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Studies directed toward the synthesis of the A-ring of taxol

Hamilton, Pauline McDonald, Ph.D.

City University of New York, 1992

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Studies Directed Toward the Synthesis of the A-ring of Taxol

By

Pauline McDonald Hamilton

A dissertation submitted to the Graduate
Faculty in Chemistry in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy, The City University
of New York.

1992

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

9/22/92 — William Frost Berkowitz
Date — Chair of Examining Committee

9/22/92
Date — Executive officer

A. D. Baker

Klaus Grohmann

Supervisory Committee

The City University of New York

Abstract

Studies Directed Toward the Synthesis of the A-ring of Taxol

By

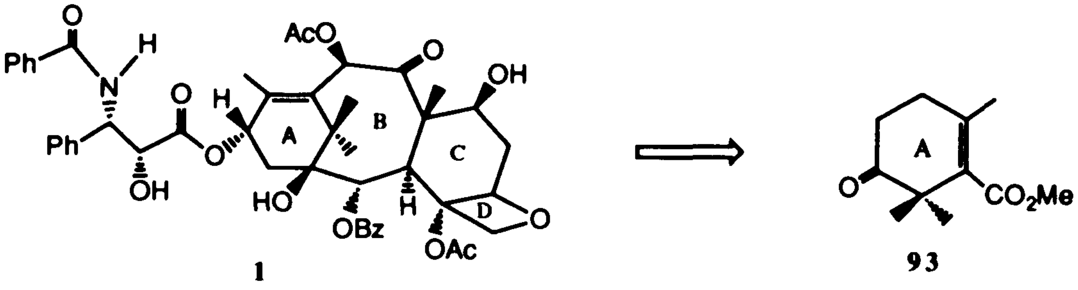
Pauline McDonald Hamilton

Advisor: Professor **W.F. Berkowitz**

Taxol **1**, a novel anticancer agent, isolated from Taxus *brevifolia*, is a member of the class of taxane diterpenes. Since its isolation and characterization (in 1971 by Wall and collaborators) many groups around the world using varied approaches have made significant contributions toward the assembly of the taxane framework and ultimately to taxol itself.

The focus of this investigation was directed towards making a fully functionalized A-ring synthon of taxol. Toward this end three approaches were explored. These approaches to the A-ring involve a Robinson annulation, an alkoxide accelerated vinylcyclobutane to cyclohexenol rearrangement (developed by Danheiser), and acid catalyzed electrophilic cyclization of geranyl acetate and its derivatives. Early difficulties with the alkoxide accelerated ring expansion approach resulted in it being aborted. The other two approaches led to interesting intermediates with the requisite

number of carbon atoms and latent functionalities. However, later efforts to transform these intermediates to the targeted A-ring synthon were futile.



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I would like also to acknowledge my colleagues (especially Irina and my lab-mates), and all members of the Chemistry Department at Queens College, for the warm and caring work environment that they shared with me. Thanks to the Chemistry Department for providing financial support through teaching assistantships throughout my stay at Queens College.

Finally, I would like to thank my friends and family for the good encouragements that they have always given me. To my wonderful husband, Uton Clive, I say thanks for the indispensable support that he has given me and for his great faith in me. Thanks also to Almighty God for life, health and a sound mind.

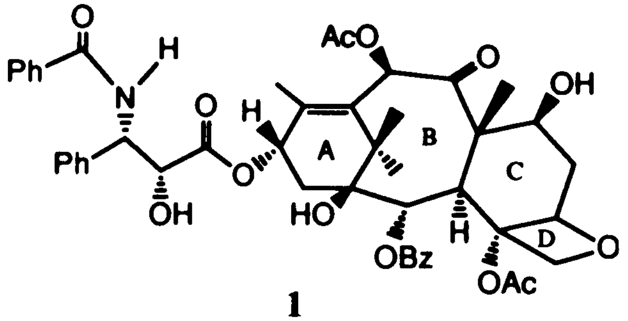
Contents

Chapter One

A brief introduction to taxol and the taxanes

1.1 Background

Taxol (**1**) and structurally related compounds[1,2] are members of a group of diterpenoids known as the taxanes. The diterpenes[3] are C_{20} compounds biogenetically derived from geranylgeranyl pyrophosphate and the taxanes are a particularly interesting group with the tricyclo [9.3.1.0]pentadecane skeleton shown by **2**. Taxol, the most complex member of this group is an important anticancer agent[4]. It has been isolated in low yield from several species (T. *cuspidata*, T. *baccata* L, T. *wallichiana* and T. *brevifolia*) of Taxus plants[1]. However, the main source has been from the bark of the pacific yew, Taxus *brevifolia*[1]. Interest in taxol started in the late 1960s when a crude extract of bark from the pacific yew was tested by the National Cancer Institute (NCI) in a large scale screening test. A few years later, taxol, the active component of the bark extract, was isolated and characterized by Wall[1] and collaborators. Extensive phase II and III clinical studies[4] with taxol confirmed activity against ovarian cancer and some leukemias, and gave indication of activity against other types of cancers[5]. The effectiveness of taxol in these studies has heightened public awareness and led to increased demand. Taxol, however, is toxic, has poor aqueous solubility and the procedure for extracting it is long, tedious and low yielding. These factors initially hampered the NCI's investigations[6] and consequently slowed the development of taxol as a drug.



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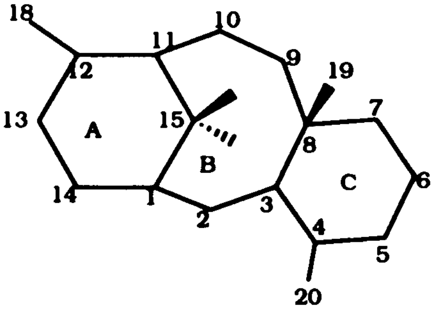
1.2 Mechanism of action

Taxol is a confirmed antimicrotubule agent with a novel mechanism of action. Microtubules are ubiquitous cellular constituents that consist of α- and β- tubulin protein subunits. They are the primary constituents of mitotic spindles (the rod-like material that is responsible for the equal partitioning of chromosomes to daughter cells). The first report of taxol's novel mechanism of action was by Horowitz[7] who in 1979 indicated that taxol was an antimicrotubule agent whose mechanism of action differs from existing antimicrotubule agents such as colchicine[8]. Taxol binds to microtubules and promotes the polymerization of tubulin dimers to stable, non-functional microtubules while other antimicrotubule agents act as promoters of microtubule depolymerization. Cells treated with taxol (0.1-10 µmol/L) form disorganized microtubules and abnormal spindles during mitotic cell division. This disrupts the substructure of cancer cells and somehow prevents their rapid division and spread. The exact mechanism of this anticancer action is not yet known but it has been speculated that taxol acts as an alkylating agent[9].

1.3 Approaches to the synthesis of taxol and the taxanes

The taxane diterpenes taxol and taxusin have been the targets of numerous synthetic efforts. The tricyclic ring system **2a** is the basic framework of these compounds.

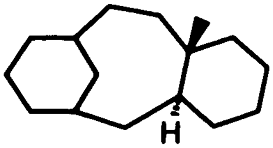
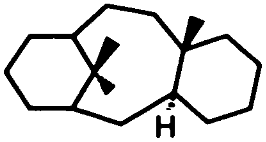
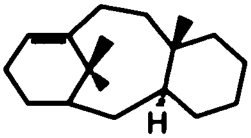


2a

The most synthetically demanding features of the taxane diterpenes are the bridgehead C_{11}-C_{12} double bond, the congested eight-membered B-ring and the trans B/C ring junction. These features and their overall complexity make the synthesis of taxanes as a group a great challenge. Another serious challenge is a possible problem with the stability of these systems. This potential problem has been addressed by Swindell[10] using MM2 force field calculations. These indicated that the taxane skeleton is relatively stable and as shown in Table 1 the A-ring is relatively unstrained despite the gem-dimethyl group and the bridgehead double bond.

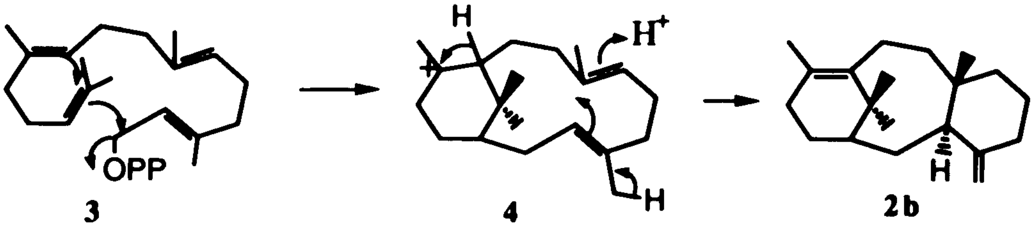
This finding is also consistent with degradative studies of Lythgoe[11a,b], as well as Halsall and Della Casa de Marcano[11c].

Table 1: Swindell's MM2 calculations (kcal/mol)

taxane skeleton	ΔH^{o}_{f}	strain energy
	-46.05	33.09
	-51.20	43.72
	-27.11	42.21

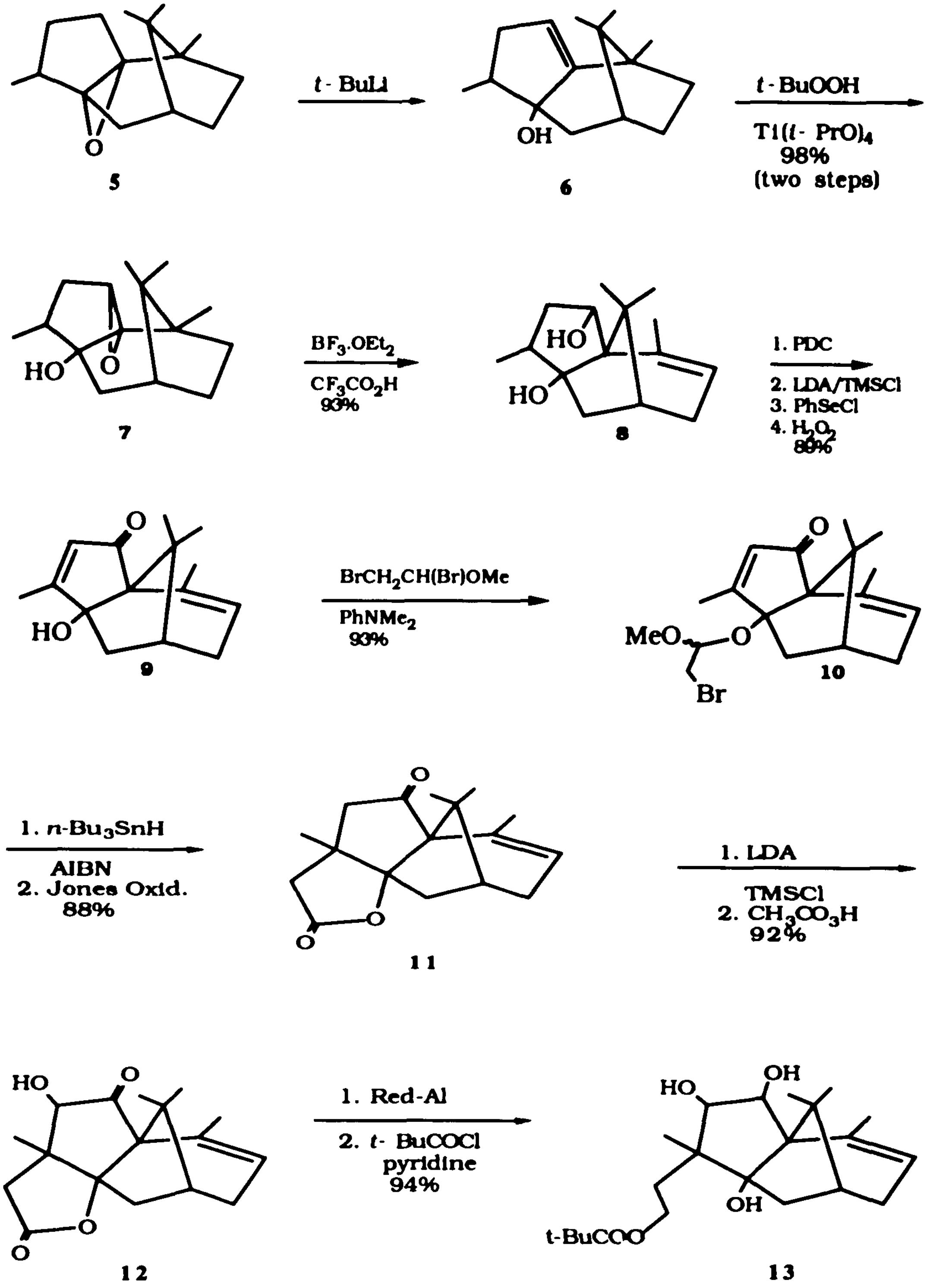
The biosynthetic route to biologically active naturally occurring compounds such as the taxanes is usually of interest to synthetic chemists[12]. The first investigation of biosynthesis (of the taxanes) was by Lythgoe[11b] who in 1966 indicated that there was a biogenic link between the taxane diterpenes and cembrene[13] (the first naturally occurring C_{14}-monocyclic diterpene to be characterized). He also proposed a biogenetic route (Scheme 1) to the taxanes that involves the cyclization of geranylgeranyl pyrophosphate, but to date there has been no confirmation.

Scheme 1: Proposed biosynthesis of the taxane diterpenes

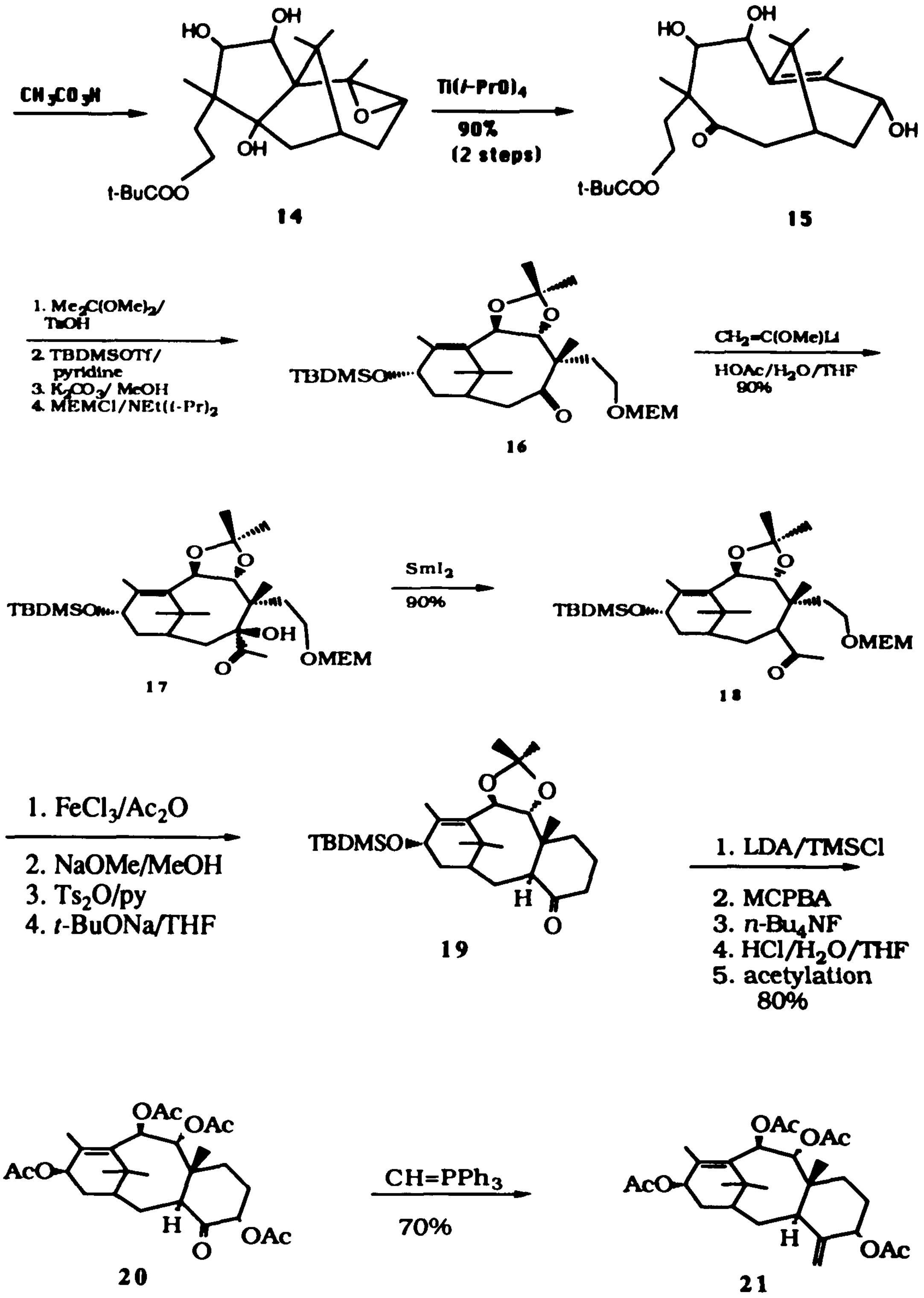


Unlike the biosynthesis, the total synthesis of the taxanes has received much attention and the chemical literature is replete with significant contributions from researchers around the world. In most of these syntheses, however, the emphasis is on assembling the taxane skeleton[14,15] rather than taxol itself. The types of reactions employed in the construction of the taxane systems include Diels-Alder[15a-d], intramolecular carbonium ion induced cyclization[15e-g], rearrangement (oxy-Cope, Claisen and fragmentation)[15h-k], photochemical[14a,15l-r], and nickel catalyzed cycloaddition[15s-t]. So far, the only total synthesis of a naturally occurring taxane diterpene, taxusin(**21**), has been achieved by Holton[15k] via carbonium ion induced fragmentation of patchoulene oxide **5**. The key step in this synthesis (Scheme 2) is the fragmentation of the unstable bicyclic epoxy alcohol **14** in the presence of $Ti(i\text{-}PrO)_4$ to give the AB-ring system **15**. Subsequent modification led to compound **21**.

Scheme 2: Holton's total synthesis of taxusin, **21**

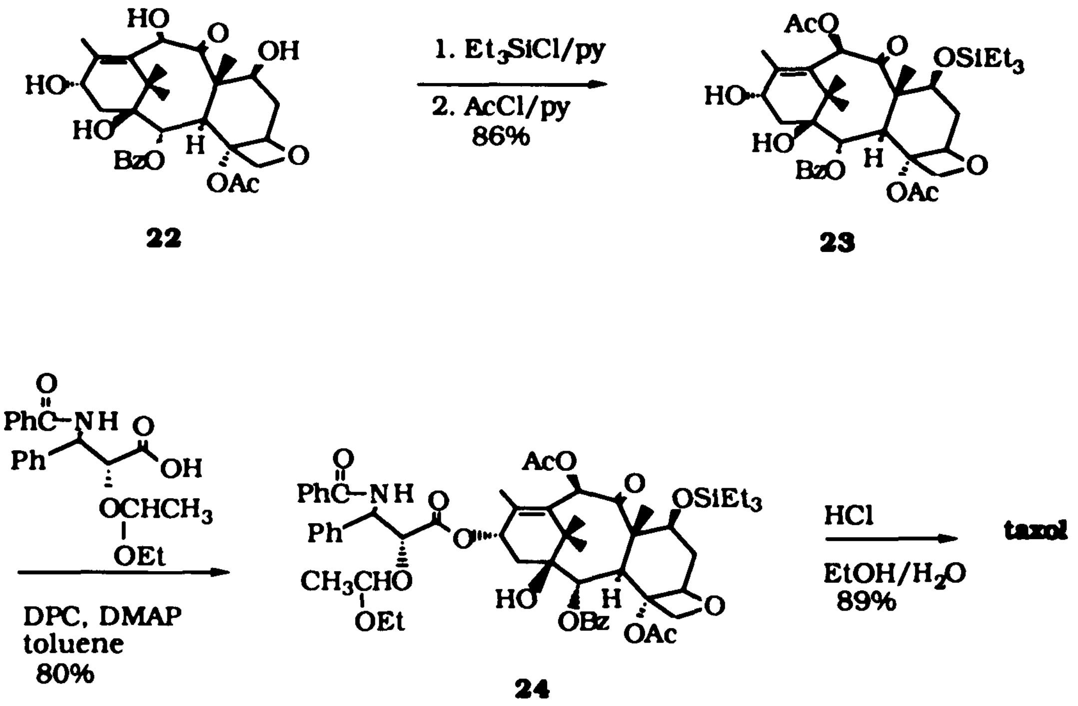


Scheme 2 (contd.)



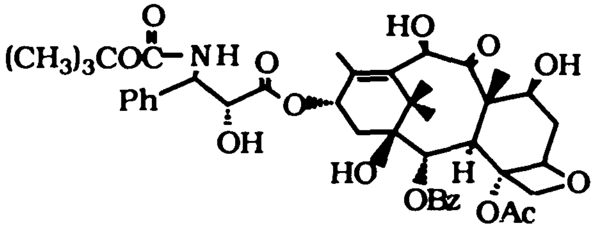
The total synthesis of taxol remains as yet an unattained goal. However, Greene[16] has reported the partial synthesis from naturally occurring 10-deacetyl baccatin III (**22**) as shown in Scheme 3.

Scheme 3: Greene's hemisynthesis of taxol



There have also been reports of very efficient syntheses of the taxol side chain[17]. With the availability of 10-deacetyl baccatin III (obtained from easily regrown Taxus leaves) and the improved syntheses of the taxol side chain, the hemisynthesis of taxol is a feasible alternative to the total synthesis as a way to provide taxol to meet clinical demands.

In addition to the partial synthesis of taxol there are several reports of semisyntheses of closely related analogues of taxol[18]. To date, the most interesting analogue is taxotere (**25**)[17b], a very potent anticancer agent also prepared from the naturally occurring 10-deacetyl baccatin III in a manner similar to Scheme 3.

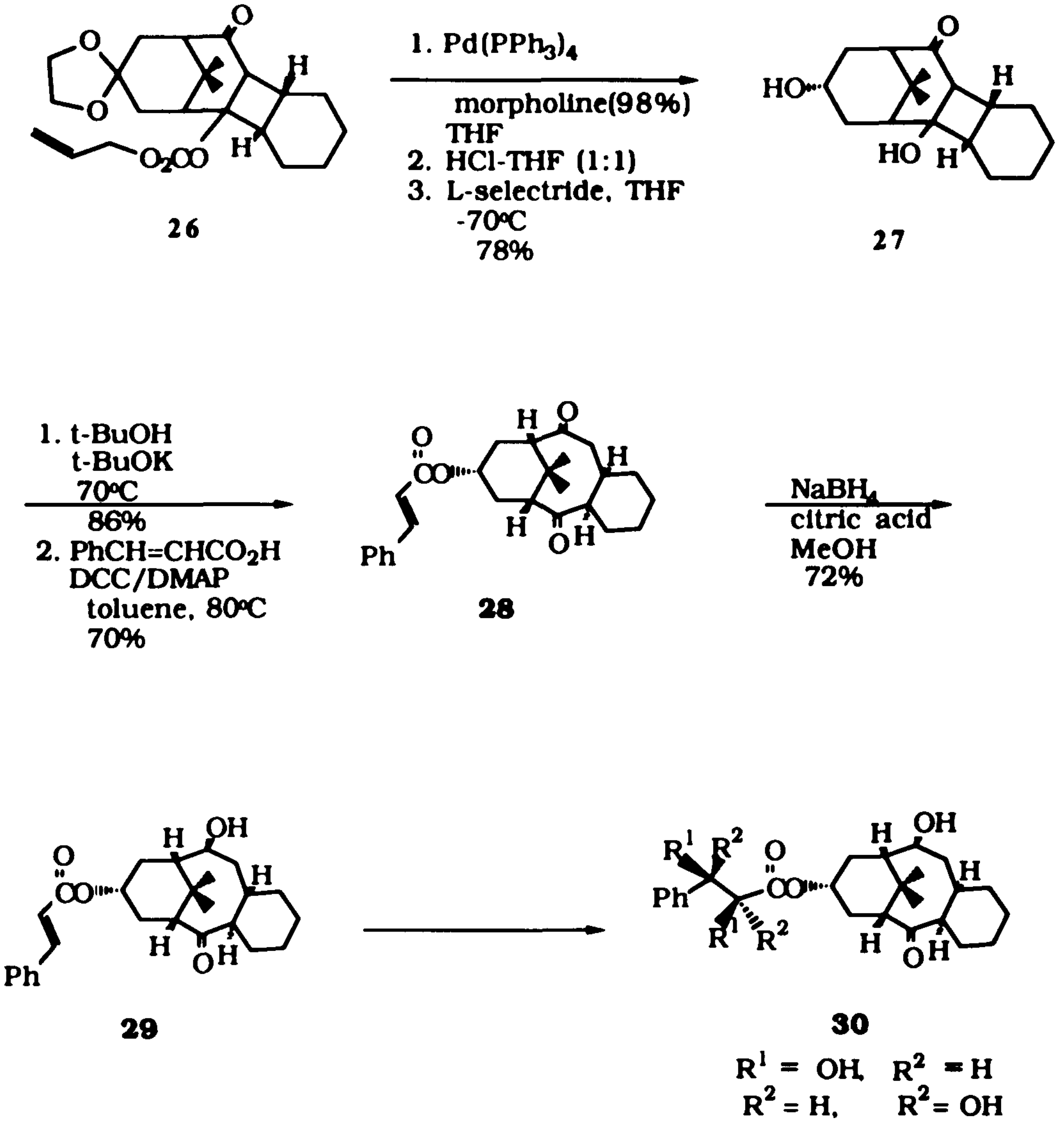


25

Taxotere differs from taxol only in the C_{13} ester side chain and at C_{10} where a hydroxyl group is in place of the acetoxy group. However, taxotere shows greater aqueous solubility and is presumably more potent[19] than taxol. Most of the analogues prepared so far differ only in the side chain[18] hence they, like taxol, show (varying degrees of) biological activity.

Recently however, Blechert[15r] reported the synthesis (Scheme 4) of a less functionalized analogue, **30** that inhibited the depolymerization of tubulin. That report is very encouraging as it shows that it is possible to develop simplier, yet biologically active analogues.

Scheme 4: Blechert's synthesis of a less functionalized analogue



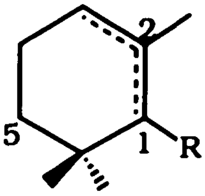
Although there has been some progress in the efforts directed toward the synthesis of taxol (and related species), to date the only source of taxol for clinical studies is the bark of the pacific yew tree. Stripping the trees of the bark in order to isolate taxol is a threat to this plant species (it takes about three trees to provide enough drug to treat each patient). This threat is a serious concern to environmentalists who are concerned not only about the massive distruction of the yew population but also about disturbing its natural habitat. This concern has prompted many researchers to start investigating alternate sources[20] of taxol. Some of these include extraction from Taxus leaves {leaves have (20-70 ppm) lower concentration than bark (70-400 ppm) but are quickly regrown}, large scale cultivation of yew plants[20b] and cell and tissue culture production[20b]. These investigations are essentially in the developmental stages but in the long term might lead to "an environmentally correct" as well as a convenient source of taxol for clinical use.

Chapter Two

Approaches to the A-ring of taxol and related compounds

The A-ring of taxol with its bridgehead double bond, gem-dimethyl and oxygen functions at C_1 and C_{13} (taxol numbering) presents an enormous synthetic challenge. Adding to this challenge is the fact that both the C_1 hydroxyl and the C_{13} ester side chain are essential for biological activity. It is not surprising then that the emphasis of several investigations has been on the synthesis of the A-ring either by itself or as part of the ABC-ring framework. In this chapter the syntheses of some A-ring type species will be reviewed.

A literature search reveals that six-membered ring moieties such as **31** are present in many natural products[3], and that many such species have been synthesized by a number of groups.



31

However, in most of these systems the C_5 position as shown by **31** is unsubstituted, whereas a suitably functionalized A-ring synthon of taxol needs an oxygen function at this position in order to generate the C_1 hydroxyl (of taxol). The remainder of this chapter will focus on the syntheses of some systems that have C_5 substituents which may or may not be oxygen.

2.1 Substituted cyclohexanes from geranyl acetate and derivatives

There are many reports of attempts to convert geranyl acetate and derivatives to systems closely related to the A-ring, although for the most part without regard to their application in the synthesis of the taxanes[21]. For many of these cyclization reactions complex mixtures of products are reported. Table 2 lists a number of these reactions that give isolable products in low to moderate yields.

Table 2: Cyclization of geranyl acetate and derivatives

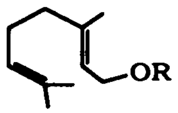
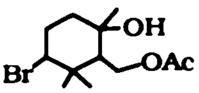
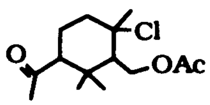
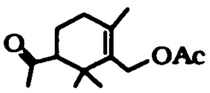
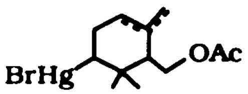
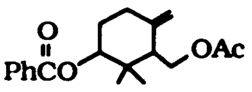
compound	conditions	product(s)/(%yield)	references
 **32** R= Ac	$Br_2/SnBr_4$, CH_3NO_2/H_2O	 **33** (16%)	22
	$AlCl_3/AcCl$ $CH_2Cl_2/0°C$	 **34** (44%)	21
	$SnCl_4/AcCl$ $CH_3NO_2/0°C$	 **35** (31%)	21
	$Hg(TFA)_2$ CH_3NO_2	 **36** (24%)	23
	 $\mathrm{Ph\overset{\overset{O}{\|}}{C}OO\overset{\overset{O}{\|}}{C}Ph}$ CuCl $(PhCOO)_2Cu$ PhH/reflux	 **37** (58%)	24

Table 2 (contd.)

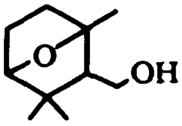
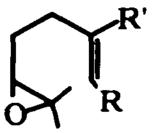
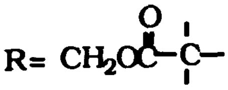
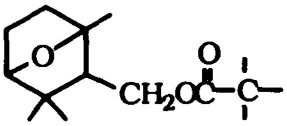
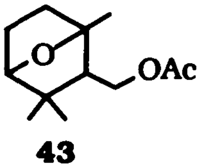
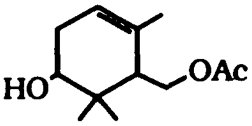
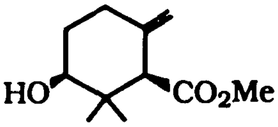
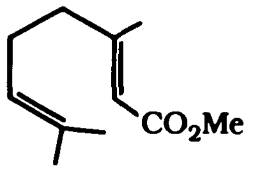
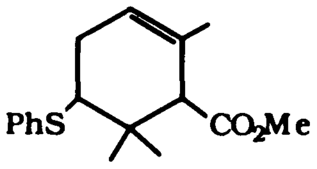
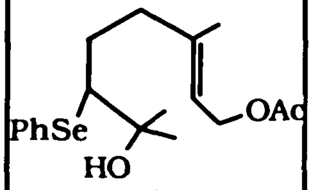
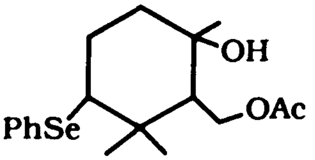
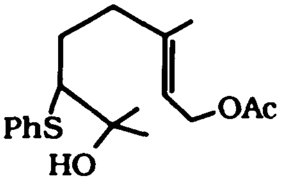
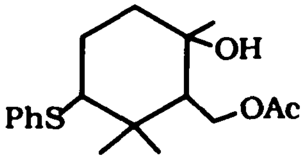
compound	conditions	product(s)/(% yield)	references
38 R=H	$Tl(ClO_4)_3$	 **39** (31%)	25
  $\mathrm{R= CH_2O\overset{O}{\overset{\|}{C}}-\overset{\|}{\underset{\|}{C}}-}$ R'=Me; **40**	$SnCl_4$/0°C CH_2Cl_2	 **41** (85%)	26
R= CH_2OAc R'= Me; **42**	$SnCl_4$/0°C CH_2Cl_2	 **43**	26
	85%H_3PO_4 0°C	 **44**	27
R= CO_2Me R'= CH_2TMS **45**	$BF_3.OEt_2$ or $SnCl_4$	 **46** (80%)	28

Table 2 (contd.)

compound	conditions	product(s)/(% yield)	references
 **47**	PhSBF$_4$ CH$_3$NO$_2$ -25°C	 **48** (57%)	29
 **49**	TFA/CH$_2$Cl$_2$ 0°C	 **50** (65%)	30
 **51**	TFA/CH$_2$Cl$_2$ 0°C	 **52** (53%)	31

Although most of the cyclized products in Table 2 possess the basic framework of the A-ring, further elaboration is necessary in order to obtain a suitably functionalized A-ring synthon of taxol. Furthermore, these results indicate that good yields of the cyclized products are obtained only when geranyl acetate is derivatized as shown by the pivalate **40** and the allylsilane **45**. Compounds **43** and **44** both have oxygen functions at C$_5$ but they were formed from geranyl acetate in only very low yield.

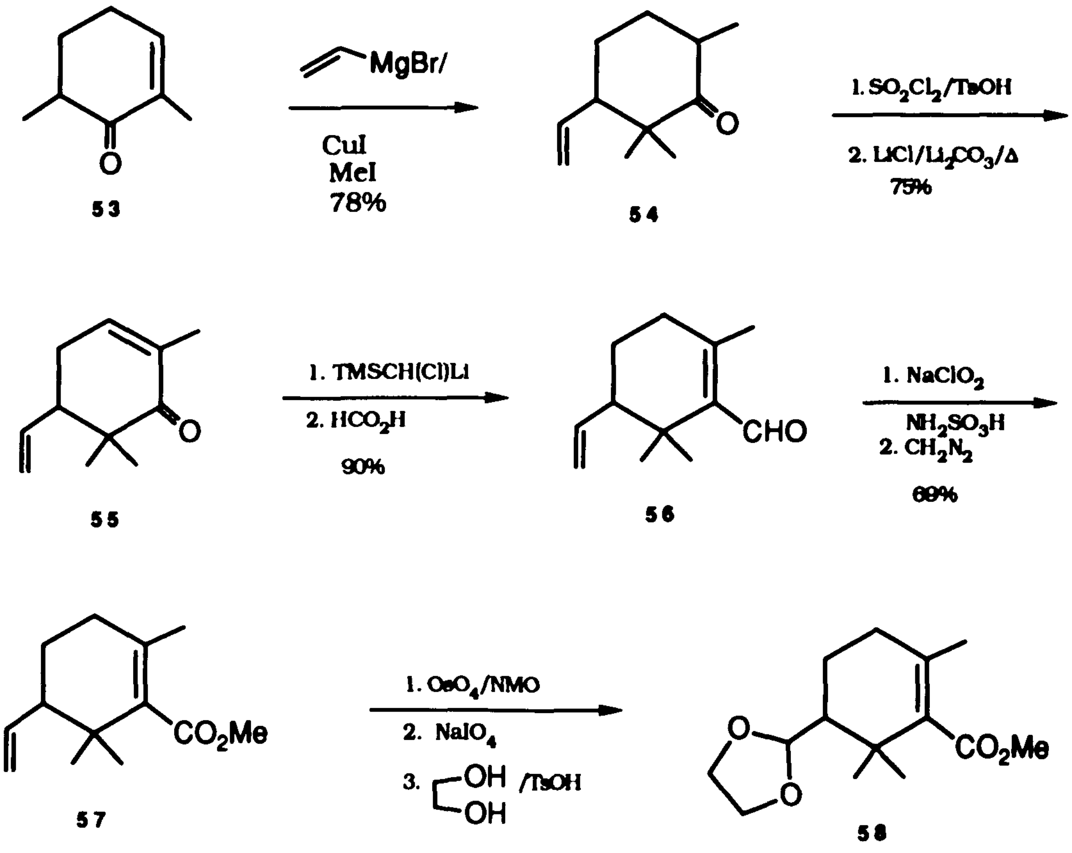
2.2 Modification of cyclic systems

In this section some approaches to the A-ring of the taxanes involving the modification of other ring systems will be briefly mentioned.

2.2.1 Kende's approach

In 1986 Kende[15e] reported the synthesis of a taxane triene obtained through the coupling of A and C ring intermediates. The initial focus of his work was on the preparation of the A-ring **58** from commercially available 2,6-dimethyl-cyclohexenone as shown in Scheme 5.

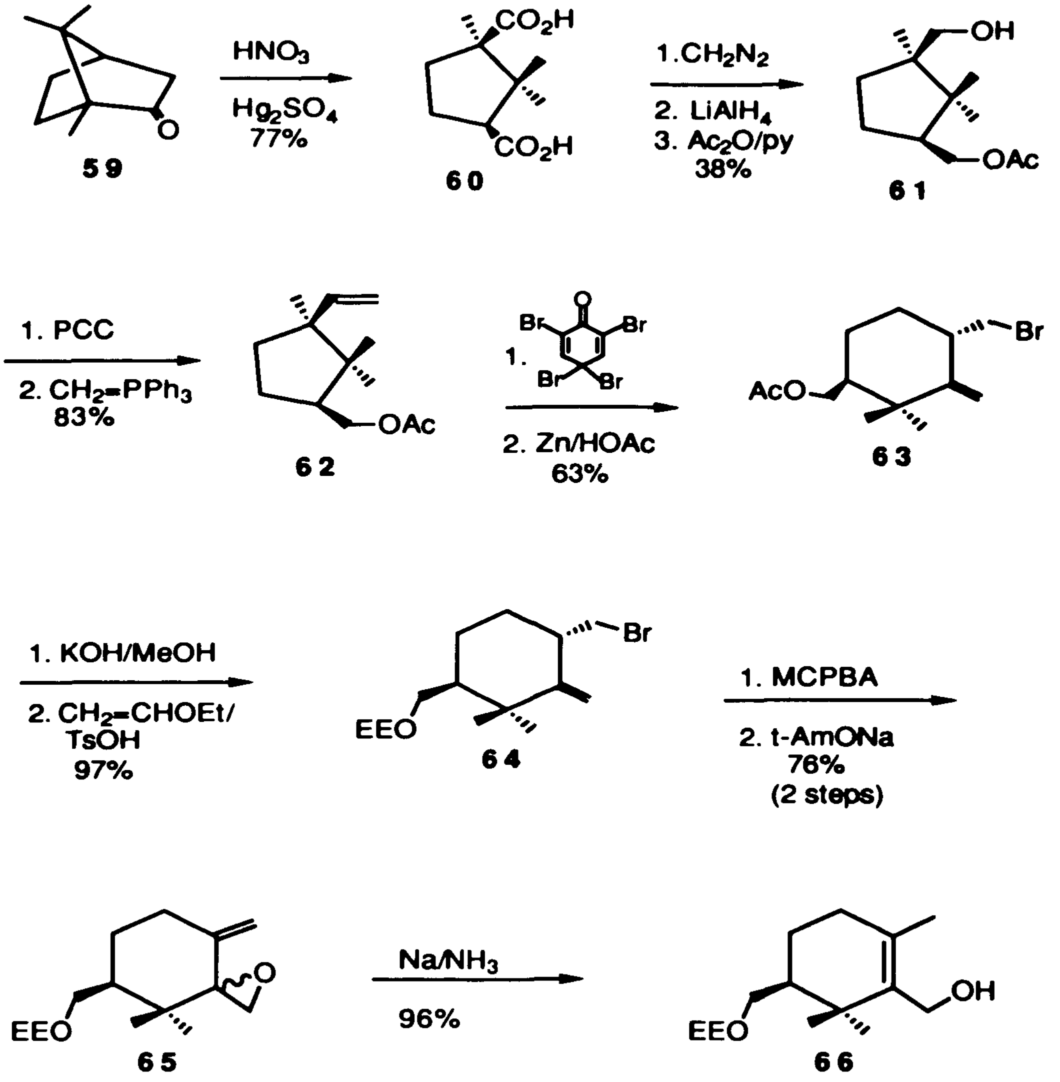
Scheme 5: Kende's approach to the taxane A-ring



2.2.2 Kitagawa's approach

In another approach to the A-ring of the taxanes Kitagawa[32] prepared compound **66** from d-camphor **59** as shown in Scheme 6. The key step in this approach is the ring expansion rearrangement reaction of **62** involving the migration of the less substituted homoallylic cyclopentane carbon to the cyclohexane system **63**.

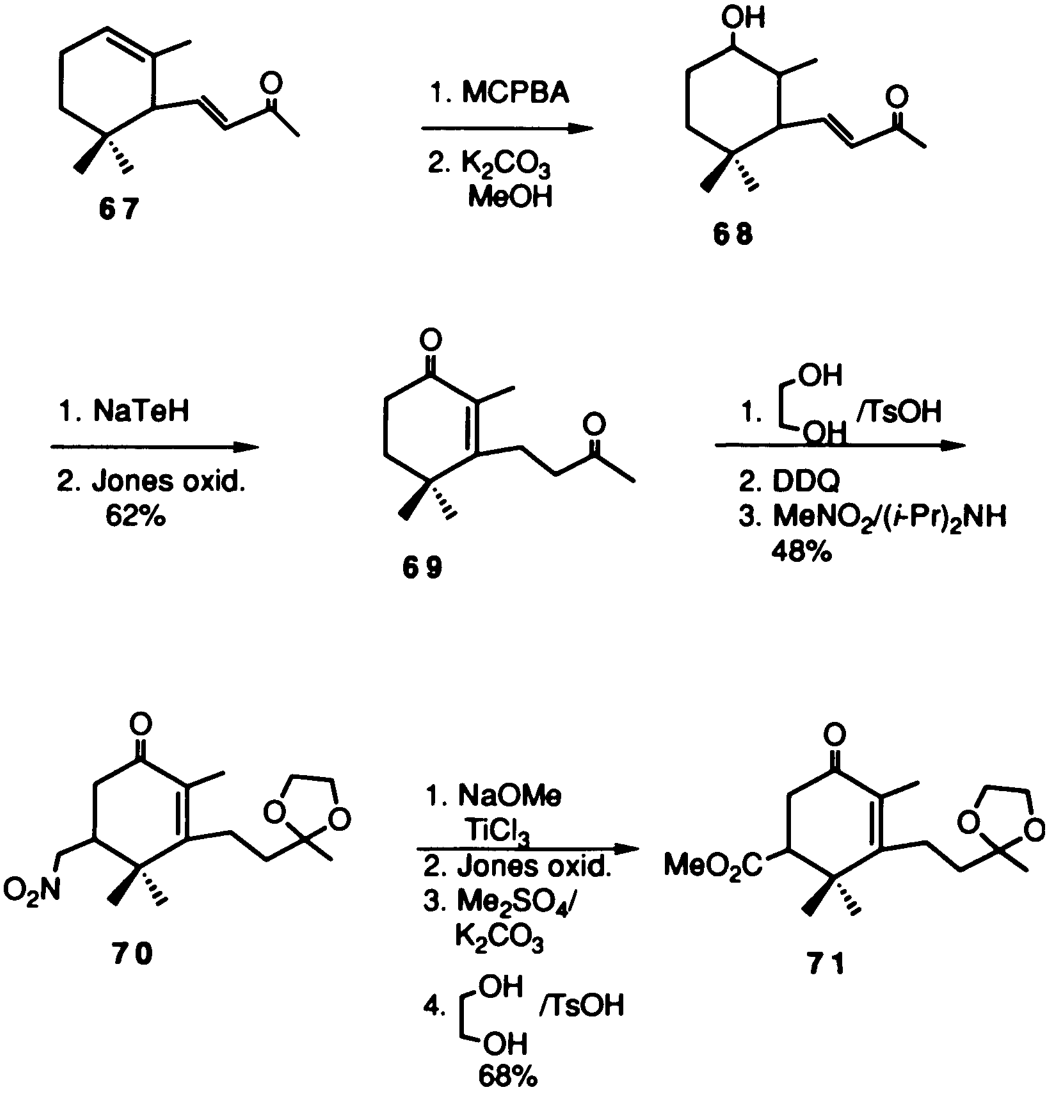
Scheme 6: Kitagawa's approach to the A-ring of taxanes



2.2.3 Oishi and Ohtsuka's approach

Another structurally related compound (**71**) was prepared by Oishi and Ohtsuka[15f] from α-ionone as shown in Scheme 7.

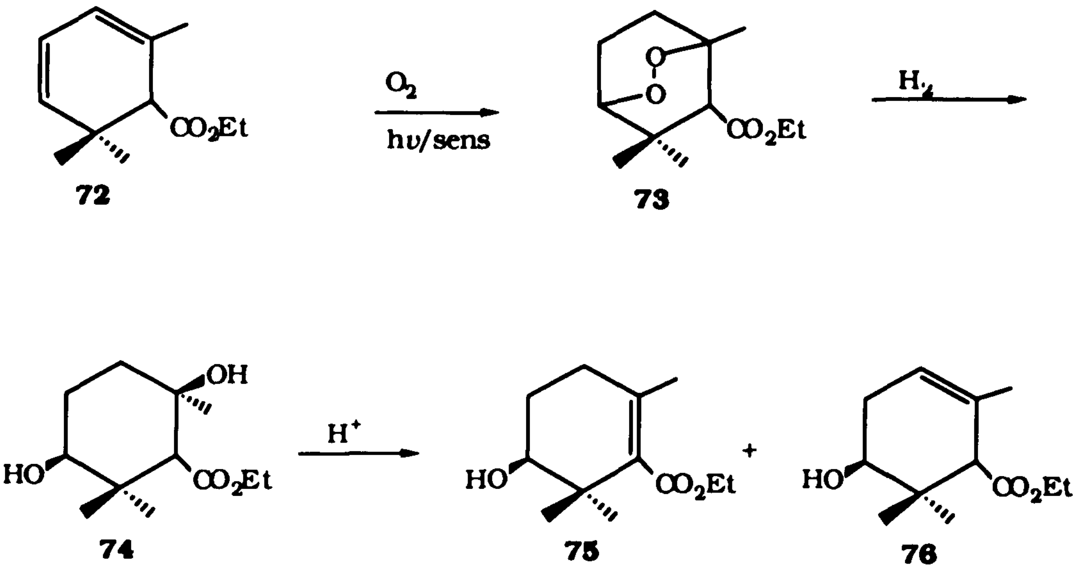
Scheme 7: Oishi and Ohtsuka's approach to the taxane A-ring



2.2.4 Kaiser's approach

In 1978 Kaiser and Lamparsky[33] reported the synthesis of the ester **75** (~7%) and its double bond isomer **76** (53%) via photo-oxidation and subsequent reduction of ethyl α- safranate as outlined in Scheme 8. This synthesis however, appeared to have been conducted without regard to any involvement in the synthesis of the taxanes.

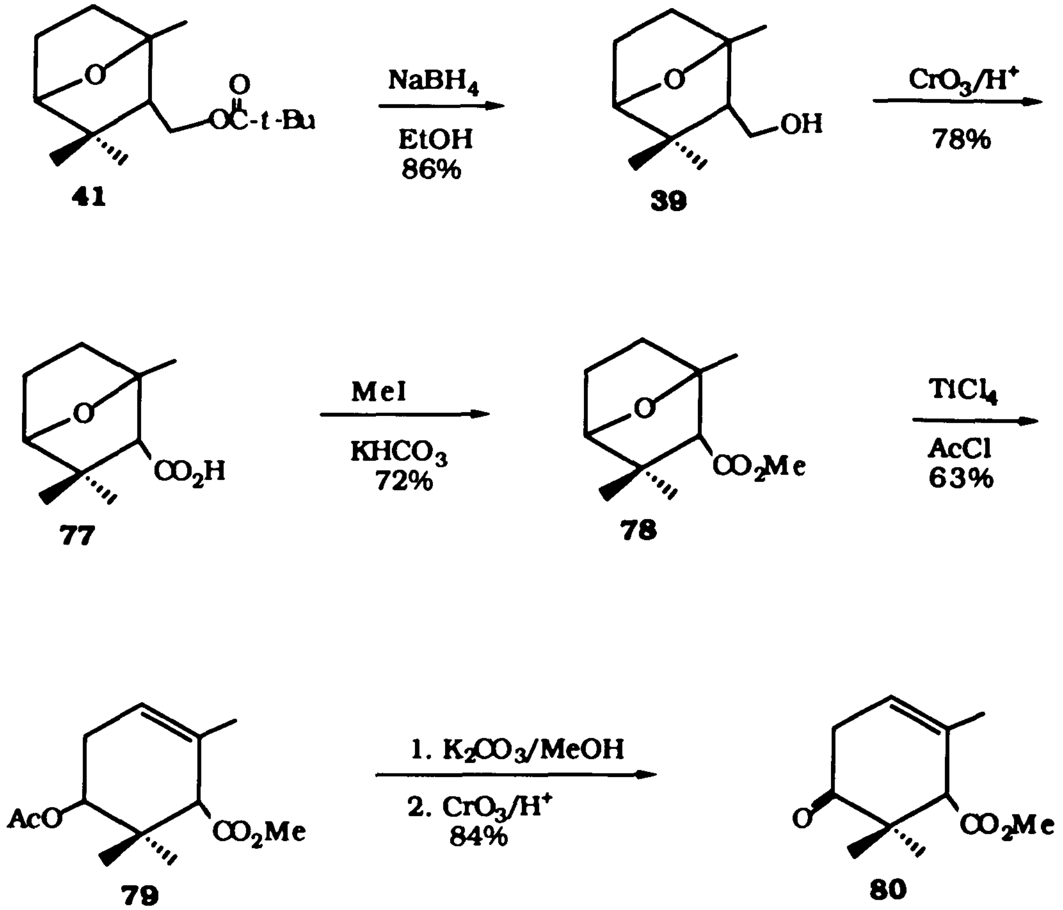
Scheme 8: Kaiser and Lamparsky's synthesis of related species



2.2.5 Berkowitz's approach

Recently Berkowitz and Wilson[34] prepared the A-ring synthon **80** according to Scheme 9. In this series of reaction the bicyclic ether **41** (originally prepared by Rouessac[26], see Table 2), was modified through conversion of the pivalate to the methyl ester followed by cleavage of the ether bridge with $TiCl_4$ and acetyl chloride.

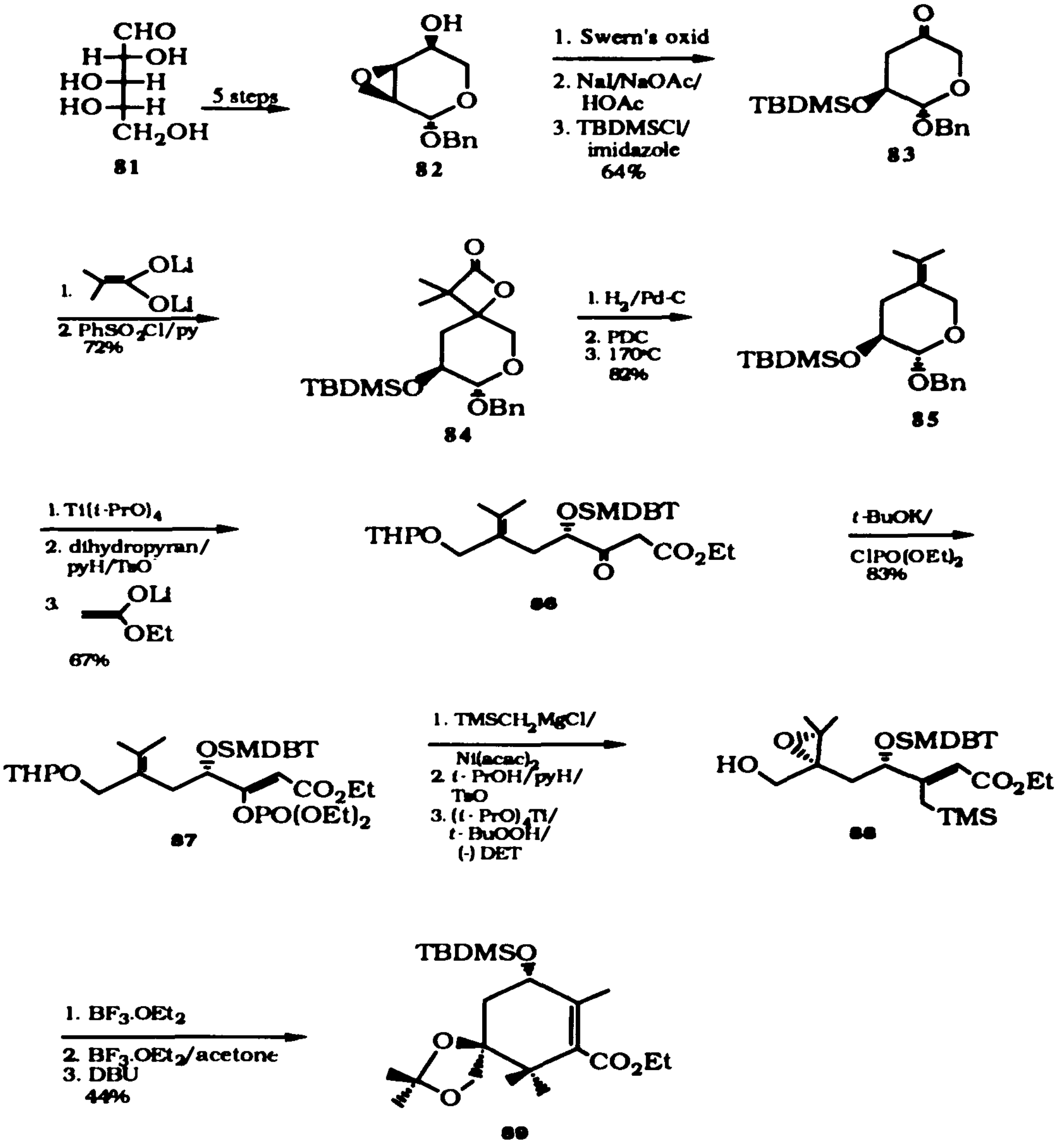
Scheme 9: Berkowitz's approach to the A-ring of taxol



2.2.6 Frejd's approach

To date the most functionalized A-ring synthon, **89** has been prepared by Frejd^{35}. Compound **89** was prepared via a 23-step enantioselective synthesis from L-arabinose as shown in Scheme 10.

Scheme 10: Frejd's approach to the A-ring of the taxanes



One of the key steps in Frejd's synthesis of the A-ring moeity **89** is the Lewis acid catalyzed cyclization of the acyclic intermediate **88**. This reaction, however, does not give the desired product unless the trimethylsilyl group is present.

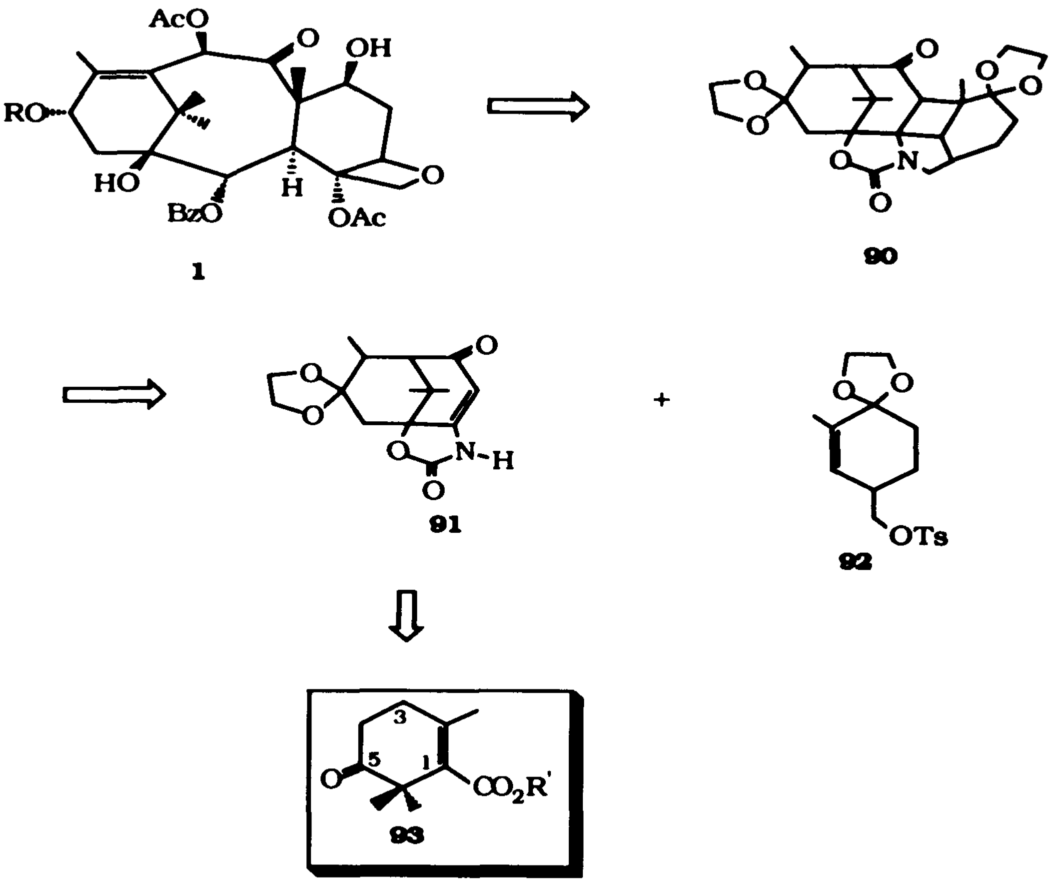
In addition to the syntheses outlined above, the A-ring has also been prepared via intramolecular Diels-Alder reaction[15a,b] as part of the ABC-ring system.

Chapter Three

Results and Discussion

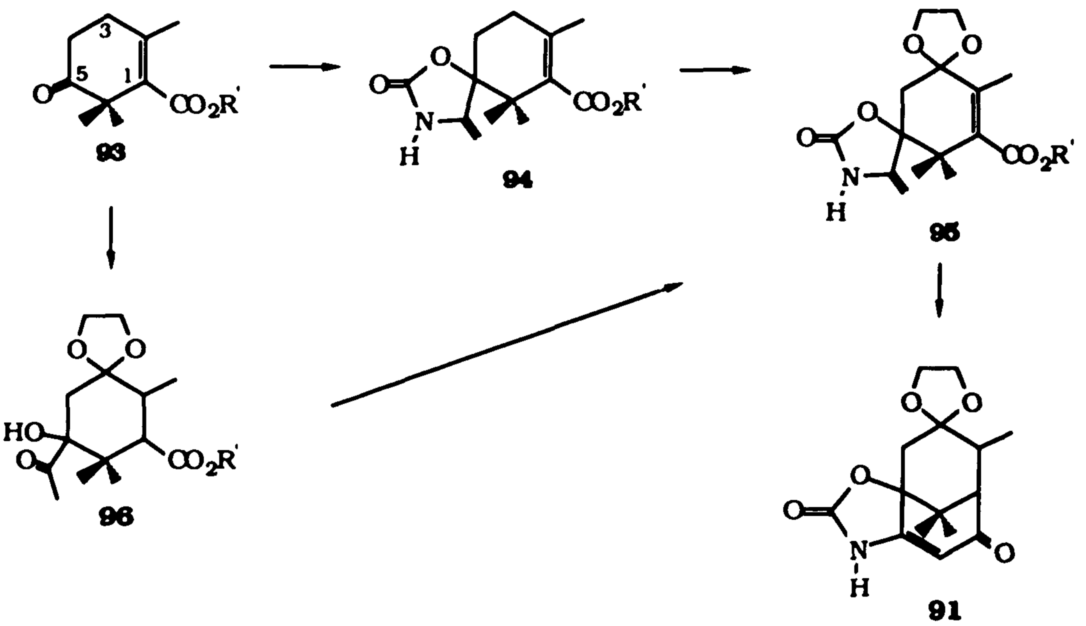
The focus of this investigation was to develop an approach to the A-ring of taxol. In order to do that a retrosynthetic analysis was performed as shown in Scheme 11. The target compound **93** was required as part of a larger goal[14a] which is to effect a total synthesis of taxol. The key step in this approach to taxol involves a photochemical [2+2] addition[36] and subsequent de Mayo[37] type fragmentation.

Scheme 11: A retrosynthetic analysis for taxol



Compound **92**, the C-ring synthon, has been prepared in our laboratory by Subasinghe[31]. The carbamate **91**, however, has not yet been prepared but a convenient route to its synthesis has been proposed as outlined in Scheme 12. Compound **93** was chosen as the A-ring synthon because it is expected to give upon further elaboration the fully functionalized A-ring of taxol, that is, the keto group at C_5 will provide the C_1 hydroxyl of taxol, a key feature which is not incorporated in the total syntheses of the taxane skeletons reported to date. Also an oxygen function can be introduced at C_3 through allylic oxidation to provide the C_{13} side chain of taxol, another feature which is absolutely essential for biological activity.

Scheme 12: A design for the synthesis of compound **91**

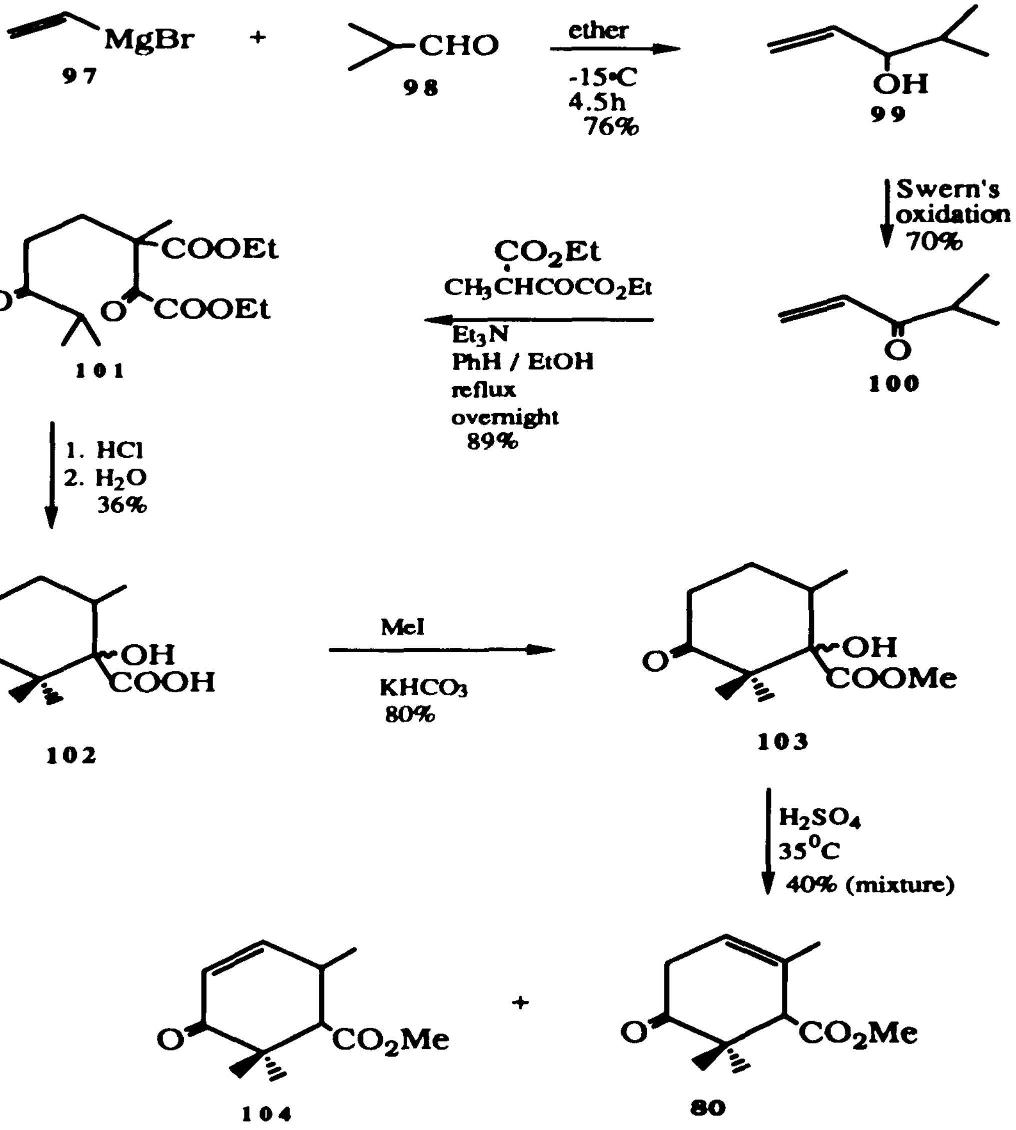


As pointed out above the goal of this investigation was to make the A-ring synthon **93**. Toward this end three approaches employing (a) Robinson annulation (b) alkoxide accelerated vinylcyclobutane rearrangement and (c) acid catalyzed cyclization of geranyl acetate derivatives were investigated. At this juncture however, one might ask why target a compound (see compound **75**) that has essentially been made? The answer simply is that the reported yields in the case of compound **75**[33] and closely related analogues (**44**, **76** and **80**) are inadequate. In addition, (except for **75**) no one has yet made an A-ring synthon that can easily generate a fully functionalized taxol A-ring that can be incorporated in our proposed total synthesis. Furthermore it was hoped that this investigation would lead to a convenient synthesis of the A-ring synthon in a minimum number of steps.

The Robinson annulation approach

Our initial approach to the preparation of the A-ring synthon involved a Robinson annulation (Scheme13). This approach was previously pursued by Rao[38,39]. However, there were some changes. The oxidation of the allylic alcohol **99** was conducted via Swern oxidation in 70% yield and not by Jones oxidation (38% yield) as reported by Rao. The oxidation was also conducted with γ-MnO_2, and sodium hypochlorite but a low yield of product was obtained with the former and addition to the double bond occurred with the latter. The α-hydroxy acid **102**, formed by tandem Michael-Aldol condensation of compound **100** was expected to dehydrate under the reaction conditions to give the corresponding α, β- unsaturated acid, according to a similar reaction of Goldsmith[39]. This dehydration, however, did not occur. The acid was then converted to the methyl ester **103** (because it was easier to work with and to analyze by GC-MS) and dehydration (with P_2O_5, HMPA, and CH_3SO_2Cl/DMAP) attempted. A complex mixture

Scheme 13: The Robinson's annulation approach to the A-ring



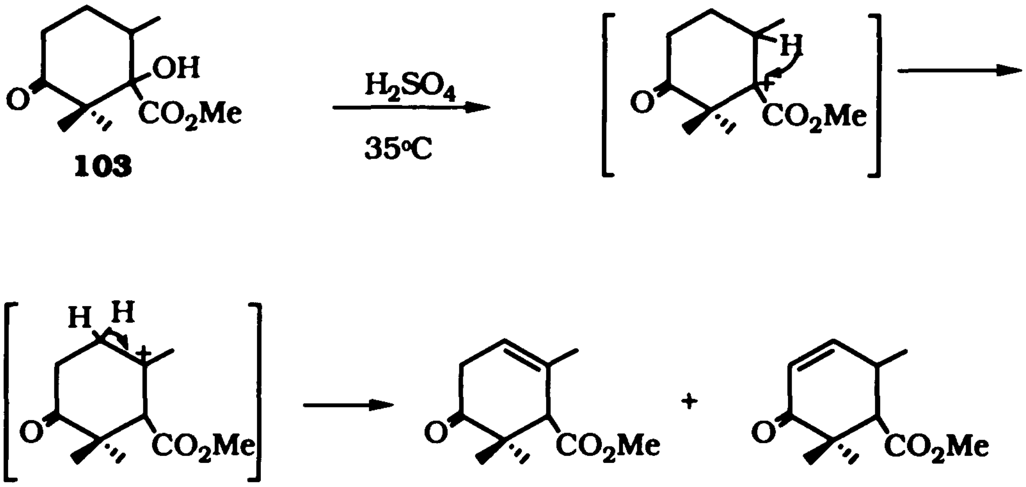
resulted with P_2O_5, and no reaction was observed with the others. Prior attempts by Rao[38] (with $SOCl_2$, SO_2Cl_2, $POCl_3$, and MsCl/DBU) to execute the dehydration were also unsuccessful. Only in concentrated sulfuric acid was there any detectable dehydration product. With warm concentrated sulfuric acid, Rao observed by GC-MS two dehydrated components which supposedly were the target compound **93** and its double bond isomer **80**, as well as a number of other components, none of which was isolated and characterized. With concentrated sulfuric acid at 35 °C from 2-4 hours, we were able to obtain a less complicated mixture (of three new components plus starting material) as shown by TLC. Purification by PLC and then by HPLC gave one major and a minor component each with a molecular mass of 196 (m/e 214-18(H_2O)), corresponding to the dehydration product. The IR of the major compound showed two carbonyl absorptions at 1730 and 1680 cm^{-1} indicating the presence of a saturated and a conjugated carbonyl group, respectively. The proton 60 MHz NMR spectrum showed peaks at δ 1.10 (m, 9H, triplet of 3H on narrow doublet of 6H), 2.40 (m, 2H), 3.75 (s, 3H), 5.80 (dd, 1H), and 6.60 (dd, 1H). The spectral data fit the structure assigned to compound **104**. The structure was also authenticated by $UV_{(MeOH)}$ which gave λ max at 223 nm (ε, 9,939). This compared with the calculated value of 227 nm ± 5 nm indicating the presence of a conjugated enone system.

The minor compound showed peaks in the proton NMR at δ 1.10 and 1.17 (two s, 3H each), 1.83 (s, 3H), 2.90 (m, 3H), 3.65 (s, 3H) and 5.65 (br. s, 1H) corresponding to compound **80**, also prepared by Wilson[34] via Lewis acid catalyzed electrophilic cyclization as shown in Scheme 9.

The resistance of the α-hydroxy ester **103** to dehydration was probably due in-part to the electron withdrawing effect of the ester group since formation of a carbonium ion alpha to an ester group is expected to lead to an unfavorable transition state. The resistance to dehydration could also be due to steric hindrance since attempts to replace the hydroxyl group with a better (though bulkier) leaving group also failed.

The proposed mechanism for the dehydration reaction to the isomeric mixture of compounds (Scheme 14) shows an hydride transfer to C_1 giving a more stable carbonium ion intermediate which loses a proton to give compound **80**. Compound **104** was most likely obtained through the isomerization of **80**.

Scheme 14: Mechanism for the dehydration of compound **103**



103

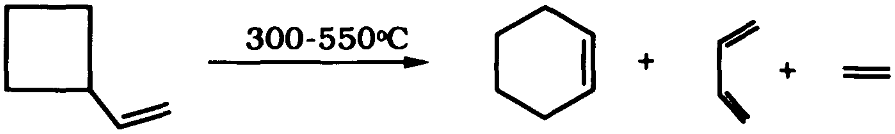
80

104

Although there was good indication that both compound **80** and its double bond isomer **104** were synthesized via the Robinson annulation approach outlined in Scheme 13, the yields were very poor and therefore not adequate for further work. Failing to satisfactorily complete the synthesis of compound **93** via Scheme 13 we turned our attention to a four to six-membered ring expansion rearrangement reaction developed by Danheiser[40].

Alkoxy accelerated vinylcyclobutane rearrangement

Although the vinylcyclobutane to cyclohexene rearrangement[41] shown in eqn.1 has been known for a long time, it is only recently that this method has been made synthetically useful[40].

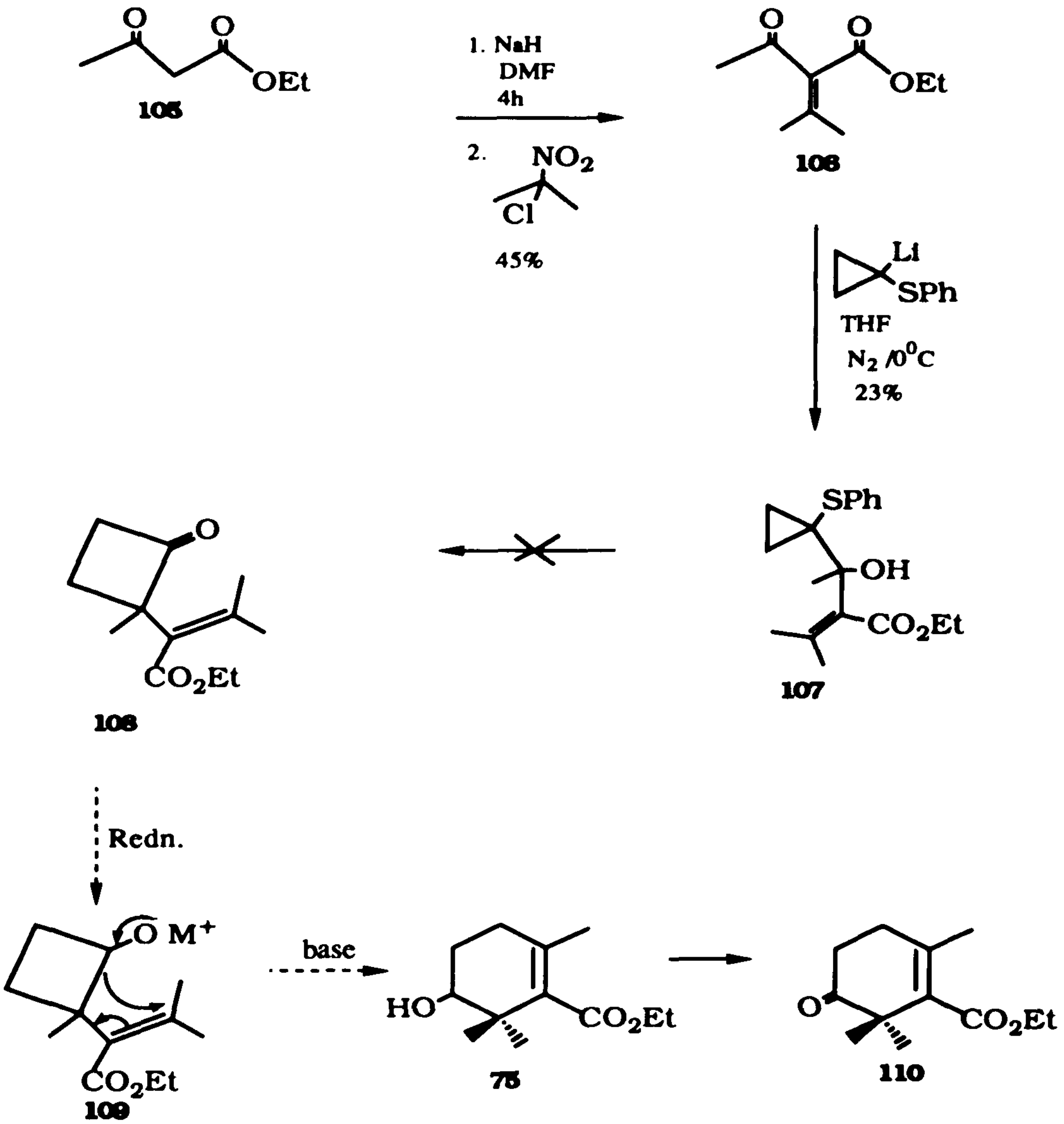


eqn.1

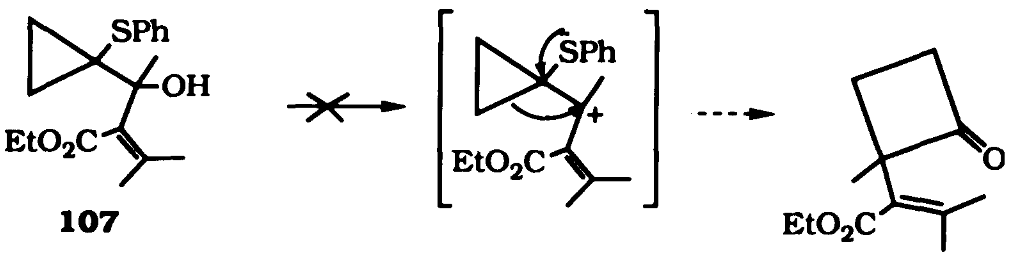
Our next approach to the A-ring synthon **93** is outlined in Scheme 15. It involves the alkoxide accelerated vinylcyclobutane to cyclohexenol rearrangement developed by Danheiser[40] (whose work was based on the studies of Evans[43a]). The keto-ester **106** was prepared via an $S_{RN}1$ reaction[43] from ethyl acetoacetate and 2-

chloro-2-nitropropane. The 2-chloro-2-nitropropane, prepared through a modified procedure of Seigle[44], was used as acetone equivalent in this reaction because acetone gives poorer yield due to

Scheme 15: Alkoxy accelerated vinylcyclobutane rearrangement



a side reaction with ethyl acetoacetate. The reaction of compound **106** with lithiocyclopropyl phenyl sulfide in THF at -78 °C gave a major compound in 23% yield (plus unreacted starting materials). The IR showed absorptions at 3500 (br., OH), 1718 (CO_2Et), 1640 (ArC=C), and 1560 cm^{-1} and the proton 200 MHz NMR gave peaks at δ 0.90 (m, 4H), 1.60 (t, 3H), 2.20 (s, 3H), 2.80 (s, disappear in D_2O, 1H), 4.40 (q, 2H) and 7.50 (m, 5H), corresponding to compound **107**. The rearrangement of compound **107** was attempted with 50% aqueous fluoboric acid, $BF_3.OEt_2$, and $SnCl_4$ but no reaction was observed in each case (TLC and IR). The rearrangement was expected to proceed as follows:

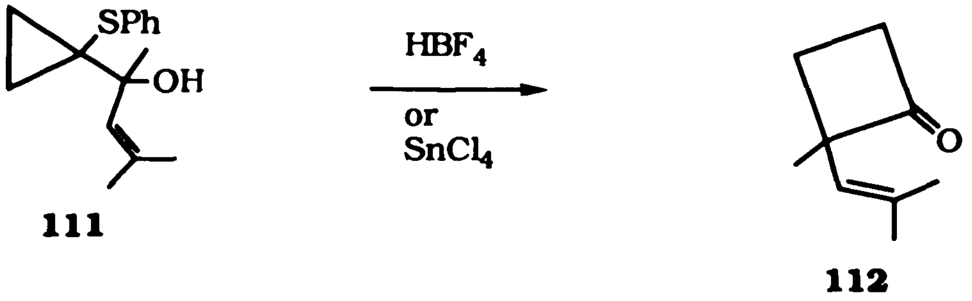


107

108

eqn.2

The lack of reactivity in compound **107** was probably due to the destabilizing effect of the electron withdrawing ester group on the allylic cationic intermediate, since its close relative, compound **111**, prepared by Trost[45] rearranged to **112** in 47% yield (eqn.3), under the same reaction conditions.



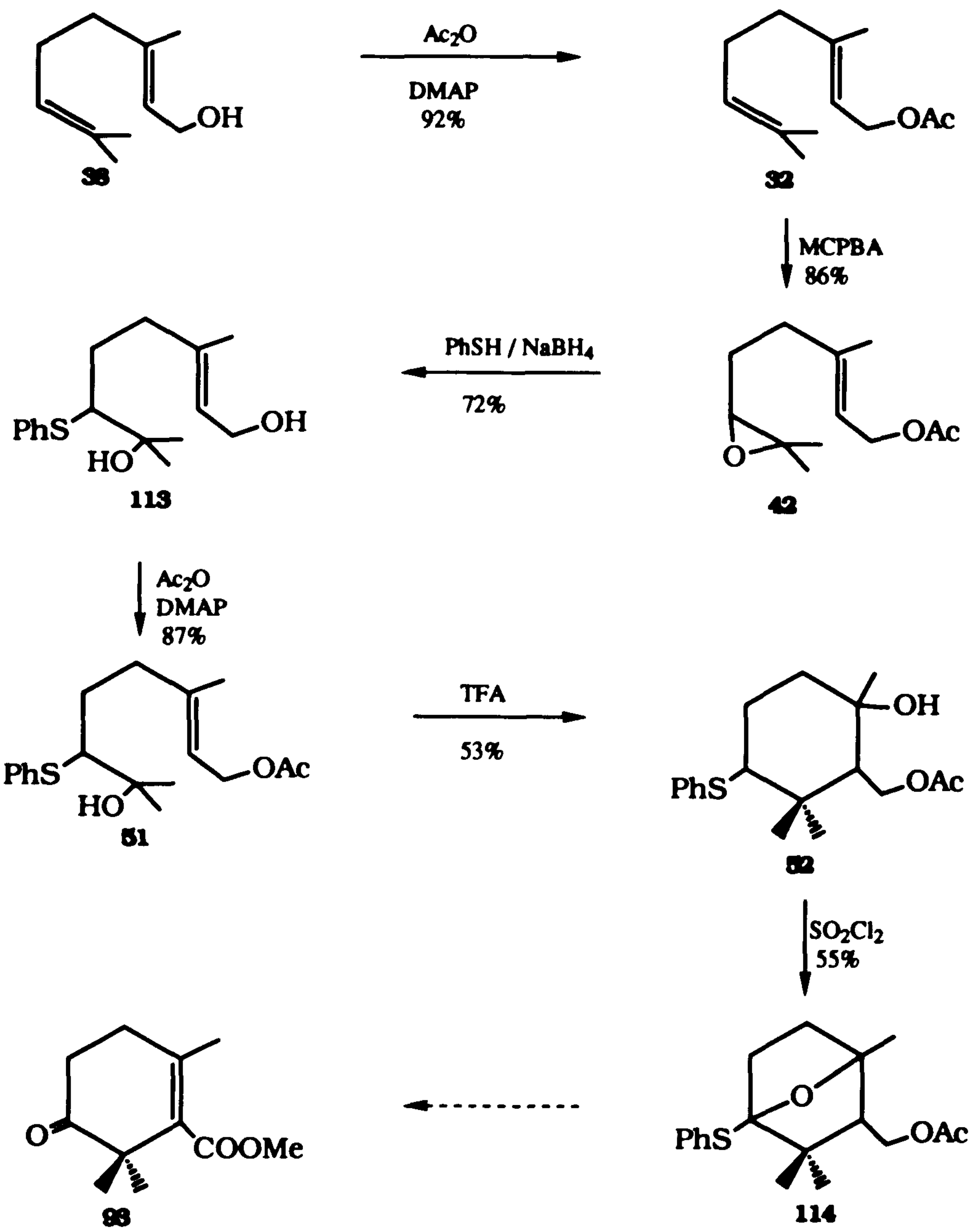
eqn.3

Since it was not possible to effect the rearrangement of compound **107** to the vinylcyclobutanone **108**, Scheme 15 was aborted.

Electrophilic cyclization of geranyl acetate derivatives

After both the Robinson annulation and the ring expansion rearrangement approaches failed to provide a convenient route to the A-ring synthon **93**, the focus of this investigation was shifted to the cyclization of the geranyl acetate derivative **51** shown in Scheme 16. Much of this work, however, is repetition of the efforts of Subasinghe[31] and Jiang (from our laboratory) who had previously worked on this project. Geranyl acetate **32** was prepared in good yield from commercially available geraniol. Epoxidation of **32** with m-chloroperbenzoic acid (MCPBA) in dichloromethane gave the 6,7-epoxy-geranyl acetate, **42** regioselectively. It should be noted that geranyl acetate and not geraniol was used in the epoxidation reaction because the acetate is more selective. It gives the 6,7-mono-epoxide while the alcohol gives a mixture. The reason for the selectivity is not clear but it can be argued that the electron withdrawing acetate group being closer to the C_2-C_3 double bond, makes it less reactive.

Scheme 16: Cyclization of geranyl acetate derivative 51



Also, the greater steric hindrance around the C_2-C_3 double bond might contribute to the observed regioselectivity. The epoxide was used because studies done in our laboratory[38], as well as by Kametani[30] revealed that geranyl acetate does not undergo cyclization to the corresponding cyclohexane derivative. There are, however, reports[21,22,23] (Table 2) of Lewis acid catalyzed cyclizations of geranyl acetate. In most of these cases, however, complex mixtures resulted and the cyclized products were obtained in very low yields.

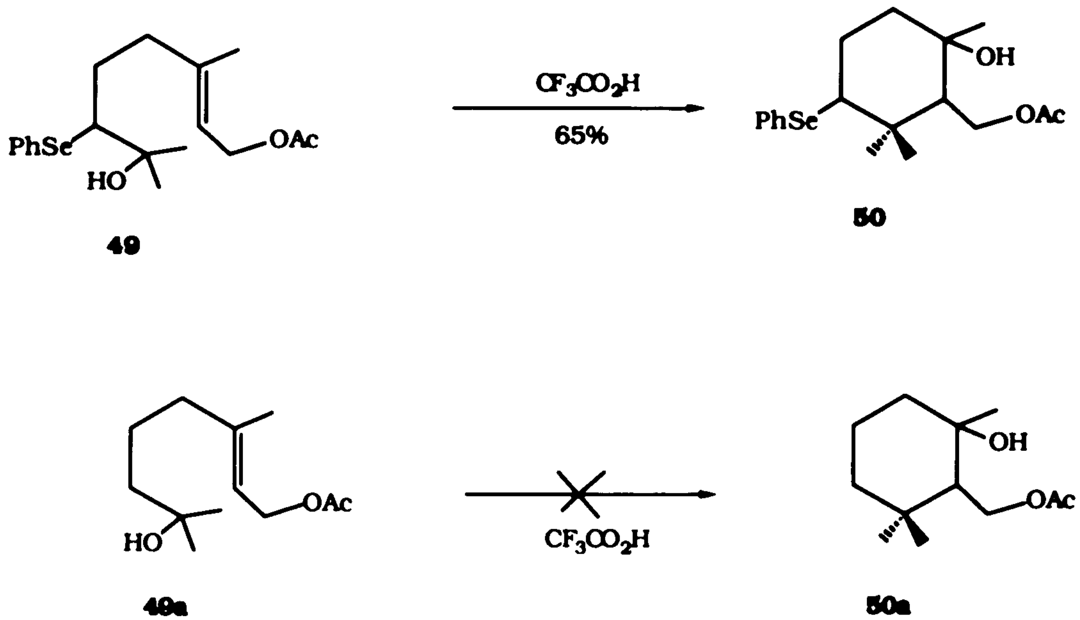
Attempts to cyclize the epoxide **42** (with Lewis acids) were unsuccessful. With $SnCl_4$, $BF_3.OEt_2$, and CF_3CO_2H apparently the same complex mixture was formed (as shown by TLC). Partial separation by column chromatography and analysis by NMR gave no indication of the cyclized product. This result is consistent with other attempts[30,31,46] to effect a similar cyclization of the mono-epoxide **42**. It should be noted though, that there are reports[26,27] (Table 2) indicating that the epoxide **42** undergoes the required cyclization (see **43** and **44**) but no yields have been reported.

Prior to this investigation, Subasinghe[31] (who also investigated ways to make the A-ring synthon of taxol), failed to effect cyclization of epoxide **42**. In searching for a way to effect the cyclization of geranyl acetate derivatives Berkowitz and Subasinghe[31] turned to the work of Kametani[30] (**49** ⟶ **50**, Table 2). Subasinghe repeated Kametani's work then tried to oxidatively remove the PhSe group from **50** in an effort to develop a route to the

A-ring of taxol. Subsequently, the selenide **50** was converted to the corresponding selenoxide[30], and a Pummerer rearrangement attempted. The rearrangement attempts resulted in the decomposition of the selenoxide. Failing to oxidatively remove the PhSe group, the investigation turned to the use of sulfur instead of selenium. The rationale for this was that the analogous sulfoxide is more stable and therefore the Pummerer rearrangement might be possible without the concomitant decomposition. In addition, the sulfur compounds are cheaper and less harmful, hence the use of sulfur instead of selenium in this investigation. The sulfide **51** was therefore prepared, via nucleophilic attack of PhS^- on the epoxide **42**, followed by reacetylation. As expected (compare with **49**) the sulfide **51** underwent facile cyclization in CF_3CO_2H at -15 °C to give **52** in moderate yield.

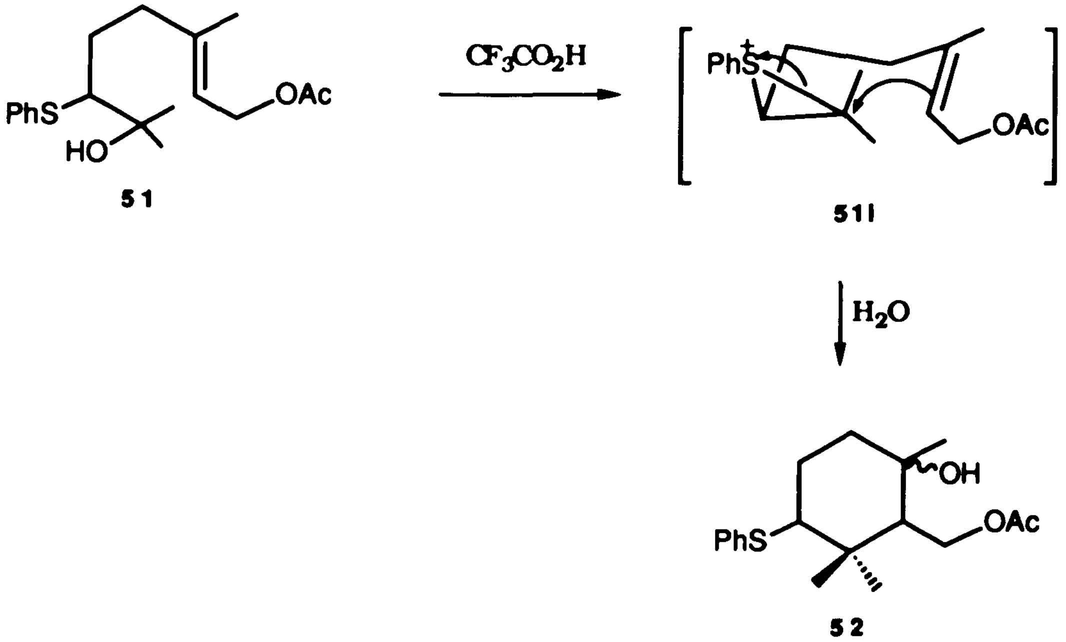
The question at this point is why did compound **51** cyclize (under acidic condition) but compound **32** (or even **42**) did not? Both Kametani[30] (Figure 1) and Rouessac[26] have invoked the participation of the phenyselenyl group in the stabilization of the incipient carbonium ion to account for this difference in reactivity.

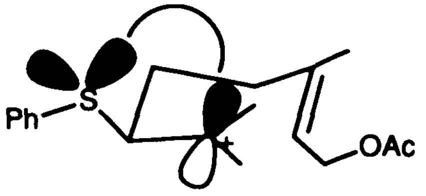
Figure 1: Kametani's supporting evidence for the involvement of the PhSe group.



As evident from Table 2, stabilizing the incipient cation[26,30,31] or enhancing the nucleophilicity of the C_2-C_3 double bond[28] results in good yield of the cyclized product. Cyclization, however, is limited by the need to obtain good orbital overlap in the transition state. It can be envisioned that the transition state for ionization of both geranyl acetate and its mono-epoxide **42** are too short-lived or too reactive to engage in proper orbital overlap. When the sulfide group (or selenide) is present the β-carbonium ion can be stabilized by the sulfur lone pair interaction as illustrated in Scheme 17. Oxygen (of the epoxide **42**) is not able to stabilize the β- carbonium ion as sulfur can. In the case of the allylsilane **45** the transition state can be stabilized by the TMS group. The pivalate **40** and the acetate **42** cyclized to the bicyclic ethers **41** and **43**, respectively (evidently from neighboring group participation of oxygen). However, since the yields of **41** and **43** are not comparable, carbonium ion stabilization appears to be only partly responsible for the difference in reactivity. Further investigation is therefore needed in order to completely address this problem.

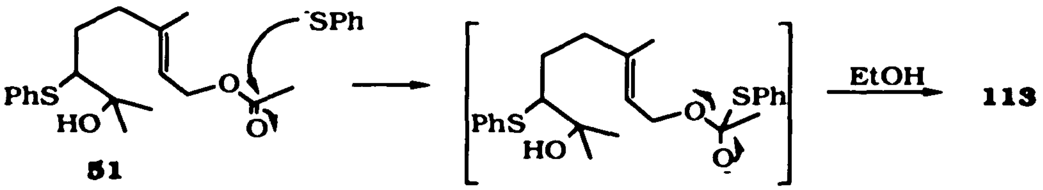
Scheme 17: Mechanism of cyclization of compound **51**





lone pair--p-orbital interaction

As indicated in Scheme 16, nucleophilic attack of the PhS^- species on the epoxide **42** gave predominantly the diol **113** instead of the acetate **51** (possibly through the attack of the PhS^- anion on the acetate group as shown by eqn.4). This is not commonly expected but a similar reaction with the $PhSe^-$ anion has been reported[47]. Reacetylation, however, proceeded efficiently to the acetate **51**.

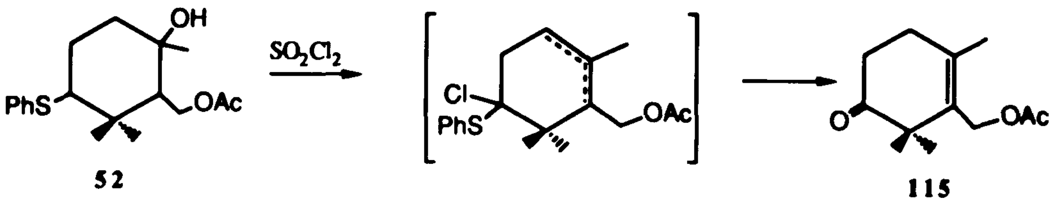


eqn.4

As mentioned earlier, the sulfide **52** was prepared (instead of the analogous selenide **50**) because it was thought that its sulfoxide would be stable enough to undergo the Pummerer rearrangement. As with the selenoxide, however, attempts to oxidatively cleave the sulfoxide via a Pummerer rearrangement resulted in decomposition[30]. It should be borne in mind that for the Pummerer rearrangement to occur a methylene or methyl group is usually required next to the sulfur. In the case of both the selenoxide and sulfoxide there is only one very hindered methine hydrogen.

The reaction with sulfuryl chloride (SO_2Cl_2), was done with the intent to produce the keto-acetate **115** according to eqn. 5.

Precedent for this reaction was obtained from the work of Chu[48], who in 1983 reported that sulfuryl chloride reacts with phenylsulfides to give α-chlorophenyl sulfides which upon treatment



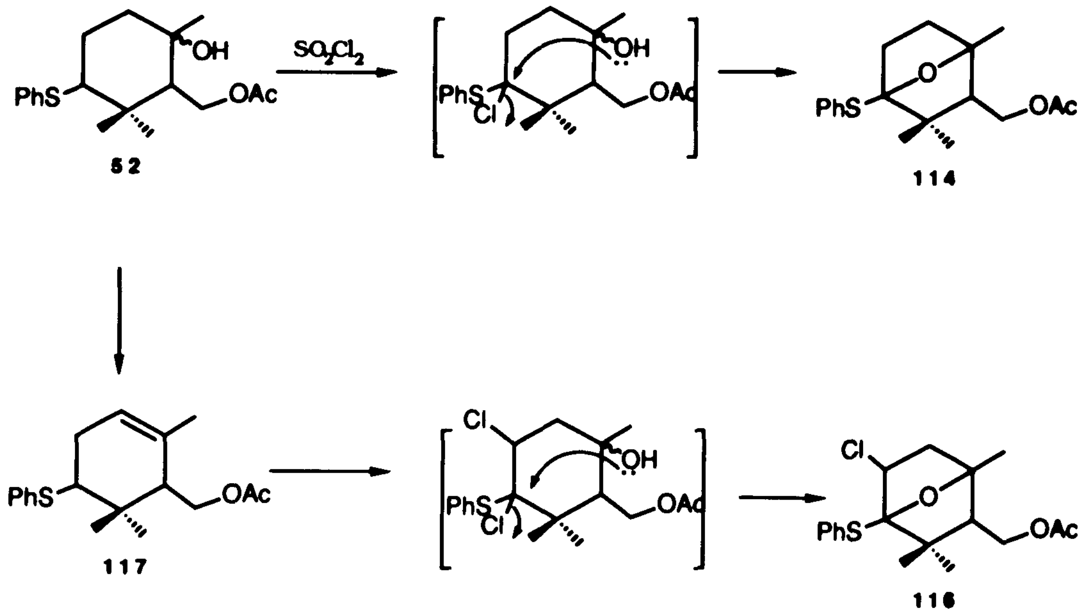
52

115

eqn.5

with water deactivated silica gel give the corresponding aldehydes. This reaction resulted in the formation of the bicyclic ether **114** (and its chlorinated analogue **116** as a minor component)[31]. The mechanism of this reaction is speculated to proceed as outlined in Scheme 18. Apparently cleavage of the chloride generates a carbocation which is then stabilized by oxygen.

Scheme 18: Mechanism for the formation of **114** and **116**



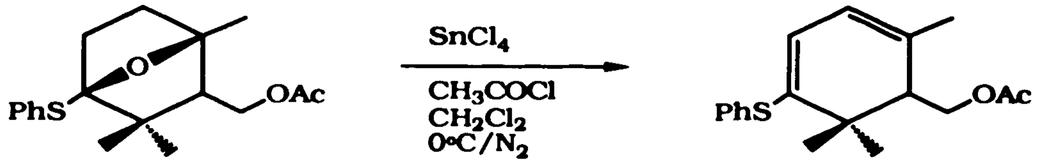
Compound **116** was not synthetically useful in this investigation, but conceivably **114** can be made to unmask the keto group at C_5 to give the keto-acetate **115** (eqn.5) upon hydrolysis of the hemithioacetal group. For this hydrolysis, the feasibility of several of the known methods were explored.

***Hydrolysis of compounds* 114 *and* 121**

A number of methods[49] are available for the conversion of thioacetals, acetals and hemithioacetals (as well as vinyl sulfides) to the corresponding parent carbonyl compounds. Using some of these, the hydrolysis of compound **114** was attempted and the results obtained are as follows:

i) with anhydrous $TiCl_4$ and acetyl chloride[50] in methylene chloride at 0°C there was no reaction. This reaction was repeated a few times (in some cases the $TiCl_4$ was in excess and others as a catalyst) but in all cases the starting material was recovered (as shown by TLC and NMR).

ii) with a catalytic amount of $SnCl_4$ under the same conditions as with the $TiCl_4$ a mixture of products (as shown by TLC) was obtained. The major component was isolated (16% yield) by column chromatography on silica gel. The IR showed absorptions at 3030 (ArC-H), 1730 (carbonyl) and 1565 cm^{-1} (C=C-C=C) and the proton NMR gave the following peaks at δ 1.20 (d, 6H), 1.90 (s, 3H), 2.10 (m, 4H), 4.40 (ABq, 2H), 5.60 (m, 2H) and 7.60 (m, 5H). The GC-MS gave m/e at 302. Based on these spectral data the structure of the major compound was assigned as **118** (eqn.6).



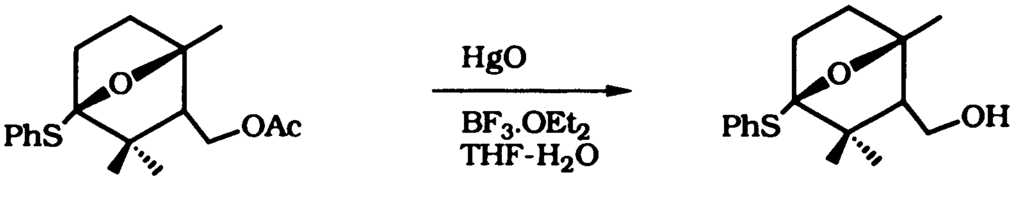
114 **118**

eqn.6

The $SnCl_4$ probably promoted ring opening of the ether by coordinating with the bridged oxygen. Since the thiophenyl group was not cleaved this indicates that there was no assistance from the sulfur lone pairs in the opening of the ether bridge leading to the vinyl sulfide. However, vinyl sulfides are known to hydrolyze under similar conditions as thioacetals. Since compound **118** contains a vinyl sulfide group (although as part of a diene system) its hydrolysis was attempted with $TiCl_4$ according to the procedure of Mukaiyama[51]. From this reaction, a mixture (of four components by TLC) was obtained and three components were isolated by flash column chromatography using silica gel but the phenyl sulfide group was present in all. In addition, there was no indication of a second carbonyl group in any. The hydrolysis of compound **118** was also attempted with $HgCl_2$ in water/acetonitrile at 45 °C but there was no reaction even after 24 hours.

iii) with $ZrCl_4$ and acetyl chloride in methylene chloride at 0 °C compound **114** showed no sign of reaction. It should be noted that Ti and Zr are in the same group of transition metals. Tin on the other hand is a group IV metal. With both $TiCl_4$ and $ZrCl_4$ there were no reaction but $SnCl_4$ opened the ether bridge. Both Sn(IV) and Zr(IV) have covalent radii of about 1.45 Å, while Ti(IV) has a somewhat smaller radius of 1.36 Å. If the size of the metal was important then $ZrCl_4$ should also cleave the ether bridge. It is therefore reasonable to conjecture that the $SnCl_4$ is more oxophillic than $TiCl_4$ and $ZrCl_4$.

iv) with $HgO-BF_3.OEt_2$[52] *in THF/water for 7 days* there was a trace of a new component as shown by TLC. However, isolation and NMR analysis showed the presence of the (thio) phenyl group. What appeared to have happened was the hydrolysis of the acetate to the corresponding alcohol (eqn.7) since the IR showed absorptions at 3600 (sharp), 3460 (broad) and no peaks between 1600-1800 cm^{-1}. The proton 60 MHz NMR spectrum was also consistent with the formation of the alcohol since the acetate CH_3 disappeared and the methylene protons adjacent to the acetate group were shifted up-field. Sulfur being a soft base was expected to donate a pair of electrons to the soft acid, mercury, thereby making the C-S bond more susceptible to cleavage. The fact that cleavage did not occur underscores the stability of the bridgehead sulfur.



114 **119**

eqn.7

v) with $LiAlH_4$-$AlCl_3$[53] in refluxing anhydrous ether for 27 hours the reaction also gave alcohol **119** (based on spectral comparison with the hydrolysis product of Scheme 19).

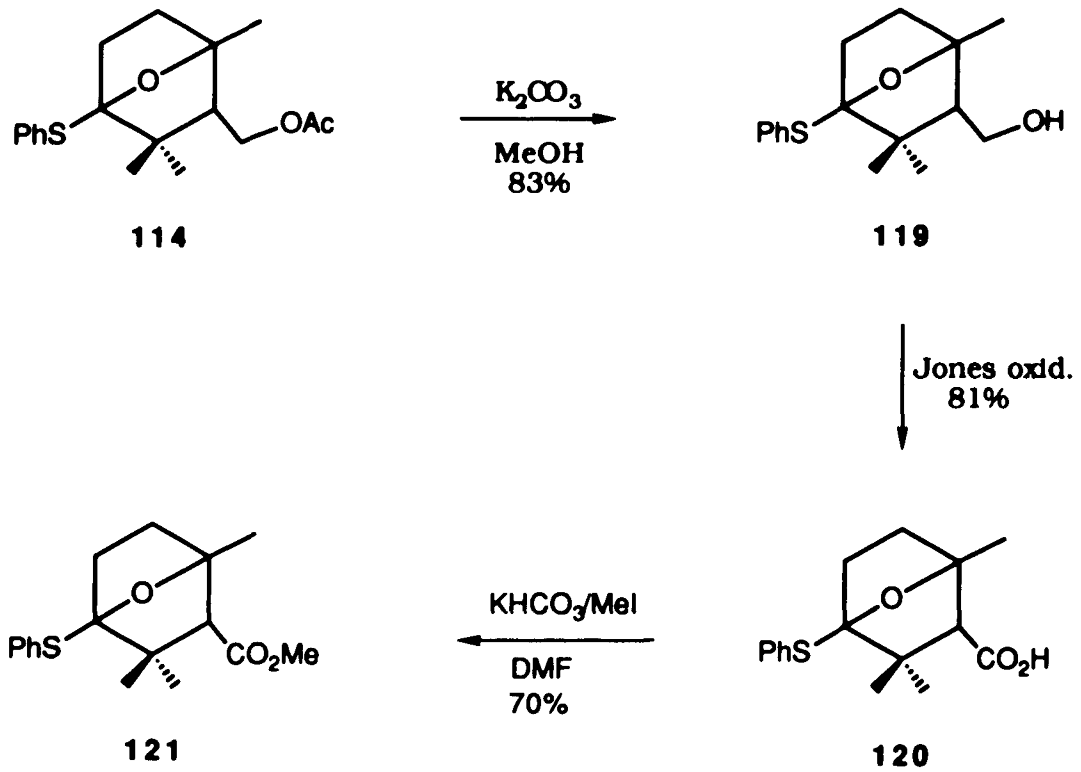
vi) with concentrated sulfuric acid[54] *in refluxing dioxane/water overnight*, a complex mixture of products (as shown on TLC) was obtained. Three components were isolated from this mixture but they all had the thiophenyl group (based on NMR). In addition, the GC-MS spectra for the three components showed low molecular weights species that were not consistent with any meaningful product.

vii) with DMSO/dil.HCl/H_2O/dioxane[55] there was no reaction (based on TLC).

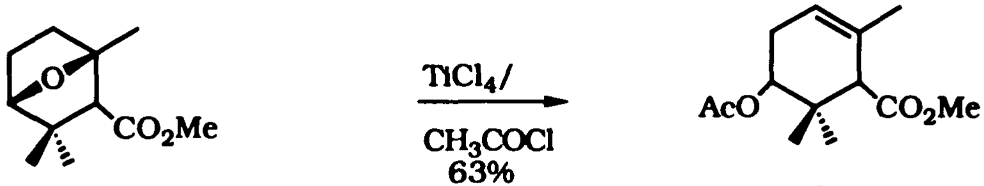
viii) with $SO_2Cl_2/SiO_2/H_2O/CH_2Cl_2$[56] the hydrolysis did not occur but one new compound was isolated (by column chromatography using silica gel). Based on the similarity of the proton NMR to compound **116** it appeared that the chlorination of compound **114** had occurred.

As a result of the difficulty encountered with the hydrolysis of the thioacetal group, compound **114** was modified to the methyl ester **121** (Scheme 19) and the hydrolysis attempted. The rationale

Scheme 19: Conversion of the acetate **114** to the ester **121**



for this modification is that coordination to both the ether oxygen and the carbonyl oxygen of the ester might facilitate cleavage. If coordination occurs, the methyl ester would be preferred over the acetate since the former would lead to (a more stable) six-membered ring while the latter would give an eight-membered ring. In addition, Wilson[34] (using earlier studies[50] from our laboratory) successfully cleaved the closely related compound **78** with $TiCl_4/CH_3COCl$ as shown by eqn.8. It should be pointed out that other attempts[34] to cleave the ether bridge of **78** (LDA, NaOMe and $BF_3.OEt_2$) resulted in



78

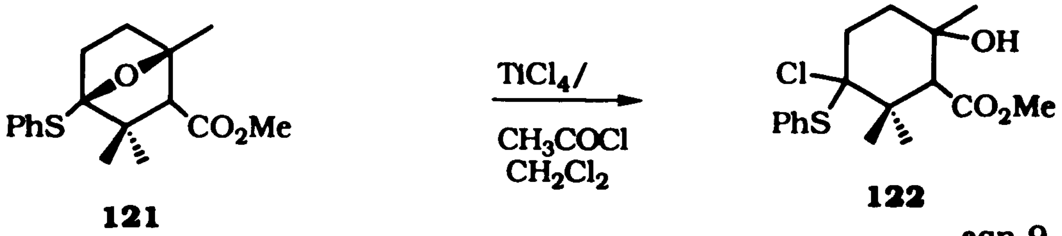
79

eqn.8

the re-isolation of the starting material. Compound **78** was also unsuccessfully treated with $LiN(SiMe)_2$ (which was used by Koizumi[57] to cleave a related bridged-ether system).

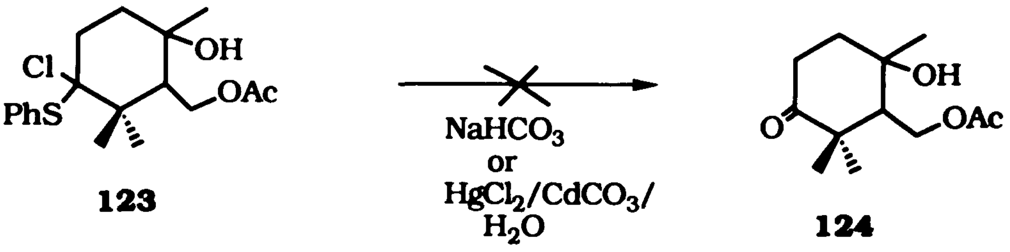
The results of the attempted hydrolysis of compound **121** are as follows:

i) with $TiCl_4$ and acetyl chloride in methylene chloride at 0 °C for 90 minutes a new compound was formed and some starting material remained. Purification by column chromatography using silica gel gave a pale yellow solid with m.p. at 102.5 °C. The IR showed absorptions at 3600 (free OH), 3480 (br., OH), 2980, 2962, 2880, 1728 and 1580 cm^{-1} and the proton NMR gave peaks at δ 1.10 (s, 3H), 1.43 (narrow d, 6H), 1.90 (d, 2H), 2.78 (d, 2H), 2.95 (s, 1H), 3.60 (s, 3H) and 7.05 (m, 5H). The GC-MS gave m/e at 342 consistent with compound **122** (eqn.9).



eqn.9

Based on the spectral data it was assumed that compound **122** had the chlorine alpha to the sulfur. As a result, its hydrolysis was attempted with boiling water for one hour. Analysis by TLC and NMR showed that no reaction had taken place (starting material was recovered). This result is similar to that obtained by Subasinghe[31] as shown by eqn.10. Her attempts to hydrolyze the α-chloro sulfide **123** failed. In addition, it is known that it is difficult to prepare ketones (aldehydes are readily formed) from α-halo sulfides. In such reactions vinyl sulfides are often formed[58].



eqn.10

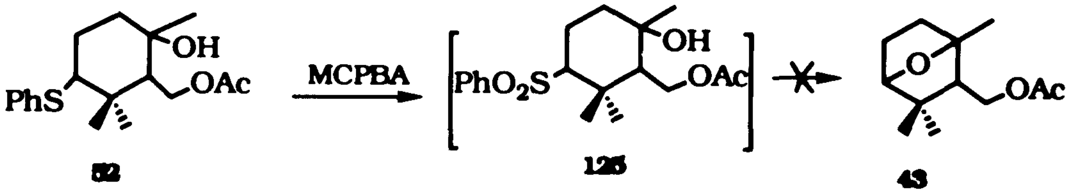
ii) with excess $TiCl_4/SnCl_4$ (1:1 mol equiv.) and acetyl chloride compound **122** was obtained (IR and NMR were identical to the compound obtained from the reaction shown by eqn.9).

iii) with $POCl_3$[59] *and sodium iodide in acetonitrile and DMF at room temperature (overnight)* an unidentified mixture of products was formed.

The resistance of compound **121**, like compound **114**, to hydrolysis can be attributed in part to the hydrolytic stability[60] of the bicyclic system. In addition, both the bridgehead positions are substituted (with the relatively bulky methyl and thiophenyl groups). Furthermore, it seems that the adjacent gem-dimethyl group creates a sterically hindered environment around the sulfur resulting in its inertness in these reactions. It is not surprising then, that the only apparent reaction of compounds **114** and **121** is the cleavage of the C-O bond (due to Lewis acid coordination to oxygen) to give **118** and **122**, respectively. It is however, not clear why the vinyl sulfide **118** and the α -chloro sulfide are so resistant to hydrolysis.

Cleavage of the sulfoxide and sulfone

Failing to successfully hydrolyze the hemithioacetal (of **114** and **121**) to the corresponding ketone, cleavage of the thiophenyl group was attempted instead. Since an oxygen function is required to replace the sulfide, **114** was converted to the sulfoxide(**126**) and sulfone(**125**) with the hope that the hydroxyl group would displace either or both groups to give compound **43** (eq.11).



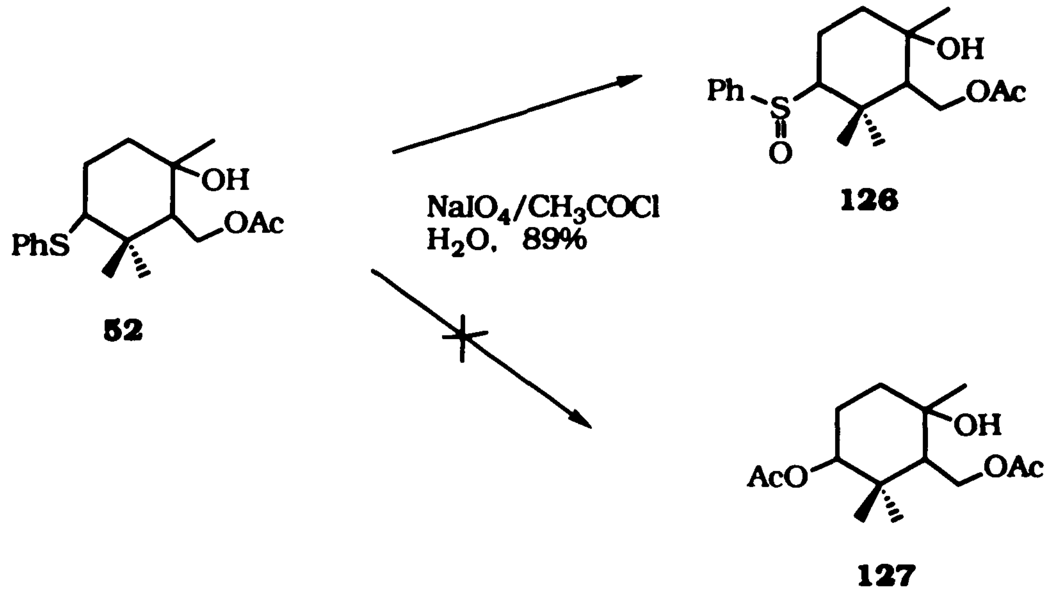
eqn.11

However, neither the sulfoxide nor the sulfone (with MCPBA/aqueous $NaHCO_3$) gave compound **43**. It should be noted that the analogous reaction[26] with selenium instead of sulfur gave the acetate **43**.

Oxidative substitution of the PhS moiety

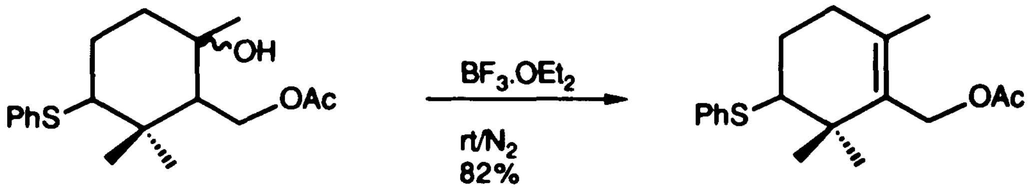
In a recent article Uemura[61] reported that oxidative substitution of PhSe and PhTe moieties in alkyl phenyl selenides and tellurides with $NaIO_4$ in aqueous acetic acid (at 20-80 °C for 0.5-24 h) led to esters and alcohols in moderate yields. Subsequently, this reaction was attempted with the phenyl sulfide **52** (Scheme 20) with the hope of making compound **127**. TLC, however, showed the formation of a single compound which was identified as the sulfoxide **126**. The sulfoxide was also produced via MCPBA oxidation of **52** (in 64% yield).

Scheme 20: attempted oxidative substitution of the PhS moiety



Miscellaneous reactions

Since the hemithioacetal group in both the acetate **114** and the methyl ester **121** was resistant to hydrolysis it was hoped that by preventing its formation the sulfide would be able to undergo α-chlorination and subsequent hydrolysis to the desired ketone. Hence, dehydration of the alcohol **52** was attempted with $BF_3.OEt_2$[62] (eqn.12) to remove the "offending" OH group.

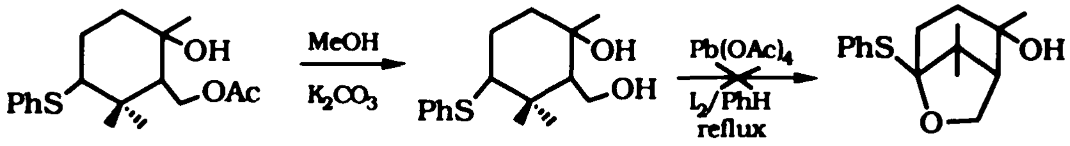


52 **128**

eqn.12

Based on the NMR data and the GC-MS spectrum, compound **128** was tentatively assigned. Its conversion to compound **115** (see eqn.5) was attempted but the results are inconclusive.

In another attempt to prevent the formation of the hemithioacetal group, the acetate **52** was hydrolyzed to the diol **129** and then reacted with lead tetraacetate and iodine^{63a} as catalyst with the intent to form the ether **130** (eqn.13).



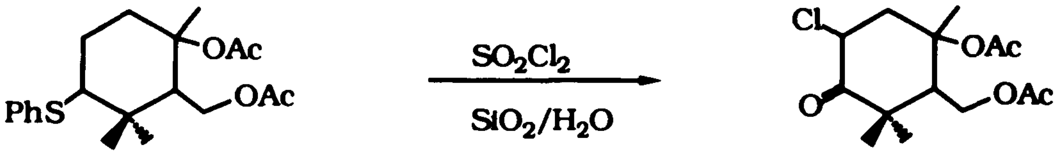
52 **129** **130**

eqn.13

The reaction with Pb(OAc)$_4$ and iodine was run overnight. TLC analysis of the reaction mixture showed two components plus starting material. The two new components were analyzed by GC-MS. The major compound had m/e of 322 and its IR and NMR spectra were identical to compound **52**. The other compound showed unidentifiable fragments in the GC-MS spectrum as well as turned brown on standing at room temperature indicating that it contained iodine (possibly resulting from substitution of the primary OH group with iodine). The reaction with $Pb(OAc)_4$ was attempted because it is known to cause alcohols with hydrogens in the δ position to cyclize to the corresponding ether[63b]. However, there are two ways that cyclization could occur, to give compound **119** or **130**, but it was expected that compound **130** would be favored due to the reaction mechanism[63]. However, intramolecular hydrogen abstraction leading to the cyclic ether is influenced not only by the distance between the attacking hydroxylic oxygen and the δ-carbon but also by steric hindrance. In the case of compound **129**, the gem-dimethyl group apparently hinders the attack of the primary OH group. In addition, molecular mechanics (MMX) calculation indicates that both compounds **119** and **130** are of comparable stability with heats of formation (ΔH_f) calculated to be 40 Kcal/mole. Both of these compounds are expected to be more strained than the acetate **52**, hence the observance of the acetate and not the ethers (**119** and **130**). If compound **130** had been formed it would then hopefully be oxidized to the corresponding lactone which would be subsequently hydrolyzed and modified to compound **93**.

The reaction of the hydroxy acetate **52** with NCS followed by $HgO/BF_3.OEt_2$ was also tried in an effort to replace the thiophenyl group with a keto group but instead the bicyclic ether **114** was formed (NMR identical to previously obtained **114**). Subasinghe[31] also tried to react compound **52** with NCS but the product obtained could not be hydrolyzed.

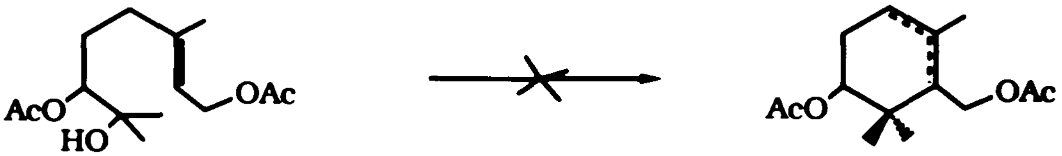
Another attempt to prevent the hydroxyl group of compound **52** from participating in the hemithioacetal formation was to protect it. The protection of the alcohol as the acetate **131** was conducted by Subasinghe[31] but attempts to replace the sulfide with a keto group using $SO_2Cl_2/SiO_2/H_2O$ resulted in the formation of compound **132**.



131 **132**

eqn.14

As a result of the difficulty encountered to remove the thiophenyl group, one might ask why not use an oxygen nucleophile instead of sulfur? Unfortunately, the acetoxy group instead of the phenyl sulfide group was used as shown by eqn.15 but the cyclized product **134** could not be obtained[31].



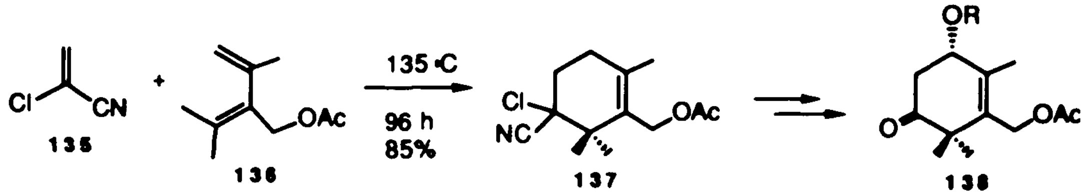
133 **134**

eqn.15

$BF_3.OEt_2$ catalyzed cyclization of **133** failed to show any reaction at room temperature and upon heating resulted in a complicated mixture. Although acetals are easier to cleave than the corresponding sulfur compounds, the oxygen cannot provide the same stabilization of the β-carbonium ion as the sulfur can.

Conclusion and Future Prospects

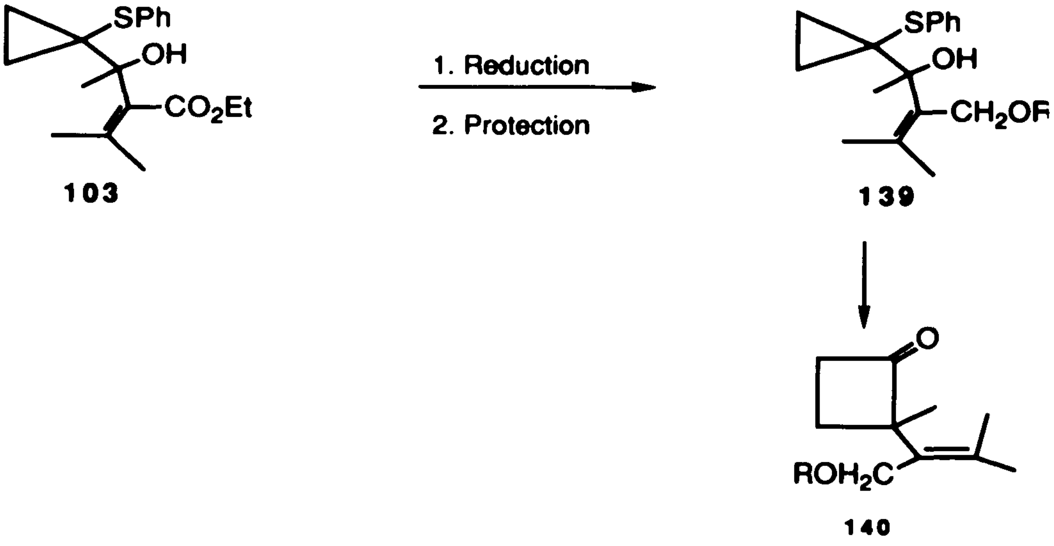
As pointed out earlier, the goal of this project was to synthesize a fully functionalized A-ring synthon of taxol. Based on a retrosynthetic analysis (Scheme 11) of natural taxol, this synthon was chosen to be the ester **93**. Despite the efforts expended in our laboratory[31,34,38] to develop a convenient route to this compound, its synthesis remains an unattained goal. In a very recent communication, however, Nicolaou[70] reported an attractive enantioselective synthesis of a fully functionalized A-ring of taxol (a system closely related to our target **93**). His A-ring synthon **138** (eqn.16) was obtained via a short route featuring Diels-Alder and Corey oxazaborolidine reactions.



eqn.16

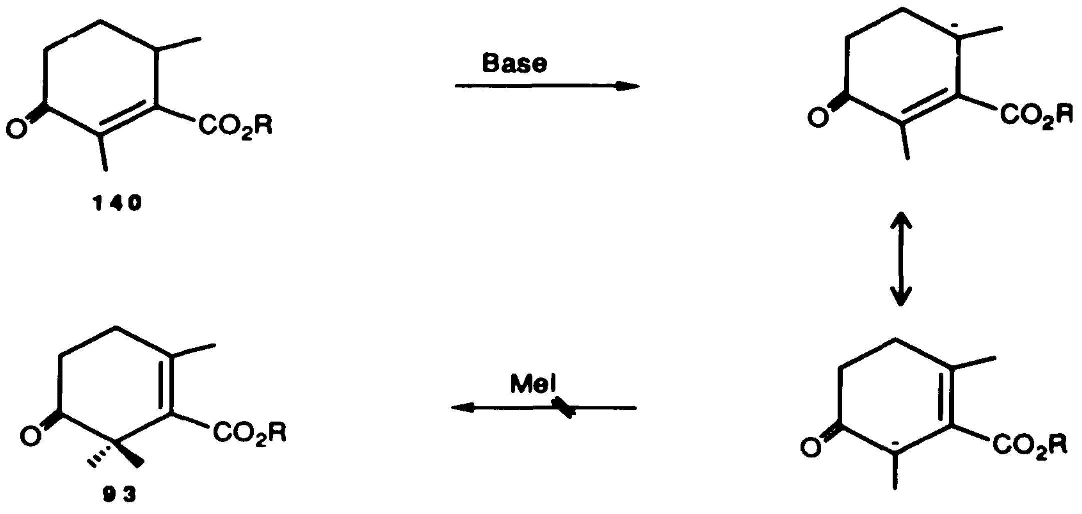
Although our investigation had its share of difficulties, it is not far-fetched to envision that with "new energies" some of these problems can be solved. For instance, Scheme 15 involving the alkoxide accelerated ring expansion was aborted because the cyclopropyl phenylsulfide **107** failed to rearrange to the desired cyclobutanone system. The most plausible reason for this failure to rearrange is destabilization of the carbocation transition state due to the electron withdrawing ester group. In the future, this problem might be solved by converting the ester to a less destabilizing group (as shown in Scheme 21) prior to the Lewis acid mediated rearrangement reaction.

Scheme 21: Ester functional group modification



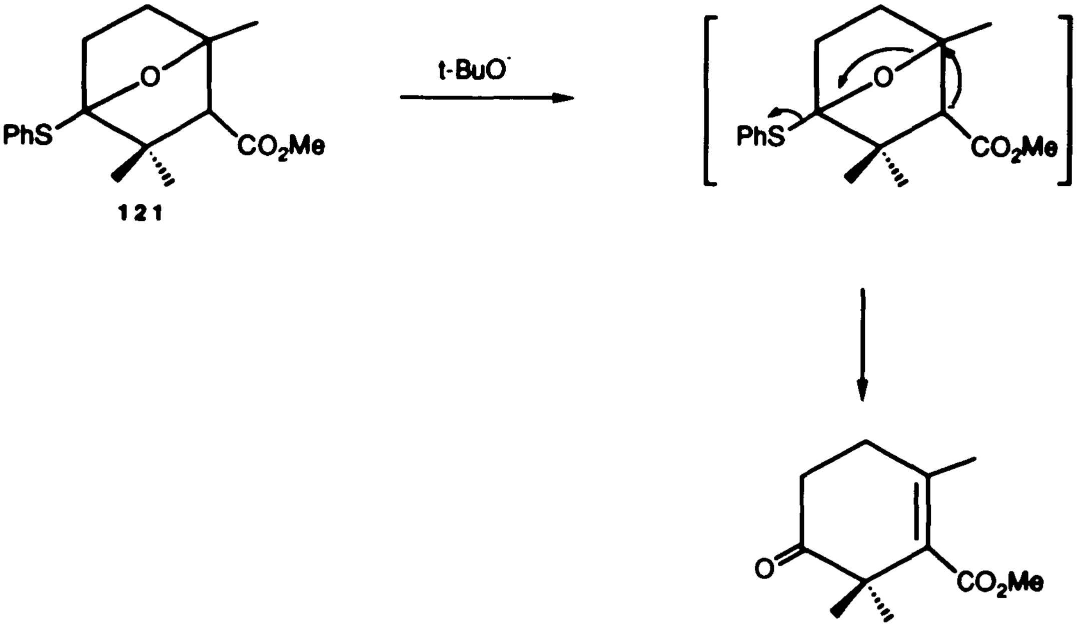
In the case of the Robinson annulation approach (Scheme 13) to the A-ring synthon **93**, the low yield of the cyclized product **102**, resulting from Aldol condensation and the resistance of the α-hydroxy ester **103**, to dehydration are factors which disfavor any future prospects. The resistance of compound **103** to dehydration can be attributed in-part to the destabilizing effect of the electron withdrawing ester group on the developing carbocation in the transition state. This problem might be alleviated by converting the ester to the primary alcohol (which may or may not be protected) before dehydrating the tertiary alcohol. On the other hand, the low yield of the cyclization step appears to be due to steric congestion which arise from the formation of contiguous quaternary centers in the product. Although it maybe possible to solve the dehydration problem, the low yield of the cyclization step makes this sequence of reactions not worthwhile pursuing, especially since an earlier attempt[38] (Scheme 22) to solve the problem of steric congestion by introducing the gem-dimethyl group (via monoalkyation) after the cyclization step resulted in polyalkylated products.

Scheme 22: Attempted alkylation of an α,β-unsaturated ketone



In terms of future prospects, the most promising part of this investigation involves the cyclization of geranyl acetate derivatives (Scheme 16). The starting material is commercially available and inexpensive, and the cyclic intermediates **52** and **114** are easy to handle, air stable solids. Compounds **114** and its close relative **121**, however, are unexpectedly very stable to heavy metal and acid-mediated hydrolysis (of their respective hemithioacetal groups). With further work though, it might be possible to cleave the hemithioacetal group under basic condition as shown in Scheme 23. It should be borne in mind though, that according to Wilson[34] the closely related bicyclic ether **78** did not cleave under basic condition. However, the presence of the PhS group in **121** might provide the pull necessary for the cleavage of the hemithioacetal group.

Scheme 23: Proposed cleavage of hemithioacetal group



121

93

Chapter Four

Experimental Section

Melting points (uncorrected) were determined in open capillaries on a Thomas Hoover Uni-melt apparatus. Infrared (IR) spectra were recorded on a Perkin-Elmer 598 infrared spectrometer. The IR samples were run in $CDCl_3$ (~5% solution) and calibrated with a polystyrene film. Nuclear magnetic resonance (NMR) spectra were run in $CDCl_3$ (~10% solution) with tetramethyl silane (TMS) as internal standard. The proton 60 MHz spectra were determined on a Varian EM 360 NMR spectrometer and high resolution proton and carbon-13 spectra on a 200 NMR Bruker/IBM NMR spectrometer. Chemical shifts are reported in parts per million (ppm). Splitting patterns are abbreviated as s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants are given in Hertz. GC-MS spectra were obtained using a Hewlett-Packard 5988A GC/MS system with a Hewlett-Packard 1000 data system. The GC column was a 50 m x 0.32 m id, fused silica capillary with a cross-linked bonded polyethylene glycol stationary phase. The carrier gas was helium. The oven temperature program was 35 °C initially for 1 minute, then 20 °C per minute to 100 °C, held 1 minute, then up 10 °C per minute to 250 °C and held 10 minutes. GC samples were loaded using splitless injection. The mass range was 40 - 400 and 70 eV electron impact ionization was used. Thin layer chromatography (TLC) and preparative layer chromatography (PLC) were carried out on precoated Kodak chromatogram sheets with fluorescent indicator. Flash column[64] chromatography was carried out on kieselgel 60

(230-400 mesh ASTM) and high performance liquid chromatography (HPLC) with a Waters Associates system consisting of a model U6K injector, a model 6000A solvent delivery system, a differential refractometer R401, a model 141 recorder and two columns with Lichromsorb Si 60 (10 μm). An Harrison Research Chromatotron model 7924T was also used in the purification of a few samples. Solvents used for TLC, flash column chromatography and work-up were reagent grade. All solvents used in reactions were dried according to existing procedures and distilled. Compounds prepared by known routes were identified by comparison with IR and NMR spectra when available. Microanalyses were done by Galbraith Laboratories, Knoxville, TN.

Preparation of **4-methylpent-1-en-3-ol (99)**[38,65].

Isobutyraldehyde (15.0 mL, 11.9 g, 160 mmol) was dissolved in 150 mL of anhydrous ether in a three-necked flask equipped with a nitrogen inlet-tube, a mechanical stirrer and an addition funnel. The flask was stirred, flushed with nitrogen and cooled (dry ice/CCl_4) for 20 minutes. Vinyl magnesium bromide in THF (200 mL, 200 mmol) was added dropwise during a 25 minute period. After the addition was completed the cooling bath was removed and the reaction mixture was allowed to warm to room temperature while being stirred for about 4 hours. The reaction mixture was then acidified by adding 110 mL of cold 3M hydrochloric acid and the organic layer was separated. The aqueous layer was further extracted with ether (6x40 mL). The combined organic layers were washed with saturated aqueous $NaHSO_3$ (4x50 mL), followed by saturated aqueous $NaHCO_3$ (6x50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a yellow oil. Vacuum distillation gave 12.2 g (76%) of compound **99** as a colorless oil, b.p. 53-62 °C at 20 mm Hg. $IR_{(neat)}$ (cm^{-1}) 3450, 2950, 2870 and 1635. ^1H NMR (60 MHz, $CDCl_3$, ppm) 0.80 (d, 6H), 1.75 (m, 1H), 1.90 (s, 1H), 3.70 (t, 1H), 5.20 (dd, 2H) and 5.85 (m, 1H). GC-MS (m/e) 100.

Preparation of **isopropyl vinyl ketone (100)**[38,66] (via Swern oxidation)[67]

Oxalyl chloride (10.0 mL, 14.6 g, 110 mmol) was dissolved in 50 mL of dry CH_2Cl_2 in a three-necked flask equipped with a mechanical stirrer and two addition funnels then cooled (dry ice/acetone) for 5 minutes. DMSO (17.0 mL, 18.7 g, 220 mmol) was dissolved in 50 mL of dry CH_2Cl_2 in one of the funnels, and added dropwise during 5 minutes. The allylic alcohol, **99** (10.0 g, 100 mmol) was dissolved in 25 mL of CH_2Cl_2 in the other funnel and added dropwise during 5 minutes, after which the flask was stirred for 15 minutes. Triethylamine (35.0 mL, 24.4 g, 250 mmol) was added and the reaction mixture was allowed to warm to room temperature while being stirred for two hours. The contents of the flask were then poured into cold brine and the organic layer was separated. The aqueous layer was further extracted with CH_2Cl_2 (3x40 mL). The combined organic layers were washed with 1% HCl (3x50 mL) followed by saturated aqueous $NaHCO_3$ (3x50 mL) and brine (60 mL) then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a yellow oil. Vacuum distillation gave 6.86 g (70%) of **100**, as a pale yellow oil, b.p. 55-61 °C at 32 mm Hg. $IR_{(neat)}$ (cm^{-1}) 2960, 2940, 2885, 1720 and 1610. ^1H NMR (60 MHz, $CDCl_3$, ppm) 1.15 (d, 6H), 2.60 (m, 1H), 5.75 (dd, 1H), and 6.45 (m, 2H).

Preparation of the 1,5-diketo-diester **101**[38,39]

Isopropyl vinyl ketone, **100** (2.8 g, 30 mmol) and commercially obtained diethyl oxalpropionate (4.0 mL, 4.3 g, 20 mmol) were dissolved in 100 mL of a 1:1 mixture of dried benzene/absolute ethanol. Five drops of triethylamine were added and the mixture was refluxed overnight, then concentrated under reduced pressure. The residue was dissolved in 50 mL of ether and washed with saturated aqueous $NaHSO_3$ (4x20 mL) followed by brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 8.0 g (89%) of compound **101** as a yellow oil. $IR_{(neat)}$ (cm^{-1}) 2980, 2940, 2880, 1760, and 1730. ^1H NMR (60 MHz, $CDCl_3$, ppm) 1.15 (t, 6H), 1.45 (slightly split d, 9H), 2.40 (m, 5H) and 4.30 (doublet of q, 4H).

1-hydroxy 2,2,6-trimethyl 3-oxo-cyclohexane carboxylic acid (102)[38,39]

Compound **101** (5.6 g, 20 mmol) was dissolved in 50 mL of cold concentrated hydrochloric acid and the solution was stirred at room temperature overnight. Water (50 mL) was then added and the mixture was refluxed for 23 hours. The cooled reaction mixture was diluted with cold water (75 mL) and extracted with ether (6x25 mL). The combined ether layers were washed with brine until the aqueous extract was no longer acidic, then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 2.3 g of the crude product as a pale yellow solid. Recrystallization from methylene chloride gave 1.4 g (36%) of a white solid, m.p. 156.0-156.5 °C. $IR_{(DMSO)}$ (cm^{-1}) 3678 (sharp), 3440 (broad), 2980, 2940, 1710 and 1700. ^1H NMR (60 MHz, DMSO, ppm) 0.90 (s, 6H), 1.20 (d, 3H), 1.80 (m, 3H), 2.35 (m, 2H) and 6.50 (variable br. s, 2H). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found C, 59.81; H, 8.12.

methyl 1-hydroxy 2,2,6-trimethyl 3-oxo-cyclohexane carboxylate (103)[38,39]

The hydroxy acid, **102** (0.79 g, 4.0 mmol) was dissolved in 50 mL of dry DMF and potassium bicarbonate (0.70 g, 7.0 mmol) was added, followed by methyl iodide (0.50 g, 4.0 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was then diluted with water (50 mL) and extracted with ether (3x25 mL). The combined ether extracts were washed with saturated aqueous $NaHCO_3$ (25 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 0.69 g (80%) of **103** (isomeric mixture), as a pale yellow oil. $IR_{(neat)}(cm^{-1})$ 3520, 2950, 2880 and 1720. ^1H NMR (60 MHz, $CDCl_3$, ppm) 0.75 (d, 3H), 0.95 (s, 3H), 1.25(s, 3H), 1.80 (m, 3H), 2.35 (m, 2H), 3.25 (br. s, 1H) and 3.80 (s, 3H). GC-MS (m/e) 214.

Dehydration of compound 103

The hydroxy ester, **103** (80 mg, 0.37 mmol) was dissolved in 2.0 mL of concentrated sulfuric acid and stirred at room temperature for 4 hours. Iced-cold water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (5x10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (5x10 mL) followed by water (10 mL) and brine (20 mL), then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 60 mg a pale yellow oil. Purification by PLC followed by HPLC (hexane/ethyl acetate) gave compounds **80** and **104** in a 1:5 ratio respectively. Compound **104** gave the following spectral data: $UV_{(\lambda\ max,}$

MeOH) 223 nm (ε, 9,939). (calc. 227± 5 nm). IR (cm^{-1}) 2980, 2980, 2960, 2940, 1730, 1680 and 1570. ^{1}H NMR (60 MHz, $CDCl_3$, ppm) 1.10 (m, 9H), 2.40 (m, 2H), 3.75 (s, 3H), 5.80 (dd, 1H), and 6.60 (dd, 1H). GC-MS (m/e) 196. The minor compound **80** gave the following data: ^{1}H NMR (200 MHz, $CDCl_3$, ppm) 1.10 (s, 3H), 1.17 (s, 3H), 1.83 (s, 3H), 2.90 (m, 3H), 3.65 (s, 3H) and 5.65 (br. s, 1H). GC-MS (m/e) 196.

ethyl 2-isopropylidene 3-hydroxy 3-methyl 3 (1'-phenylthiocyclopropyl)propionate (107)[68]

A dry 250 mL three-necked flask was fitted with a nitrogen inlet-tube, a stopper and a rubber septum. Cyclopropyl phenyl sulfide (1.78 g, 10.0 mmol) and 70 mL of dried THF were placed in the flask via syringe. The flask was cooled (ice/salt) for 15 minutes. n-BuLi (0.02 mol) was added and the mixture was stirred at 0 °C for a further 2 hours. Ethyl α-isopropylidene acetoacetate **106** (2.0 g, 10 mmol) was added via syringe and the mixture was stirred at 0 °C for a further 30 minutes. The mixture was quenched with water (5 mL) and ether (100 mL) was added. The mixture was filtered and washed with brine (2x10 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure to give 3.9 g of a yellow oil. Purification on silica gel gave 0.73 g (23%) of compound **107**. IR (cm^{-1}) 3500, 1718, 1640 and 1560. ^{1}H NMR (200 MHz, $CDCl_3$, ppm) 0.90 (m, 4H), 1.60 (t, 3H), 2.20 (s, 3H), 2.80 (s, 1H, disappeared in D_2O), 4.40 (q, 2H) and 7.50 (m, 5H).

Preparation of **2-chloro-2-nitropropane**[44]

Reagent grade 2-nitropropane (24.8 g, 280 mmol) was dissolved in 150 mL of 10% sodium hydroxide in a three-necked flask equipped with a chlorine inlet-tube, a mechanical stirrer and a gas outlet-tube. The flask was cooled in an ice bath for 40 minutes, then chlorine was bubbled into the rapidly stirred reaction mixture for 2 hours. An oily layer was formed during the reaction and it was separated. The aqueous layer was extracted with CH_2Cl_2 (3x25 mL). The combined organic layers were washed with 10% sodium hydroxide (3x50 mL) followed by brine (2x25 mL) then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give 21.6 g of a colorless oil. Distillation gave 18.2 g (52%) of 2-chloro-2-nitropropane, b.p. 130-134 ° C (Lit. b.p. 134 ° C). ^1H NMR (60 MHz, $CDCl_3$) gave a singlet at 2.20 ppm.

Preparation of **α-isopropylidene acetoacetate (106)**[43]

Sodium hydride (4.30 g, 100 mmol; calculated from 57% oil dispersion) was placed in a three-necked flask and rinsed with anhydrous ether which was decanted. The flask was fitted with a thermometer, a septum, and an addition funnel carrying a nitrogen inlet-tube. Dried DMF (60 mL) was added and the mixture was stirred while ethyl acetoacetate (13.0 mL, 13.3 g, 100 mmol) was added dropwise during 1 hour followed by an additional 3 hours of stirring at room temperature. 2-Chloro-2-nitropropane (5.4 mL, 6.6 g, 50 mmol) was added via syringe and the reaction mixture was stirred overnight at room temperature. The reaction mixture was then poured into 400 mL of cold water and the organic layer was extracted with 5% sodium hydroxide (4x50 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give 7.7 g of a yellow oil. Vacuum distillation gave 3.8 g (45%) of a pale yellow oil, b.p. 67-69 °C at 1.5 mm Hg. IR (cm^{-1}) 2980, 2940, 1720, 1690 and 1625. ^1H NMR (60 MHz, $CDCl_3$, ppm) 1.35 (t, 3H), 2.05 (s, 3H), 2.20 (s, 3H), 2.40 (s, 3H) and 4.35 (q, 2H). GC-MS (m/e) 170.

Preparation of **geranyl acetate (32)** (commercially available)

Commercially available geraniol (49.2 g, 320 mmol) was dissolved in acetic anhydride (35.7 g, 350 mmol) and cooled in an ice bath. 4-N,N-dimethylaminopyridine (40.0 mg) was added and the reaction mixture was stirred at room temperature overnight. Water (200 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3x50 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (3x50 mL) followed by brine (50 mL), then dried over anhydrous Na_2SO_4. The solvent was removed on the rotavapor to give 57.6 g (92%) of a slightly yellow oil. ^1H NMR (60 MHz, $CDCl_3$, ppm) 1.55 (s, 4H), 1.65 (s, 6H), 2.0 (s, 6H), 4.50 (d, 2H) and 5.20 (m, 2H).

6,7-epoxy-3,7-dimethyl 2-octenyl acetate (42)[31]

Geranyl acetate (25.0 g, 120 mmol) was dissolved in CH_2Cl_2 (500 mL). Saturated aqueous sodium bicarbonate (400 mL) was added and the mixture was stirred while being cooled in an ice bath. M-Chloroperbenzoic acid (40.8 g, 130 mmol; calculated from 50-60% MCPBA) was added in small portions and after the addition was completed the ice bath was removed. The mixture was then stirred at room temperature for 1.5 hours. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (100 mL) followed by brine (100 mL), dried over anhydrous sodium sulfate and concentrated on the rotavapor to give a pale yellow oil. Reduced pressure distillation gave 23.0 g (86%) of **42** as a colorless oil, b.p. 98-104 °C at 0.5 mm Hg. IR (cm^{-1}) 2970, 2930, 1730, 1670, 1230 and 1120. ^1H NMR (60 MHz, $CDCl_3$, ppm) 1.28 (narrow d, 6H), 1.75 (m, 5H), 2.10 (m, 5H), 2.70 (t, 1H), 4.70 (d, 2H) and 5.60 (t, 1H).

3,7-dimethyl 7-hydroxy 6-thiophenyl 2-octenol (113)

Freshly distilled thiophenol (15.7 g, 140 mmol) was dissolved in absolute ethanol (500 mL) in a dry three-necked flask equipped with a nitrogen inlet-tube, a mechanical stirrer and an addition funnel. The flask was flushed with nitrogen and cooled in an ice bath for 15 minutes. Sodium borohydride (1.34 g, 35.0 mmol) was slowly added after which the cooling bath was removed and the mixture was stirred for 30 minutes. The epoxy acetate (**42**) was dissolved in absolute ethanol (50 mL), added dropwise, and the resulting mixture was kept overnight at room temperature. The mixture was concentrated on the rotavapor and the residue was dissolved in CH_2Cl_2 (200 mL), washed with water (150 mL) and dried over anhydrous Na_2SO_4. The solvent was removed on the rotavapor to give a pale yellow viscous oil which crystallized upon addition of hexane and ethyl acetate (4:1) to give 28.8 g (72%) of a white solid, m.p. 71.0-72.0 °C. IR (cm^{-1}) 3610, 3500 and 2990. ^{1}H NMR (60 MHz, $CDCl_3$, ppm) 1.20 (d, 6H), 1.60 (s, 3H), 2.60 (br. s, 1H), 3.90 (d, 2H), 5.10 (t, 1H) and 7.20 (m, 5H).

3,7-dimethyl 7-hydroxy 6-thiophenyl 2-octenyl acetate (51)

The diol, **113** (14.3 g, 51.0 mmol) and acetic anhydride (6.0 mL, 6.5 g, 61 mmol) were dissolved in dry methylene chloride (30 mL). The mixture was cooled in an ice bath, DMAP (~5 mg) was added and the mixture was stirred at room temperature overnight. Water (100 mL) was added and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2x30 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (3x50 mL), dried over anhydrous Na_2SO_4 and concentrated on the rotavapor to give a yellow oil. Purification by column chromatography (hexane and ethyl acetate/2:1) gave 14.2 g (87%) of a pale yellow oil. IR (cm^{-1}) 3500, 2990, 1725 and 1655. ^{1}H NMR (60 MHz, $CDCl_3$, ppm) 1.20 (d, 6H), 1.70 (s, 3H), 2.20 (s, 3H), 2.80 (br.s, 1H), 4.55 (d, 2H), 5.24 (t, 1H) and 7.50 (m, 5H).

2-acetoxymethyl-4-phenylthio-1,3,3-trimethylcyclohexenol (52)[31]

The hydroxy acetate, **51** (7.0 g, 20 mmol) was dissolved in dry methylene chloride (500 mL) in a round-bottomed flask equipped with a nitrogen inlet-tube and an addition funnel. The flask was cooled (dry ice/CCl_4) for 10 minutes and trifluoroacetic acid added dropwise during 15 minutes. After addition was completed the cooling bath was removed and the mixture was stirred for about 20 minutes. The reaction mixture was then carefully poured into 1 L of cold aqueous $NaHCO_3$. The organic layer was separated and washed with more saturated aqueous $NaHCO_3$ (3x50 mL), followed by brine, then concentrated on the rotavapor to give 3.4 g (53%) of a pale yellow oil which crystallized on standing. Recrystallization from hexane/ethyl acetate gave white crystals, m.p. 86.0-86.5 °C. ^1H NMR (60 MHz, $CDCl_3$, ppm) 0.97 (s, 3H), 1.20 (d, 6H), 1.65 (m, 5H), 2.40 (br.s, 1H), 4.40 (d, 2H) and 7.20 (m, 5H). ^{13}C NMR (200 MHz, $CDCl_3$, ppm) 16.5 (CH_3), 20.5 (CH_3), 22.8 (CH_2), 28.0 (CH_3), 29.0 (C), 38.3 (CH_3), 42.4 (CH_2), 56.8 (CH), 59.5 (CH), 61.8 (CH_2), 71.0 (C), 126.2 (CH), 131.0 (CH), 136.0 (CH) and 170.5 (C). GC-MS (m/e) 322.

2-acetoxymethyl-4-phenylthio-1,3,3-trimethyl-7-oxabicyclo [2.2.1]heptane (114)[31]

The hydroxy acetate, **52** (3.39 g, 12.0 mmol) was dissolved in dry methylene chloride (150 mL) in a two-necked flask equipped with a nitrogen inlet-tube and a rubber septum. The flask was flushed with nitrogen and cooled (ice/salt) for 15 minutes. Sulfuryl chloride (20.0 mL, 20.0 mmol; calculated from a 1M solution in CH_2Cl_2) was added and the mixture was stirred for 20 minutes, then filtered through deactivated[48] silica gel (120 g/60 mL H_2O). The filtrate was washed with brine (50 mL) then dried over anhydrous $MgSO_4$ and concentrated on the rotavapor to give a pale yellow oil. Purification by flash column chromatography on silica gel gave 2.1 g (55%) of compound **114** as white solid, m.p. 82.5 °C and compound **116**, also white solid, m.p.108.0-109.5 °C. Spectral data for **114**: ^{1}H NMR (60 MHz, $CDCl_3$, ppm) 1.00 (s, 3H), 1.35 (s, 3H), 1.68 (s, 3H), 2.25 (s, 3H), 4.25 (d, 2H), 4.85 (dd, 1H), 7.63 (m, 3H) and 8.10 (m, 2H).

6-acetoxymethyl-4-phenylthio-1,5,5-trimethylcyclohexa-1,3-diene (118)

The bicyclic acetate **114** (1.16 g, 3.60 mmol) was dissolved in dry methylene chloride (60 mL) in a 250 mL round-bottomed flask equipped with a nitrogen inlet-tube, a rubber septum and an addition funnel. The flask was cooled (ice/salt) for 30 minutes and flushed with nitrogen. Acetyl chloride (0.7 mL, 0.7 g, 0.01 mol) was dissolved in dry CH_2Cl_2 (10 mL) and added dropwise via syringe followed by anhydrous $SnCl_4$ (0.2 mL, 1 mmol) and the mixture was stirred for 45 minutes. Potassium carbonate (4.0 g, 30 mmol) was added followed by methylene chloride (100 mL), water (1.0 mL) and stirring was continued for 3 hours. The red reaction mixture was decanted and the flask was rinsed with CH_2Cl_2 (2x25 mL). The combined organic layers were washed with saturated aqueous sodium carbonate (5x50 mL) followed by brine (2x50 mL), then dried over anhydrous $MgSO_4$. The solvent was removed on the rotavapor to give a pale yellow oil. Purification by column chromatography on silica gel (hexane/ethyl acetate, 5:1) gave 0.17 g (16%) of compound **118**, as a pale yellow oil. A second compound (80 mg) was isolated but its structure could not be assigned based on the spectral data. **118**: IR

(cm^{-1}) 3030, 2970, 1730, 1580 and 1565. ^1H NMR (60 MHz, $CDCl_3$, ppm) 1.20 (d, 6H), 1.90 (s,3H), 2.10 (m, 4H), 4.40 (overlapping AB q, 2H), 5.60 (m, 2H) and 7.60 (m, 5H). GC-MS (m/e) 302.

4-phenylthio-1,3,3-trimethyl-7-oxabicyclo [2.2.1]heptane-2-methanol (119)

The bicyclic acetate, **114** (1.0 g, 3.0 mmol) was dissolved in anhydrous methanol (30 mL) in a 50 mL round-bottomed flask equipped with a nitrogen inlet-tube. Potassium carbonate (0.48 g, 3.0 mmol) was added and the mixture was stirred at room temperature for 2 hours then neutralized with 1% HCl and extracted with ether (3x50 mL). The combined ether extracts were washed with water (50 mL) and dried over anhydrous $MgSO_4$. The solvent was removed on the rotavapor and 0.87 g (83%) of a white solid was formed on standing. IR (cm^{-1}) 3620, 3480, 3060, 2970, 2930, 2880 and 1580. ^1H NMR (60 MHz, $CDCl_3$, ppm) 1.15 (d, 3H), 1.60 (s, 6H), 1.80 (m, 5H), 3.75 (d, 3H), 7.55 (m, 3H) and 7.80 (m, 2H). GC-MS (m/e) 278.

4-phenylthio-1,3,3-trimethyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (120)

Alcohol **119** (1.0 g, 3.5 mmol) was dissolved in acetone (30 mL) and the solution was cooled in an ice bath. Jones reagent (3.0 mL) was added dropwise until the orange color persisted. The reaction mixture was then stirred at room temperature for 2.5 hours. The organic layer was carefully poured off and the aqueous layer was washed with ether (3x30 mL). The ether layers were combined and washed with 1.5M HCl until all the green color disappeared, then with water (50 mL) followed by brine (50 mL), then dried over anhydrous $MgSO_4$. The solvent was removed on the rotavapor to give a very pale yellow solid 0.85 g (81%), with m.p. 122.0-123.0 °C. IR (cm^{-1}) 3500-3200, 3060, 2975 and 1705. ^1H NMR (60 MHz, $CDCl_3$, ppm) 1.25 (m, 6H), 1.45 (narrow d, 3H), 1.70 (m, 4H), 2.20 (s, 1H), 2.45 (s, 1H), 7.10 (m, 2H) and 7.40 (m, 3H).

methyl 4-phenylthio-1,3,3-trimethyl-7-oxabicyclo [2.2.1]heptane-2-carboxylate (121)^{69}

Acid **120** (0.85 g, 2.9 mmol) was dissolved in DMF (20.0 mL) in a 100 mL round-bottomed flask. Potassium carbonate (0.3 g, 3 mmol) was added to the flask and then the mixture was stirred under nitrogen. Methyl iodide (0.2 mL, 3 mmol) was added via syringe and the mixture was stirred at room temperature overnight. The reaction mixture was then diluted with water (40 mL) and extracted with ether (4x40 mL). The combined ether extracts were washed with water (50 mL) followed by brine (50 mL), then dried over anhydrous $MgSO_4$. The solvent was removed on the rotavapor to give a pale yellow oil 0.62 g (70%). IR (cm^{-1}) 3060, 2975, 2935, 2880, 1728 and 1580. ^1H NMR (200 MHz, $CDCl_3$, ppm) 1.20 (d, 6H), 1.50 (s, 3H), 1.75 (m, 4H), 2.50 (s, 1H), 3.74 (s, 3H), 7.30 (m, 3H) and 7.60 (m, 2H). GC-MS (m/e) 306.

2-acetoxymethyl-4-phenylsulfinyl-1,3,3-trimethylcyclohexanol (126)[31]

a) Compound **52** (1.1 g, 3.0 mmol) was dissolved in 50 mL methylene chloride in a 250 mL round-bottomed flask and 50 mL of saturated aqueous sodium bicarbonate was added. The reaction mixture was then cooled in an ice bath and vigorously stirred for 5 minutes, and MCPBA (1.3 g, 4.0 mmol) was then added in small portions. The reaction mixture was stirred for 2 hours at room temperature, the organic layer was then separated and the aqueous layer was extracted with CH_2Cl_2 (2x25 mL). The organic layers were combined and washed with saturated aqueous $NaHCO_3$ (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated on the rotavapor to give the sulfoxide, a white solid (0.65 g, 64% yield), m.p. 152-155 °C. IR(cm^{-1}) 3600 (sharp, free OH), 3480 (br. OH), 1730 (CO, acetate), 1145, 1080 and 1035 (SO). ^1H NMR (60 MHz, $CDCl_3$, ppm) 1.20 (narrow doublet, 6H), 1.50 (m, 5H), 1.55 (s, 3H), 2.00 (s, 3H), 2.75 (m, 2H), 4.28 (m, 2H) and 7.45 (m, 5H).

b) Sodium metaperiodate[61] (4.28 g, 20.0 mmol) was placed in a 100 mL round-bottomed flask and 400 mL of cold (0 °C) 50% aqueous acetic acid was added. Compound **52** (1.3 g, 4.0 mmol) was added in small portions. After addition was completed the cooling bath was removed and the reaction mixture was stirred overnight. The reaction mixture was then extracted with $CHCl_3$ (4x25 mL). The organic layers were combined and washed with (3x30 mL) water, followed by 50 mL of 5% aqueous $NaHCO_3$ and brine (30 mL), then dried over anhydrous $MgSO_4$. The solvent was removed on the rotavapor to give 1.4 g (89%) of a white solid, m.p. 152-155 °C. The IR and ^{1}H NMR spectra were the same as part *a* above.

2-acetoxymethyl-4-phenylsulfonyl-1,3,3-trimethylcyclohexanol (125)

Sulfoxide **126** (0.52 g, 1.5 mmol) was dissolved in 50 mL methylene chloride and 50 mL of saturated aqueous $NaHCO_3$ was added. The flask was cooled in ice and MCPBA (0.65 g, 2.0 mmol; cal. from 50-55% MCPBA) was added in small portions. The cooling bath was removed and the reaction mixture was stirred at room temperature for 3 hours. (TLC showed that a new compound was formed.) The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2x15 mL). The organic layers were combined and washed with 50 mL of saturated aqueous $NaHCO_3$, then dried over anhydrous $MgSO_4$. The solvent was removed on the rotavapor to give the sulfone, a white solid (0.48 g, 90% yield). IR(cm^{-1}) 3580 (sharp, free OH), 3500 (br., OH), 1720 (CO, acetate), and 1290, 1360 (SO_2-). ^{1}H NMR (60 MHz, $CDCl_3$, ppm) 1.20 (d, 6H), 1.50 (s, 3H), 1.60 (m, 5H), 1.95 (s, 3H), 2.6 (m, 2H), 4.20 (m, 2H), and 7.50 (m, 5H).

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