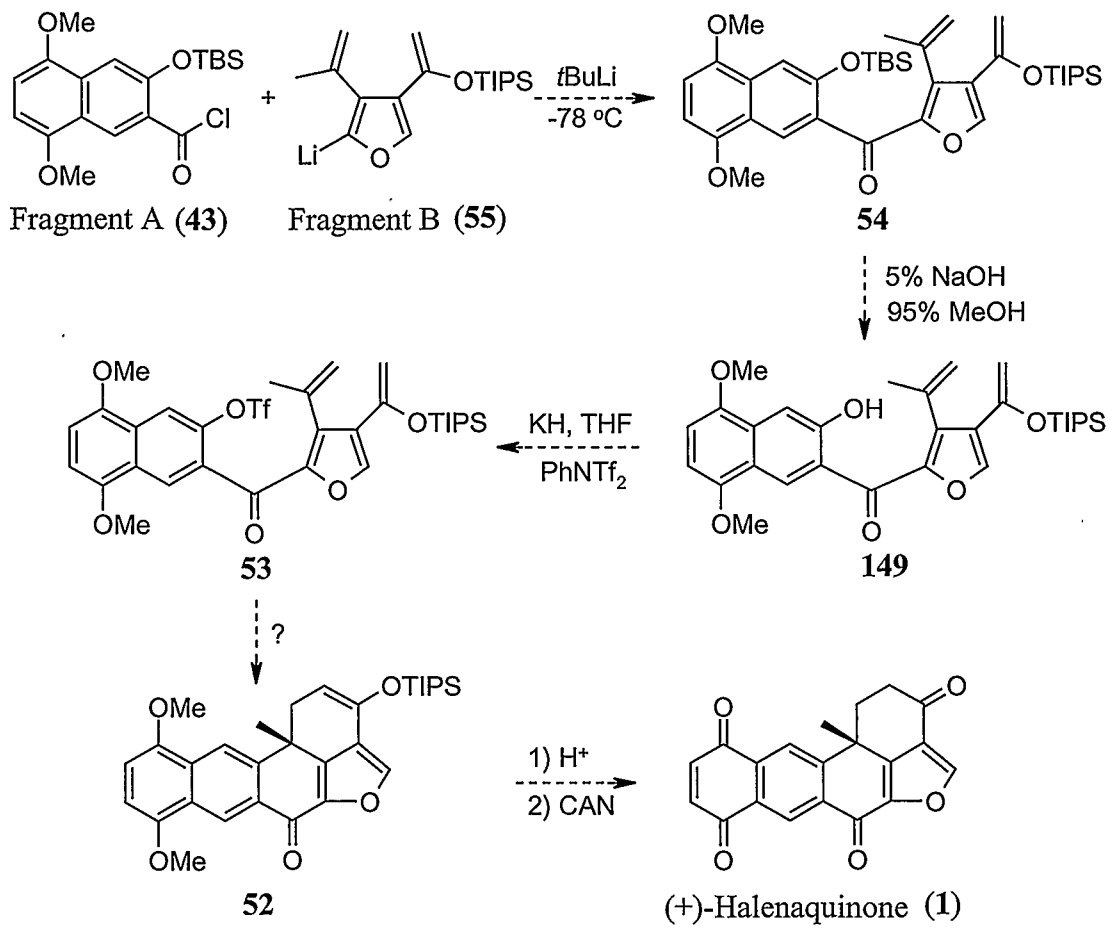
Using this model, conditions for the coupling of Fragment B (**55**) to truncated analogue of Fragment A (**135**) and isolation of disilane **132** were developed. Effective conditions for the selective deprotection of **132** to yield phenol **140** were also determined. Finally, conditions for preparation of triflate **133** in the presence of the sensitive TIPS enol ether substituent were also successfully developed. Unfortunately, conditions for the key Pd-catalyzed cyclization of **133** to **134** remained elusive.

3.7 Future Work

Once successful cyclization conditions are determined, two possible routes can be followed in the preparation of halenaquinone (**1**). The first route, based on the initial

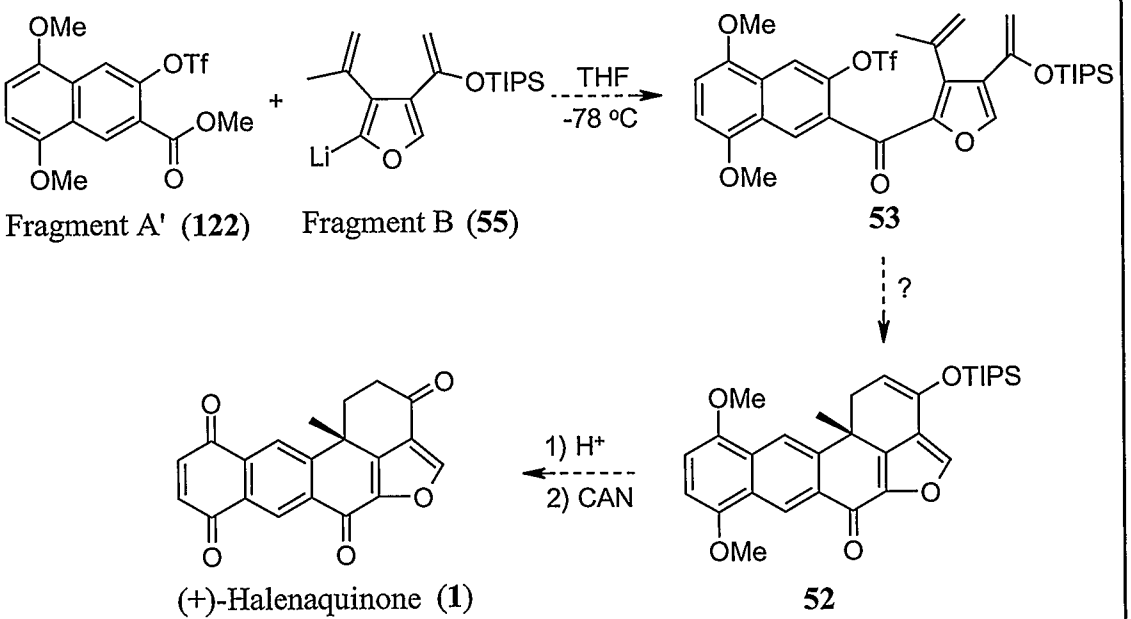
synthetic strategy, would involve the use of Fragment A (**43**) and Fragment B (**55**). Since, by extension of the work performed on the model system, conditions for the coupling of Fragment A to Fragment B to yield disilane **54**, selective deprotection and triflate formation have been resolved, only two new steps remain in the synthesis of halenaquinone *via* this route (Scheme 3.28). After cyclization to **52**, cleavage of the TIPS group using acidic conditions[22,38] followed by a known oxidation[9] would complete the first convergent total synthesis of halenaquinone (**1**).

Scheme 3.28



Alternatively, coupling Fragment A' (**122**) with Fragment B (**55**) eliminates the need for selective deprotection and triflate formation in the presence of the sensitive TIPS enol ether. Overall, this strategy would reduce the length of the synthesis by an additional 2 steps (Scheme 3.29).

Scheme 3.29



Fragment A' (**122**) Fragment B (**55**) **53**

(+)-Halenaquinone (**1**) **52**

By using this second route, only coupling of the two subunits, cyclization to **52**, cleavage of the TIPS group and oxidation are required to complete the synthesis of halenaquinone (**1**).

Chapter 4

4. Experimental Methods

4.1 Experimental Conditions

All glassware used in anhydrous reactions was dried overnight in a 120 °C oven and was subsequently cooled in a desiccator containing Drierite® or under an atmosphere of nitrogen. Moisture or oxygen sensitive reactions were performed under an atmosphere of nitrogen gas or through the use of Schlenk techniques. All solvents and reagents were purified *via* standard methods[72] when required. Tetrahydrofuran was distilled immediately prior to use from sodium benzophenone ketyl. Dichloromethane, toluene and diethyl ether were freshly distilled from calcium hydride. *N*,*N*-Dimethylformamide was purchased as an anhydrous solvent in a Sure/Seal bottle from the Aldrich Chemical Company. Other reagents including benzene, triethylamine, diisopropylamine and dimethoxyethane were dried by distillation from calcium hydride and were stored in Sure/Seal bottles. Iodomethane was passed through a plug of activated basic alumina immediately before use. *n*-Butyllithium and *t*-butyllithium were titrated prior to use with *N*-benzylbenzamide as an indicator. Aqueous solutions of NaCl (brine), Na_2CO_3 and NH_4Cl used for quenching and washing were saturated unless otherwise specified.

4.2 Chromatographic Techniques

Analytical TLC was carried out on aluminum sheets coated with a uniform thickness of 0.2 mm or Merck silica gel 60 F_{254} and the spots were visualized under UV light, or using a stain solution (0.56 g *p*-anisaldehyde, 180 mL 95% EtOH, 4 mL concentrated H_2SO_4, and 0.2 mL glacial acetic acid) or (118.4 g $(NH_4)_8Mo_7O_{24}{\cdot}4H_2O$, 200 mL concentrated H_2SO_4 and 2 L deionized water) followed by heat development.

Flash column chromatography was performed using silica gel 60 (E. Merck, 0.04-0.063 mm, 230-400 mesh) unless stated otherwise.

4.3 Compound Characterization and Identification

Melting point determinations were made using an Electrothermal® melting point apparatus in sealed capillary tubes and are reported uncorrected. Boiling points were determined using a Kugelrohr short path distillation apparatus and are reported, uncorrected, as the air-bath temperatures measured.

Infrared spectra were obtained using a Nicolet Nexus 470FT-IR E.S.P. spectrometer. Liquid samples were analyzed neat between KBr plates while solid samples were handled as chloroform or dichloromethane thin films. Characteristic absorptions are listed in wavenumbers followed by the assignment in parentheses.

Proton and carbon spectra were recorded using a Bruker ACE 200 (^{1}H 200 MHz, ^{13}C 50 MHz), a Bruker AC 300 (^{1}H 300 MHz, ^{13}C 50 MHz) or a Bruker DRK 400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometer. Unless otherwise stated, chloroform-*d* was used as the standard NMR solvent and the residual chloroform peak used for chemical shift referencing. Spectral data are listed according to the following formats: ^{1}H-NMR data as chemical shift (multiplicity, coupling constant, number of protons, assignment) and ^{13}C-NMR data as chemical shift (multiplicity, coupling constant (Hz), methyl (CH_3), methylene (CH_2), methane (CH), or quaternary (C), assignment) as determined by DEPT experiments.

GC-MS analysis was performed on a Hewlett Packard 5890 Series II gas chromatograph using a Hewlett Packard OV101, low polarity, 12 m x 0.2 mm column, equipped with a Hewlett Packard 5971A mass selective detector. Low resolution mass spectra on non-volatile samples were recorded on a Micromass VG 7070F or a Kratos MS80 mass spectrometer using 70 eV ionization with direct probe sample introduction by Ms. Q. Wu or Ms. D. Fox. ESI mass spectra were obtained using a Bruker Esquire 3000 mass spectrometer by Ms. Q. Wu. High resolution mass spectra were obtained using a Kratos MS80 spectrometer by Ms. D. Fox. Mass spectral data are listed as: mass (relative intensity, assignment).

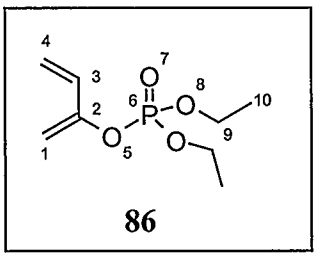
4.4 Naming Standards

Structures presented in this chapter are numbered for convenience only and do not necessarily follow IUPAC rules. Complex chemical compounds were named using Beilstein AutoNom Standard and do not necessarily follow IUPAC rules.

4.5 Experiments Pertaining to Chapter 2

Experimental procedures are listed in the approximate order of the chronology of the text pertaining to Chapter 2.

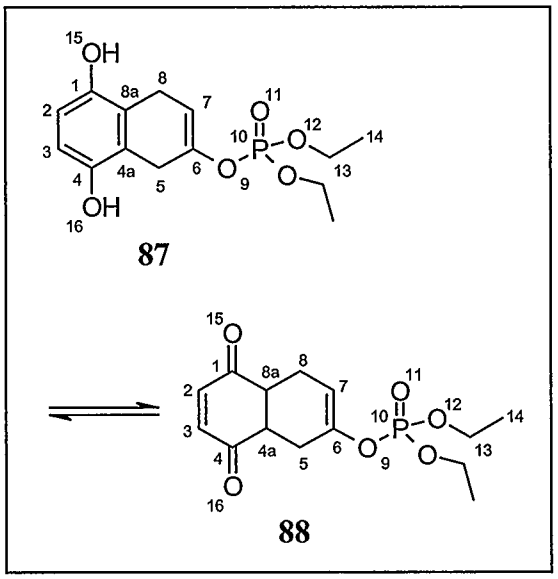
4.5.1 Preparation of 2-Diethylphosphoryloxy-1,3-butadiene (86).



86

Diisopropylamine (6.0 mL, 42 mmol) was dissolved in THF (50 ml) and cooled to –78 °C. To this solution was then added *n*BuLi (35 mL, 41 mmol) dropwise and the reaction mixture allowed to warm to 0 °C. After 30 min the LDA solution was re-cooled to –78 °C and freshly distilled methyl vinyl ketone (3.0 mL, 37 mmol) dissolved in THF (20 mL) was added dropwise over 10 min. After stirring for 10 min, diethyl chlorophosphate (9.8 mL, 80 mmol) was added in one portion and the dark brown reaction mixture allowed to warm to room temperature (1 h). The reaction was then quenched with 200 mL ice cold water and extracted into a 1:1 solution of diethyl ether and hexanes (3 x 200 mL). The combined organic layers were washed with water (2 x 200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a brown viscous material. The crude product was purified by flash column chromatography (4:1 hexanes:EtOAc) followed air bath distillation under reduced pressure (bp 76-78°C, 0.1 torr) to afford the diene (6.6 g, 32 mmol, 86%) as a colourless oil. ^{1}H NMR (200 MHz) δ 1.33 (dt, 6 H, J = 1 Hz, H-10), 4.18 (m, 4 H, H-9), 4.76 (m, 1 H, H-1a), 5.07 (m, 1 H, H-1b), 5.20 (d, 1 H, J = 10 Hz, H-4a), 5.57 (d, 1 H, J = 17 Hz, H-4b), 6.18 (ddd, 1 H, J = 3, 10, 17 Hz, H-3) ppm. Spectral and physical properties were consistent with reported data.[28b]

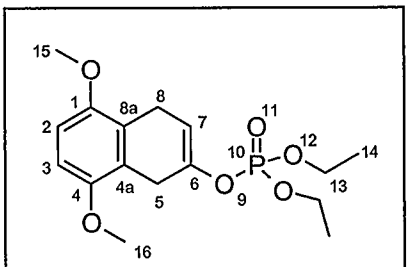
4.5.2 Preparation of 2-Diethylphosphoryloxy-5,8-dihydroxy-1,4 dihyronaphthalene (87) and 6-Diethylphosphoryloxy-4a,5,8,8a-tetrahydro-[1,4]naphthoquinone (88).



Diene **86** (3.0 g, 14.6 mmol) was dissolved in DCM (10.0 mL) and cooled to 0 °C and tin(IV) tetrachloride (1.0 M in CH_2Cl_2, 15.0 mL, 15.0 mmol) was added dropwise. After 10 min a solution of *p*-quinone (1.2 g, 11.2 mmol) dissolved in DCM (2.0 mL) was added dropwise to give a clear brown solution. After stirring 5 h at 0 °C the now black and viscous solution was diluted with DCM (5 mL) and quenched with water (5 mL). The emulsion thus formed was then subjected to suction filtration and the filtrate extracted with DCM (4 x 25 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield the addition products as a black viscous material. The crude products were isolated and purified *via* flash column chromatography (1:3:6 acetone:ether:hexanes). The combined fractions of the late eluting component were concentrated *in vacuo* to give small orange crystals which were further purified by recrystallization from a 1 : 1 solution of acetone and diethyl ether giving adduct **87** (1.42 g, 4.52 mmol, 40%) as fine white needles. ^{1}H NMR (300 MHz) δ 1.40 (t, 6 H, J = 7.2 Hz, H-14), 3.26-3.37 (m, 4 H, H-5,8), 4.23 (q, 4 H, J = 7.2 Hz, H-13), 5.58 (s, 1 H, H-7), 6.49 (s, 2 H, H-2,3) ppm. The combined fractions of the early eluting component were concentrated *in vacuo* to afford **88** (1.34 g, 4.25 mmol, 38%) as a dark viscous oil. Compound **88** tautatermorized to **87** upon standing for at least 30 days for an overall yield of 78%. ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 1.36 (t, 6 H, J = 7.0 Hz, H-14), 2.20-2.86 (m, 4 H, H-5,8), 3.10-3.28 (m, 1 H, H-4a or 8a), 3.31-3.48 (m, 1 H, H-4a or 8a), 4.17 (q, 4 H, J = 7.0 Hz, H-13), 5.51 (s, 1 H, H-7), 6.69 (s, 1 H, H-2 or 3), 6.70 (s, 1 H,

H-2 or 3) ppm. Spectral and physical properties for **87** were consistent with reported data.[28b]

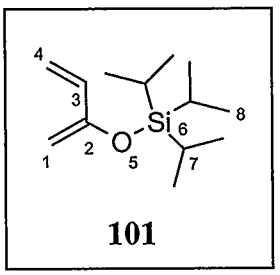
4.5.3 Preparation of 2-Diethylphosphoryloxy-5,8-dimethoxy-1,4-dihyronaphthalene (89).



89

NaH (166 mg, 6.90 mmol) was suspended in DMF (7 mL) with stirring at ambient temperature and to this was added a solution of adduct **87** (545 mg, 1.73 mmol) dissolved in DMF (0.6 mL) dropwise. After the evolution of gas ceased and the reaction mixture had re-cooled to rt (30 min) MeI (0.6 mL, 6.94 mmol) was slowly added *via* syringe. After 2.5 h the viscous reaction mixture was diluted with DMF (5 mL), quenched with ice-cold water (5 mL) and extracted into diethyl ether (4 x 25 mL). The organic layers were combined, washed with brine (4 x 50 mL), dried ($MgSO_4$), filtered and concentrated to give the crude product as a yellow oil. Purification by flash column chromatography (1:1 hexanes:EtOAc) followed by air bath distillation under reduced pressure (bp 116-117 °C, 0.10 torr) afforded the methylated product **89** (598 mg, >99%) as a bright orange oil. IR (KBr) 1258, 1034 cm^{-1}; ^1H NMR (300 MHz) δ 1.38 (t, 6 H, J = 7.1 Hz, H-14), 3.42 (s, 4 H, H-5,8), 3.78 (s, 6 H, H-15,16), 4.21 (q, 4 H, J = 7.2 Hz, H-13), 5.68 (s, 1 H, H-7), 6.65 (s, 2H, H-2,3) ppm; ^{13}C NMR (50 MHz) δ 151.1 (d, J = 11 Hz, C), 145.2 (C), 145.1 (C), 123.5 (C), 123.2 (C), 107.4 (CH), 107.2 (CH), 77.4 (CH), 64.5 (d, J = 6.1 Hz, CH_2), 55.8 (CH_3), 55.7 (CH_3), 27.4 (d, J = 4.9 Hz, CH_2), 25.1 (CH_2), 16.3 (d, J = 6.8 Hz, CH_3) ppm; mass spectrum, *m/z* (relative intensity, %) 365 (4, M^++ Na), 350 (100, M^+-CH_3), 337 (33, M^+-C_2H_7) amu; Exact mass for $C_{16}H_{23}O_6P$: calcd 342.1232, found 342.1225 amu. Anal. for $C_{16}H_{23}O_6P$: calcd C 56.14, H 6.77; found C 45.20, H 6.99 %.

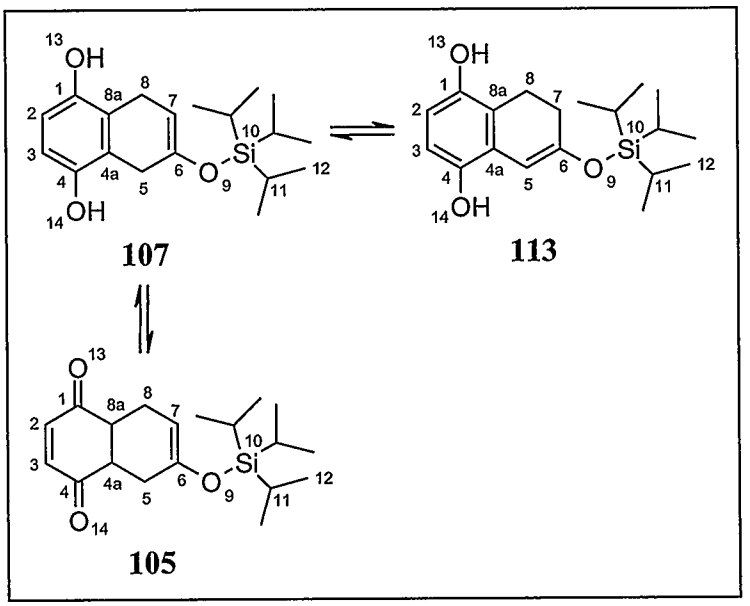
4.5.4 Preparation of Triisopropyl-(1-methylene-allyloxy)-silane (101).



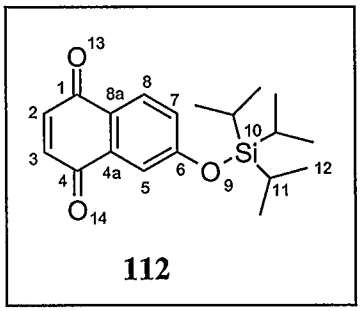
101

Diisopropylamine (3.9 mL, 27.9 mmol) was dissolved in THF (60 mL) and the resultant solution cooled to –78 °C, followed by the dropwise addition of *n*BuLi (18.3 mL, 1.5 M in hexanes, 27.9 mmol). The reaction mixture was allowed to warm to 0 °C and stirred 30 min after which time the solution was re-cooled to –78 °C. In a separate vessel, methyl vinyl ketone (2.1 ml, 24.0 mmol) was dissolved in THF (7.5 mL) and the resultant mixture added to the solution of LDA dropwise. After 1 h, TIPSOTf (7.5 mL, 27.9 mmol) was slowly added and the reaction mixture allowed to warm to room temperature overnight (16 h). The reaction was quenched with ice cold water (20 mL) and the aqueous layer extracted with 1 : 1 (hex : Et_2O) (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and reduced to yield the crude product as a yellow oil. Purification by air bath distillation under reduced pressure (bp 60-65 °C, 0.10 torr, lit.[73] 70 °C, 0.20 torr) afforded the diene (5.3 g, 23.5 mmol, 98%) as a colourless oil. ^{1}H NMR (300 MHz) δ 1.11-1.13 (m, 18 H, H-8), 1.26 (sept, 3 H, J = 6.2 Hz, H-7), 4.29 (bs, 1H, H-1a), 4.35 (bs, 1H, H-1b), 5.10 (d, 1H, J = 10.3 Hz, H-4a), 5.59 (dd, 1H, J = 2.1, 16.9 Hz, H-4b), 6.20 (dd, 1H, J = 10.3, 16.9 Hz, H-3).

4.5.5 Preparation of 6-Triisopropylsilanyloxy-5,8-dihydro-naphthalene-1,4-diol (107), 7-Triisopropylsilanyloxy-5,6-dihydro-naphthalene-1,4-diol (113) and 6-Triisopropylsilanyloxy-4a,5,8,8a-tetrahydro-[1,4]naphthoquinone (105).



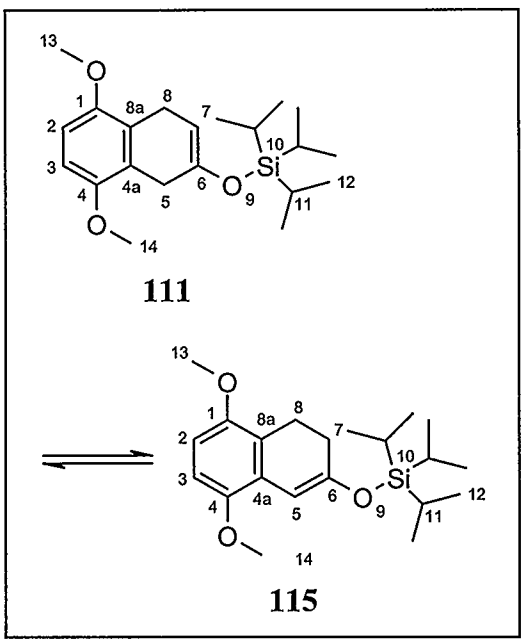
Diene **101** (1.7 g, 7.4 mmol) was dissolved in THF (40 mL) at ambient temperature. To this was then added *p*-quinone (1.8 g, 16.2 mmol) in one portion turning the clear mixture a dark brown. After 6 days the reaction mixture was concentrated under reduced pressure to yield the crude product (**105**) as a brown paste. Purification by flash column chromatography (75:1 hexanes:EtOAc) on Florisil afforded adduct **107** (1.6 g, 4.4 mmol, 60%) as a bright yellow oil and the unreacted diene (0.6 g, 2.8 mmol, 38%) as a clear colourless oil. ^{1}H NMR (200 MHz) **107** δ 0.48-1.52 (m, 21 H, H-11,12), 2.96-3.34 (m, 4 H, H-5,8), 4.92 (s, 1 H, H-7), 6.74 (s, 2 H, H-2,3) ppm. Compound **107** crystallized upon standing to yield fine yellow needles that were subsequently identified as **113**. ^{1}H NMR (300 MHz) **113** δ 1.10-1.13 (m, 18 H, H-12), 1.25-1.33 (m, 3 H, H-11), 2.43 (t, 2 H, J = 9.7 Hz, H-8), 2.77 (t, 2 H, J = 10.3 Hz, H-7), 5.77 (s, 1 H, H-5), 6.63 (d, 2 H, J = 9.7 Hz, H-2,3) ppm. ^{1}H NMR (300 MHz) **105** δ 1.06-1.08 (m, 18 H, H-12), 1.18-1.28 (m, 3 H, H-11), 2.18-2.26 (m, 2 H, H-8), 2.43-2.60 (m, 2 H, H-5), 3.11-3.17 (m, 1 H, H-4a or 8a), 3.29-3.35 (m, 1 H, H-4a or 8a), 4.85 (s, 1 H, H-7), 6.80 (s, 2 H, H-2,3) ppm; mass spectrum, *m/z* (relative intensity, %) 334 (41, M^+), 291 (16, M^+-C_3H_7) amu; Exact mass for $C_{19}H_{30}O_3Si$: calcd 334.1964, found 334.1971 amu. Spectral and physical properties for **105** were consistent with reported data.[74]



112

Distillation of adducts **105** or **107** under reduced pressure (bp 85 °C, 0.95 x 10^{-1} torr) gave a pale brown solid that that was identified as quinone **112**. Additionally, upon exposure to air, adducts **105** and **107** became progressively darker in colour to ultimately appear as dark red/black crystals that were subsequently identified as **112**. IR (KBr) 1667 (C=O) cm^{-1}; ^{1}H NMR (300 MHz) δ 1.13 (d, 18 H, J = 7.2 Hz, H-12), 1.31 (sept, 3 H, J = 5.6 Hz, H-11), 6.92 (s, 2 H, H-2,3), 7.19 (dd, 1 H, J = 2.6, 8.2 Hz, H-7), 7.48 (d, 1 H, J = 2.6 Hz, H-5), 8.00 (d, 1 H, J = 8.2 Hz, H-8) ppm; ^{13}C NMR (50 MHz) δ 185.3 (C), 184.3 (C), 161.7 (C), 139.2 (CH), 138.5 (CH), 134.1 (C), 129.2 (CH), 125.3 (CH), 123.0 (C), 116.9 (CH), 18.0 (CH_3), 12.9 (CH) ppm; mass spectrum, *m/z* (relative intensity, %) 330 (3, M^+), 287 (46, M^+-C_3H_7), 231 (100) amu. Exact mass for $C_{19}H_{26}O_3Si$: calcd 330.1651, found 330.1649 amu.

4.5.6 Preparation of (5,8-Dimethoxy-1,4-dihydro-naphthalen-2-yloxy)-triisopropyl-silane (111) and (5,8-Dimethoxy-3,4-dihydro-naphthalen-2-yloxy)-triisopropyl-silane (115).

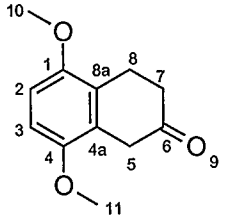


111 ⇌ **115**

Adduct **107** (1.00g, 2.99 mmol) was dissolved in THF (8 mL) and cooled to –10 °C. The bright yellow solution was then slowly added to a stirring suspension of NaH (215 mg, 9.00 mmol) in THF (7 mL) at –10 °C and the reaction mixture warmed to 0 °C. After 2 h MeI (1.90 mL, 30.0 mmol) was added dropwise and the reaction mixture was allowed to warm slowly to rt (12 h). The reaction was quenched with ice cold water (10 mL), extracted in EtOAc (3 x 50 mL) and the combined organics washed with brine (2 x 50 mL), dried (Na_2SO_4) and reduced to give the crude product as a black oil. Purification by flash column

chromatography (30:1 hexanes:EtOAc) on Florisil afforded the methylated product (1.02 g, 2.82 mmol, 94%) as a deep yellow oil. ^{1}H NMR (300 MHz) **111** δ 1.07-1.30 (m, 21 H, H-11,12), 3.29-3.36 (m, 4 H, H-5,8), 3.79, 3.80 (2s, 3 H each, H-13,14), 5.01 (s, 1 H, H-7), 6.64 (s, 2 H, H-2,3) ppm. Applying the same procedure adduct **113** resulted in the isolation of a yellow oil (69%) identified as **115**. Additionally, methylated adduct **111** converts to **115** upon standing. ^{1}H NMR (300 MHz) **115** δ 1.12-1.32 (m, 21 H, H-11,12), 2.37 (t, 2 H, J = 8.2 Hz, H-8), 2.90 (t, 2 H, J = 8.2 Hz, H-7), 3.76, 3.78 (2s, 3 H each, H-13,14), 6.03 (s, 1 H, H-5), 6.56 (d, 1 H, J = 8.7 Hz, H-2 or 3), 6.64 (d, 1 H, J = 8.7 Hz, H-2 or 3) ppm; mass spectrum, *m/z* (relative intensity, %) 362 (49, M^+), 319 (28, M^+-C_3H_7), 73 (100) amu; Exact mass for $C_{21}H_{34}O_3Si$: calcd 362.2277, found 362.2268 amu.

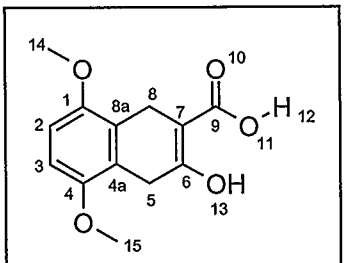
4.5.7 Preparation of 5,8-Dimethoxy-3,4-dihydro-1H-naphthalen-2-one (62).



62

O-Methylated adduct **115** (131 mg, 0.362 mmol) was dissolved in DMF (5.5 mL) and cooled to 0 °C. To this solution was then added 4 drops of 6 M HCl and the reaction mixture allowed to warm to room temperature. After stirring 2 h the solution was diluted with ether (10 mL), washed with brine (2 x 20 mL), $NaHCO_3$ (1 x 10 mL), dried ($MgSO_4$) and reduced to yield a white solid. Drying the crude product for 16 h under reduced pressure afforded the ketone **62** (66 mg, 88%) as flocculent white crystals. ^{1}H NMR (300 MHz) δ 2.55 (t, 2 H, J = 13.8 Hz, H-8), 3.09 (t, 2 H, J = 13.8 Hz, H-7), 3.52 (s, 2 H, H-5), 3.79, 3.81 (2s, 3 H each, H-10,11), 6.72 (d, 2 H, J = 2.1 Hz, H-2,3) ppm. Spectral and physical properties were consistent with reported data.[30,75]

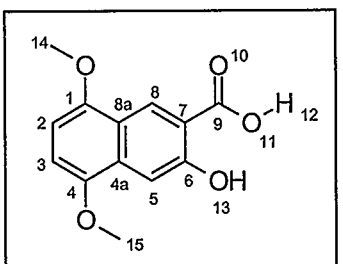
4.5.8 Preparation of 3-Hydroxy-5,8-dimethoxy-1,4-dihydro-naphthalene-2-carboxylic acid (118).



118

Ketone **62** (100 mg, 0.48 mmol) was dissolved in DMF (0.5 mL) and slowly added to a stirring solution of methyl magnesium carbonate (2 mL, 2 M in DMF). The reaction mixture was then heated to 130 °C for 3 h and then the amber solution was allowed to cool to room temperature (20 min). The gelatinous material was further cooled to -10 °C and quenched with the dropwise addition of ice-cold 10 % HCl. After the evolution of gas had ceased, and all the gelatinous material had been consumed, the newly formed pale grey precipitate was subjected to suction filtration. The crude solid was rinsed twice with ice-cold water followed by ice-cold acetone and allowed to air dry affording acid **118** (82 mg, 0.34 mmol, 72%) as a fine white powder. ^{1}H NMR (200 MHz, CD_3OD) δ 3.42-3.55 (m, 4 H, H-5,8), 3.80 (s, 6 H, H-14,15), 6.78 (s, 2 H, H-2,3), 12.67 (s, 1 H, H-12) ppm; mass spectrum, *m/z* (relative intensity, %) 250 (2, M^+), 206 (76, M^+-CO_2), 164 (100) amu; Exact mass for $C_{13}H_{14}O_5$: calcd 250.0841, found 250.0835 amu.

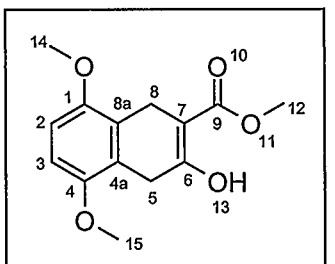
4.5.9 Preparation of 3-Hydroxy-5,8-dimethoxy-2-naphthoic acid (42).



42

Acid **118** (2-3 mg) was ground to a fine powder and mixed with benzene (0.25 mL) followed by sonication (20 min) to form a suspension. To this suspension was then added DDQ (10 mg) in one portion and the yellow mixture stirred for 20 h at room temperature. The crude reaction mixture was then reduced to give a white and yellow crystalline solid. ^{1}H NMR (200 MHz, CD_3OD) δ 3.95, 3.98 (2s, 3 H each, H-14,15), 6.68 (d, 1 H, J = 8.0 Hz, H-2 or 3), 6.90 (d, 1 H, J = 8.2 Hz, H-2 or 3), 7.53 (s, 1 H, H-5), 8.89 (s, 1 H, H-8) ppm. Spectral and physical properties were consistent with reported data.[16]

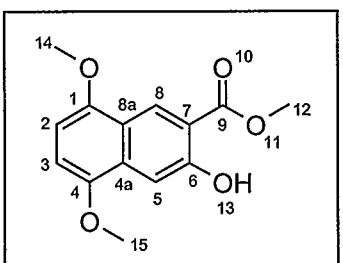
4.5.10 Preparation of 3-Hydroxy-5,8-dimethoxy-1,4-dihydro-naphthalene-2-carboxylic acid methyl ester (120).



120

Acid **118** (136 mg, 0.543 mmol) was placed in a round bottom flask which was subsequently purged with N_2 and cooled to 0 °C. Ice-cold DCM (1.5 mL) was then added to the solid and the resulting suspension vigorously stirred. To the acid mixture was then added methyl chloroformate (0.090 mL, 1.17 mmol) at 0 °C followed by the dropwise addition of Et_3N (0.090 mL, 0.642 mmol) dissolved in ice-cold DCM (0.3 mL). The reaction mixture was allowed to stir for 2 h at 0 °C at which time it was diluted with DCM (2 mL) and water (2 mL). The organic layer was then reduced to yield the crude product as a fine yellow powder. Recrystallization from acetone and hexanes afforded ester **120** (140 mg, 98%) as fine yellow crystals. mp 144 – 146 °C; IR (KBr) 1260 (C(= O)-O), 1680 (C=O), 3425 (-OH) cm^{-1}; ^1H NMR (200 MHz) δ 3.35 (s, 4 H, H-5,8), 3.80, 3.82, 3.84 (3s, 3 H, H-12, H-14, H-15), 6.68 (s, 2 H, H-2,3), 12.26 (s, 1 H, H-13) ppm. ^{13}C NMR (50 MHz) δ 172.8 (C), 169.2 (C), 151.0 (C), 150.8 (C), 123.8 (C) 122.1 (C), 107.4 (CH), 107.5 (CH), 95.1 (C), 55.8 (CH_3), 55.7 (CH_3), 51.8 (CH_3), 28.8 (CH_2), 23.5 (CH_2) ppm; mass spectrum, *m/z* (relative intensity, %) 264 (72, M^+), 232 (100, M^+-OCH_4) amu; Exact mass for $C_{14}H_{16}O_5$: calcd 264.0998, found 264.1004 amu.

4.5.11 Preparation of 3-Hydroxy-5,8-dimethoxy-naphthalene-2-carboxylic acid methyl ester (121).

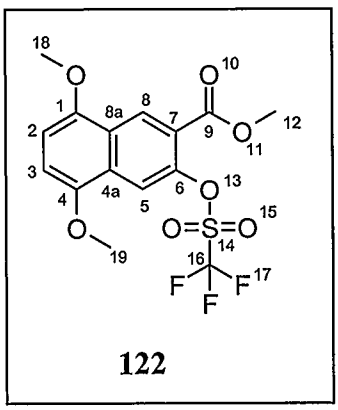


121

Ester **120** (50 mg, 0.19 mmol) was combined with DDQ (54 mg, 0.24 mmol) and mixed in DCM (2.5 mL). After stirring for 15 min at rt a dark precipitate had formed and TLC analysis showed the complete consumption of ester **121**. The crude solution was vacuum filtered and the precipitate rinsed with DCM. The resulting filtrate was reducing to yield the crude aromatized product as a brownish yellow solid. Purification

via flash column chromatography (10:1 hexanes:EtOAc) afforded the naphthol ester (32 mg, 0.12 mmol, 64%) as a yellow crystalline solid. mp 179-180 °C; IR (KBr) 1269 (C(=O)-O) 1678 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ 3.94 (s, 3 H), 3.97 (s, 3 H), 4.03 (s, 3 H), 6.53 (d, 1 H, J = 8.5 Hz), 6.73 (d, 1 H, J = 8.5 Hz), 7.66 (s, 1 H), 8.85 (s, 1 H) ppm; ^{13}C NMR (50 MHz) δ 170.7 (C), 157.2 (C), 150.6 (C), 148.3 (C), 131.5 (C), 126.9 (CH), 120.3 (C), 113.6 (C), 107.0 (CH), 106.7 (CH), 100.8 (CH), 56.1 (CH_3), 55.8 (CH_3), 52.7 (CH_3) ppm; mass spectrum, *m/z* (relative intensity, %) 262 (72, M^+), 230 (100, M^+-CH_4O), 215 (97, M^+-CH_3CH_4O) amu; Exact mass for $C_{14}H_{13}O_5$: calcd 262.0841, found 262.0844 amu. Anal. for $C_{14}H_{13}O_5$: calcd C 64.12, H 5.02; found C 63.29, H 5.30 %.

4.5.12 Preparation of 5,8-Dimethoxy-3-trifluoromethanesulfonyloxy-naphthalene-2-carboxylic acid methyl ester (122).



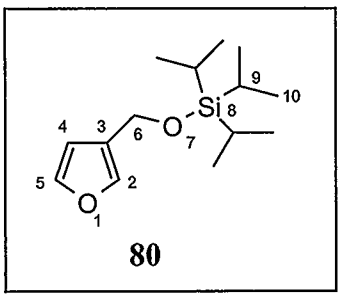
122

Naphthyl ester **121** (25 mg, 0.10 mmol) was dissolved in DCM (1 mL) and the solution cooled to -45 °C. To this mixture was then added Et_3N (30 μL, 0.26 mmol) followed immediately by the dropwise addition of Tf_2O (25 μL, 0.11 mmol). Immediately after the addition of the anhydride, TLC analysis showed the complete consumption of the starting material and the mixture was allowed to warm to rt (15 min). The reaction mixture was diluted with DCM (0.5 mL) and quenched with ice-cold water (0.5 mL). The organic layer was washed with water (10 mL), brine (10 mL) dried (Na_2SO_4) and reduced to afford the triflate (19 mg, 0.05 mmol, 50%) as a yellow crystalline solid. IR (KBr) 1712 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ 3.98, 3.99 (2s, 6 H, H-18, 19), 4.02 (s, 3 H, H-12), 6.79-6.83 (d, 1 H, J = 8.5 Hz, H-2 or 3), 6.88-6.92 (d, 1 H, J = 8.4 Hz, H-2 or 3), 8.08 (s, 1 H, H-5), 9.00 (s, 1 H, H-8) ppm; ^{13}C NMR (50 MHz) δ 164.8 (C), 150.2 (C), 149.0 (C), 145.4 (C), 129.5 (CH), 128.2 (C), 124.6 (C), 121.7 (C), 119.1 (C, J = 358.3 Hz), 116.1 (CH), 107.7 (CH), 105.5 (CH), 56.1 (CH_3), 56.1 (CH_3), 52.8 (CH_3) ppm; mass spectrum, *m/z* (relative intensity, %) 394 (60, M^+), 363 (5, M^+-OCH_3), 261 (28, M^+- SO_2CF_3), 233 (100) amu; Exact mass for $C_{15}H_{13}O_7SF_3$: calcd 394.0334, found 394.0315 amu.

4.6 Experiments Pertaining to Chapter 3

Experimental procedures are listed in the approximate order of the chronology of the text pertaining to Chapter 3.

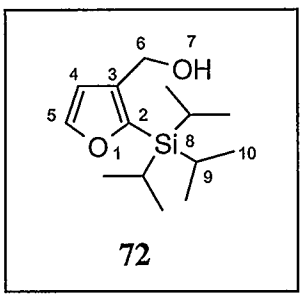
4.6.1 Preparation of (3-Furylmethoxy)triisopropyl silane (80).



80

Imidazole (8.2 g, 1.2 x 10^{-2} mol) was dissolved in DMF (40.0 mL) and the solution cooled to 0 °C. TIPSCl (12.8 mL, 60.0 mmol) was then added dropwise over 10 min. After an additional 10 minutes, 3-furanmethanol (5.3 mL, 0.6 x 10^{-2} mol) was slowly added and the reaction mixture allowed to warm slowly to room temperature (4 h). The crude product was then extracted with Et_2O (3 x 60 mL) and the combined organics dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. The crude product was purified *via* air bath distillation under reduced pressure (bp 50-55 °C, 0.10 torr) to yield silyl ether **80** as a clear colourless oil (15.1 g, 59.2 mmol, 99%). ^{1}H NMR (200 MHz) δ 1.03-1.15 (m, 21 H, H-9,10), 4.66 (s, 2 H, H-6), 6.32 (d, 1 H, J = 1.3 Hz, H-4), 7.35-7.40 (m, 2 H, H-2,5) ppm. Spectral and physical properties were consistent with reported data.[21]

4.6.2 Preparation of 2-(Triisopropylsilyl)-3-furan methanol (72).

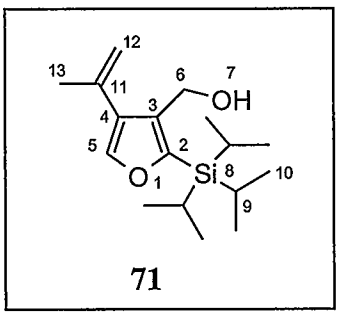


72

Silyl ether **80** (10.0 g, 39.3 mmol) was distilled and immediately dissolved in THF (120.0 mL). HMPA (7.5 mL, 4.3 x 10^{-2} mol, dried over CaH_2 , distilled and stored over 4 Å MS) was added in one portion and the solution cooled to 0 °C. After stirring 3 h, *n*BuLi (34.0 mL, 55.0 mmol) was added dropwise over 20 minutes and the reaction mixture allowed to warm slowly to rt (24 h). The reaction was quenched with $NH_4Cl_{(sat)}$ (20 mL), extracted with Et_2O (3 x 100 mL) and the combined organics washed with brine (4 x 100mL), $CuSO_{4(sat)}$ (2 x 50 mL) dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. The

crude product was purified by flash column chromatography (4:1 hexanes:EtOAc) to yield alcohol **72** as a white crystalline solid (9.9 g, 3.9 x 10^{-2} mol, 99%). mp 60.0 °C; ^{1}H NMR (200 MHz) δ 1.06 (d, 18 H, J = 7.4 Hz, H-10), 1.35 (m, 3 H, J = 7.4 Hz, H-9), 1.53 (bs, 1 H, H-7), 4.58 (s, 2 H, H-6), 6.50 (d, 1 H, J = 1.6 Hz, H-4), 7.61 (d, 1 H, J = 1.6 Hz, H-5) ppm. Spectral and physical properties were consistent with reported data.[21]

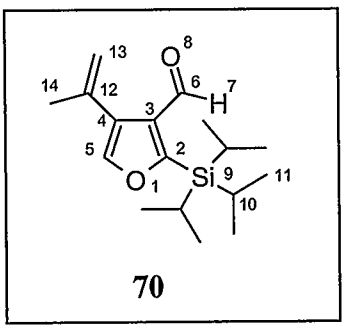
4.6.3 Preparation of 2-(Triisopropylsilyl)-4-isopropenyl-3-furan methanol (71).



71

Migration product **72** (12.5 g, 49.1 mmol) was dissolved in DME and the solution cooled to 0 °C and n-BuLi (67.5 mL, 10.8 x 10^{-2} mol) added dropwise. The reaction mixture was then warmed to rt, stirred for 1.5 h and then re-cooled to 0 °C. Trimethyl borate (12.1 mL, 10.8 x 10^{-2} mol) was then added dropwise to the stirring solution and the reaction mixture allowed to warm slowly to room temperature (20 h). The reaction was then quenched with a 2M solution of Na_2CO_3 (51.0 mL, 10.8 x 10^{-2} mol) and stirred 30 minutes. With stirring, 2-bromopropene (9.6 mL, 1.1 x 10^{-1} mol) was added followed immediately by $Pd(PPh_3)_4$ (2.9 g, 2.5 mmol). The mixture was then heated to 50 °C and stirred for 24 h at which time the clear brown solution was cooled to room temperature and quenched with $NH_4Cl_{(sat)}$ (20 mL). The organics were extracted with Et_2O (3 x 100 mL), combined, washed with brine (2 x 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. The crude oil was purified by flash column chromatography (50:1 hexanes:EtOAc) to afford the product as a waxy beige solid (11.5 g, 39.0 mmol, 80%). mp 60.0 – 61.5 °C; IR (KBr) 3317 (OH) cm^{-1}; ^{1}H NMR (200 MHz) δ 1.10 (d, 18 H, J = 7.3 Hz, H-10), 1.35 (sept, 3 H, J = 7.3 Hz, H-9), 2.06 (s, 3 H, H-13), 4.63 (s, 2 H, H-6), 5.03-5.09 (m, 1 H, H-12a), 5.41 (bs, 1 H, H-12b), 7.61 (s, 1H, H-5) ppm. ^{13}C NMR (50 MHz) δ 156.0 (C, C-11), 145.1 (CH, C-5), 135.4 (C, C-4), 133.4 (C, C-3), 126.5 (C, C-2) 112.7 (CH_2, C-12), 56.0 (CH_2, C-6), 23.5 (CH_3, C-13), 18.6 (CH_3, C-10), 11.5 (CH, C-9) ppm; mass spectrum, *m/z* (relative intensity, %) 294 (1, M^+), 251 (64, M^+-C_3H_7), 209 (100) amu; Exact mass for $C_{14}H_{23}O_2Si$: calcd 251.1468, found 251.1467 amu: calcd C 69.33, H 10.27; found C 69.45, H 10.54 %.

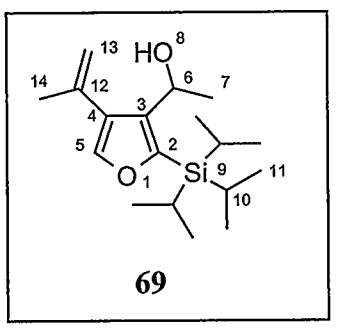
4.6.4 Preparation of 4-Isopropenyl-2-triisopropylsilanyl-furan-3-carbaldehyde (70).



70

Suzuki product **71** (5.0 g, 1.7 x 10^{-2} mol) was dissolved in DCM (50 mL) over 4 Å molecular sieves (3.0 g). NMO (3.0 g, 2.6 x 10^{-2} mol) was then added in one portion and the reaction mixture allowed to stir for 40 minutes. TPAP (0.3 g, 8.5 x 10^{-4} mol) was then added in one portion turning the beige solution black. After 2 h the crude reaction was filtered through a plug of Celite using DCM as an eluent to give a foul smelling black liquid. The crude product was purified *via* air bath distillation under reduced pressure (bp 80-82 °C, 8.0 x 10^{-2} torr) to afford the aldehyde as a clear, colourless oil (4.5 g, 1.5 x 10^{-2} mol, 91%). IR (KBr) 1689 (C=O) cm^{-1}; ^1H NMR (200 MHz) δ 1.09 (d, 18 H, J = 7.3 Hz, H-11), 1.50 (sept, 3 H, J = 7.3 Hz, H-10), 2.07 (s, 3 H, H-14), 5.12-5.17 (m, 1 H, H-13a), 5.25-5.30 (m, 1 H, H-13b), 7.60 (s, 1 H, H-5), 10.28 (s, 1H, H-7) ppm. ^{13}C NMR (50 MHz) δ 186.6 (C, C-6), 170.8 (C, C-3), 145.0 (CH, C-5), 136.1 (C, C-4), 134.8 (C, C-2) 127.2 (C, C-12), 115.9 (CH_2, C-13), 23.3 (CH_3, C-14), 18.5 (CH_3, C-11), 11.6 (CH, C-10) ppm; mass spectrum, *m/z* (relative intensity, %) 249 (100, M^+-C_3H_7), 207 (28) amu; Exact mass for $C_{14}H_{21}O_2Si$: calcd 249.1301, found 249.1311 amu: calcd C 69.81, H 9.65; found C 69.87, H 9.34 %.

4.6.5 Preparation of 1-(2-(Triisopropylsilyl)-4-isopropenyl-3-furanmethanol (69).

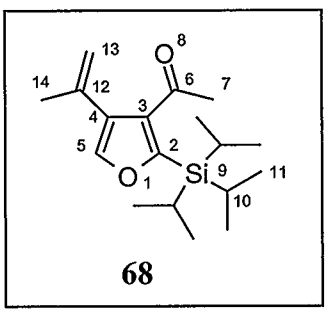


69

Aldehyde **70** (0.9 g, 3.1 mmol) was distilled and immediately dissolved in THF (11 mL) and the resulting solution cooled to 0 °C. MeLi (2.9 mL, 4.6 mmol) was added dropwise to the solution and the reaction mixture stirred 2 h at 0 °C. The reaction was quenched with $NH_4Cl_{(sat)}$ (5 mL), extracted with Et_2O (3 x 10 mL) and the combined organics dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. The crude product was purified by flash column chromatography (30:1 hexanes:EtOAc) to afford

the alcohol (0.95 mg, 3.26 mmol, >99%) as a waxy white solid. mp 57.5 – 59.0 °C; IR (KBr) 3305 (OH) cm^{-1}; ^1H NMR (400 MHz) δ 1.11 (d, 18 H, J = 7.4 Hz, H-11), 1.39 (sept, 3 H, J = 7.4 Hz, H-10), 1.54 (d, 3 H, J = 8.8 Hz, H-7), 2.12 (s, 3 H, H-14), 5.04 (q, 1 H, J = 7.2 Hz, H-6), 5.13 (bs, 1 H, H-13b), 5.50 (bs, 1 H, H-13a), 7.54 (s, 1H, H-5) ppm. ^{13}C NMR (100 MHz) δ 154.5.0 (C), 145.7 (CH), 138.1 (C), 136.7 (C), 127.1 (C) 116.1 (CH_2), 64.1 (CH), 25.0 (CH_3), 22.4 (CH_3), 18.9 (CH_3), 12.0 (CH) ppm; mass spectrum, *m/z* (relative intensity, %) 265 (100, M^+-C_3H_7) amu; Exact mass for $C_{15}H_{25}O_2Si$: calcd 265.1632, found 265.1624 amu.

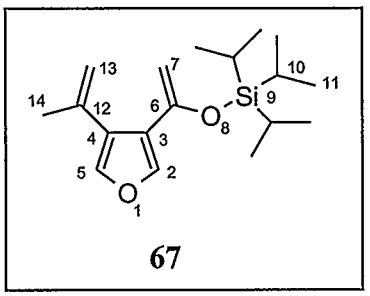
4.6.6 Preparation of 1-(2-(Triisopropylsilyl)-4-isopropenyl-3-furanmethanone (68).



68

The secondary alcohol **69** (2.169 g, 7.03 mmol) was dissolved in DCM (70 mL) and PDC (4.023 g, 10.7 mmol) added in one portion with stirring. After 48 h, the dark brown reaction mixture was filtered through a plug of basic alumina using DCM as an eluent and reduced to give a yellow oil. The crude product was purified by flash column chromatography (30:1 hexanes:EtOAc) followed air bath distillation under reduced pressure (bp 88-90 °C, 7.0 x 10^{-2} torr) to afford the ketone as a clear, colourless oil (1.981 g, 6.46 mmol, 92%). IR (KBr) 1683 (C=O) cm^{-1}; ^1H NMR (400 MHz) δ 1.07 (d, 18 H, J = 7.6 Hz, H-11), 1.41 (sept, 3 H, J = 7.6 Hz, H-10), 2.04 (s, 3 H, H-14), 2.41 (s, 3 H, H-7), 4.95 (s, 1 H, H-13a), 5.11 (s, 1 H, H-13b), 7.52 (s, 1 H, H-5) ppm. ^{13}C NMR (50 MHz) δ 198.9 (C, C-6), 160.5 (CH, C-5), 143.6 (C, C-2), 137.8 (C, C-4), 135.4 (C, C-3) 126.8 (C, C-12), 115.3 (CH_2, C-13), 30.7 (CH_3, C-14), 23.9 (CH_3, C-7), 11.5 (CH, C-10) ppm; mass spectrum, *m/z* (relative intensity, %) 263 (100, M^+-C_3H_7) amu; Exact mass for $C_{15}H_{23}O_2Si$: calcd 263.1455, found 263.1467 amu: calcd C 70.53, H 9.87; found C 69.94, H 10.01 %

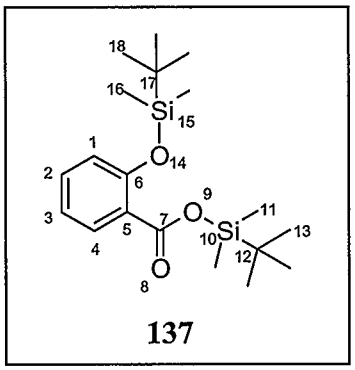
4.6.7 Preparation of [1-(4-Isopropenyl-furan-3-yl)-vinyloxy]-triisopropyl-silane (67).



67

Methyl ketone **68** (3.0 g, 9.8 mmol) was distilled and immediately dissolved in THF (50 mL) and the solution cooled to –78 °C. In a separate flask, KHMDS (2.9 g, 1.5 x 10^{-1} mmol) was dissolved in THF (200 mL) and the solution cooled to –78 °C. The ketone solution was then slowly added to the base *via* canula over 30 min. The reaction mixture was allowed to warm slowly to room temperature and after 72 h diluted with Et_2O (20 mL). The solution was then washed with brine (4 x 100 mL), dried ($MgSO_4$), filtered and reduced to give the crude product as a brown oil. Purification by flash column chromatography (100:1 hexanes:EtOAc) followed by air bath distillation under reduced pressure (bp 89-90 °C, 1.3 x 10^{-1} torr) afforded the silyl enol ether as a clear, colourless oil (1.4 g, 4.7 mmol, 48%). IR (KBr) 1634 (=C-O-) cm^{-1}; ^1H NMR (200 MHz) δ 1.07 – 1.28 (m, 21 H, H-10,11), 2.02 (s, 3 H, H-14), 4.38 (d, 1 H, J = 1.2 Hz, H-7a), 4.54 (d, 1 H, J = 1.2 Hz, H-7b), 5.03-5.08 (m, 1 H, H-13a), 5.18-5.22 (m, 1 H, H-13b), 7.25 (d, 1 H, J = 1.9 Hz, H-2), 7.48 (d, 1 H, J = 1.9 Hz, H-5) ppm. ^{13}C NMR (50 MHz) δ 150.1 (C), 139.9 (CH), 135.8 (CH), 126.6 (C), 123.9 (C), 114.9 (CH_2), 92.9 (CH_2), 22.9 (CH_3), 18.0 (CH_3), 12.7 (CH) ppm; mass spectrum, *m/z* (relative intensity, %) 306 (100, M^+), 263 (24, M^+-C_3H_7), 179 (78) amu; Exact mass for $C_{18}H_{30}O_2Si$: calcd 306.2015, found 306.2025amu: calcd C 70.53, H 9.87; found C 70.38, H 10.22 %.

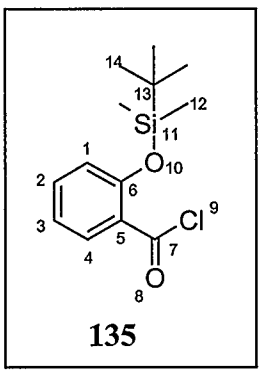
4.6.8 Preparation of *t*-Butyldimethylsilyl-2-((*t*-butyldimethylsilyl)oxy)benzoate (137).



137

TBSCl (13.7 g, 91 mmol) was dissolved in a stirring solution of DCM (50 mL) and Et_3N (12.7 mL, 91 mmol) at rt and stirred for 1 h. In a separate flask a solution of salicylic acid (5.0 g, 36.0 mmol) dissolved in a solution of DCM (50 mL) and Et_3N (5.0 mL, 36 mmol) and stirred 1 h at rt. The salicylic acid solution was then added dropwise to the TBSCl solution and allowed to stir 48 h. The reaction mixture was then diluted with toluene (500 mL) and concentrated *in vacuo* until the total volume of the solution was reduced to ~ 100 mL. The solid Et_3N·HCl was then removed using vacuum filtration and the filtrate further concentrated *in vacuo* to yield a clear lavender oil. The product was purified *via* air bath distillation under reduced pressure (bp 110-120 °C, 0.08 torr) to yield a colourless oil (10.7 g, 29 mmol, 81%). ^{1}H NMR (300 MHz) δ 0.22 (s, 6 H, H-16), 0.36 (s, 6 H, H-11), 1.01 (s, 9 H, H-13), 1.02 (s, 9 H, H-18), 6.89 (d, J = 8.2 Hz, 1 H, H-1), 6.96 (dt, J = 1.2, 7.2 Hz, 1 H, H-3), 7.36 (ddd, J = 1.5, 7.4, 8.0 Hz, 1 H, H-2), 7.75 (dd, J = 1.5, 7.7 Hz, 1 H, H-4) ppm. Spectral and physical properties were consistent with reported data.[23]

4.6.9 Preparation of 2-((*t*-Butyldimethylsilyl)oxy)benzoyl chloride (135).

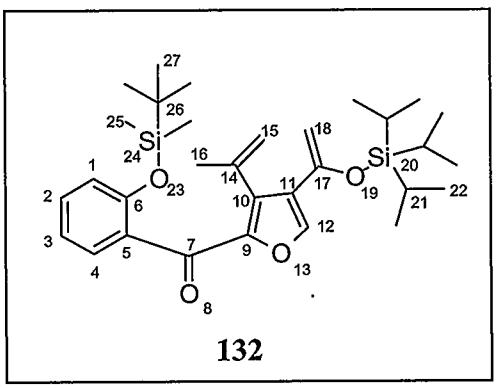


135

Disilylsalicylate **137** (3.9 g, 11.1 mmol) was dissolved in DCM (10 mL) and 3 drops of DMF were added. After cooling to 0 °C, oxalyl chloride (1.45 mL, 16.6 mmol) was added dropwise and the stirring mixture allowed to warm slowly to rt (16 h). The crude reaction mixture was then concentrated *in vacuo* to afford a yellow oil. The product was purified *via* air bath distillation under reduced pressure (bp 97-101 °C, 0.10 torr) to yield a colourless oil (2.8 g, 10.3 mmol, 92%) that was used immediately. ^{1}H NMR (300 MHz) δ 0.27 (s, 6 H, H-12), 1.03 (s, 9 H, H-14), 6.90 (d, J = 8.2 Hz, 1 H, H-1), 7.06 (t, J = 7.2 Hz, 1 H, H-3), 7.48

(ddd, J = 1.1, 7.2, 8.2 Hz, 1 H, H-2), 8.05 (dd, J = 1.5, 7.2 Hz, 1 H, H-4) ppm. Spectral and physical properties were consistent with reported data.[23,61]

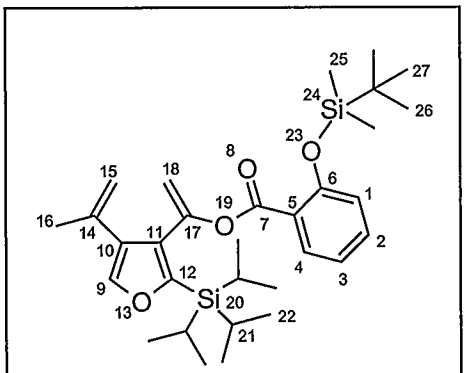
4.6.10 Preparation of [2-*t*-Butyl-dimethyl-silanyloxy)-phenyl]-[3-isopropenyl-4-(1-triisopropylsilanyloxy-vinyl)-furan-2-yl]-methanone (132) and 2-(*t*-Butyl-dimethyl-silanyloxy)-benzoic acid 1-(4-isopropenyl-2-triisopropylsilanyl-furan-3-yl)-vinyl ester (139).



132

TIPS enol ether **67** (200 mg, 0.65 mmol) was dissolved in THF (7 mL) and the resultant solution cooled to –78 °C. *t*BuLi (0.48 mL, 1.5 M in hexanes, 0.72 mmol) was then added slowly and the reaction mixture stirred for 1 h at –78 °C. The anion solution was then transferred dropwise, to a stirring solution of acid chloride **135** (190 mg, 0.70 mmol) dissolved in THF (6.5 mL) at –78 °C. The reaction mixture was then allowed to warm slowly to rt (16 h). The crude mixture was then diluted with Et_2O (20 mL), cooled to 0 °C and carefully acidified with 1 M HCl (6.5 mL). The organics were then extracted with Et_2O (3 x 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. ^{1}H NMR analysis indicated a 1.0 : 1.0 : 0.3 ratio of **132** : **139** : **67** respectively. Separation by flash column chromatography (100:1 hexanes:EtOAc) followed by a second column over neutral alumina (200:1 hexanes:EtOAc) gave two products. The less polar compound (R_f = 0.63, 15:1 hexanes:EtOAc) further purified by air bath distillation under reduced pressure (bp 143-145 °C, 0.16 torr) to yield disilane **132** as a yellow oil. IR (KBr) 1656 (C=O) cm^{-1}; ^{1}H NMR (300 MHz) δ 0.14 (s, 6 H, H-25), 0.80 (s, 9 H, H-27), 1.09-1.12 (m, 18 H, H-22), 1.23 (sept, J = 8.2 Hz, 3 H, H-21), 2.02 (s, 3 H, H-16), 4.35 (d, J = 1.5 Hz, 1 H, H-18a) 4.75 (d, J = 1.5 Hz, 1 H, H-18b), 4.95 (bs, 1 H, H-15a), 5.14 (bs, 1 H, H-15b), 6.83 (d, J = 8.7 Hz, 1 H, H-1), 7.00 (t, J = 7.7 Hz, 1 H, H-3), 7.32-7.36 (m, 2 H, H-2,4), 7.65 (s, 1 H, H-12) ppm; ^{13}C NMR (50 MHz) δ -4.3 (CH_3), 12.9 (CH), 18.1 (C), 18.2 (CH_3), 22.8 (CH_3) 25.6 (CH_3), 92.5 (CH_2), 117.7 (CH_2), 119.5 (CH), 121.2 (CH), 126.6 (C), 129.6 (CH), 131.8 (CH), 132.2 (C),

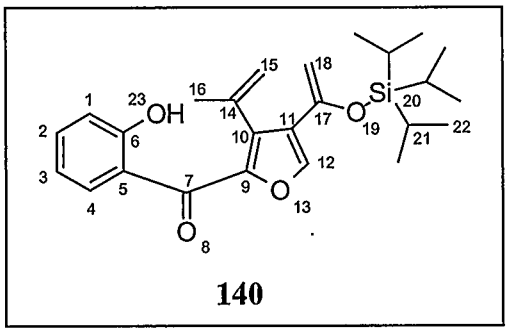
133.6 (C), 136.6 (C) 144.0 (CH), 148.6 (C), 148.8 (C), 153.4 (C), 185.5 (C) ppm; mass spectrum, *m/z* (relative intensity, %) 540 (6, M^+), 497 (6, M^+-C_3H_7), 483 (7, M^+-C_4H_9), 207 (100) amu; Exact mass for $C_{31}H_{48}O_4Si_2$: calcd 540.3091, found 540.3073 amu. Anal. for $C_{31}H_{48}O_4Si_2$: calcd C 68.84, H 8.94; found C 67.28, H 8.70 %.



139

The more polar compound (R_f = 0.86, 15:1 hexanes:EtOAc) was also further purified by air bath distillation under reduced pressure (bp 132-135 °C, 0.15 torr) to yield enol benzoate **139** as dark yellow oil. IR (KBr) 1744 (C=O) 1247 (C-O-C) cm^{-1}; ^1H NMR (300 MHz) δ 0.23 (s, 6 H, H-25), 1.04-1.10 (m, 27 H, H-22,26), 1.44 (sept, *J* = 7.7 Hz, 3 H, H-21), 2.05 (s, 3 H, H-16), 4.96, 5.21, 5.38, 5.56 (4bs, 4 H, H-15a, 15b, 18a or 18b), 6.87-6.96 (m, 2 H, H-1 or 4, H-2 or 3), 7.33 (t, *J* = 6.7 Hz, 1 H, H-2 or 3), 7.57 (s, 1 H, H-9), 7.71 (d, *J* = 6.2 Hz, 1 H, H-4) ppm; ^{13}C NMR (50 MHz) δ -4.1 (CH_3), 12.0 (CH), 18.6 (C), 19.0 (CH_3), 23.3 (CH_3) 26.0 (CH_3), 105.9 (CH_2), 113.7 (CH_2), 120.8 (CH), 121.4 (CH), 122.7 (C), 126.9 (CH), 131.4 (C), 131.6 (CH), 133.4 (CH), 135.0 (C) 143.9 (CH), 147.3 (C), 156.3 (C), 128.0 (C), 162.7 (C) ppm; mass spectrum, *m/z* (relative intensity, %) 540 (1, M^+), 235 (100, M^+-$C_{18}H_{29}O_2Si$) amu; Exact mass for $C_{31}H_{48}O_4Si_2$: calcd 540.3091, found 540.3104 amu. Anal. for $C_{31}H_{48}O_4Si_2$: calcd C 68.84, H 8.94; found C 67.16, H 8.76 %.

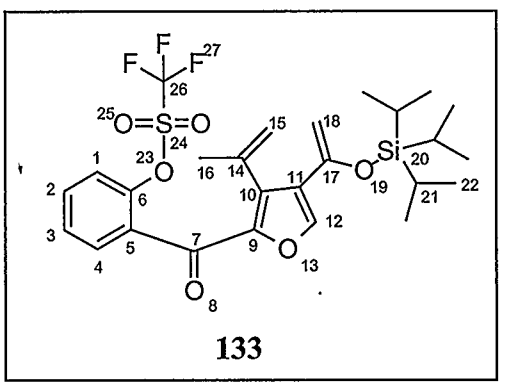
4.6.11 Preparation of (2-Hydroxy-phenyl)-[3-isopropenyl-4-(1-triisopropylsilanyloxy-vinyl)-furan-2-yl]-methanone (140).



140

Compound **132** (240 mg, 0.444 mmol) was dissolved in 40 mL of a solution of 5% NaOH in 95% MeOH with stirring. After 30 min the bright yellow reaction mixture was diluted with Et_2O (20 mL), washed with water (4 x 50 mL), dried (Na_2SO_4) and reduced to yield the crude product as a dark yellow oil. Purification by air bath distillation under reduced pressure (bp 138-141 °C, 0.13 torr) afforded the phenol (186 mg, 0.436 mmol, 98%) as a bright yellow oil. IR (KBr) 3418 (O-H) 1628 (C=O) cm^{-1}; ^1H NMR (300 MHz) δ 1.09-1.32 (m, 21 H, H-21,22), 2.14 (s, 3 H, H-16), 4.42 (d, J = 1.5 Hz, 1 H, H-18a), 4.86 (d, J = 1.5 Hz, 1 H, H-18b), 5.05 (s, 1 H, H-15a), 5.30 (s, 1 H, H-15b), 6.91-7.03 (m, 2 H, H-1,3), 7.46-7.51 (m, 1 H, H-2), 7.79 (s, 1 H, H-12), 8.23 (dd, J = 7.7, 1.5 Hz, 1 H, H-4), 12.16 (s, 1 H, H-23) ppm; ^{13}C NMR (50 MHz) δ 12.9 (CH), 18.4 (CH_3), 22.9 (CH_3), 92.9 (CH_2), 116.9 (CH_2), 118.4 (CH), 118.9 (CH), 119.4 (C), 126.6 (C), 132.3 (CH), 135.6 (CH), 136.0 (CH), 137.3 (C) 143.9 (CH), 147.7 (C), 148.3 (C), 163.6 (C), 186.4 (C) ppm; *m/z* (relative intensity, %) 426 (100, M^+), 383 (49, M^+-C_3H_7), amu; Exact mass for $C_{25}H_{34}O_4Si$: calcd 426.2255, found 426.2226 amu.

4.6.12 Preparation of Trifluoro-methanesulfonic acid 2-[3-isopropenyl-4-(1-triisopropylsilanyloxy-vinyl)-furan-2-carbonyl]-phenyl ester (133).

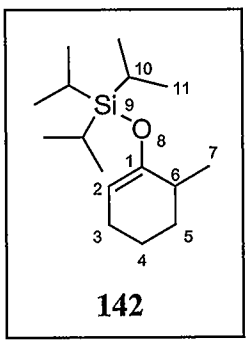


133

Compound **140** (48 mg, 0.11 mmol) was dissolved in THF (1 mL) and the solution cooled to 0 °C and slowly added to a stirring suspension of KH (5 mg, 0.12 mmol) in THF (1 mL) also at 0 °C. The bright yellow anion solution was allowed to warm to rt and stirred for 2 h. $PhNTf_2$ (44 mg, 0.12 mmol) was added in one portion

under a stream of nitrogen and the reaction mixture brought to reflux (67 °C). After 1 h TLC analysis showed the complete consumption of starting material **140** and the reaction mixture cooled to rt, diluted with Et_2O (1 mL) and quenched with water (2 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers dried (Na_2SO_4) and reduced to afford triflate **133** as a yellow oil (57 mg, 0.10 mmol, 97%). ^{1}H NMR (200 MHz) δ 1.07-1.26 (s, 21 H, H-21,22), 2.08 (s, 3 H, H-16), 4.41 (d, J = 1.7 Hz, 1 H, H-18a), 4.82 (d, J = 1.7 Hz, 1 H, H-18b), 5.06 (s, 1 H, H-15a), 5.27 (s, 1 H, H-15b), 7.35-7.66 (m, 4 H, H-1 to H-4) 7.69 (s, H-12) ppm; mass spectrum, *m/z* (relative intensity, %) 558 (19, M^+), 425 (4, M^+-SO_2CF_3), 115 (100) amu; Exact mass for $C_{25}H_{33}O_4Si$: calcd 425.2148, found 425.2143 amu.

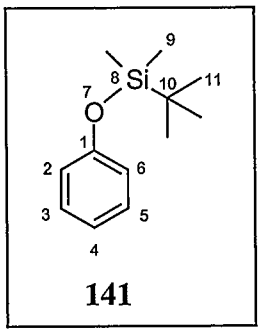
4.6.13 Preparation of 6-Methyl-1-triisopropylsilyl(oxy)-cyclohex-1-ene (142).



142

To a stirring solution of 0.5 M KHMDS in toluene (9.0 mL, 4.5 mmol) at 0 °C was added 2-methylcyclohexanone (0.28 mL, 2.3 mmol) dissolved in THF (7.5 mL) dropwise over 25 min. After stirring 35 min TIPSOTf (0.68 mL, 2.5 mmol) was added dropwise and the reaction mixture allowed to warm slowly to room temperature (18 h). The solution was then quenched with $NH_4Cl_{(sat)}$ (5 mL), washed with brine (1 x 20 mL), dried ($MgSO_4$), filtered and concentrated to give the crude product as a yellow oil. Purification by flash column chromatography (hexanes) followed by distillation (95-103°C at 20 torr) to give silyl enol ether **142** (0.83 g, 1.6 mmol, 68%) as a colourless oil. ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 1.00-1.20 (m, 24 H, H-7,10,11), 1.32-1.70 (m, 3 H), 1.72-1.84 (m, 1 H), 1.92-2.03 (m, 2 H), 2.13-2.28 (m, 1 H), 4.78 (t, 1 H, J = 3.9 Hz, H-2). Spectral and physical properties were consistent with reported data.[71]

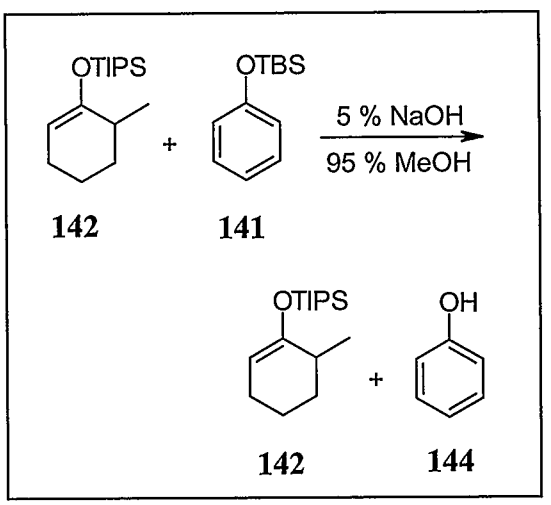
4.6.14 Preparation of *t*-Butyl-dimethyl-phenoxy-silane (141).



141

To a stirring solution of TBSCl (1.91 g, 12.7 mmol) and imidazole (1.78 g, 26.0 mmol) dissolved in DMF (50 mL) at ambient temperature was added phenol (1.00 g, 10.6 mmol) dissolved in DMF (10 mL), dropwise. After stirring 2 h the reaction mixture was cooled to 0 °C and a solution of ice-cold 5% HCl (60 mL) was slowly added. The crude material was then extracted in diethyl ether (3 x 30 mL), washed with brine (1 x 30 mL), dried and concentrated. Purification by flash column chromatography (15:1 hexanes:EtOAc) gave silyl ether **141** (1.88 g, 9.0 mmol, 85%) as a colourless oil. ^{1}H NMR (200 MHz) δ 0.14 (s, 6 H, H-9), 0.94 (s, 9 H, H-11), 6.60-7.40 (m, 5 H) ppm. Spectral and physical properties were consistent with reported data.[76]

4.6.15 Procedure for selective deprotection of a phenolic TBS group in the presence of a TIPS enol ether function.



To a 1:1 mixture of the TIPS enol ether **142** (96 mg, 0.36 mmol) and TBS phenol **141** (75 mg, 0.36 mmol) was added a solution of 5% NaOH in MeOH (19 mL) in one portion. The mixture was stirred vigorously and monitored with TLC analysis. After 20 min TLC analysis showed complete consumption of the TBS phenol concurrent with the appearance of a spot consistent in R_f and stained appearance with a known sample of phenol. A 1 mL aliquot taken, extracted with diethyl ether (3 x 25 mL), combined, dried ($MgSO_4$), filtered and concentrated to give a colourless oil which when analyzed by ^{1}H NMR gave a spectrum consistent with intact TIPS enol ether **142**.[71] Consumption of the TBS phenol was further confirmed by the absence of peaks in the aromatic region. The remaining aqueous layer was acidified

using 5% HCl, extracted with diethyl ether (3 x 25 mL), combined, dried ($MgSO_4$), filtered and concentrated to isolate deprotected phenol **144**. The while oily crystals thus obtained were analyzed by ^1H NMR and gave a spectrum consistent with commercially obtained phenol.[77]

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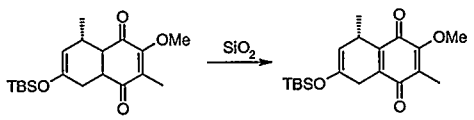
50. While attempting to isolate **105**, the formation of oxidized analogue **112** was facile. While attempting silica gel chromatographic purification on a structurally similar system:



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57. A sample of enol silyl ether **67** was prepared by dissolving the compound in $CDCl_3$, placing the sample in an NMR tube and passing dry nitrogen through the sample for 20 minutes.

58. In an attempt to confirm the results obtained by irradiation of the methyl peak, the reverse experiments were performed. Irradiation of the peak at 7.25 ppm (H_A) was hoped to result in at least a small enhancement in the methyl peak at 2.03 ppm and perhaps at 5.04 ppm (H_C) in accordance with the previous results; however, no difference in signal was observed except, of course, for that of the irradiated peak. The negative experiment was also attempted by irradiation of the peak at 7.48 ppm which, by elimination, is assumed to be $H_{A'}$ but this gave spectra showing only the irradiated peak. The negative results obtained by irradiation of the peaks at 7.25 and 7.48 ppm cannot be taken as proof that these protons are well removed from the methyl group and/or vinyl group since the difference obtained by irradiating three protons was found to be less than 1% and it is possible that the difference obtained irradiating a single proton was present but small enough to be buried in the baseline.

59. Several of the low energy conformers, including the lowest energy conformer, were found to be oriented such that the olefin of the enol silyl ether substituent and the irradiated methyl group of the propene substituent were tipped out of the plane formed by the furan ring to different degrees in the same direction as depicted for structure **67b** (Figure 3.1). This orientation, with the olefins necessarily twisted out of the plane dictated that one vinyl proton *trans* to the silyl group, H_D, be in closer proximity, on average, to the irradiated methyl protons.

60. Subsequent attempts were made to duplicate the NOE difference experiment with modest results. The effect was seen consistently in subsequent experiments at 7.25 ppm as high as 2.12% while the size of the effect tended to fluxuate at 5.04 and 4.54 ppm with signals nearly buried in the baseline and not exceeding 0.79%. The hydrogen atom at C5 could thus be assigned while further study would be required to unambiguously assign the remaining peaks.

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62. Unfortunately, the separation of the products was problematic. Successive columns were required: silica gel using 100:1 hexane:EtOAc and neutral alumina 200:1 hexane:EtOAc. Although better separation was observed with the silica gel, prolonged exposure to the acidic stationary phase resulted in partial desilation of the compound later identified as **132**. As a result, although pure samples of the two compounds were obtained, complete separation was not achieved. ^{1}H NMR analysis of the crude product of the coupling reaction showed 43.5% conversion to compound I and 43.5% conversion to compound II (13% SM).

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