APPLICATIONS OF ARYL ISOTHIOCYANATES IN ONE-POT ELIMINATION REACTIONS, SYNTHESIS AND ANTI-OXIDANT ACTIVITY OF SEVERAL NOVEL CAPSIATES AND PROGRESS TOWARDS THE TOTAL SYNTHESIS OF THREE ICETEXANE AND ONE NORICETEXANE DITERPENOIDS

by

THOMAS COMBS IRVIN

(Under the Direction of George Majetich)

ABSTRACT

An alternative to the Chugaev reaction has been developed. This new method utilizes aryl isothiocyanates in a one-pot elimination process and gives yields comparable to the Chugaev reaction. Additionally, this new procedure eliminates a purification step. Forty-four novel capsiates were prepared from vanillyl alcohol and the corresponding carboxylic acid. The capsiates were tested for anti-oxidant activity by an ORAC assay. Eight capsiates exhibited ORAC values above 5,000 μmol Trolox/gram. The first total synthesis of rosmaridiphenol has been completed using a cyclialkylation strategy. The progress towards the total syntheses of salvimultine, perovskone B, and hydrangenone is presented as well.

INDEX WORDS: Chugaev, isothiocyanate, elimination, capsiates, anti-oxidant, ORAC, salvimultine, rosmaridiphenol, perovskone B, hydrangenone

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LIST OF ABBREVIATIONS

ABBREVIATION	**FULL NAME**
AAPH	2-2’-azobis(2-amidinopropane) dihydrochloride
Acac	acetylacetonate
Ac_2O	acetic anhydride
AIBN	azobisisobutyronitrile
BHT	butylhydroxytoluene
Boc	*tert*-butoxycarbonyl
BTFP	3,5-*bis*(trifluoromethyl)phenyl
BzCl	benzoyl chloride
CAN	ceric ammonium nitrate
CBS	Corey–Bakshi–Shibata
Cbz	carboxybenzyl
DCC	*N*-*N’*-dicyclohexylcarbodiimide
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAE	dimethylaminoethanol
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide

DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethylsulfoxide
EAS	electrophilic aromatic substitution
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
EtSH	ethanethiol
FDA	Food and Drug Administration
HMPA	hexamethylphosphoramide
KO-*t*-Bu	potassium *tert*-butoxide
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
m-CPBA	*meta*-chloroperoxybenzoic acid
MeOH	methanol
MOM	methoxymethyl
NBS	*N*-bromosuccinimide
NaHMDS	sodium hexamethyldisilazide
NaOEt	sodium ethoxide
NaOMe	sodium methoxide
NaSEt	sodium ethanethiolate
n-BuLi	*n*-butyllithium
OAc	acetate
ORAC	oxygen radical absorbance capacity

PMB	*para*-methoxybenzyl
PPA	polyphosphoric acid
p-TsOH	*para*-toluenesulfonic acid
Py·HOTf	pyridinium triflate
SAR	structure-activity relationship
sec-BuLi	*sec*-butyllithium
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TCBC	2,4,6-trichlorobenzoyl chloride
TEA	triethylamine
TES	triethylsilyl
THF	tetrahydrofuran
TIPDS	tetraisopropyl disiloxyl
TMS	trimethylsilyl
TRPV1	transient receptor potential vanilloid type-1
TsCl	*para*-toluenesulfonyl chloride
VEGF	vascular endothelial growth factor

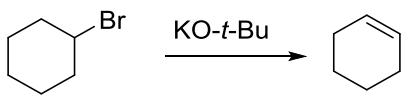
CHAPTER 1

APPLICATION OF ARYL ISOTHIOCYANATES IN ONE-POT ELIMINATION REACTIONS

1.1 Introduction

The formation of a carbon–carbon double bond has always been a challenging yet desired transformation in organic synthesis. The most commonly used procedure is the acid-catalyzed dehydration of an alcohol. Unfortunately, this procedure requires harsh conditions which do not lend itself to late stage use in a synthesis of an acid-sensitive molecule; this reaction proceeds through a carbocation intermediate which opens the possibility of a skeletal rearrangement leading to undesired products. The search for a suitable alternative has been ongoing for over 100 years.

Perhaps the most common subset of these olefination reactions is the β-elimination. The simplest form of this reaction is the base-catalyzed E_2 elimination of HX from a halo-alkane (Scheme 1.1). This simple elimination is one of the first reactions taught to undergraduate organic students because of its wide utility and simplicity. However, the use of strong base limits the function group tolerance of the reaction.



Scheme 1.1

Several of these eliminations are thermally driven such as the pyrolysis of an acetate and the Chugaev xanthate elimination (Figure 1.1).[1,2] These thermally driven eliminations proceed nearly exclusively via a *syn*-elimination mechanism.

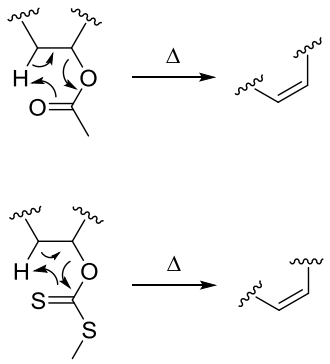


Figure 1.1

Not all elimination reactions are thermally driven. The Peterson olefination (Figure 1.2) utilizes acidic or basic conditions to facilitate the elimination of a β-hydroxy silane to yield an olefin.[3] Hudrlik showed that under acidic conditions the reaction proceeds via an *anti*-elimination mechanism and under basic conditions a *syn*-elimination occurs.[4] The different mechanisms allow for control of the stereochemistry of the resulting olefin.

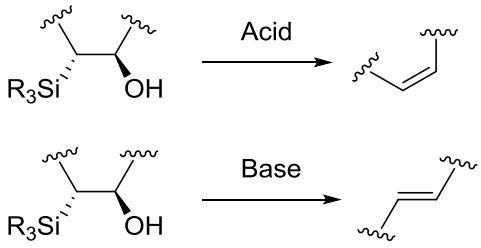
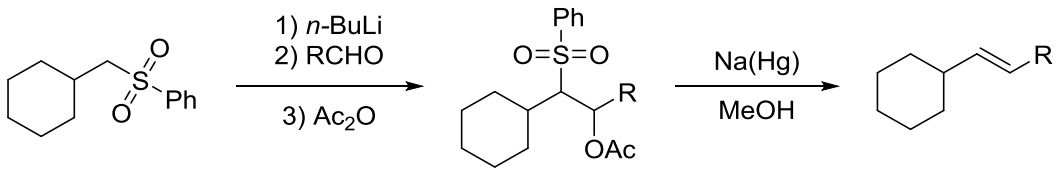


Figure 1.2

Another alternative to pyrolysis is a β-elimination that involves a reductive elimination step. One of the most popular is the Julia–Lythgoe olefination.[5] This reaction uses a reducing agent to effect the elimination of a β-alkoxy sulfone (Scheme

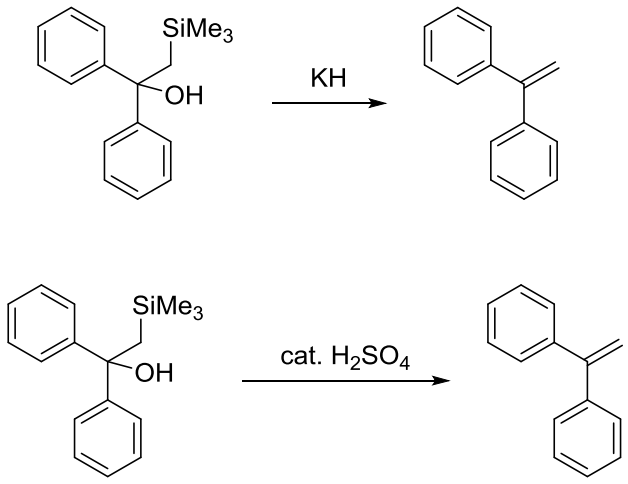
1.2). This reaction typically results in only the (*E*)-alkene being formed. Because of the hazards of working with sodium-mercury amalgam, several alternatives have been discovered. One of those, using SmI_2, has found widespread use in the reductive elimination of not only sulfones but other functional groups as well.



Scheme 1.2

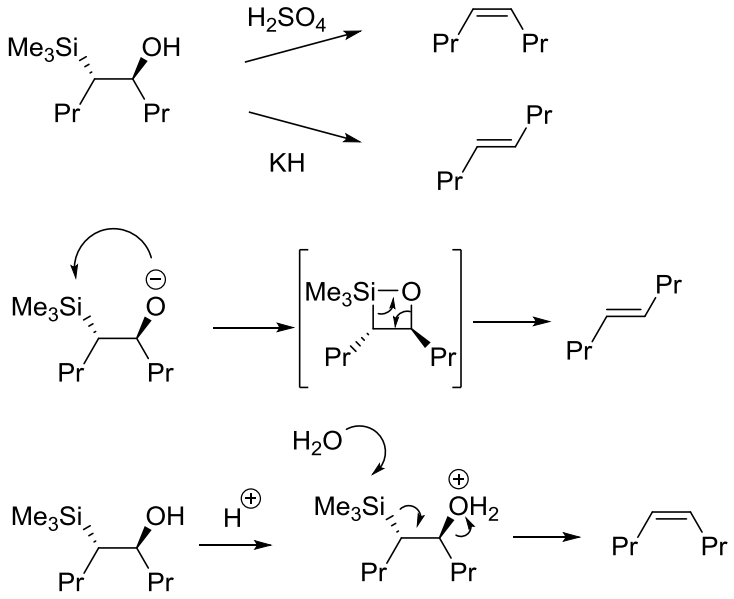
1.2 The Peterson Olefination

The Peterson olefination was first reported in 1968 and involves the attack of a silyl organometallic compound on a carbonyl to yield a β-hydroxy silane.[3] This compound can then undergo β-elimination to yield an olefin in either acidic or basic conditions (Scheme 1.3). This initial report sought to build on the trends noted for β-hydroxy phosphines. The olefins were obtained in reasonable yield but there was very little *E*/*Z* selectivity in the products.



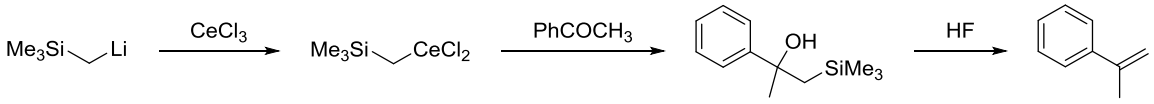
Scheme 1.3

In 1975, Peterson reported a stereoselective elimination. When 5-trimethylsilyl-4-octanol was treated with base (*E*)-4-octene was the major product. If the same compound was treated with acid the *Z* isomer was the major product (Scheme 1.4) which suggests that the acid-catalyzed elimination proceeds via an anti pathway whereas the base-catalyzed proceeds via a syn route.



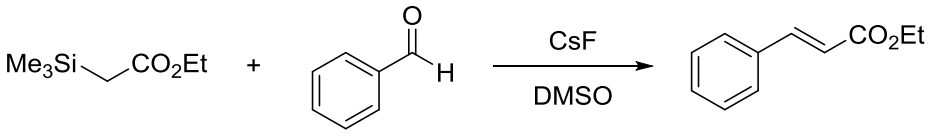
Scheme 1.4

The Peterson olefination has been modified for the methylenation of carbonyls. One problem with using the alkylsilyllithium reagents typically seen in the Peterson olefination is their high level of basicity which leads to low levels of chemoselectivity and lower yields. Johnson discovered that if the alkylsilyllithium reagent was combined with $CeCl_3$ the basicity is reduced and the resulting terminal olefins can be isolated in high yield (Scheme 1.5).[6] This suggests that a transmetallation occurs between the alkyllithium and the cerium leading to an alkylcerium species. These compounds are much less basic but still very nucleophilic. Similar to the original Peterson conditions, the elimination can be catalyzed by either an acid or base.



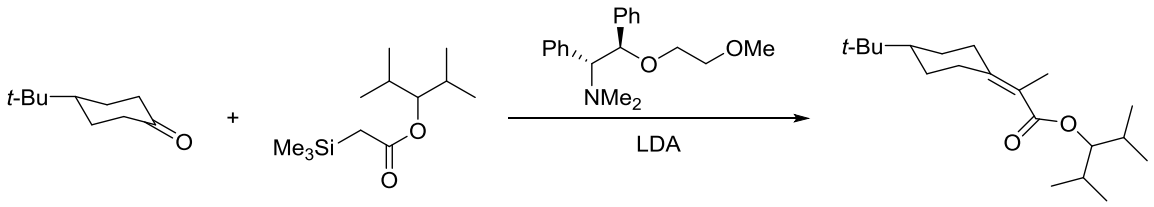
Scheme 1.5

The Peterson olefination has also been improved to a one-pot process. When a methylsilane containing an electron withdrawing group was combined with a series of aldehydes with catalytic CsF in DMSO, a high yield of the *E*-olefin resulted (Scheme 1.6).[7] This eliminates the need for an acidic or basic workup; however, this one-pot process only creates *E*-olefins. For the preparation of *Z*-olefins the traditional Peterson olefination is superior; however, this reaction is very solvent dependent. For example, when performed in THF no olefin is observed. Additionally, when TBAF was substituted for CsF a significant amount of the β-hydroxy ester was observed. This has been attributed to the residual water present in commercially available TBAF solutions.



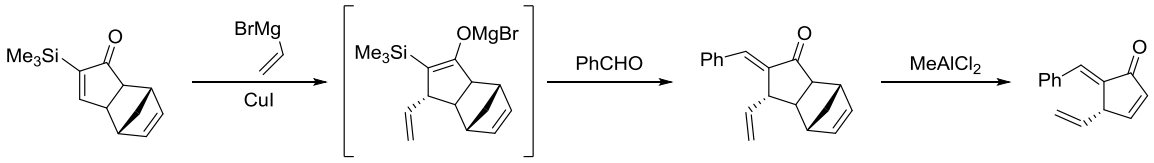
Scheme 1.6

In addition to a one-pot process, the Peterson Olefination has been performed asymmetrically. Through the use of a chiral ligand, a series of axially chiral olefins has been prepared (Scheme 1.7).[8] Moreover, an excess of ligand is required for the formation of the olefin in good yield and stereoselectivity. When excess siloxide was added to the ketone the yield was decreased. This can be attributed to the siloxide complexing with the ligand and preventing the chiral silanoate from forming.



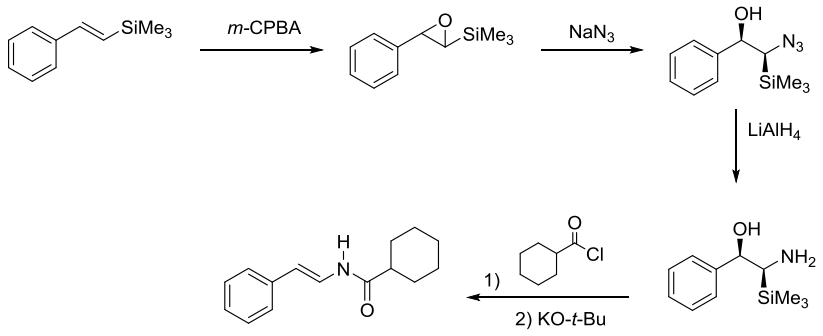
Scheme 1.7

Cross-conjugated dienones are an important structural component of several natural products. Several of these compounds form important precursors to a range of prostaglandin derivatives. The Peterson olefination provided a concise route to several derivatives. A conjugate addition of a Grignard reagent followed by quenching the resulting enolate with benzaldehyde resulted in the desired exocyclic olefin. A retro Diels–Alder reaction furnished the cross-conjugated dienone in good yield (Scheme 1.8).[9] Excitingly, the organometallic addition occurs asymmetrically and the stereocenter remains untouched when the Lewis acid–promoted retro Diels–Alder was performed.



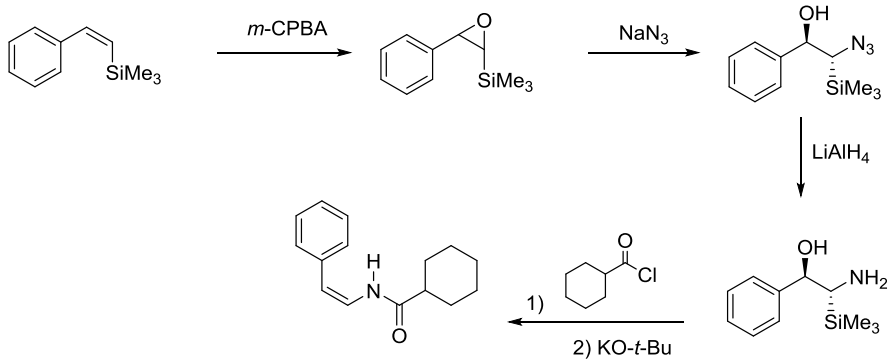
Scheme 1.8

Enamides have been shown to be critical to the biological activity of several cyclic and acyclic peptides.[10] These functional groups are also very sensitive especially to acidic conditions under which they readily succumb to hydrolysis. In order to prepare these linkages, only neutral or basic conditions may be used. The Peterson olefination satisfies all of these requirements. Fürstner was able to prepare a series of both *E*- (Scheme 1.9) and *Z*- (Scheme 1.10) enamides from the respective vinyl silanes.[10]



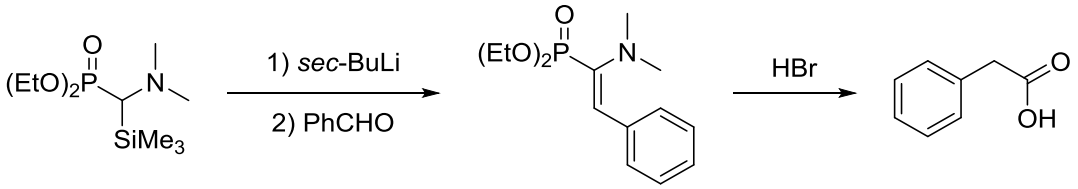
Scheme 1.9

Once the amine had been prepared, a one-pot process was used to facilitate the Peterson olefination. First, the amine was acylated with a series of acyl chlorides and then potassium *tert*-butoxide promoted the elimination to give the enamide.



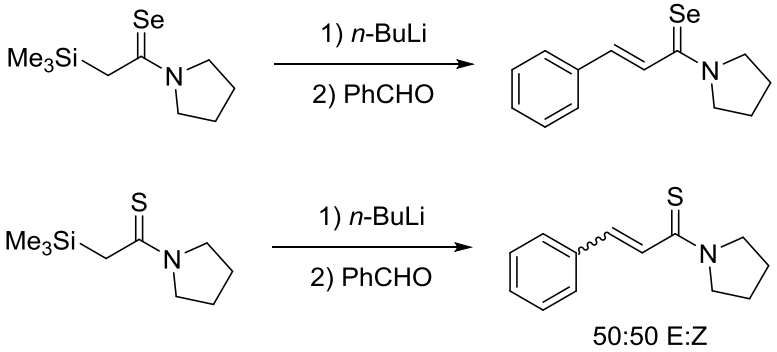
Scheme 1.10

The preparation of α-phosphonoenamines has been desirable because of their use as peptide mimetics. They can also form homologated carboxylic acids from the starting aldehydes when subjected to hydrolysis. This second application is useful because it only requires two steps whereas other methods required more. McNulty was able to form these enamines from a range of aldehydes (Scheme 1.11).[11] The advantage of using the Peterson olefination is the mildness of reagents used. The α-phosphonoenamines are quite labile and stronger reagents may lead to their decomposition.



Scheme 1.11

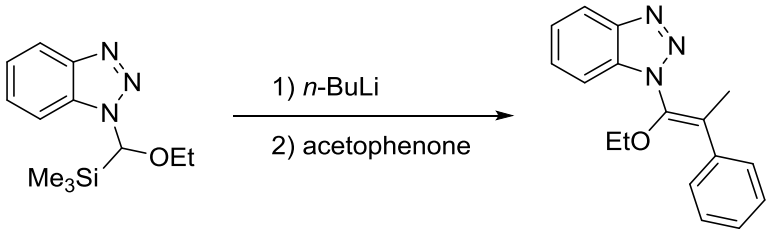
Organoselenium compounds and especially selenocarbonyls have been targeted for their potential use as anti-cancer drugs;[12] however, they are notoriously difficult to prepare. Murai was able to use a Peterson Olefination to prepare a series of α,β-unsaturated selenoamides from the corresponding selenoacetamide (Scheme 1.12).[13] Surprisingly, only the *E*-isomer was observed. When the corresponding thioacetamide was subjected to the same reaction conditions a 50:50 mixture of the *E*-and *Z*-isomers resulted. This suggests that the increased size of the selenium compared to sulfur causes steric repulsion which precludes *Z*-olefin formation.



Scheme 1.12

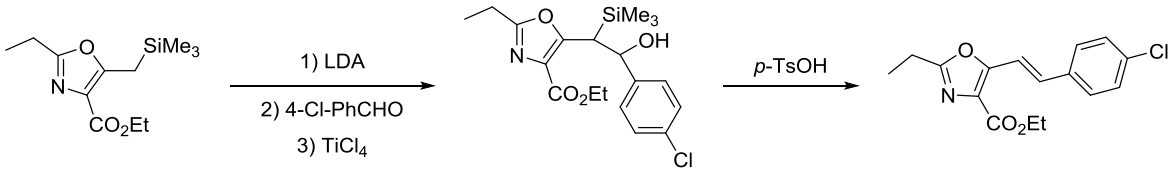
1-(1-Alkenyl)benzotriazoles are key intermediates in the preparation of pyrimidines, carbazoles, and indoles. As such, a general method of preparing these compounds is very important for the synthesis of natural products containing these functional groups. The difficulty in preparing these compounds is the formation of the olefin. Previous work has employed the Wittig reaction and other eliminations but all

suffered from poor yield. Pleynet and co-workers were able to use a Peterson olefination to prepare these compounds in good yield (Scheme 1.13).[14] The advantage of using the Peterson olefination on these substrates is that the triazole stabilizes the anion formed on the adjacent carbon. Surprisingly, when LDA was used to create the anionic intermediate, only minimal olefin formation was observed. By changing to the less hindered *n*-butyllithium, the olefins were prepared cleanly in high yield.



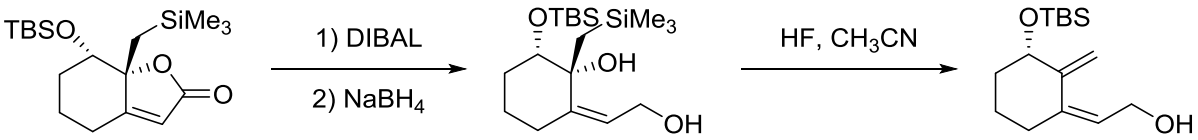
Scheme 1.13

Another class of heterocyclic compounds accessible via the Peterson olefination are 5-alkenyloxazoles. Oxazoles have been shown to exhibit high levels of biological activity.[15] However, very few methods to prepare these compounds are known. Chau was able to take several 5-(trimethylsilyl)-methyloxazoles and combine them with aromatic and aliphatic aldehydes to produce an olefin (Scheme 1.14).[15] To form the α-hydroxysilane the harsh Lewis acid $TiCl_4$ was required. This can be attributed to the poor nucleophilicity of the lithium anions formed. Fortunately, these silanes readily underwent elimination to the olefins upon treatment with *p*-toluenesulfonic acid.



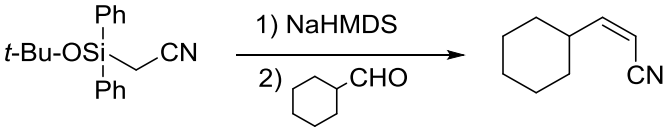
Scheme 1.14

In several Vitamin D derivatives, a sensitive exocyclic methylene olefin is present. As such the Peterson olefination has proven to be quite useful because of the mild reagents required. Harsher methods often lead to a mixture of the exo- and endocyclic olefins. Miles was able to use the Peterson Olefination to install this alkene (Scheme 1.15).[16]



Scheme 1.15

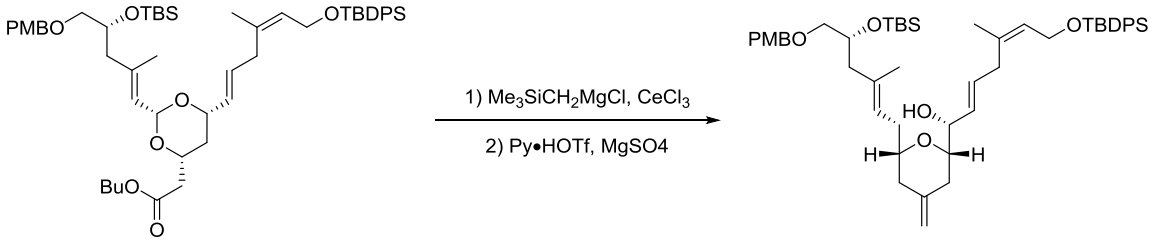
In addition to α,β-unsaturated carbonyls, α,β-unsaturated cyanides can also be formed by the Peterson olefination. Of particular interest is forming the less stable *Z*-olefin. Kojima and co-workers were able to selectively prepare a series of (*Z*)-α,β-unsaturated cyanides from a specially developed silicon reagent and the corresponding aldehyde (Scheme 1.16).[17] It suggests that making the silicon more electronegative favors *Z* olefin formation.



Scheme 1.16

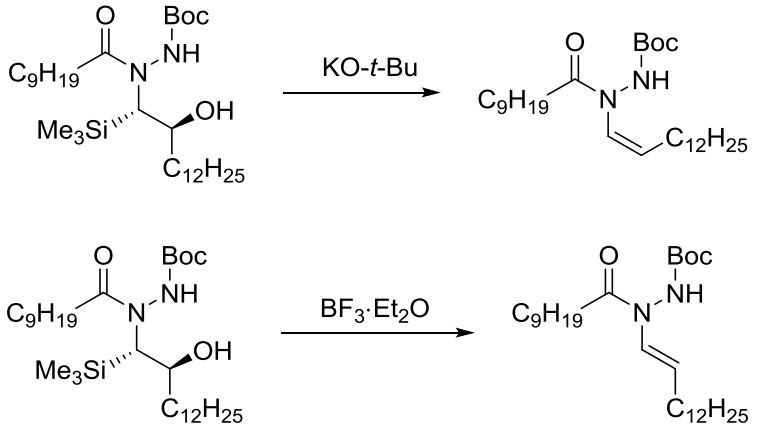
The Peterson olefination has also been used in tandem with other reactions in natural product synthesis. In the synthesis of (+)-dactylolide, a macrocyclic lactone, Aubele and co-workers used a sequential Peterson-Prins process to prepare the tetrahydropyran ring (Scheme 1.17).[18] The conditions employed for the sequential

process [pyridinium triflate and $MgSO_4$] were quite mild. This was necessary to prevent *in situ* protodesilylation of the allylsilane generated.



Scheme 1.17

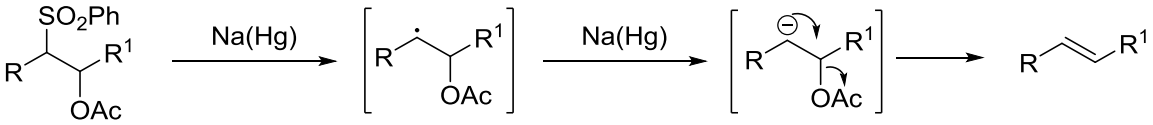
While uncommon in natural products, compounds containing a hydrazine group have been shown to be very biologically active. In the preparation of hydrazidomycin A, Beveridge used a Peterson olefination to install the critical *Z*-enehydrazide (Scheme 1.18).[19] The attractiveness of the Peterson olefination is evident in this synthesis. By changing the conditions from basic to acidic, the stereochemistry of the resulting olefin was changed from *Z* to *E*. This allowed for the preparation of the isomeric *trans*-hydrazidomycin A.



Scheme 1.18

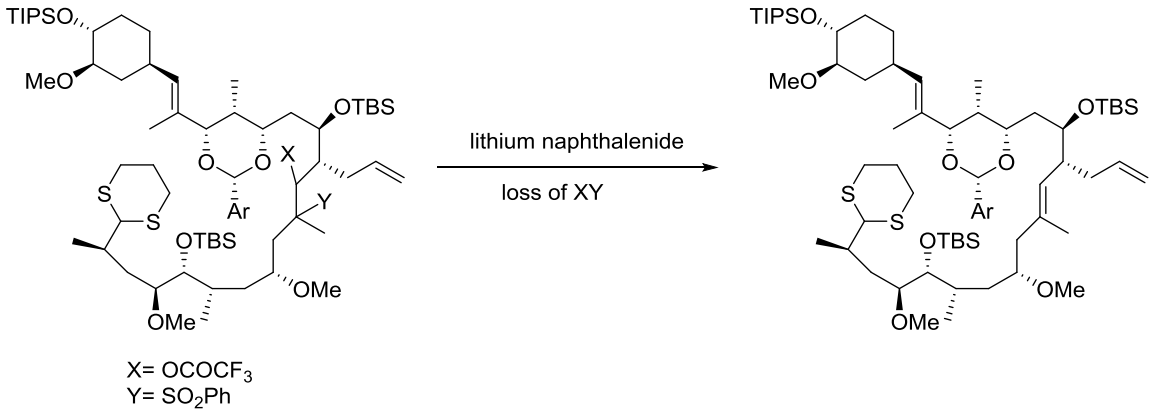
1.3 Julia-Lythgoe Olefination and Related Reductive Eliminations

The Julia–Lythgoe olefination was first reported in 1973 and involves the addition of a phenyl sulfone to an aldehyde, or ketone, followed by a reductive elimination to yield an olefin.[5] During the reductive elimination step, a carbanion is formed which leads to nearly exclusive formation of *E*-alkenes. This is due to the preference of carbanions to eliminate in an anti fashion (Scheme 1.19).[20] A protic solvent mixture is required for the elimination to occur.[5] Kociensky, Lythgoe, and Waterhouse established that methanol was preferable to ethanol because the reduction in ethanol occasionally led to the formation of a vinyl sulfone rather than the intended olefin. When methanol was used, only the desired olefin was formed.[21,22]



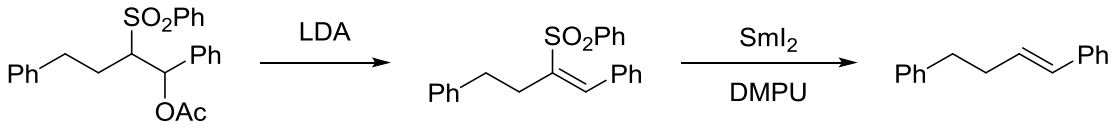
Scheme 1.19

One drawback of the original conditions of the Julia–Lythgoe olefination is the toxicity of the sodium-mercury amalgam. Extensive research was performed on finding an alternative. Lithium napthalenide was used in Danishefsky's formal synthesis of FK-506, an immunosuppressant macrolide (Scheme 1.20).[23] While the acetate underwent elimination, several side products were observed due to a radical fragmentation process occurring preferentially to the elimination of the acetate. As a result the trifluoroacetate was used to create a better leaving group for the elimination and reduce the competing pathways. Unfortunately, lithium napthalenide is often difficult to handle which decreases its utility as a reducing agent. So while lithium napthalenide efficiently reduces the β-alkoxy sulfones, there are drawbacks which make other reducing agents more desirable.



Scheme 1.20

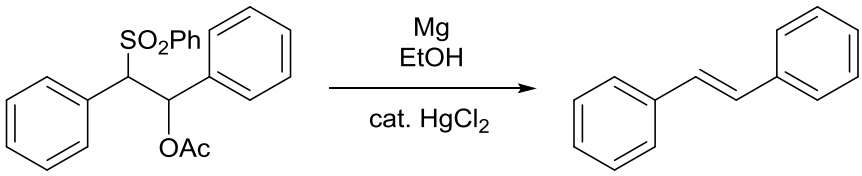
Samarium iodide was also used as an alternative to sodium-mercury amalgam. Ihara and co-workers were able to use a mixture of SmI_2 and HMPA to effect the elimination of several β-acetoxy sulfones.[24] This new method resulted in a higher yield of olefin formation than the original Julia method using sodium-mercury amalgam. However, one disadvantage to this method is the need to use HMPA. This drawback was slightly eased by substituting DMPU for HMPA.[25] Unfortunately, when DMPU was employed, direct reduction of the β-acetoxy sulfones was unsuccessful. This was overcome by first performing an elimination to yield the vinyl sulfone and then using the SmI_2 for the reduction to the olefin (Scheme 1.21).



Scheme 1.21

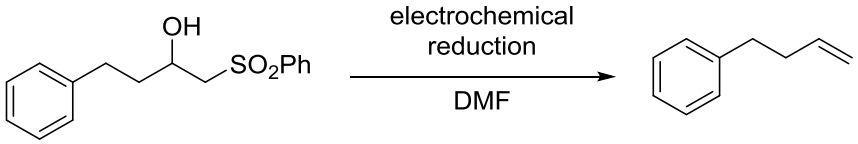
One of the least toxic methods developed uses magnesium in absolute ethanol. Lee was able to efficiently reduce a range of β-alkoxy sulfones using this method (Scheme 1.22).[26] This process has the advantage that even the use of unactivated magnesium at room temperature affords the elimination products. Unfortunately, this process is quite slow and involves reaction times greater than 24 hours. This was solved

by adding a catalytic amount of mercuric chloride to create a catalytic amount of magnesium-mercury amalgam *in situ* which was a vast improvement over the original conditions where an excess of sodium-mercury amalgam is required. Unfortunately, the use of toxic reagents was not able to be completely eliminated in this process. As such, there is room for improvement on the conditions to eliminate the use of toxic mercury compounds. This process is very efficient and excitingly does not lead to the over-reduction products that are often found in magnesium reductions.



Scheme 1.22

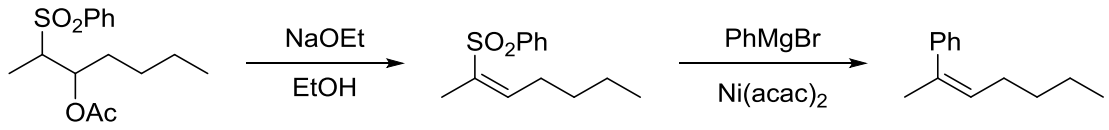
Shono was able to use electrochemical reduction to reduce a series of β-hydroxy sulfones to the olefins (Scheme 1.23).[27] This method has several advantages, most prominently the absence of any toxic reagents. All that is required is a solution of the β-hydroxy sulfone in DMF. This method gives comparable yields of the olefin when compared with other reducing agents.



Scheme 1.23

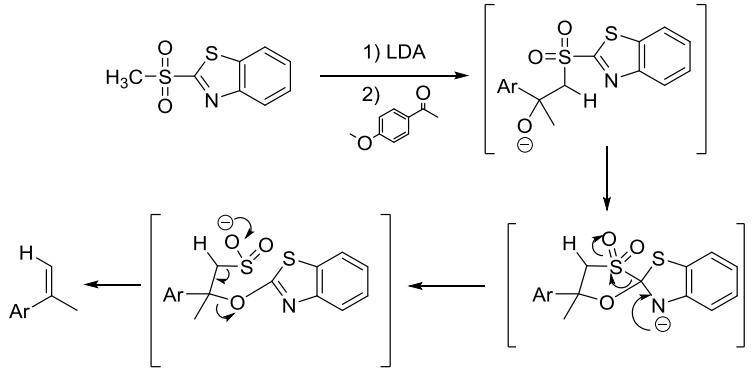
While the initial reports only focused on the addition of aldehydes to result in di-substituted olefins, ketones may be employed as well. These reactions result in tri-substituted olefins. Unfortunately, the desired olefins could not be reached directly. First the reduction of the β-acetoxy sulfone resulted in the vinylic sulfone.[28] A further reaction

of the vinylic sulfone with a Grignard reagent resulted in the trisubstituted olefin (Scheme 1.24).[29] The configuration of the final olefin is dependent on the stereochemistry of the vinylic sulfone. The Grignard reagent substitutes the sulfone with nearly complete retention of configuration.



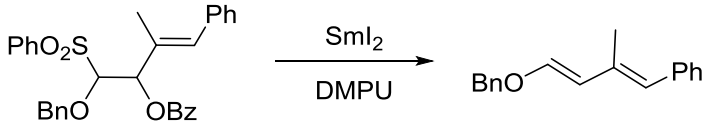
Scheme 1.24

This process was improved when a one-pot process was developed to prepare a range of di- and tri-substituted olefins. The key to this development was the replacement of phenyl sulfones with a range of heteroaryl sulfones. The first iteration employed a benzothiazole sulfone and further improvements were made when the tetrazole sulfones were used.[30,31,32] The key to this process is an *in situ* transfer of the heteroaryl group from the sulfur to the oxygen of the carbonyl. Elimination of SO_2 and the heteroaryl oxide results in formation of the olefin (Scheme 1.25). The benzothiazole sulfones decomposed when combined with LDA rather than react with the aldehydes which resulted in reduced yields. The tetrazole sulfones were stable to LDA and only reacted with the aldehydes in the desired fashion.[31]



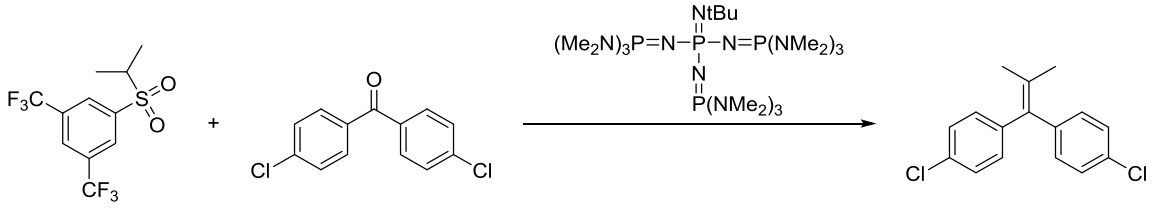
Scheme 1.25

The Julia–Lythgoe olefination has also been used to prepare conjugated dienyl ethers. These compounds provide important precursors for Diels–Alder reactions which are quite common in natural product synthesis. In this variation the alkoxide, resulting from addition to the aldehyde, is trapped with benzoyl chloride to yield β-benzoyl sulfones. Reductive elimination afforded by treatment with SmI_2 and DMPU gave the dienyl ether in high yield (Scheme 1.26).[33] Interestingly, changing the alkoxide group from the acetoxy to the benzoyl allowed for the reductive elimination to occur in one step which can be attributed to the much more reactive benzoyl group.



Scheme 1.26

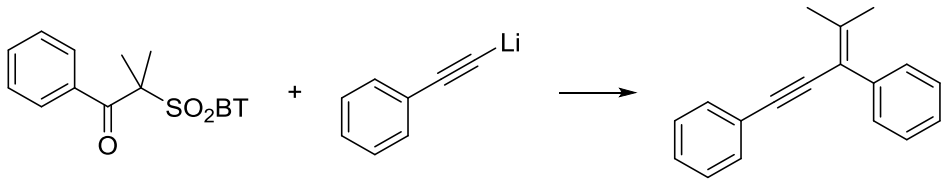
By changing the aryl group on the sulfone from phenyl to BTFP the technique was expanded to synthesize several tri- and tetra-substituted olefins. Perhaps the greatest attribute of this technique is the absence of a reducing agent. Simply heating a solution of the sulfone and ketone with an excess of Schwesinger's base gave the olefins (Scheme 1.27).[34]



Scheme 1.27

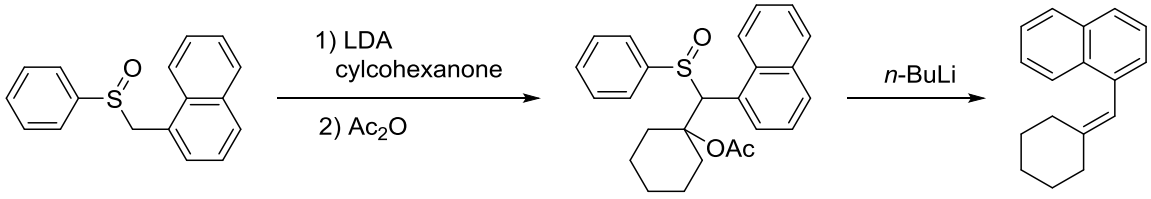
In 2013, Ou and co-workers modified this reaction further to prepare a range of tetra-substituted olefins. A series of β-carbonyl benzothiazo-2-yl sulfones was prepared with the idea that instead of adding the sulfone to the ketone, a nucleophile would add to

the carbonyl and *in situ* create the precursor to the Julia olefination. Unfortunately, oxygen and nitrogen based nucleophiles did not result in any olefin formation. However, alkynyl lithium nucleophiles readily gave the olefins in good yield (Scheme 1.28).[35]



Scheme 1.28

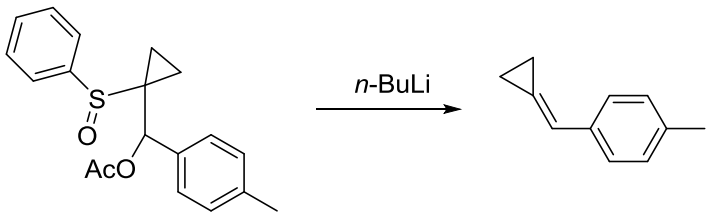
Sulfones are not the only sulfur containing functional group that can undergo the Julia olefination. Several different sulfoxide groups have been shown to be very active in this reaction especially in the formation of trisubstituted olefins. Because of the reduced acidity of the hydrogen on the α carbon of the sulfoxide, the reaction between the carbanion and the ketone is irreversible so that this reaction proceeds without the use of reducing agents.[36] The first report combined arylmethyl sulfoxides and cyclohexanone to yield a range of tri-substituted olefins (Scheme 1.29).[36] Once the β-acetoxy sulfoxide was formed the addition of 4 equivalents of *n*-BuLi afforded the olefin in excellent yield. Similarly to the use of the BTFP sulfones, no reducing agent was required. However, a one-pot process could not be used here and the reaction had to be completed step-wise.



Scheme 1.29

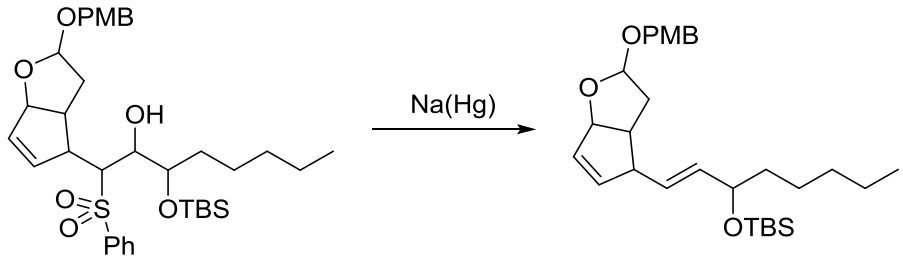
This technique is not limited to arylmethyl sulfoxides. Several cyclopropyl sulfoxides have been used to create a range of trisubstituted olefins. In this example

phenyl cyclopropyl sulfoxide was used to prepare a few cyclopropyl styrene derivatives (Scheme 1.30).[37] Here the two different elimination conditions were compared. The traditional Julia conditions and the new *n*-BuLi conditions both resulted in formation of the olefin but the new conditions gave a higher yield.



Scheme 1.30

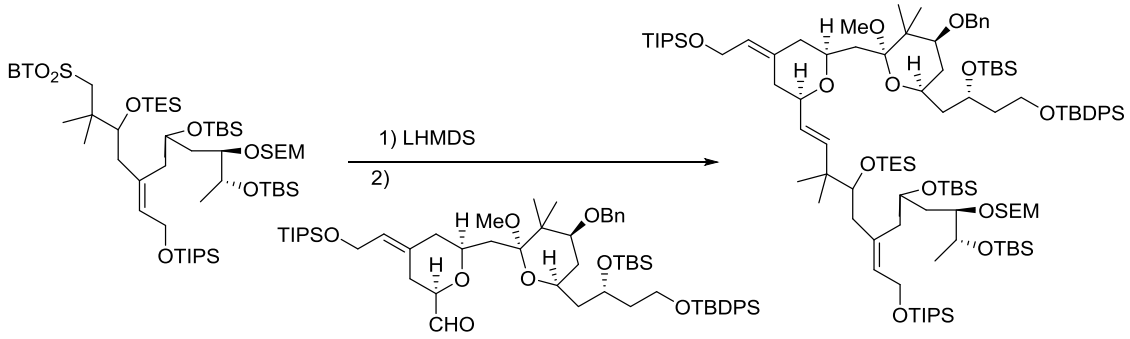
The Julia olefination has also been a key technique in natural product synthesis. For example, the Julia olefination was used in the key olefination step during the total synthesis of A_2 Isoprostane, a prostaglandin derivative.[38] Here, Zanoni used the original Julia conditions where the reductive elimination of the β-hydroxy sulfone was performed with sodium-mercury amalgam (Scheme 1.31). Additionally, both PMB and TBS protecting groups survived the olefination conditions.



Scheme 1.31

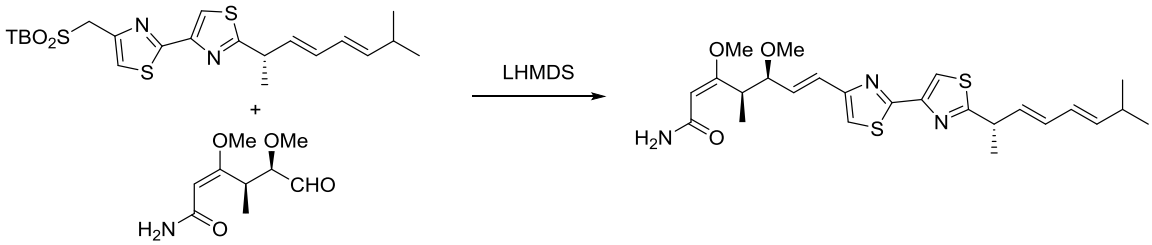
The Julia olefination has been featured in the preparation of several bryostatin derivatives; however, under classic conditions a poor yield is obtained. Allen was able to incorporate a modified Julia–Kocienski olefination to obtain the key macrocyclic olefin

in 71% yield (Scheme 1.32).[39] The key to this transformation was changing the sulfone to the benzothiazole derivative.



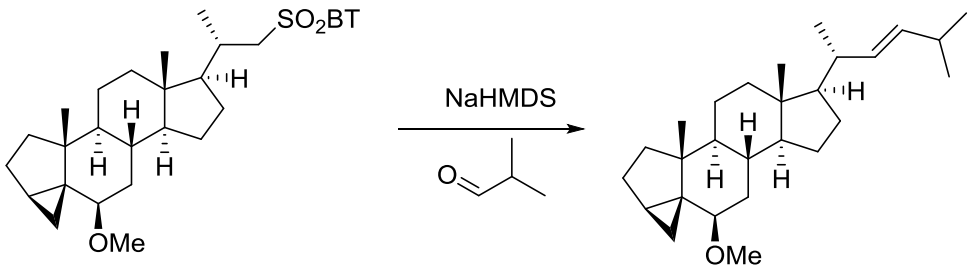
Scheme 1.32

Iwaki used similar conditions to Allen and co-workers to synthesize (+)-myxothiazole A. A one-pot Julia–Kocienski olefination was employed to couple the left and right halves of the molecule (Scheme 1.33).[40] These conditions did not affect the diene or the three stereocenters of the molecule.



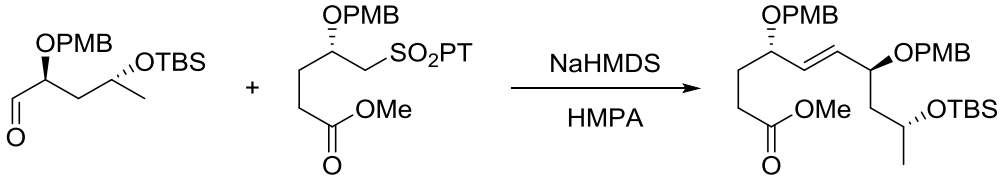
Scheme 1.33

Another class of molecules which have been prepared using a Julia olefination is steroid derivatives. In the synthesis of several sea lamprey pheromones, Izgu, Burns, and Hoye employed a Julia olefination in the preparation of the steroidal side chains.[41] Even though the sulfone precursor and the aldehyde are quite bulky, the Julia olefination proceeded quite efficiently (Scheme 1.34). Interestingly, the counter-ion of the base was quite important. When KHMDS was employed, only a trace amount of olefin was detected. However, NaHMDS gave the olefin in reasonable yield.



Scheme 1.34

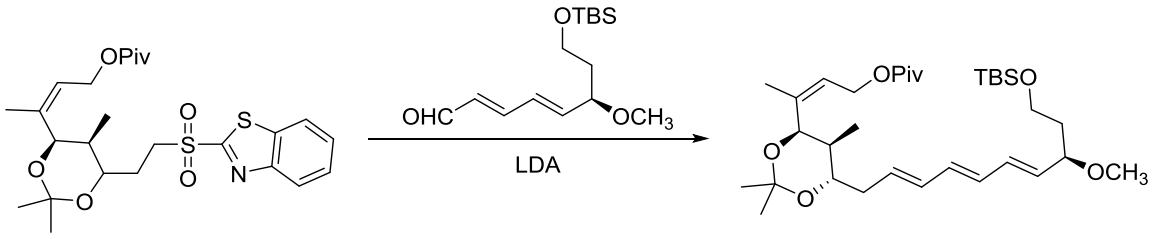
Wu and co-workers were also able to use a Julia olefination to prepare stagonolide C. Like Izgu and co-workers, only NaHMDS afforded the olefin in decent yield.[42] However, HMPA was required for the reaction to proceed (Scheme 1.35). Additionally, a slow addition of the aldehyde was required to minimize any aldol condensation side products.



Scheme 1.35

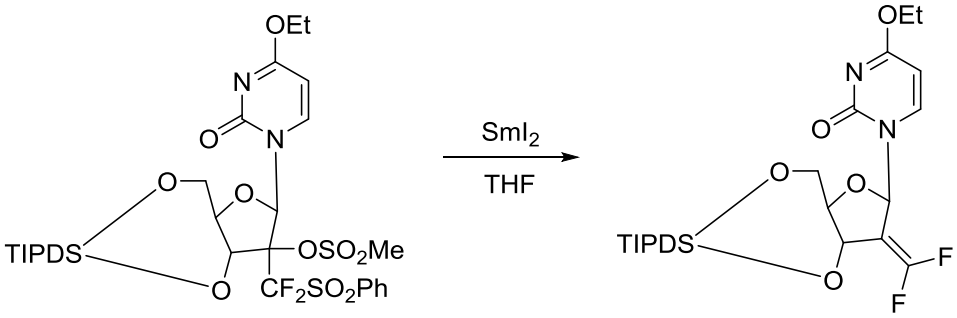
In the synthesis of (+)-thiazinotrienomycin E, a Julia olefination was used to synthesize the triene motif. A major problem with polyene units is that many of the typical protocols to synthesize these groups lead to unstable products which subsequently polymerize or decompose. This compound was no exception. The first attempt used a Stille coupling to prepare the triene and that led to decomposition of the product. The next attempt used a Horner–Wadsworth–Emmons reaction but the product isomerized from the desired *E,E,E* configuration to a complex mixture of *E*- and *Z*-isomers. Fortunately, a Julia olefination led to the desired configuration in reasonable yield with

no isomerization or decomposition (Scheme 1.36). This shows that the Julia olefination provides a reasonable and mild way to prepare sensitive olefins.



Scheme 1.36

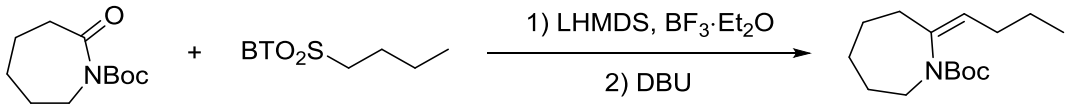
In addition to sensitive polyene containing compounds, the Julia olefination has been used to synthesize exocyclic olefins which are often unstable and prone to isomerization. The two most common methods of forming exocyclic double bonds are either a Wittig reaction or a Horner–Emmons reaction. In the synthesis of a series of 2'-deoxy-2'-difluoromethylene nucleosides both methods did not result in formation of the desired product. However, when a Julia olefination was employed the desired exocyclic olefin was formed in reasonable yield (Scheme 1.37).[43]



Scheme 1.37

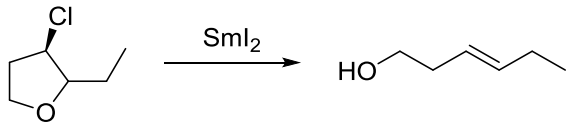
Recently, this technique has been extended to prepare a range of exocyclic enamides which are important precursors in alkaloid synthesis. Previous work has been limited to only preparing un-substituted or mono-substituted exocyclic olefins. The main

drawback is that in the preparation of mono-substituted derivatives, the use of Grignard reagents typically leads to isomerization to the endocyclic olefin. Gigant was able to prepare a range of exocyclic enamides from the Boc-protected lactam using a modified Julia olefination (Scheme 1.38).[44] Excitingly, no isomerization to the endocyclic olefin was observed.



Scheme 1.38

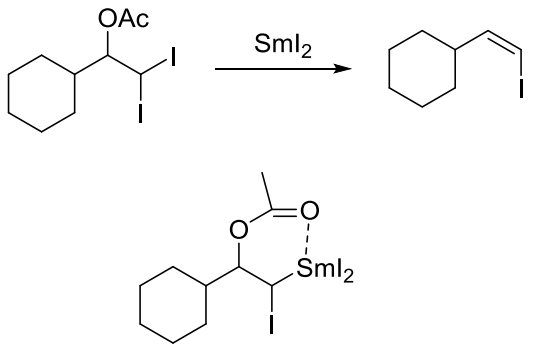
In addition to the Julia olefination, SmI_2 has found widespread use in β-elimination reactions. Sodium has been known to promote a ring opening in β-halogenoethers. However, over-reduction products are often seen. When SmI_2 is used only the olefin is observed (Scheme 1.39).[45] This can be attributed to the slower reaction of the ether with SmI_2 compared to sodium.



Scheme 1.39

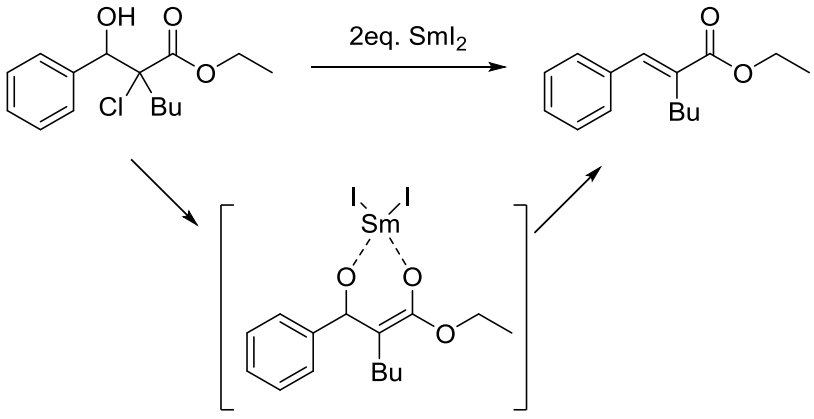
SmI_2 has also been used in the β-elimination of 1,2-diiodoalcohols to yield vinyl iodides. When the acetoxy protected alcohols were treated with 2 equivalents of SmI_2 the major product observed is the *Z* olefin (Scheme 1.40).[46] This can be rationalized by looking at the intermediate after trans-metallation. Once the SmI_2 replaces the *syn* iodide, it chelates with the acetate to promote the elimination. This cannot occur if the *anti* iodide is transmetallated. When the desired product is a conjugate olefin a lower

level of selectivity is observed. This can be attributed through resonance stabilization of the allylic carbocation generated if the C–O bond cleaves before elimination of the SmI_2.



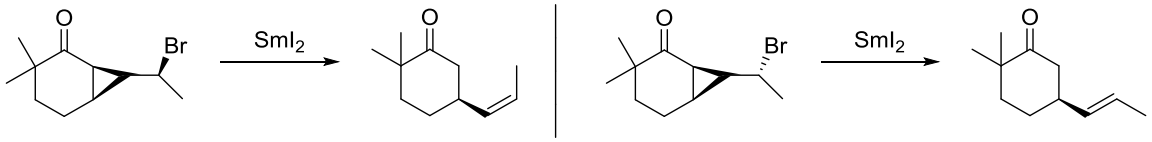
Scheme 1.40

The preparation of α,β-unsaturated carbonyls has also been efficiently performed using SmI_2. When a range of 2-chloro-3-hydroxy esters were exposed to two equivalents of SmI_2 the *E*-olefins were isolated in good yield (Scheme 1.41).[47] The observed selectivity can again be explained by a chelation effect. The SmI_2 chelates to the carbonyl oxygen and the hydroxyl group. This activates the hydroxyl making it a better leaving group and allows the *anti* elimination to occur. For the analogous amides, similar selectivity was observed.



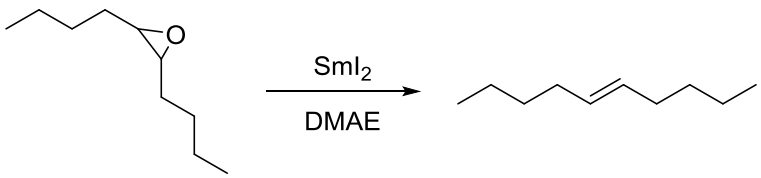
Scheme 1.41

Additionally, SmI_2 has been shown to promote the cleavage of C–C bonds in a range of bromo-cyclopropyl ketones. The stereochemistry of the alkene appears to be completely dependent on the orientation of the bromide. When the bromide is on the α-face the *E*-olefin is the major product and when the bromide is on the β-face the *Z*-olefin is the major product (Scheme 1.42)[48] which suggests that the mechanism proceeds through a transmetallation of the bromide followed by elimination. If a radical process were taking place, the olefin produced would much more likely be a mixture.



Scheme 1.42

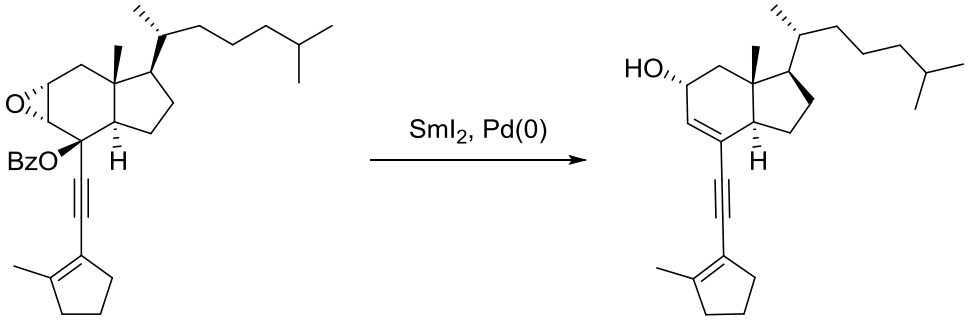
Epoxides can also be reduced by SmI_2 to yield olefins (Scheme 1.43).[49] Unfortunately, this reaction does not proceed with SmI_2 alone as an additive is needed to facilitate the elimination. This reaction proceeds by first opening the epoxide to yield a β-iodoalkoxide. The additive, DMAE, then activates the alkoxide and further reduction by SmI_2 affords the β-elimination product.



Scheme 1.43

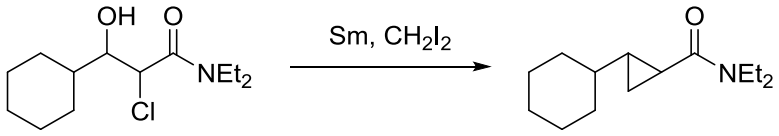
SmI_2 is also quite tolerant of the presence of other metals. In the preparation of several Vitamin D analogues, SmI_2 was used in conjunction with palladium(0) to open an epoxide in the reduction of a propargylic acetate to yield the allylic alcohol (Scheme 1.44). In this reaction, the palladium promotes the elimination of the benzoate to yield an

allenyl-palladium species and further reduction by SmI_2 opens the epoxide and forms the allylic alcohol.



Scheme 1.44

These elimination reactions have also been used to prepare precursors for Simmons–Smith type cyclopropanations. When a series of α-chloro-β-hydroxyamides were treated with SmI_2 elimination to the olefin was observed. When this was combined into a one-pot process where Sm metal and CH_2I_2 were added to the amide to generate SmI_2 *in situ*. The cyclopropyl derivative was produced in good yield (Scheme 1.45).[50]



Scheme 1.45

1.4 Pyrolysis Reactions

The pyrolysis of various functional groups to yield olefins has been a very active area of research. The two most common functional groups that undergo pyrolysis are xanthates and esters prepared from the corresponding alcohol. It was first observed in 1876 that the pyrolysis of an ester resulted in an olefin product.[2] However, it was not until 1938 that the necessity of a β-hydrogen (Figure 1.3) was established.[51] At the time,

the mechanism of pyrolysis was postulated to involve radical intermediates but this was disproven by careful study of the pyrolysis products.[51] Several of the products that would have arisen from a radical mechanism were not detected.[51] It was not until later study by Sir Derek Barton on xanthate pyrolysis that the mechanism of ester pyrolysis was determined to be concerted.[52] The pyrolysis of an ester proceeds relatively cleanly. Generally, the only product besides the olefin is the carboxylic acid derived from the starting ester.

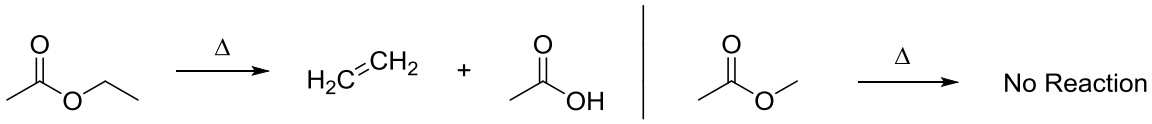
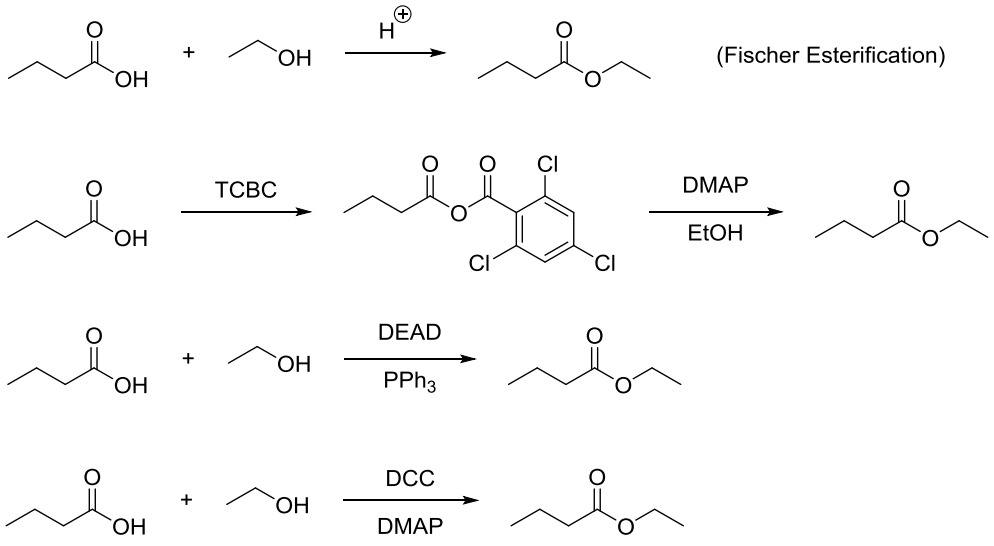


Figure 1.3

While nearly any ester can undergo the pyrolysis the most commonly used is an acetate. Because an acetate lacks a β-hydrogen, the main side product is acetic acid which can be easily extracted away from the desired olefin



Scheme 1.46

Additionally, these esters can be easily prepared from the corresponding alcohol (Scheme 1.46). The first method employed was the Fischer esterification.[53] This

procedure is very simple and the desired ester can be prepared on a large scale. However, the requirement of a strong acid catalyst limits the functional groups on both the alcohol and carboxylic acid that can tolerate the reaction. Also the Fischer esterification must be refluxed which limits the use of compounds with sensitive functional groups.

In the last 50 years several methods have been developed to synthesize these esters under much milder conditions. The Yamaguchi esterification was one method that eliminated the need for an acid catalyst (Figure 1.4).[54] Combining a carboxylic acid with the Yamaguchi reagent (TCBC) yields the much more reactive anhydride. This anhydride can be treated with one equivalent of DMAP and an alcohol to give the desired ester. The greatest advantage of the Yamaguchi esterification is that it can be performed at room temperature which greatly increases the range of functional groups tolerated. However, one downside to this procedure is that it is a two-step process and the carboxylic acid and alcohol cannot be directly combined.

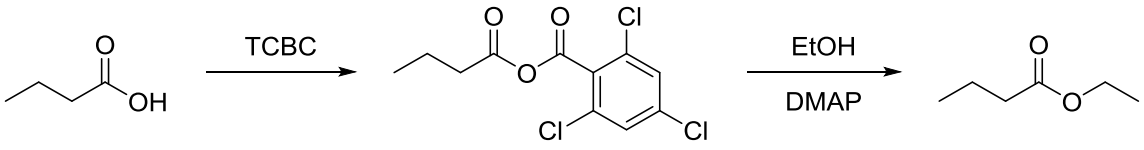


Figure 1.4

One way to shorten the esterification to one step is to employ a coupling reagent. One example which has become widely used is the Mitsunobu reaction (Figure 1.5).[55] Instead of an acid catalyst, the carboxylic acid and alcohol are combined with one equivalent each of PPh_3 and DEAD to yield the ester.

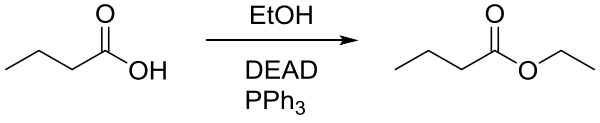


Figure 1.5

Developed 11 years after the Mitsunobu reaction, the Steglich esterification has also become a popular method of preparing esters (Figure 1.6). In this procedure, the carboxylic acid and alcohol are combined with the solid coupling reagent DCC and DMAP.[56] The Steglich esterification is usually performed with DCM as the solvent. One advantage to this is that the dicyclohexyl urea byproduct of the esterification is insoluble in DCM and can be easily filtered away leading to a simpler purification process.

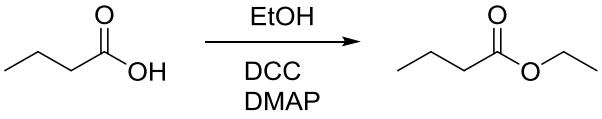
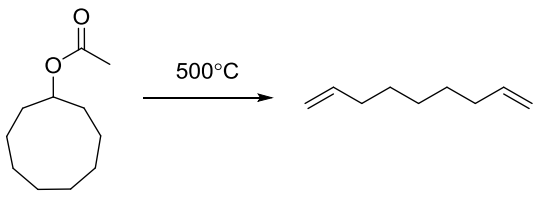


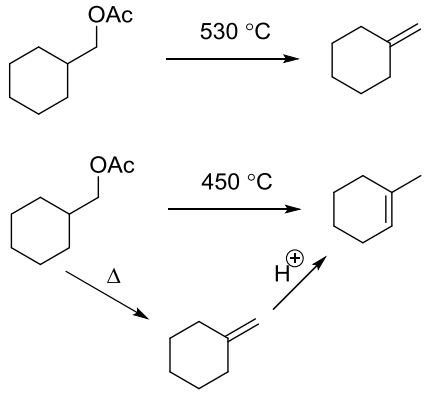
Figure 1.6

One disadvantage of ester pyrolysis is the extreme temperatures required. Depending on the substrate, temperatures ranging from 300°C to 1100°C were necessary to perform the pyrolysis.[51] Because of these high temperatures, compounds containing sensitive groups are usually not suitable for these conditions and the resulting olefins may not be stable at the required temperatures. For example, when cyclononyl acetate was pyrolyzed at 500 °C, the major product was the linear 1,8-nonadiene and not the expected cyclononene (Scheme 1.47).[57] The decomposition of cyclononene was proven when Blomquist heated a sample to 500 °C and only 1,8-nonadiene was obtained. This shows that the elimination occurred and further decomposition led to the observed product mixture.



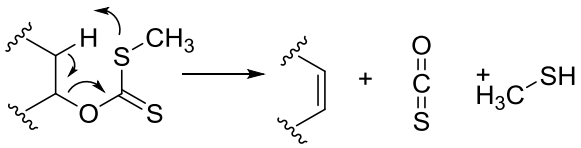
Scheme 1.47

The product mixtures obtained from an ester pyrolysis initially appeared to be very temperature dependent. When cyclohexylcarbinyl acetate was heated to 530 °C, methylene cyclohexane was the only product.[58] However, when the temperature was lowered to 450 °C, 1-methylcyclohexene was the major product in a 3:1 ratio.[59] It was subsequently shown that the temperature was not responsible for the differing product mixtures. Instead, the production of 1-methylcyclohexene was a result of residual acid present on the pyrolysis column (Scheme 1.48).[58]



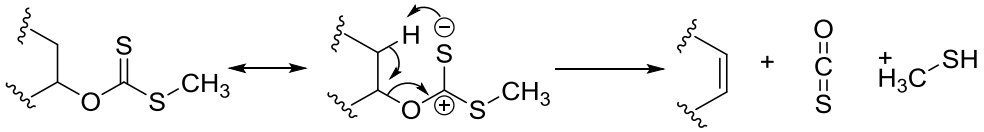
Scheme 1.48

The pyrolysis of a xanthate was first reported by Tschugaeff in 1899 and subsequently named the Chugaev reaction.[60] Similarly to ester pyrolysis, a *cis*-β-hydrogen is necessary for the reaction to occur.[61] The mechanism was first hypothesized to be a concerted, single step mechanism that incorrectly involved the thioether sulfur (Scheme 1.49). One advantage of the Chugaev reaction over ester pyrolysis is the lower temperature at which the reaction occurs. While ester pyrolysis requires temperatures in the 300-600 °C range, the Chugaev reaction generally undergoes pyrolysis in the 150-250 °C range. The greatly lowered temperatures allow for a much wider range of functional groups that can tolerate the conditions required for pyrolysis.



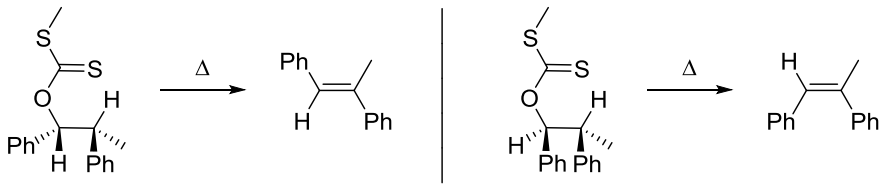
Scheme 1.49

Cram proposed an alternative mechanism in 1949 (Scheme 1.50).[62] In his mechanism, Cram postulated that the thiocarbonyl sulfur was more nucleophilic because of a resonance form which placed a formal negative charge on that atom. Additionally, the thiocarbonyl sulfur is much less sterically hindered which makes nucleophilic attack much more likely.



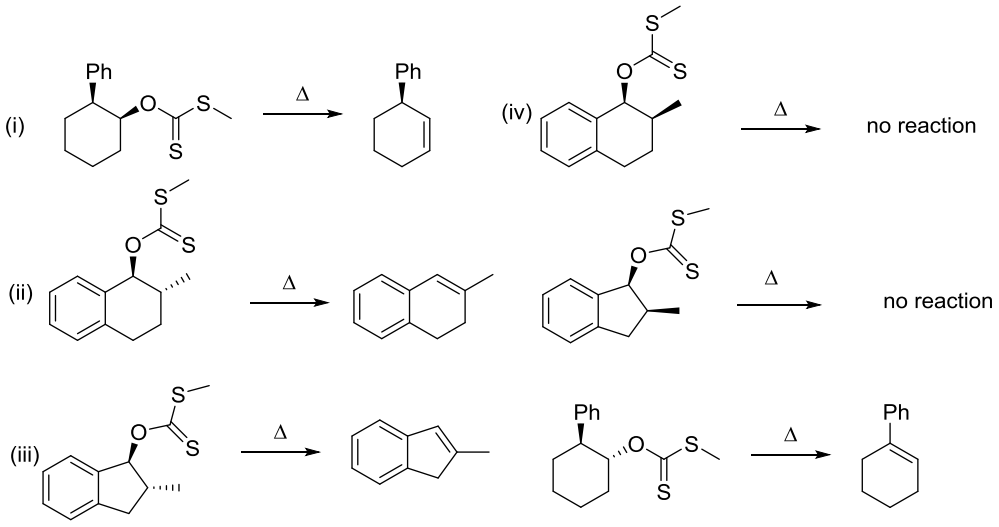
Scheme 1.50

Cram provided evidence for his mechanism in his studies on open chain compounds. When compared to cyclic compounds where the configuration of the compound is locked, the pyrolysis of acyclic xanthates resulted in compounds that could only be achieved by cis elimination.[62,63] Cram also showed that the configuration of the product of the Chugaev reaction could be predicted by analyzing the stereochemistry of the starting xanthate. The xanthates of *threo* and *erythro* 1,2-diphenyl-1-propanol were pyrolyzed and the only products isolated were (*Z*)-1,2-diphenylpropene and (*E*)-1,2-diphenylpropene respectively (Scheme 1.51).



Scheme 1.51

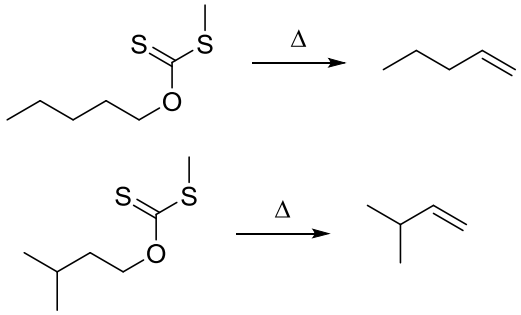
Additional studies by Alexander and Mudrak on the xanthates of several cyclic compounds supported Cram's postulated mechanism. The pyrolysis of the xanthates of 2-phenylcyclohexanol[i], 2-methyl-1-tetralol[ii] and 2-methyl-1-indanol[iii] all resulted in products resulting from *cis*-elimination only.[64,65,66] Critically pyrolysis did not occur when a *cis*-β-hydrogen was not present (cf iv, Scheme 1.52).[65]



Scheme 1.52

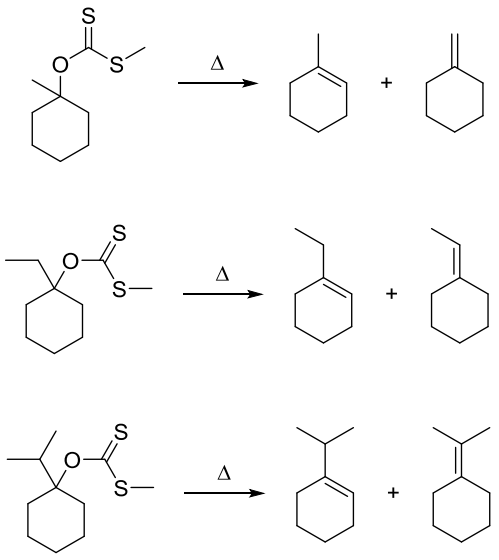
Further proof of Cram's mechanism was obtained when Bader and Bourns performed a series of kinetic isotope effect studies on *S*-methyl-*trans*-2-methyl-1-indanyl xanthate.[67] This substrate was chosen because there was only one β-hydrogen present and only *cis*-elimination can occur. Their study showed that no isotope effect was observed for the carbonyl carbon and a minimal effect was observed for the thioether sulfur. This data coupled with the significant isotope effect observed for the thiocarbonyl sulfur definitively proves that the bonds formed and broken during the Chugaev reaction center on the thiocarbonyl sulfur. If the mechanism postulated by Huckel were correct the data should have been reversed. A significant isotope effect should have been observed for both the carbonyl carbon and the thioether sulfur.

Very few reports have been published on the Chugaev reaction of primary alcohols. When the xanthates of 1-pentanol and 3-methyl-1-butanol were subjected to pyrolysis the only products observed were 1-pentene and 3-methyl-1-butene, respectively (Scheme 1.53).[68] Whitmore observed that a much higher temperature was necessary to afford the elimination products for the primary alcohols. This is reflected in the relatively poor yields for these reactions (~15%). There does not appear, however, to be any justification for why the xanthates of primary alcohols are more resistant to Chugaev elimination than secondary or tertiary alcohols.



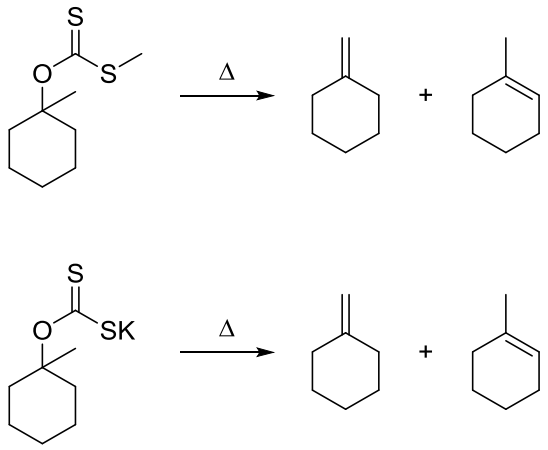
Scheme 1.53

Like primary alcohols, there are very few examples of using the Chugaev reaction to dehydrate open chain tertiary alcohols. The pyrolysis of the xanthate of 2-cyclopropyl-2-propanol yielded only 2-cyclopropyl-1-propene.[69] However, the 24% yield was rather poor. Most of the research has been performed on cyclic tertiary alcohols. A series of the xanthates of 1-alkylcyclohexanols readily underwent pyrolysis to yield the corresponding olefins (Scheme 1.54).[70] While tertiary xanthates underwent pyrolysis more readily than primary xanthates a side effect of this was that a mixture of products resulted. While the major products were the endocyclic olefins (~40% yield) a significant amount of the exocyclic olefins were observed (~10% yield).[70]



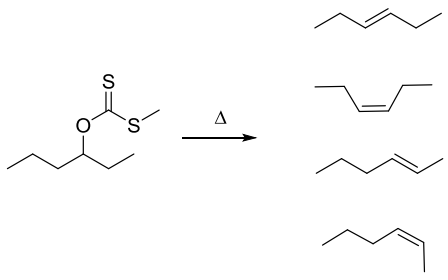
Scheme 1.54

Rutherford provided an interesting extension of the Chugaev reaction on tertiary alcohols. Instead of adding iodomethane to create the *S*-methyl xanthate, he isolated the potassium salt of the xanthic acids.[71] When these salts were pyrolyzed the resulting olefin mixture was nearly identical to that obtained from the pyrolysis of the corresponding *S*-methyl xanthates. For example the pyrolysis of the xanthate of 1-methylcyclohexanol resulted in a 79:21 mixture of 2-methylcyclohexene and methylenecyclohexane. The pyrolysis of the potassium salt resulted in a virtually identical 82:18 mixture (Scheme 1.55). This is an exciting development because it eliminates one step from the process and thus eliminates a purification step. The potassium salts may be filtered off, washed with ether and dried under vacuum. Unfortunately, this chemistry was unable to be extended to primary and secondary alcohols.



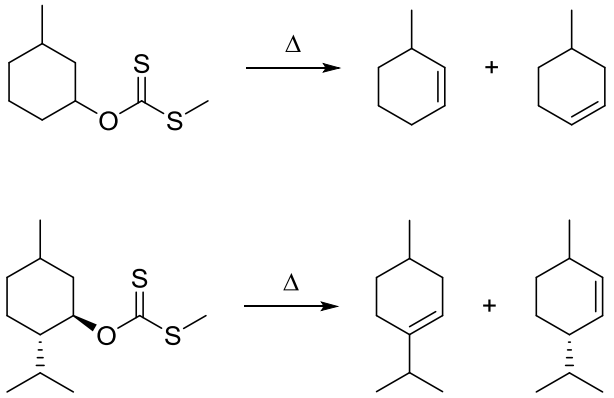
Scheme 1.55

While there has been limited experimentation with primary and tertiary alcohols, the Chugaev reaction has found the most utility in the dehydration of secondary alcohols. Similar to tertiary alcohols, the Chugaev reaction of secondary xanthates can yield multiple products. An additional complication is that not only are there two possible directions of elimination but *cis*/*trans* isomers are formed. This has reduced the synthetic utility of the Chugaev reaction in acyclic alcohols where multiple β-hydrogens are present. For example, when the xanthate of 3-hexanol was subjected to pyrolysis, four products resulted (Scheme 1.56).[72] The major products were *trans*-2-hexene and *trans*-3-hexene in approximately equal yield (28%) which is statistically probable because of the two β-hydrogens on either side of the xanthate. The *cis*-isomers were also observed in a significant amount.



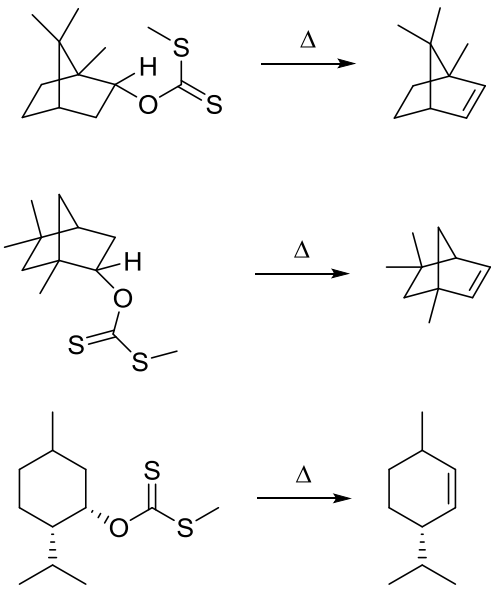
Scheme 1.56

This problem is somewhat ameliorated when the Chugaev reaction is used for the elimination of the xanthates of cyclic secondary alcohols. The restricted rotation caused by the ring eliminates the *cis*/*trans* isomer problem in most small to medium sized rings. However, the problem of multiple directions of elimination has not been completely solved. For example when the xanthate of 3-methyl-cyclohexanol was pyrolyzed, a mixture of 3-methyl-cyclohexene and 4-methyl-cyclohexene resulted.[73] Additionally, the xanthate of (–)-menthol resulted in a mixture of menthenes (Scheme 1.57).[74]



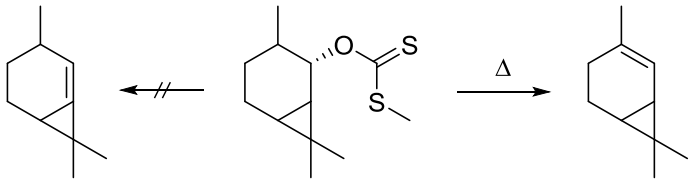
Scheme 1.57

The Chugaev reaction has been used extensively in terpene synthesis. The xanthate of borneol yielded only bornylene upon pyrolysis (Scheme 1.58).[75] Since borneol only has one *cis*-β-hydrogen this precludes the formation of multiple products. Another example involving a xanthate with only one *cis*-β-hydrogen is the pyrolysis of the xanthate of α-isofenchyl alcohol which yields isofenchylene.[76] Similarly, the xanthate of (+)-neomenthol resulted in only 2-menthene.[61]



Scheme 1.58

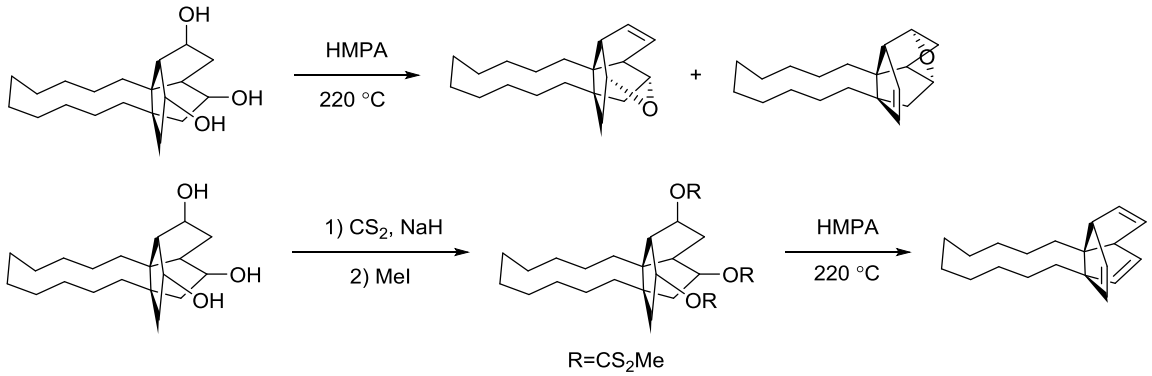
Even in cases where multiple *cis*-β-hydrogens exist there may only be one product. When the xanthate of (–)-carenol was pyrolyzed only one olefin was isolated (Scheme 1.59) [77] because it would not be favorable to form an alkene on the bridgehead carbon in carenol.



Scheme 1.59

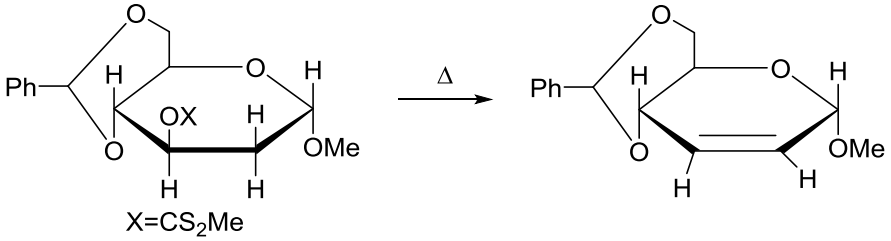
The true test of the Chugaev reaction's use comes during the synthesis of complex molecules. Cook's synthesis of ellacene employed a Chugaev reaction in the key dehydration of a tris-alcohol (Scheme 1.60).[78] The Chugaev protocol proved to be superior to other methods of dehydration because the steric bulk of the twelve-membered ring caused preferential ether formation over the desired triene. It is noteworthy that a

solvent was required during the Chugaev reaction in order to dilute the reaction and minimize polymerization of the triene product.



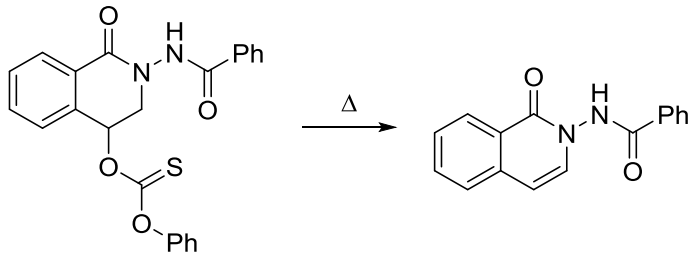
Scheme 1.60

Traditionally, carbohydrates have been resistant to pyrolysis by the Chugaev reaction, even in cases with multiple *cis*-β-hydrogens.[79] Most commonly instead of an elimination reaction, a rearrangement of the xanthate is the only product. This has been attributed to the hydrogens being stabilized by lone pairs on the oxygens.[80] Ferrier exploited this when he performed a Chugaev reaction on a glucopyranoside (Scheme 1.61) whereby the elimination only occurred in the direction of the hydrogen that was attached to a carbon not bearing an oxygen atom. This would augment the hypothesis that a mesomeric effect between a lone pair on the oxygen and the resulting double bond caused the resistance of carbohydrates to the Chugaev reaction.



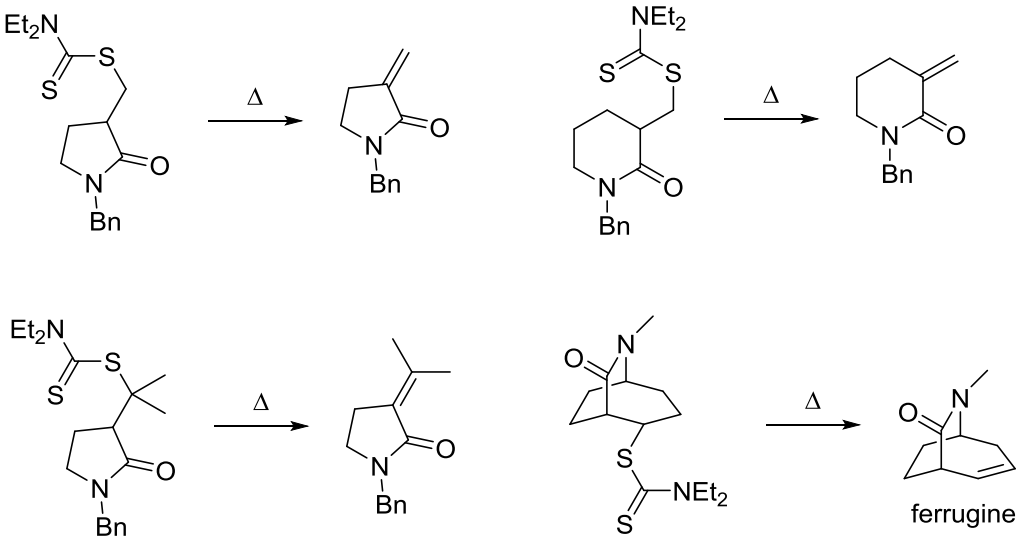
Scheme 1.61

Ray and Manning used a Chugaev-type reaction in their synthesis of 2-benzamidoisoquinolin-1(2H)-one. Instead of a xanthate, a thiocarbonate was subjected to pyrolysis (Scheme 1.62).[81] This was employed because *p*-toluenesulfonic acid did not afford the desired dehydration product as only decomposition occurred.



Scheme 1.62

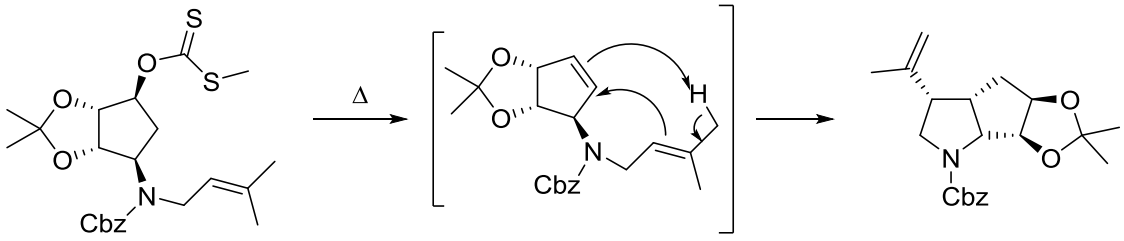
Similarly, it has been shown that dithiocarbamates also undergo Chugaev-type thermal eliminations. Ahmed and co-workers investigated the thermal elimination of a wide range of dithiocarbamates (Scheme 1.63).[82] Interestingly, they discovered that the elimination of the dithiocarbamates proceeded only at higher temperatures than typically required for the Chugaev reaction.



Scheme 1.63

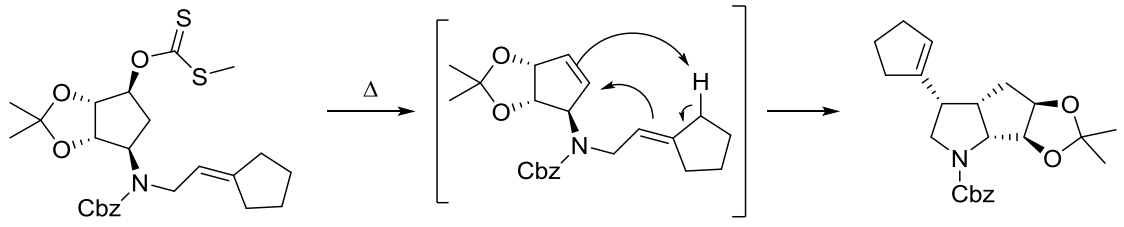
To demonstrate the applicability of this Chugaev-type elimination, they used this reaction in their synthesis of (±)-ferrugine.[82] Even though there are two *cis*-β-hydrogens, elimination only occurs in one direction due to Bredt's rule which states that there cannot be a double bond on a bridgehead carbon in rings smaller than eight carbons.

Nakagawa and co-workers employed a Chugaev reaction as the key step in his synthesis of (–)-kainic acid to exploit a Chugaev reaction to create an alkene in the starting five-membered ring. This allowed him to perform an ene-reaction in the same step to form the fused five-membered rings and generate the isopropylene group (Scheme 1.64).[83] This shows the great utility that the Chugaev reaction has in creating alkenes which can be further exploited to introduce other functional groups to the molecule.



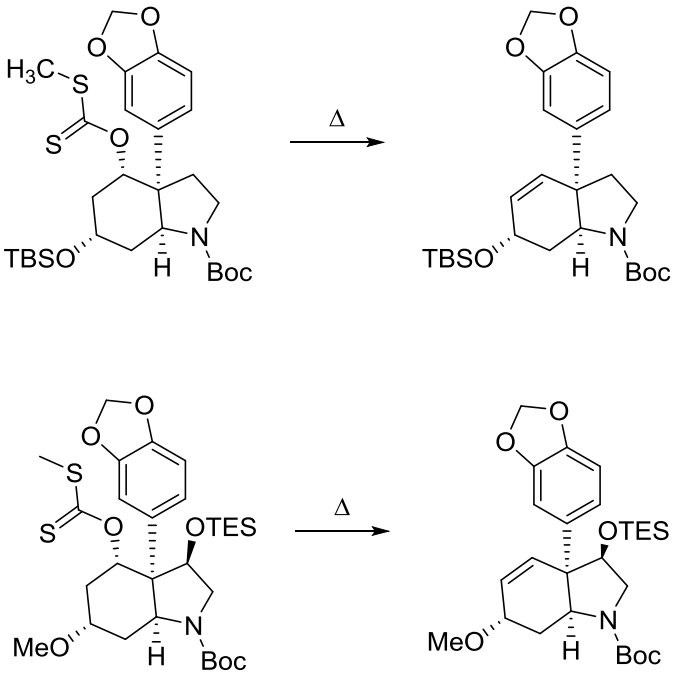
Scheme 1.64

He employed the same tandem Chugaev-ene approach in his synthesis of several acromelic acids.[84] However, in this case rather than inserting an isopropylene group, a cyclopentene was introduced (Scheme 1.65).



Scheme 1.65

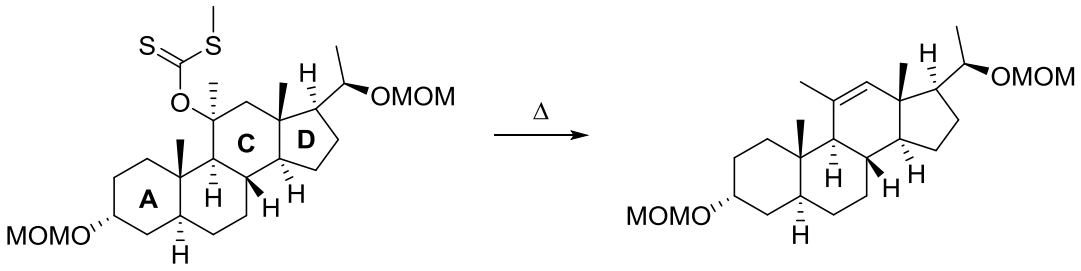
The Chugaev reaction has also been featured in alkaloid synthesis. In Bohno's synthesis of (+)-vittatine and (+)-haemanthamine, the Chugaev reaction introduced the requisite olefin in the six-membered ring to form the precursor to the allylic alcohol in (+)-vittatine and the allylic ether in (+)-haemanthamine (Scheme 1.66).[85,86] Because there was only one *cis*-β-hydrogen, the elimination could only proceed in one direction. Additionally, these syntheses highlight the fact that the Chugaev reaction does not affect many protecting groups as a Boc, a TES, and a TBS group survived the elimination conditions.



Scheme 1.66

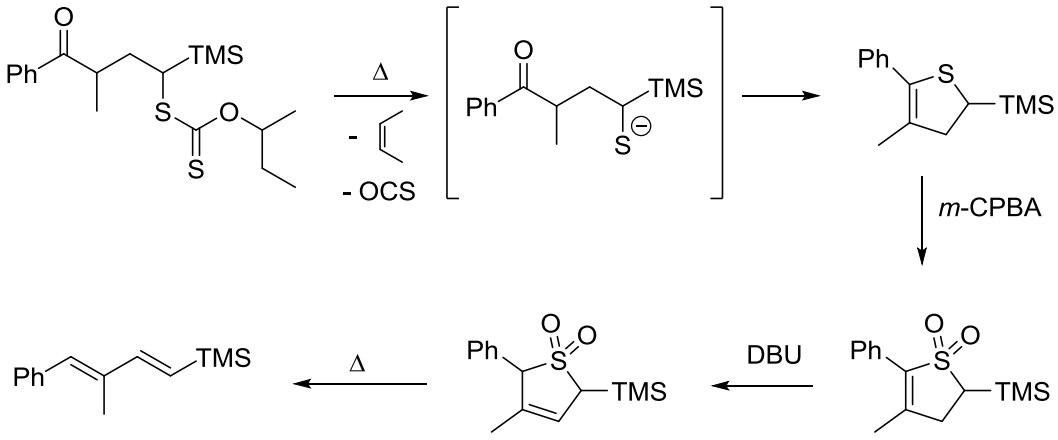
Zhang and co-workers extended the utility of the Chugaev reaction to the synthesis of steroids.[87] They introduced the alkene into the C-ring of the steroid skeleton and use that to further manipulate the steroid skeleton (Scheme 1.67). This reaction is favorable because the methane of the B/C ring fusion is on the α face of the carbocyclic skeleton while the tertiary xanthate is on the β face. This ensures that the elimination can

only occur away from that ring fusion to give a trisubstituted alkene rather than a tetra-substituted one. Interestingly, elimination in the direction of the methyl group would lead to the less stable exocyclic double bond. This ensures that the Chugaev reaction yields only the desired endocyclic product.



Scheme 1.67

The Chugaev reaction is typically used to introduce an olefin into a molecule. However, in addition to the olefin, another product of the Chugaev reaction is the sulfide anion obtained after pyrolysis. Goh took advantage of this and used the sulfide to prepare a series of dihydrothiophenes.[88] These compounds could then be oxidized and pyrolyzed to yield 1,3-TMS dienes (Scheme 1.68).

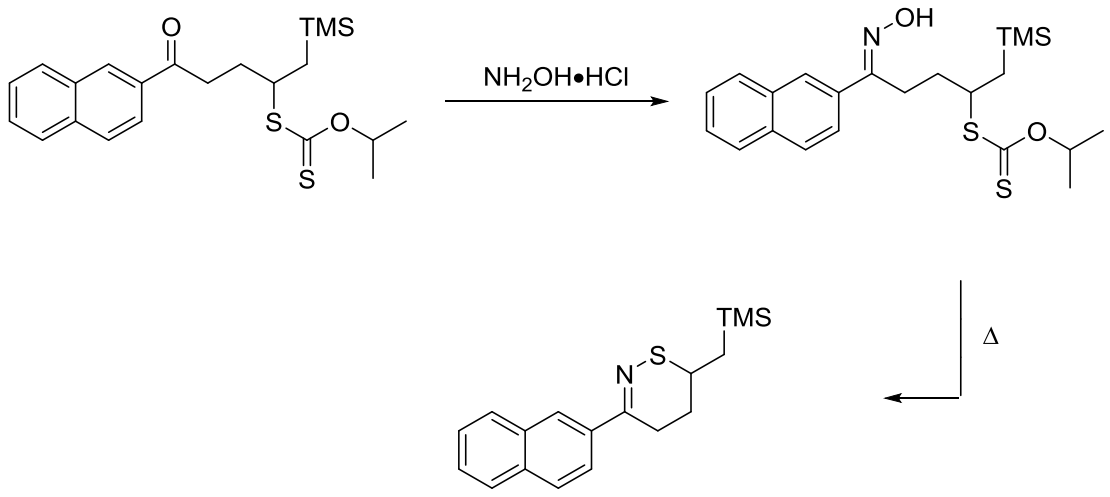


Scheme 1.68

Because the TMS group is very sensitive to acidic conditions, many of the typical dehydration techniques could not be used. By using the pyrolysis of a xanthate to effect

the cyclization and dehydration, Goh avoided using any conditions which would remove the TMS group. Additionally, the resulting dienes are prone to polymerization over time. By creating the shelf-stable sulfolenes in a one-pot process, the precursor may be stored until the diene is required.

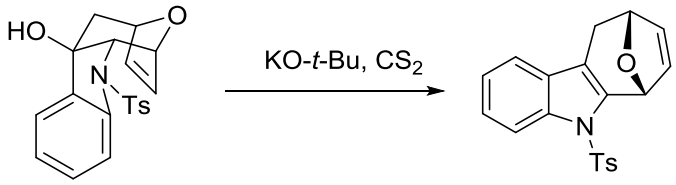
Another protocol involving the sulfide anion was developed to prepare a library of dihydrothiazines, a relatively rare heterocycle.[89] The oxygen analogue, dihydrooxazine, has found widespread use in forming biologically active compounds. It is therefore possible that the dihydrothiazine will find similar utility. In this case instead of a ketone, the electrophile for the sulfide is an oxime (Scheme 1.69). Interestingly, the major side product is the dihydrothiophene which was observed by Goh and suggests that both reactions proceed via a similar mechanism.



Scheme 1.69

One class of compounds that has been the subject of extensive research is indoles, a structural feature which has been found in several natural products. The cyclohepta[b]indoles where a seven-membered ring is fused to the pyrrole ring of indole. He and co-workers were able to use a one-pot process where the xanthate intermediate

was formed followed by elimination to yield the indole (Scheme 1.70).[90] While there are multiple *cis*-β-hydrogens, the driving force behind this reaction appears to be the formation of the aromatic indole. This process is superior to other dehydration methods because only the indole is formed, whereas when other methods were used, only fragmentation products are observed.



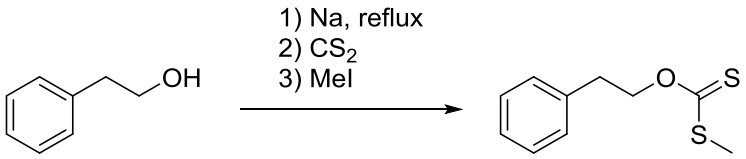
Scheme 1.70

1.5 Development of a New Elimination Protocol

The Chugaev reaction has been widely used for over 100 years despite having several drawbacks.[91] For example, it is often difficult to prepare and sufficiently purify the xanthates. The temperatures required for these eliminations (~200 °C) limit the use of the Chugaev reaction in the latter stages of a complex synthesis. The long reaction times required are also undesirable. These reactions are plagued by the formation of sulfur-containing impurities which can be difficult to separate from the desired olefin or have a stench which makes these compounds less than desirable to work with. Thus, even when the olefin can be purified, the yield is often quite low over the two steps from the alcohol precursor. Recognizing these difficulties, we set out to improve the Chugaev reaction.

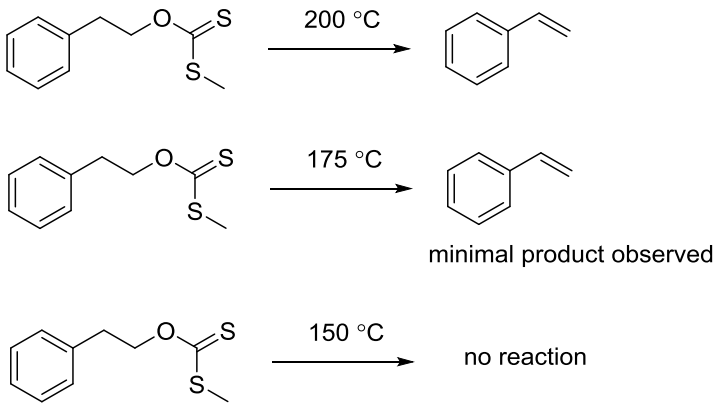
2-Phenylethanol was chosen as our model substrate for several reasons. First, this compound is inexpensive and commercially available and there is only one possible

elimination product due to the presence of only one *cis*-β-hydrogen. The *S*-methyl xanthate of 2-phenylethanol was easy to prepare (Scheme 1.71).



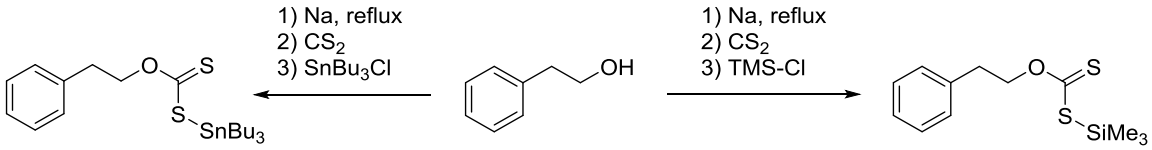
Scheme 1.71

With the xanthate in hand, the next step was to determine qualitatively at what temperature elimination occurred. The xanthate was heated neat in a sealed tube at 150 °C, 175 °C, and 200 °C (Scheme 1.72). After heating the xanthate overnight at 150 °C no elimination was observed. Minimal elimination was observed at 175 °C and significant elimination was observed at 200 °C. Additional experiments were performed at 225 °C, but after heating overnight, decomposition of the silicone oil bath occurred. As a result, 200 °C was chosen as our standard elimination temperature.

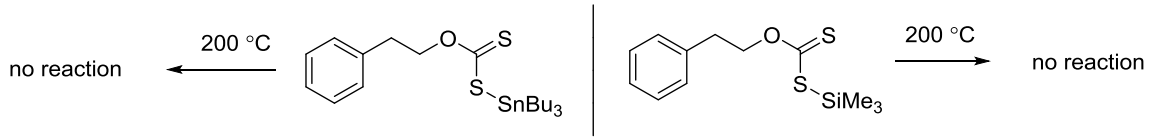


Scheme 1.72

We first attempted to modify the xanthate in the hope that the elimination temperature could be lowered. We hypothesized that the β-hyperconjugation effects of either tin or silicon could lead to a lower elimination temperature.[92] The *S*-$SnBu_3$ and *S*-$SiMe_3$ xanthates of 2-phenylethanol were prepared (Scheme 1.73).



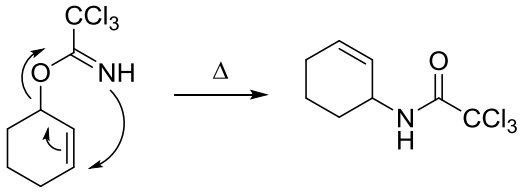
Scheme 1.73



Scheme 1.74

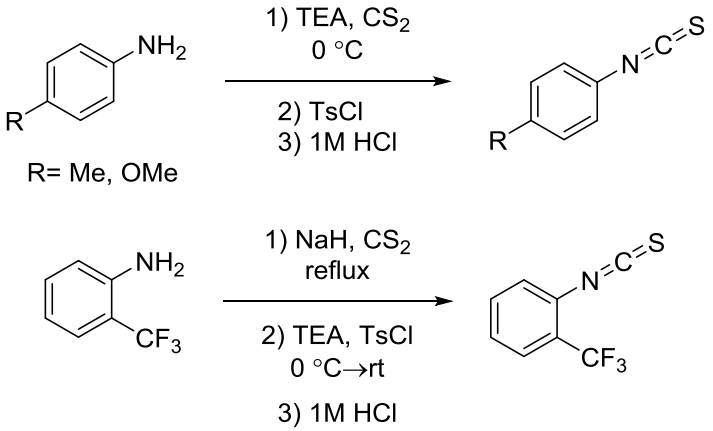
Surprisingly, when these xanthates were heated to 200 °C no elimination was observed (Scheme 1.74). When the reactions were repeated at 225 °C minimal elimination was observed. As a result, further efforts to achieve elimination were terminated.

With this result in hand we turned our attention to trichloroacetonitrile. Trichloroacetonitrile is well-known for its applications in Overman rearrangements of allylic alcohols (Scheme 1.75).[93]



Scheme 1.75

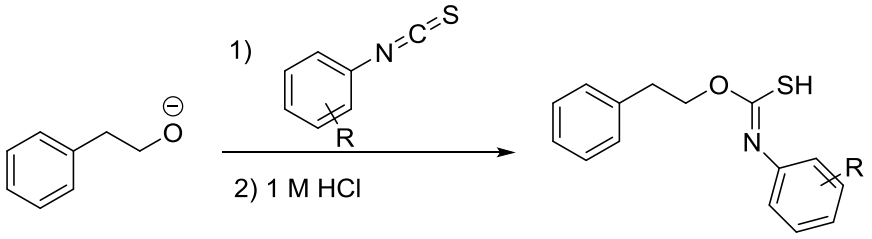
We hypothesized that heating the trichloroacetimidate would result in a Chugaev-type thermal elimination. Unfortunately, even at 225 °C no elimination was observed. This could simply be attributed to the imine nitrogen not being sufficiently basic enough for the reaction to occur under Chugaev conditions. Undeterred by this negative result, we then turned our attention to aryl isothiocyanates.



Scheme 1.76

Aryl isothiocyanates have the advantage of being commercially available or easily prepared[94] and there are no β-hydrogens to complicate the elimination. Three derivatives were prepared from the corresponding aniline in addition to the commercially available phenyl isothiocyanate (Scheme 1.76). We hypothesized that an electronic effect may lower the elimination temperature and isothiocyanates were prepared with either electron-donating or electron-withdrawing groups on the aryl ring.

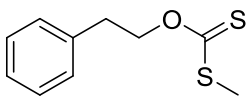
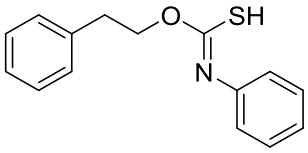
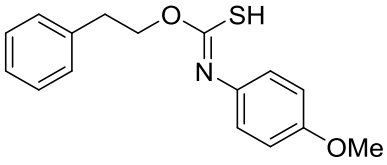
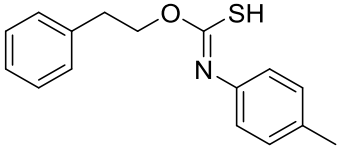
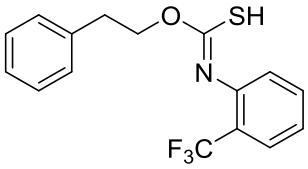
With these isothiocyanates in hand, they were converted to the corresponding carbonimidothioates (Scheme 1.77). This was achieved by combining the sodium salt of 2-phenylethanol with the isothiocyanate. Subsequent quenching of the reaction with 1 M HCl led to the carbonimidothioates.



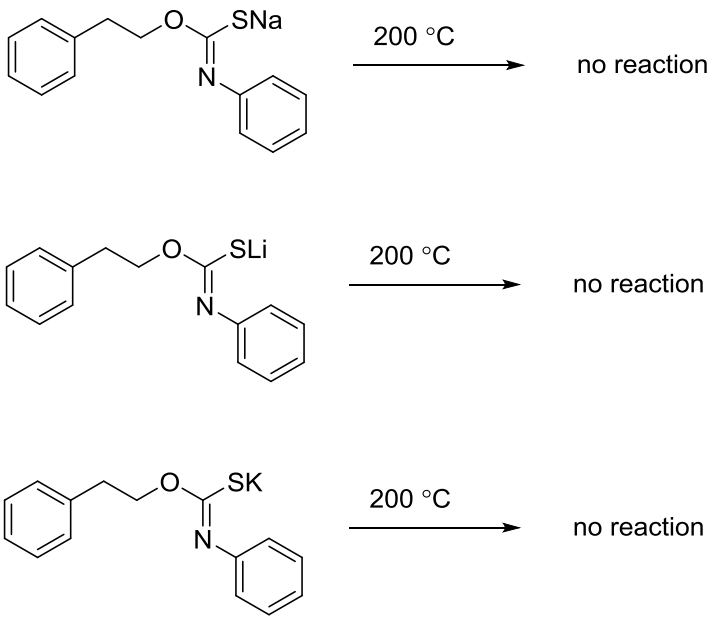
Scheme 1.77

When these carbonimidothioates were heated at 150 °C no elimination was observed. However, when these compounds were heated to 200 °C elimination occurred with similar yields of styrene compared to the *S*-methyl xanthate. These results are summarized in Table 1.1.

Table 1.1

Entry	Compound	Isolated % Yield
1		18
2		15
3		17
4		7
5		16

Interestingly, there does not appear to be a significant difference in yield when the aryl isothiocyanate is substituted with either electron-donating or electron-withdrawing groups. Only phenyl isothiocyanate was selected for further study because it is commercially available and that there is no significant decrease in yield compared to the other aryl isothiocyanates.

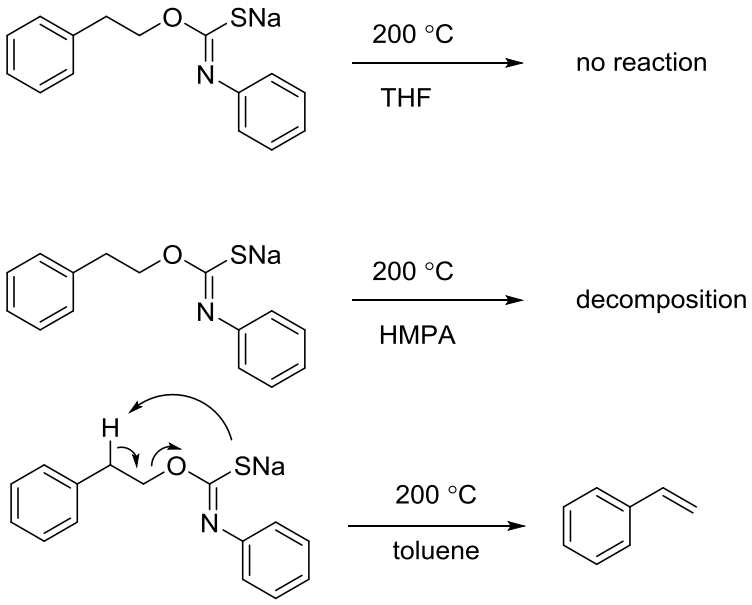


Scheme 1.78

Buoyed by the discovery of an alternative method to the Chugaev reaction, we set out to improve upon it. We hypothesized that by making the thiol sulfur more basic, a more facile elimination would result. The sodium salt of 2-phenylethanol was combined with phenyl isothiocyanate and rather than working up with 1 M HCl, the sodium salt was isolated. When this salt was heated neat to 200 °C no elimination occurred. Unfortunately, when the counter ion was changed from sodium to potassium or lithium no elimination was also observed (Scheme 1.78).

With the observations that the protonated thiol underwent elimination at 200 °C but heating the salts neat to the same temperature did not result in elimination, we

concluded that a solvent was necessary. When the salts were suspended in THF and heated to 200 °C in a sealed tube no elimination was observed. Changing the solvent to HMPA unfortunately led to an inseperable mixture of decomposition products at 200 °C and no elimination at 150 °C. However, when the solvent was changed to toluene a significant amount of elimination product resulted (Scheme 1.79).

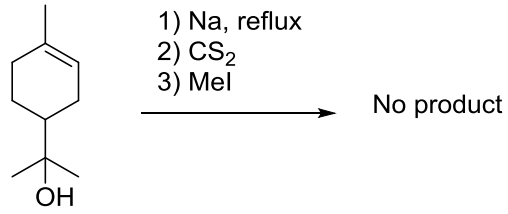


Scheme 1.79

We then hypothesized that this procedure could be shortened to a one-pot process. The sodium salt of 2-phenylethanol was combined with 1.1 eq of phenyl isothiocyanate in toluene and heated to 200 °C in a sealed tube. Excitingly, the same yield of styrene was observed as in the two-step process! While we had eliminated one step from the procedure, the reaction times were still quite long. Previous work in the Majetich lab had determined that microwave heating can significantly decrease the time required for a reaction.[95] Unfortunately, heating the reaction mixtures in microwave reaction vessels at 200 °C for up to four hours did not lead to an appreciable amount of styrene. Even when the solvent was changed from toluene to DMSO or DMF minimal elimination was

observed. We attempted to heat the sealed tubes in the microwave but this resulted in an explosive decomposition of the apparatus. As a result, we abandoned microwave heating and focused on conventional heating methods.

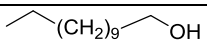
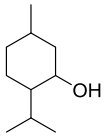
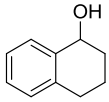
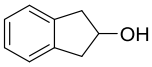
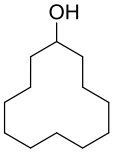
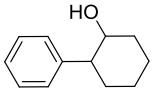
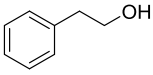
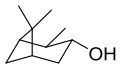
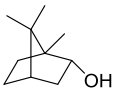
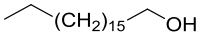
The *S*-methyl xanthates of ten commercially available primary or secondary alcohols were prepared. Unfortunately, the *S*-methyl xanthates of several tertiary alcohols, including α-terpineol, were unable to be isolated (Scheme 1.80). This is in agreement with previous reports which have noted the inherent instability of tertiary xanthates.[91]



Scheme 1.80

The ten xanthates were then heated neat at 200 °C overnight and the olefin products were isolated via column chromatography. Interestingly, the olefin yields did not increase with heating of up to three days. With these results in hand, the same ten alcohols were treated with 1 eq of NaH in toluene in thick-walled glass tubes to prepare the sodium salts. The salts were then treated with 1.1 eq of phenyl isothiocyanate, the tubes were sealed under a slight negative pressure and heated to 200 °C overnight. As in the Chugaev reactions, the olefins were able to be isolated and purified via column chromatography. The results are summarized in Table 1.2.

Table 1.2

Entry	Alcohol	Xanthate Yield	Chugaev Yield	Overall Chugaev Yield	Isothiocyanate Elimination Yield
1		50	14	7	8
2		43	41	18	15
3		89	64	57	67
4		65	25	16	5
5		42	73	31	31
6		48	72	35	16
7		46	18	8	6
8		63	11	7	10
9		53	31	16	11
10		66	44	29	7

In nearly all cases, the overall yields of the Chugaev reaction are comparable with the yields obtained in the one-pot isothiocyanate eliminations. In the cases where multiple *cis*-β-hydrogens were present, i.e. entries 2 and 6, an inseparable mixture of regioisomers were obtained; the product ratios were nearly identical in the Chugaev reactions and the one-pot isothiocyanate eliminations. In entries 4 and 7, a significant amount of polyindene and polystyrene were detected in both procedures. Just as in the Chugaev reaction, primary alcohols were the most resistant to elimination. This is hypothesized to be a result of an unfavorable accumulation of positive charge on the primary carbon.

While we were unable to reduce the temperature or the reaction time, the greatest advantage of the new procedure is the fact that the reaction may be performed in a one-pot process. This eliminates the preparation and purification of the intermediate xanthates and phenyl isothiocyanate is quite inexpensive, < $0.20/gram. Crucially, this new procedure proceeds with comparable yields to the Chugaev reaction. While the conversion of the alcohol is lower than in the Chugaev reaction, the starting material may be easily isolated and resubmitted to the elimination conditions.

1.6 Summary and Conclusions

In summary, a new one-pot alternative to the Chugaev reaction has been developed. This new procedure eliminates the tedious synthesis and purification of the intermediate xanthates required for the Chugaev reaction. Additionally, the overall yields of this new procedure are comparable to those obtained through the Chugaev reaction.

This new procedure has been shown to be effective on a range of primary and secondary alcohols.

1.7 Experimental Data and Procedures

General Procedures: All reactions were run under an argon atmosphere and monitored by TLC analysis. Unless otherwise noted all extractive workups consisted of the following procedure: the crude reaction mixture was diluted with diethyl ether and deionized water. The aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed twice with deionized water, once with brine and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the organic layers concentrated on a rotary evaporator. The crude residue was placed under vacuum at 1 torr until a constant weight was observed. The residue was subsequently purified by flash column chromatography using silica gel 60 (230-400 mesh ASTM) and distilled reagent grade hexanes and ethyl acetate. Melting points were recorded on a DigiMelt MPA 160. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVB-400 MHz spectrometer with a ^{13}C operating frequency of 100 MHz. ^{1}H NMR spectra were obtained in $CDCl_3$ and normalized using trace $CHCl_3$ present (δ 7.27 ppm) as an internal reference. ^{13}C NMR spectra were obtained in $CDCl_3$ using trace $CHCl_3$ present (δ 77.23 ppm) as an internal reference. IR spectra were obtained on an Avatar 360FT-IR and are reported in frequency of absorption (cm^{-1}). Only selected IR frequencies are reported.

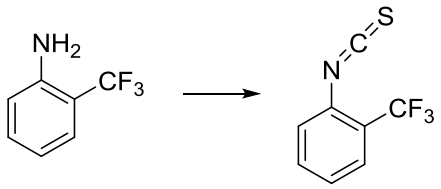
General Procedure for Preparation of *S*-methyl xanthates: 5.47 g (44.7 mmol) 2-phenyl ethanol was dissolved in 40 mL dry toluene. 1.133 g (49.2 mmol) Na metal sliced into small pieces was slowly added to the solution. The solution was heated to reflux for 14 hours. The solution was cooled to 0 °C and 6 mL (100 mmol) CS_2 was added dropwise. The solution was stirred and allowed to warm to room temperature over 1 hour. 2.9 mL (46.5 mmol) was added dropwise and the solution was stirred for 30 minutes. Standard workup followed by purification by column chromatography (30:1 hexanes/ethyl acetate) gave 4.36 g (20.5 mmol, 46% yield) *S*-methyl-*O*-2-phenylethyl carbonodithioate as a yellow oil [R_f = 0.73, 30:1, hexanes/ethyl acetate]

General Procedure for Preparation of Electron-Rich Isothiocyanates: p-Anisidine (5.05 g, 41.0 mmol) and triethylamine (25 mL, 179 mmol) were dissolved in 100 mL dry THF. The solution was cooled to 0 °C. Carbon disulfide (5 mL, 82.8 mmol) was added dropwise over the course of one hour. The solution was allowed to warm to room temperature and was stirred overnight during which a precipitate formed. The solution was cooled back to 0 °C and p-toluenesulfonyl chloride (8.76 g, 45.9 mmol) was added. The solution was allowed to warm to room temperature then stirred for one hour. The solution was acidified with 1.0 M aqueous HCl. Extraction with ether was followed by successive washings with water and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield a brown oil. The crude isothiocyanate was purified using column chromatography (100% hexanes) to yield 2.79 g (16.9 mmol, 41 % yield) of 4-methoxyphenyl isothiocyanate as a yellow oil [R_f = 0.52 100% hexanes].

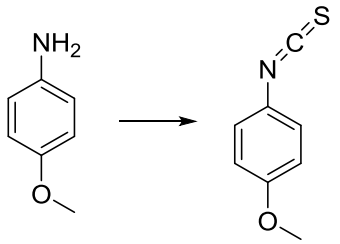
General Procedure for the Synthesis of Electron-Poor Isothiocyanates: 2-Amino benzotrifluoride (4.68 g, 29.0 mmol) dissolved in 50 mL of dry THF. 1.8155 g Sodium hydride (60% dispersion in oil, 1.82 g, 45.3 mmol) was slowly added to the flask. The solution was cooled to 0 °C and carbon disulfide (5.25 mL, 86.8 mmol) was added dropwise over a one-hour period. The solution was refluxed for 24 hours during which a precipitate formed. The solution was then cooled to 0 °C and triethylamine (9.0 mL, 64.5 mmol) was added followed by *p*-toluene sulfonyl chloride (6.11 g, 32.0 mmol). The solution was stirred and warmed to room temperature over 1 hour. The solution was acidified with 1.0M aqueous HCl and then extracted twice with 50 mL diethyl ether. The organic extracts were washed with water, brine and then dried over anhydrous $MgSO_4$. The crude mixture was concentrated under reduced pressure and then purified by column chromatography (8:1 hexanes : ethyl acetate) to give 1.08 g pure 2-trifluoromethyl phenyl isothiocyanate (5.3 mmol, 18.3% yield). [R_f = 0.48, 100% hexanes].

General Procedure for Chugaev Reaction of Xanthates: *O*-Cyclododecyl-*S*-methyl carbonodithioate (149 mg, 0.5 mmol) was added to a thick-walled tube. The tube was sealed and heated at 200 °C for 14 hours. The tube was cooled to room temperature and then carefully opened and the crude reaction mixture was diluted in 10 mL diethyl ether. Standard workup, followed by column chromatography (100% hexanes) gave 65.5 mg (0.4 mmol, 73% yield) of 1-cyclododecene as a colorless oil. [R_f = 0.93, 100% hexanes].

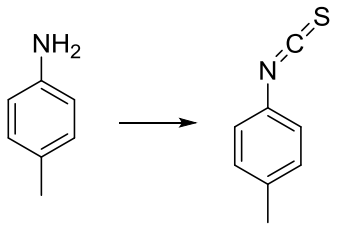
General Procedure for New Isothiocyanate Elimination: Cyclododecanol (166 mg, 0.9 mmol) was dissolved in 2 mL dry toluene and placed in a thick walled glass tube. A 60% dispersion of NaH (37 mg, 0.9 mmol) was then added. The solution was stirred at room temperature for 1 hour. The tube was then sealed and heated at 200 °C overnight. After cooling to room temperature the tube was carefully opened and the crude reaction mixture was dissolved in 10 mL diethyl ether. Standard workup, followed by column chromatography (100 % hexanes), gave 46.6 mg (0.3 mmol, 31% yield) of 1-cyclododecene as a colorless oil [R_f = 0.93, 100% hexanes].



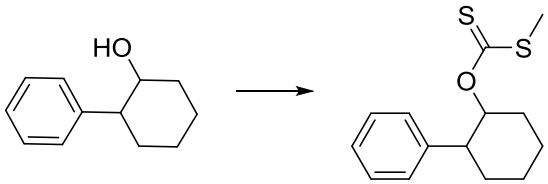
Preparation of 2-trifluoromethylphenyl isothiocyanate: Yield 18%; ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.40 (m, 2H), 7.57 (t, 1H), 7.67 (d, *J*= 8 Hz); ^{13}C NMR (100 MHz, $CHCl_3$) δ 29.9, 128.7, 129.9, 130.1, 131.3, 131.6, 169.9, 194.2.



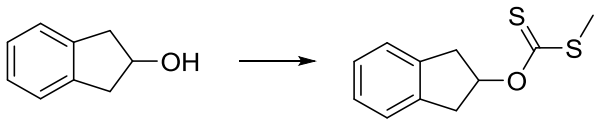
Preparation of 4-methoxyphenyl isothiocyanate: Yield 41%; ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.82 (s, 3H), 6.86 (d, *J*= 8 Hz, 2H), 7.18 (d, *J*= 8 Hz, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 55.8, 115.0, 123.8, 127.2, 134.0, and 158.77; IR (film) λ_{max} 2055 cm^{-1}.



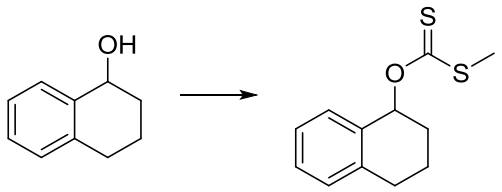
Preparation of 4-methylphenyl isothiocyanate: Yield 35%; [R_f = 0.63, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 2.36 (s, 3H), 7.12 (d, *J*= 8 Hz, 2H), 7.15 (d, *J*= 8 Hz, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 21.4, 125.7, 128.6, 130.3, 134.8, and 137.2; IR (film) λ_{max} 2118 cm^{-1}.



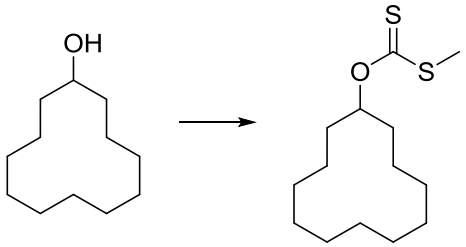
Preparation of *S*-methyl-2-phenylcyclohexyl carbonodithioate: Yield 48%; [R_f = 0.68, 30:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.40-1.67 (m, 11H), 1.65-1.89 (m, 3H), 1.97-2.01 (m, 2H), 2.13-2.17 (m, 1H), 2.34 (s, 3H), 2.39-2.45 (m, 1 H), 2.49 (s, 3H), 2.90-3.02 (m, 2H), 5.75-5.61 (m, 1H), 5.97 (s, 1H), 7.21-7.29 (m 10H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 18.6, 18.9, 20.6, 24.7, 26.0, 26.9, 29.9, 31.4, 34.4, 47.0, 49.8, 83.3, 86.0, 110.2, 126.8, 127.6, 127.9, 128.5, 128.6, 142.5, 215.0. (Note: This was a 1:1 mixture of *cis*/*trans* isomers which accounts for the higher number of peaks)



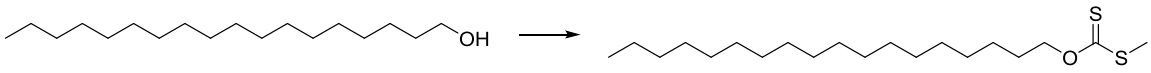
Preparation of *O*-(2,3-dihydro-1H-inden-2-yl) *S*-methyl carbonodithioate: Yield 65%; [R_f = 0.70, 30:1 hexanes/ethyl acetate]: MP = 54-65 °C; ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.22 (d J=10Hz, 2H), 3.43 (dd J= 12 Hz, 2H), 6.21-6.23 (m, 1H), 7.23-7.27 (m, 4H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 19.2, 39.6, 84.9, 124.9, 127.1, 140.4, 215.7.



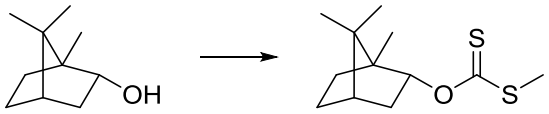
Preparation of *S*-methyl *O*-(1,2,3,4-tetrahydronaphthalen-1-yl) carbonodithioate: Yield 89%; [R_f = 0.61, 30:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.88-1.97 (m, 2H), 2.07-2.11 (m, 1H), 2.21-2.24 (m, 1H), 2.56 (s, 3H), 2.77-2.83 (m, 1H), 2.89-2.96 (m, 1H), 6.87 (t, 1H), 7.16-7.20 (m, 2H), 7.27 (d J = 8Hz, 2H) 7.33 (d J = 8Hz, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 23.4, 27.7, 110.2, 126.1, 126.6, 127.0, 127.7, 128.0, 128.9, 134.4, 135.7, 169.9.



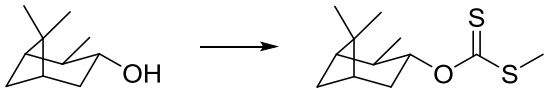
Preparation of *O*-cyclododecyl *S*-methyl carbonodithioate: Yield 42%; [R_f = 0.55, 30:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.35-1.42 (m, 18H), 1.71-1.75 (m, 2H), 1.82-1.86 (m, 2H), 2.55 (s, 3H), 5.83-5.87 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 18.9, 21.2, 23.5, 23.7, 23.9, 24.2, 29.0, 83.1, 215.6.



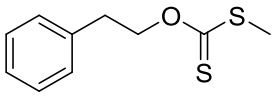
Preparation of *S*-methyl *O*-octadecyl carbonodithioate: Yield 66%; [R_f = 0.80, 30:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.89 (t, 3H), 1.26-1.40 (m, 30H), 1.80 (pentet, 2H), 2.57 (s, 3H), 4.59 (t, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 14.4, 19.1, 23.0, 26.1, 28.5, 29.4, 29.6, 29.7, 29.8, 29.9, 29.9, 29.9. 29.9, 29.9, 29.9, 29.9, 29.9 (overlapping signals), 32.1, 74.5, 169.9.



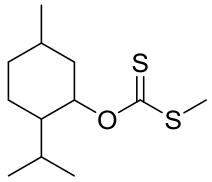
Preparation of *O*-bornyl *S*-methyl carbonodithioate: Yield 53%; [R_f = 0.73, 30:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.90-0.93 (m, 9H), 1.08-1.12 (m, 2H), 1.39-1.43 (m, 1H), 1.72-1.78 (m, 2H), 2.03 (m, 1H), 2.45-2.49 (m, 1H), 2.57 (s, 3H), 5.48-5.51 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 13.8, 19.1, 19.8, 27.9, 28.1, 33.8, 36.6, 45.1, 48.1, 49.7, 90.6, 215.9.



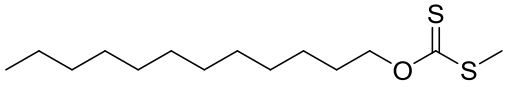
Preparation of *O*-isopinocamphenyl *S*-methyl carbonodithioate: Yield 63%; [R_f = 0.67, 30:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.98 (s, 3H), 1.12-1.16 (m, 4H), 1.25 (s, 3H), 1.73-1.77 (m, 1H), 1.88 (t, 1H), 1.95-1.99 (m, 1H), 2.35-2.41 (m, 2H), 2.57 (s, 3H), 2.70-2.74 (m, 1H), 5.81-5.85 (m, 1H);^{13}C NMR (100 MHz, $CHCl_3$) δ 19.2, 20.8, 24.1, 27.6, 33.6, 35.4, 38.5, 41.4, 43.5, 47.7, 84.8, 215.7.



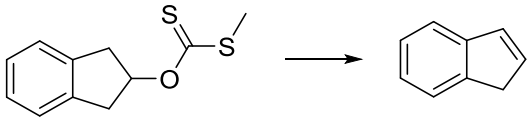
Preparation of *S*-methyl *O*-phenethyl carbonodithioate: Yield 46%; [R_f = 0.84, 30:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 2.54 (s, 3H), 3.13 (t, 2H), 4.81 (t, 2H), 7.25-7.27 (m, 3H), 7.32-7.35 (m, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 19.1, 34.9, 74.2, 127.0, 128.8, 129.2, 137.4, 215.9.



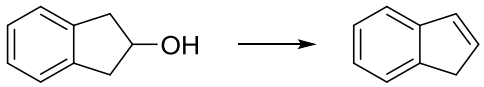
Preparation of *O*-(2-isopropyl-5-methylcyclohexyl) *S*-methyl carbonodithioate: Yield 43%; [R_f = 0.80, 30:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.81 (d J= 8Hz, 3H), 0.94 (d J= 8Hz, 6H), 1.11-1.16 (m, 2H), 1.50-1.54 (m, 1H), 1.71-1.75 (m, 3H), 1.86-1.92 (m, 1H), 2.24 (d J= 12Hz, 1H), 2.56 (s, 3H), 5.49-5.55 (m, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 17.2, 19.0, 20.8, 22.2, 24.0, 26.9, 31.6, 34.4, 39.8, 47.5, 84.7, 215.7.



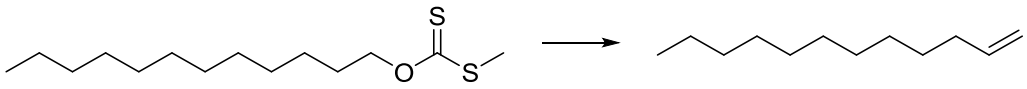
Preparation of O-dodecyl S-methyl carbonodithioate: Yield 50%; [R_f = 0.85]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.89 (t, 3H), 1.27-1.40 (m, 18H), 1.80 (pentet, 2H), 2.56 (s, 3H), 4.59 (t, 2H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 14.4, 19.1, 22.9, 26.1, 28.5, 29.4, 29.6, 29.7, 29.8, 29.8 [Note: Overlapping signals], 29.9, 32.1, 74.5, 216.2.



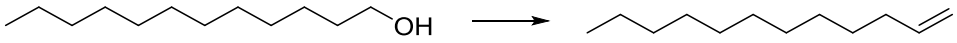
Chugaev Elimination of *O*-(2,3-dihydro-1H-inden-2-yl) *S*-methyl carbonodithioate: Yield 25%; [R_f = 0.95, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.40 (s, 2H), 6.56 (d J= 8Hz, 1H), 6.89 (d J= 8Hz, 1H), 7.19 (t, 1H), 7.33 (t, 1H), 7.41 (d J=8 Hz, 1H), 7.48 (d J= 8Hz, 1H).



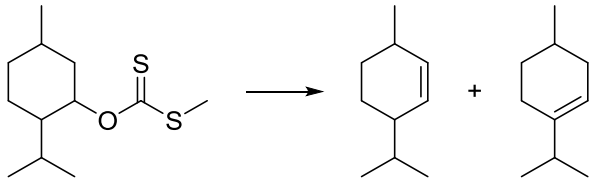
Isothiocyanate Elimination of 2-indanol: Yield 5%; [R_f = 0.95, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.40 (s, 2H), 6.56 (d J= 8Hz, 1H), 6.89 (d J= 8Hz, 1H), 7.19 (t, 1H), 7.33 (t, 1H), 7.41 (d J=8 Hz, 1H), 7.48 (d J= 8Hz, 1H).



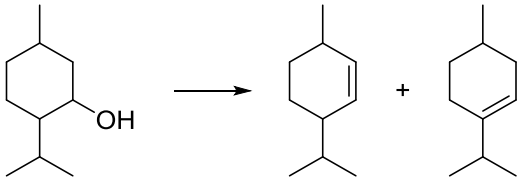
Chugaev Elimination of *O*-dodecyl *S*-methyl carbonodithioate: Yield 14%; [R_f= 0.97, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.89 (t, 3H), 1.27-1.40 (m, 16H), 2.02-2.08 (m, 2H), 4.93 (d J=12 Hz, 1H), 5.00 (d J= 16Hz, 1H), 5.78-5.86 (m, 1H).



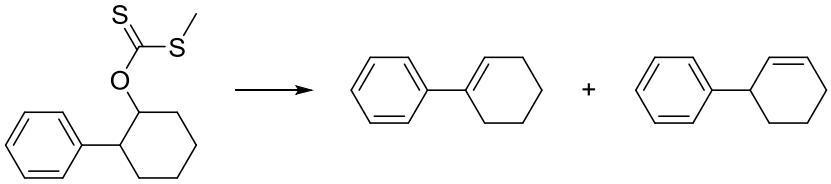
Isothiocyanate Elimination of 1-dodecanol: Yield 8%; [R_f= 0.97, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.89 (t, 3H), 1.27-1.40 (m, 16H), 2.02-2.08 (m, 2H), 4.93 (d J=12 Hz, 1H), 5.00 (d J= 16Hz, 1H), 5.82 (m, 1H).



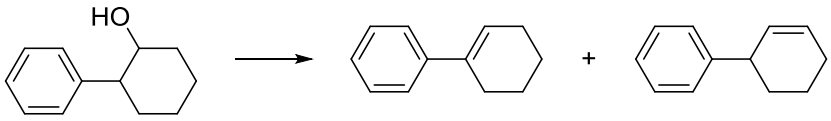
Chugaev Elimination of *O*-(2-isopropyl-5-methylcyclohexyl) *S*-methyl carbonodithioate: Yield 41%; [R_f = 0.93, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.88 (d J= 8Hz, 2H), 0.90 (d J= 8Hz, 2H), 0.95-0.96 (m, 6H), 0.97-0.99 (m, 1H), 0.99-1.01 (m, 10H), 1.10-1.30 (m, 3H), 1.60-1.64 (m, 4H), 1.70-1.74 (m, 2H), 2.14-2.18 (m, 3H), 5.38 (m, 2H), 5.54 (t, 1H).



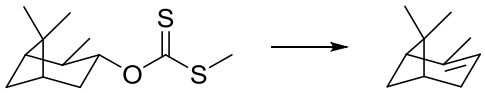
Isothiocyanate Elimination of menthol: Yield 15%; [R_f = 0.93, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.88 (d J= 8Hz, 2H), 0.90 (d J= 8Hz, 2H), 0.95-0.96 (m, 6H), 0.97-0.99 (m, 1H), 0.99-1.01 (m, 10H), 1.10-1.30 (m, 3H), 1.60-1.64 (m, 4H), 1.70-1.74 (m, 2H), 2.14-2.18 (m, 3H), 5.38 (m, 2H), 5.54 (t, 1H).



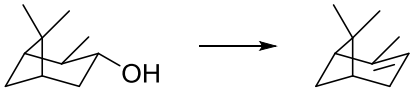
Chugaev Elimination of *S*-methyl-2-phenylcyclohexyl carbonodithioate: Yield 72%; [R_f = 0.88, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.60-1.86 (m, 9H), 2.08-2.12 (m, 1H), 2.26-2.27 (m, 2H), 2.47 (s, 2H), 3.45-3.47 (m, 1H), 5.78-5.80 (m, 1H), 5.94-5.96 (m, 1H), 6.18 (s, 1H), 7.26-7.29 (m, 4H), 7.34-7.38 (m, 4H), 7.44 (d J= 8Hz, 2H).



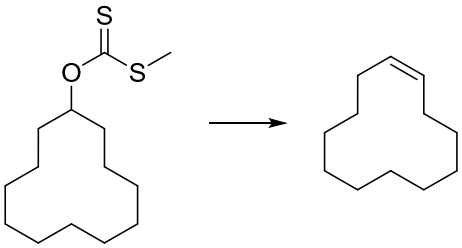
Isothiocyanate Elimination of 2-phenylcyclohexanol: Yield 16%; [R_f = 0.88, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.60-1.86 (m, 9H), 2.08-2.12 (m, 1H), 2.26-2.27 (m, 2H), 2.47 (s, 2H), 3.45-3.47 (m, 1H), 5.78-5.80 (m, 1H), 5.94-5.96 (m, 1H), 6.18 (s, 1H), 7.26-7.29 (m, 4H), 7.34-7.38 (m, 4H), 7.44 (d J= 8Hz, 2H).



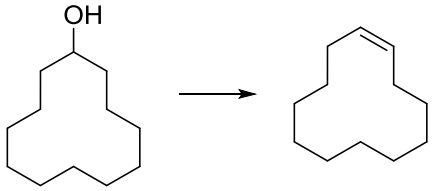
Chugaeve Elimination of *O*-isopinocamphenyl *S*-methyl carbonodithioate: Yield 11%; [R_f = 0.92, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.84 (s, 3H), 1.09 (d J= 8Hz, 1H), 1.16 (d J= 8Hz, 1H), 1.27 (s, 3H), 1.30 (m, 1H), 1.67 (s, 3H), 1.92-1.96 (m, 1H), 2.20-2.22 (m, 1H), 2.33-2.36 (m, 1H), 5.19 (s, 1H).



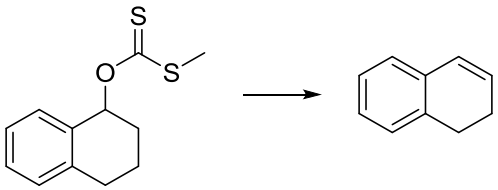
Isothiocyanate Elimination of isopinocampheol: Yield 10%; [R_f = 0.92, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.84 (s, 3H), 1.09 (d J= 8Hz, 1H), 1.16 (d J= 8Hz, 1H), 1.27 (s, 3H), 1.30 (m, 1H), 1.67 (s, 3H), 1.92-1.96 (m, 1H), 2.20-2.22 (m, 1H), 2.33-2.36 (m, 1H), 5.19 (s, 1H).



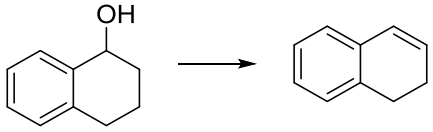
Chugaev Elimination of *O*-cyclododecyl *S*-methyl carbonodithioate: Yield 73%; [R_f = 0.94, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.30 (m, 10H), 1.42-1.46 (m, 6H), 2.04-2.08 (m, 4H), 5.37-5.39 (m, 2H).



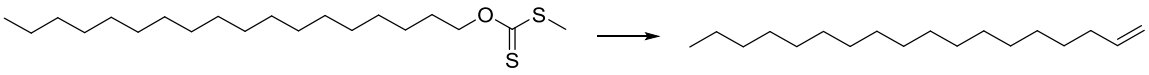
Isothiocyanate Elimination of cyclododecanol: Yield 31%; [R_f = 0.94, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.30 (m, 10H), 1.42-1.46 (m, 6H), 2.04-2.08 (m, 4H), 5.37-5.39 (m, 2H).



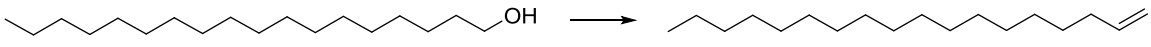
Chugaev Elimination of *S*-methyl *O*-(1,2,3,4-tetrahydronaphthalen-1-yl) carbonodithioate: Yield 64%; [R_f = 0.82, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 2.30-2.36 (m, 2H), 2.81 (t, 2H), 6.02-6.05 (m, 1H), 6.48 (d J= 12Hz, 1H), 7.07-7.17 (m, 4H).



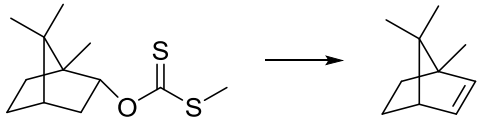
Isothiocyanate elimination of 1,2,3,4-tetrahydronaphthalen-1-ol: Yield 67%; [R_f = 0.82, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 2.30-2.36 (m, 2H), 2.81 (t, 2H), 6.02-6.05 (m, 1H), 6.48 (d J= 12Hz, 1H), 7.07-7.17 (m, 4H).



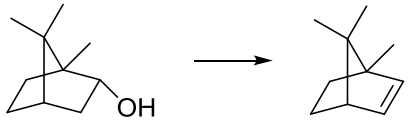
Chugaev Elimination of *S*-methyl *O*-octadecyl carbonodithioate: Yield 44%; [R_f = 0.91, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.89 (t, 3H), 1.26-1.40 (m, 28H), 2.01-2.07 (m, 2H), 4.94 (d J= 8Hz, 1H), 5.00 (d = 16Hz, 1H), 5.77-5.88 (m, 1H).



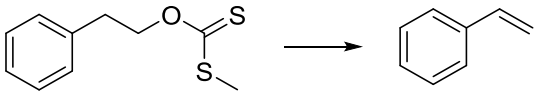
Isothiocyanate Elimination of 1-octadecanol: Yield 7%; [R_f = 0.91, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.89 (t, 3H), 1.26-1.40 (m, 28H), 2.01-2.07 (m, 2H), 4.94 (d J= 8Hz, 1H), 5.00 (d = 16Hz, 1H), 5.77-5.88 (m, 1H).



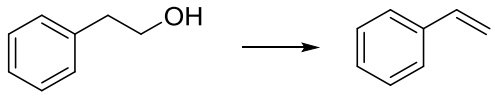
Chugaev Elimination of *S*-methyl *O*-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl) carbonodithioate: Yield 31%; [R_f = 0.90, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.77 (s, 3H), 0.83 (s, 3H), 1.03 (s, 3H), 1.53-1.57 (m, 2H), 1.65-1.72 (m, 2H), 1.77-1.83 (m, 1H), 5.66 (d J = 8Hz, 1H), 5.90-5.92 (m, 1H).



Isothiocyanate Elimination of borneol: Yield 11%; [R_f = 0.90, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.77 (s, 3H), 0.83 (s, 3H), 1.03 (s, 3H), 1.53-1.57 (m, 2H), 1.65-1.72 (m, 2H), 1.77-1.83 (m, 1H), 5.66 (d J = 8Hz, 1H), 5.90-5.92 (m, 1H).



Chugaev Elimination of *S*-methyl *O*-phenethyl carbonodithioate: Yield 18%; [R_f = 0.84, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.27 (d J = 12 Hz, 1H), 5.78 (d J = 16Hz, 1H), 6.75 (dd J = 16 Hz, 1H), 7.28 (t, 1H), 7.35 (t, 2H), 7.44 (d J = 8 Hz, 2H).



Isothiocyanate elimination of 2-phenylethanol: Yield 6%; [R_f = 0.84, 100% hexanes]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 5.27 (d J = 12 Hz, 1H), 5.78 (d J = 16Hz, 1H), 6.75 (dd J = 16 Hz, 1H), 7.28 (t, 1H), 7.35 (t, 2H), 7.44 (d J = 8 Hz, 2H).

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CHAPTER 2

SYNTHESIS AND ANTI-OXIDANT ACTIVITY OF SEVERAL NOVEL CAPSIATES

2.1 Introduction

The genus *Capsicum* has been used in cooking for thousands of years and is well known to the modern hot sauce enthusiast. The desirable property of this genus is the pungent spiciness of its fruits. However, it was not until the 19th century that work started on the identification of the compound responsible for the pungency. In 1876 Thresh was able to isolate and crystallize the compound which he named capsaicin.[1] The structure was partially elucidated by Micko in 1898.[2] He determined that capsaicin contained a phenol and a methoxy group which supported the theory that a vanillyl group was present. Nelson postulated that the chemical structure was *N*-(4-hydroxy-3-methoxybenzyl)-8-methylnon-6-enamide[3] by hydrolyzing capsaicin which resulted in the isolation of vanillyl amine and 8-methylnon-6-enoic acid. Note that because of the position of the olefin in capsaicin of *cis*/*trans* isomers were possible. It was not until 1955 that the configuration of the olefin was definitively proven to be *trans*.[4] A surprising twist occurred when it was discovered that the samples of capsaicin isolated previously were actually 2:1 mixtures of two compounds. Kosuge identified the second

compound as being structurally similar to capsaicin except for the lack of an olefin. He named this second compound dihydrocapsaicin (Figure 2.1).[5]

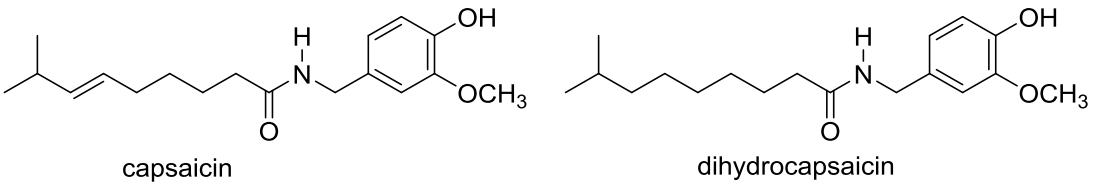
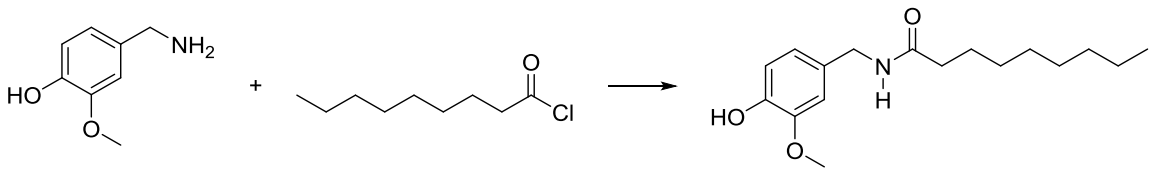


Figure 2.1

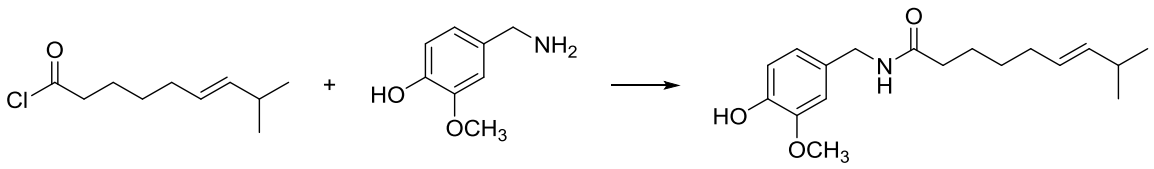
2.2 Syntheses of Capsaicinoids

In addition to determining the structure of capsaicin, Nelson was also the first to synthesize a set of analogues (Scheme 2.1).[6] He combined vanillylamine with several acyl chlorides to prepare the capsaicinoids. Importantly, all synthesized analogues possessed the pungent sensation of natural capsaicin.



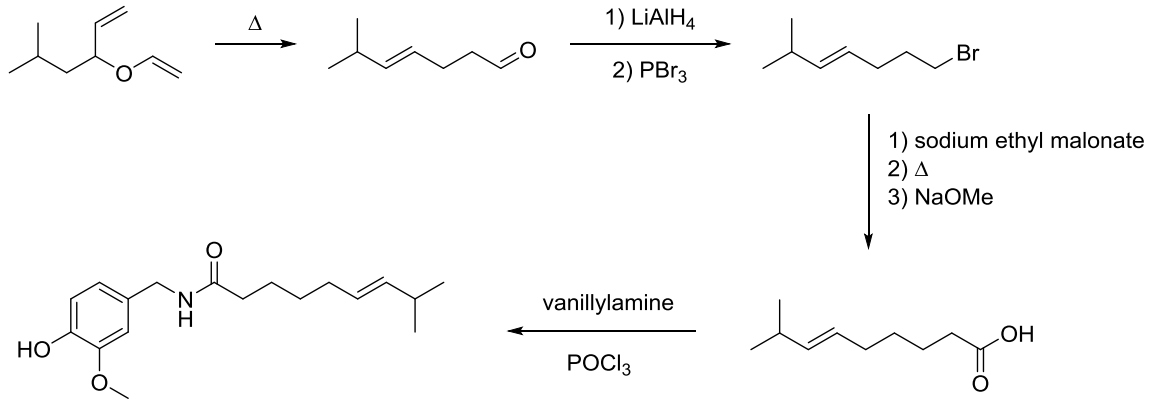
Scheme 2.1

Crombie was able to prepare capsaicin[4] through a similar method to Nelson.[3] He prepared (*E*)-8-methylnon-6-enoic acid using a malonic ester synthesis and treated that carboxylic acid with thionyl chloride to yield the acyl chloride. He then combined the acyl chloride with vanillylamine to yield capsaicin (Scheme 2.2). Unfortunately, the overall yield (4.7%) was quite poor which left much room for improvement.



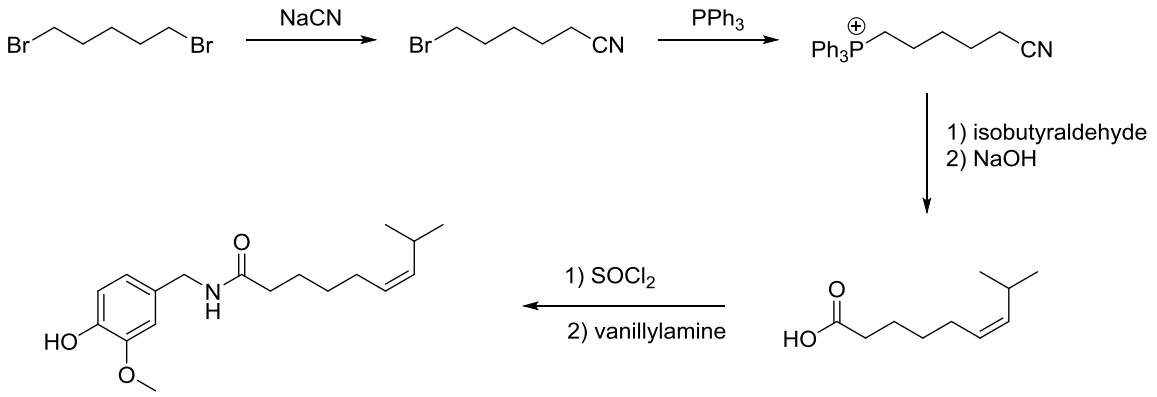
Scheme 2.2

Vig improved on Crombie's synthesis by preparing the fatty side chain in a slightly different manner.[7] The key step in his preparation is a Claisen rearrangement which installs the olefin in the correct location, with the correct geometry, and results in an aldehyde. This aldehyde was reduced to the alcohol with $LiAlH_4$ which was converted to a primary bromide. A two-carbon homologation was achieved via a malonic ester synthesis. The synthesis was completed by combining the acid and vanillylamine in the presence of phosphorus oxychloride to yield capsaicin (Scheme 2.3).



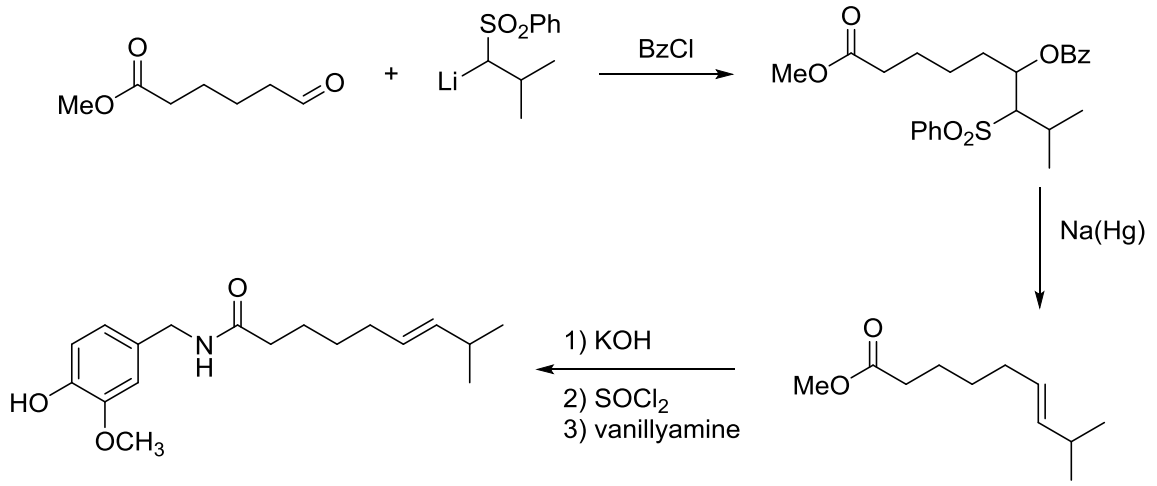
Scheme 2.3

The isomeric *cis*-capsaicin was first prepared by Rangoonwala in 1979[8] when he synthesized (*Z*)-8-methyl-non-6-enoic acid from 1,5-dibromopentane. The key step in Rangoonwala's synthesis was a Wittig reaction to install the *Z*-olefin. He then converted the carboxylic acid to an acyl chloride and combined it with vanillylamine to yield *cis*-capsaicin (Scheme 2.4).



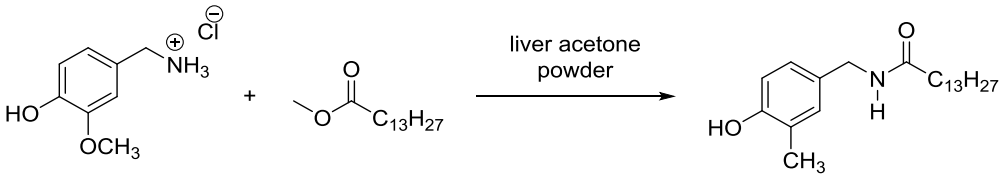
Scheme 2.4

Gannett was able to improve on this synthesis even further by employing a Julia olefination to introduce the required olefin. Gannett's procedure also allowed for several analogues to be prepared in good yield. In this synthesis, lithiated isobutyl phenyl sulfone was treated with methyl 6-oxohexanoate to yield an alcohol. This alcohol was trapped with benzoyl chloride and treated with sodium amalgam to yield the *E*-olefin nearly exclusively. The resulting ester was saponified and then converted to the acyl chloride; condensation with vanillylamine led to capsaicin in good yield (Scheme 2.5).[9]



Scheme 2.5

Methods of ester and amide formation have been developed involving enzyme catalysis. The advantage of these procedures is that the reagents required are non-toxic and there is good selectivity of the substrates. Kobata was able to use the commercially available chicken liver acetone powder to catalyze the coupling of vanillylamine hydrochloride with several methyl esters (Scheme 2.6).[10] While the yields for the reaction were low (~17%), this reaction was scalable and reproducible. Additionally, when no enzyme was present the reaction did not proceed.

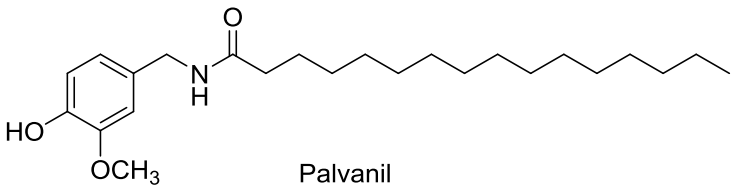


Scheme 2.6

2.3 Pharmacological Properties of Capsaicinoids

Capsaicin and its analogues have been used extensively for their pharmacological properties; the most common use is for pain relief. The TRPV1 receptor has been shown to be involved in pain perception,[11] which has led to extensive study of agonists of the TRPV1 receptor of which capsaicin is one. Capsaicin initially activates the TRPV1 receptor but prolonged exposure causes a desensitization effect.[12] This effect seems to result from the receptor neurons going into a refractory state. As a result, the neurons are resistant to stimuli and the feeling of pain is reduced.[13] It has been shown that application of capsaicin results in a calcium overload inside the cell. These high levels of calcium result in a loss of mitochondrial function which in turn causes the nerve ending to collapse. This has been hypothesized as an explanation for the desensitization effect of capsaicin.[14] For its pain relieving properties, a patch containing 8% capsaicin has been

approved by the FDA as a treatment for postherpetic neuralgia.[15] A non-pungent analogue, palvanil (Figure 2.2), has been shown to exhibit a much more potent desensitizing effect compared to capsaicin.[16] Palvanil also exhibits slower kinetics of TRPV1 activation than capsaicin which has been attributed to its higher lipophilicity. This suggests that modifying the side chain of capsaicin may result in a more effective drug.



Palvanil

Figure 2.2

Obesity is a major health concern today. It has been hypothesized that capsaicin may aid in weight reduction. One of the major causes of obesity is over consumption; suppressing the appetite should lead to an overall reduction in body weight. A 1 g oral dose of red pepper has been shown to result in an increase in energy expenditure and a decrease in appetite in both regular consumers and non-consumers of spicy food.[17] These results suggest that capsaicin might aid in weight reduction through appetite suppression. Obesity has also been linked to several diseases including type 2 diabetes, fatty liver disease, and insulin resistance. Two signs of type 2 diabetes are abnormally high blood levels of glucose and lipids. Kang tested a 0.015% capsaicin supplement on obese mice being fed a high fat diet. In the mice being treated with capsaicin, a decrease in fasting glucose and triglyceride levels was observed.[18] Additionally, capsaicin has been shown to reduce glucose intolerance and enhance fatty acid oxidation in the liver of these obese

mice.[19] These findings suggest that capsaicin may prove to be an effective treatment of type 2 diabetes.

Another major health concern is cardiovascular disease. Cardiovascular disease has become the leading cause of mortality in the developed world.[20] As such, research is ongoing into treatments to prevent or delay the onset of this disease. Capsaicin has been shown to inhibit platelet aggregation and the activity of two clotting factors.[20] While these experiments were performed on whole blood samples, capsaicin has yet to be tested in living organisms for these effects. Nonetheless, these results suggest that capsaicin or a capsaicin derivative might serve as a treatment for cardiovascular disease.

Perhaps the largest area of pharmacological research is in developing and testing compounds for their anti-cancer properties. Gastric cancer has become one of the more common types of cancer, especially in Asia[21] has become resistant to the most common treatment, cisplatin, and has led to investigation into alternative treatments. One reason for the resistance is the overexpression of the Aurora-A protein. Cisplatin resistance has been noted in SNU-668 cells containing high levels of this protein. However, treatment with a combination of capsaicin and cisplatin led to apoptosis.[21] Additionally, Aurora-A levels were much lower in cells treated with capsaicin and cisplatin compared to cells treated only with cisplatin. This suggests that capsaicin reduces production of Aurora-A and in turn decreases resistance to cisplatin.

In addition to gastric cancer, capsaicin has also been shown to be effective against colon cancer cells. Lu treated colo 255 cells with capsaicin both *in vitro* and *in vivo*.[22] In the *in vitro* study, capsaicin induced apoptosis and cytotoxic activity. In the mouse models, the mice treated with capsaicin had much smaller cancer masses and a slower

growth rate compared to the control. This suggests that capsaicin may prove to be an effective treatment.

One feature common to several breast cancer cell lines is a downregulation of the caspase-3 protein. This has been posited as an explanation for why many lines are resistant to most chemotherapy techniques. This has led to the search for a treatment that induces apoptosis of these cells via a caspase-3 independent pathway. Chang and co-workers have shown that capsaicin induced apoptosis in MCF-7 breast cancer cells.[23] Because this cell line is caspase-3 deficient, these results suggest that the apoptosis is induced via an alternative pathway. Unfortunately, capsaicin was cytotoxic only at concentrations above 100 μM. While this result is disappointing, it suggests that perhaps a capsaicin analogue may prove to be more effective.

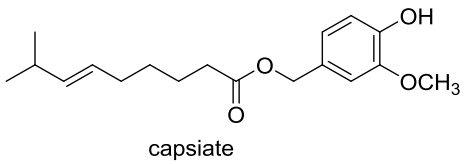
Lung cancer remains as the most common type of cancer in humans. Two of the hallmarks of lung cancer are an elevated white blood cell and mast cell count. Anandakumar showed that treatment of mice with benzo(a)pyrene induced lung cancer with capsaicin reduced the white blood cell and mast cell counts of these animals.[24] While the capsaicin did not induce apoptosis in the lung cancer cells, the reduced counts suggest that capsaicin was acting in a chemoprotective manner, which suggests that a combined treatment of capsaicin and a chemotherapy drug will serve to induce apoptosis and reduce the tumor size.

Capsaicin has also been shown to be active against certain human leukemia cell lines. Tsou showed that HL-60 cells treated with capsaicin underwent apoptosis.[25] Interestingly, capsaicin appeared to increase Ca^{2+} levels within the cells which resulted in a decrease in the mitochondrial membrane potential which induced the apoptosis

pathway. Similarly to the MCF-7 cell line, capsaicin was only effective at concentrations above 75 μM. Again, these preliminary results suggest that an analogue of capsaicin may prove to be more effective at inducing apoptosis.

2.4 Capsiates

The recently discovered chili breed CH-19 Sweet has been the subject of much interest due to the lower pungency of these peppers when compared to other chili pepper varieties. The main component of these peppers is capsiate, the ester analogue of capsaicin (Figure 2.3).[26] Interestingly, capsiate has also been shown to activate TRPV1 pathways. This suggest that capsiate could prove to have similar pharmacological properties to capsaicin.



capsiate

Figure 2.3

While capsiate activates the TRPV1 receptors, it lacks the pungency of capsaicin! This is due to the ester linkage between the vanillyl ring and the fatty side chain. In capsaicin this linkage is an amide. The ester hydrolyzes when crossing the oral mucosa which eliminates any pungency.[27]

Because of the similar structures of capsaicin and capsiate, research was begun into the pharmacological applications of capsiate. Haramizu et al. administered capsiate to mice being fed an *ad libitum* diet.[28] In the mice treated with capsiate the accumulation of body fat was inhibited and energy expenditure increased. Excitingly, the inhibition of fat accumulation and the increase in energy expenditure in mice treated with capsiate and

no exercise were similar to mice being exercised with no capsiate supplementation. This suggests that capsiate supplementation when paired with exercise could lead to significant weight reduction. Additionally, because capsiate is non-pungent, it may serve as a more tolerable treatment compared to the very pungent capsaicin.

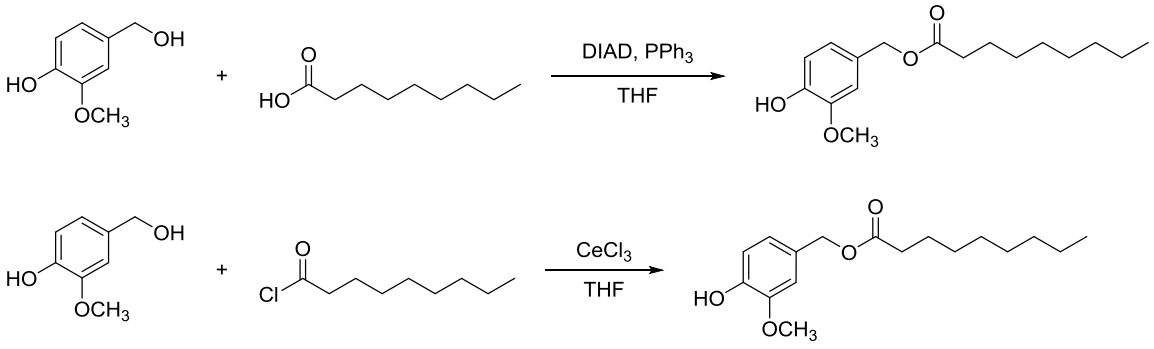
VEGF has been shown to be an important factor in tumor growth and migration. As such any compound that inhibits VEGF could potentially lead to an anti-tumor treatment. Pyun showed that both capsaicin and capsiate inhibit VEGF at similar concentrations *in vitro*.[29] This indicates that the activity is not dependent on the linkage between the vanillin ring and the side chain. Excitingly, capsiate also inhibits angiogenesis *in vivo*,[29] which suggests that capsiate or an analogue may prove to be an effective anti-tumor treatment.

Reactive oxygen species have been shown to cause oxidation of poly-unsaturated fatty acids. These acids are particularly prevalent in neuronal tissue and oxidation has been shown to lead to a variety of neurodegenerative diseases.[30] The main method of combating this oxidation is with anti-oxidant compounds, specifically radical scavengers. Reddy and co-workers prepared and tested the anti-oxidant activity of capsiate and a few linear fatty analogues.[30] Excitingly, these analogues exhibited similar levels of anti-oxidant activity to BHT and α-tocopherol, two known radical scavengers. However, as the chain length increased the anti-oxidant capacity was reduced.

Inflammatory bowel disease is a quite painful condition affecting the human colon. The transcription factor NF-κB has been shown to be quite active in immune response and inflammation.[31] As such, treatments for inflammatory bowel disease have centered on suppressing this factor. When mice with inflammatory bowel disease were

treated with capsiate, fewer inflammatory cells were present in the lamina propria of the colon.

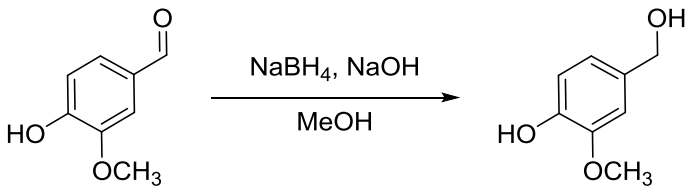
While capsiate is available naturally in CH-19 Sweet peppers, a synthetic route is necessary for any potential therapeutic use. The two most common methods of preparing capsiate and its analogues are the Mitsunobu esterification[32] and cerium(III)-catalyzed esterification. Appendino and co-workers were able to prepare vanillyl nonanoate under typical Mitsunobu conditions, albeit in modest yield (Scheme 2.7)[33] without having to protect the phenol in vanillyl alcohol. This one-step procedure provides an efficient way to prepare a large number of capsiate analogues. Appendino et al. prepared vanillyl nonanoate by coupling vanillyl alcohol and nonanoyl chloride with catalytic cerium(III) chloride.[34] This method is quite mild but may not be applicable to more complicated carboxylic acids because of the harsh conditions required to prepare the acyl chloride. Reddy was also able to prepare a few capsiate analogues via enzymatic catalysis.[30]



Scheme 2.7

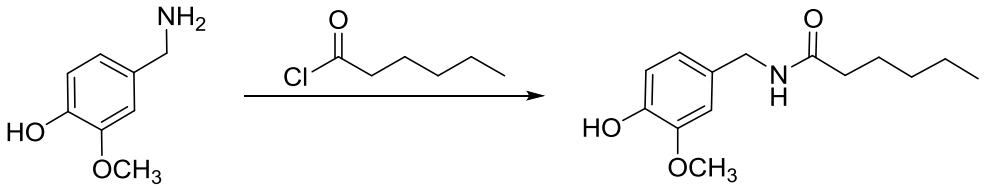
2.5 Preparation of Novel Capsiates

The common functionality in all of the capsiates is the vanillyl ring. Fortunately that moiety can be accessed from the inexpensive, commercially available vanillin. A simple reduction of vanillin with $NaBH_4$ results in vanillyl alcohol (Scheme 2.8).



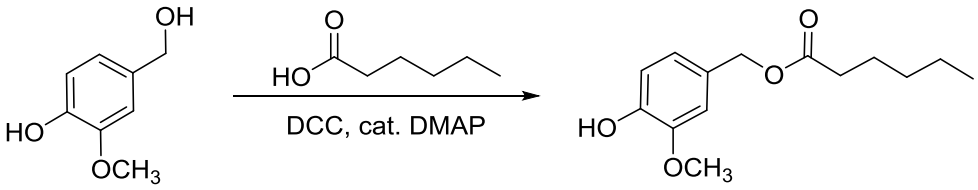
Scheme 2.8

With vanillyl alcohol in hand, the next step was to determine how to attach the side chain. In his preparation of capsaicin analogues, Gannett coupled vanillyl amine with several fatty acid chlorides (Scheme 2.9).[9] While this method is fast and high yielding, preparing the acyl chlorides requires the use of $SOCl_2$ which limits the side chain functionalities tolerated.



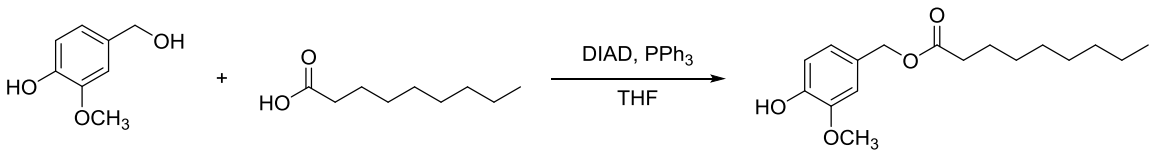
Scheme 2.9

Another possible method is the Steglich esterification which uses DCC and a catalytic amount of DMAP (Scheme 2.10). The advantage of this procedure is that the main by-product, dicyclohexylurea, is insoluble in DCM and can easily be filtered away. Vanillyl alcohol can be directly coupled with the carboxylic acid to introduce the side chain. One downside of this coupling procedure is that the reaction times needed can be quite long.



Scheme 2.10

A better alternative, and the one chosen for this study, is the Mitsunobu reaction. This procedure employs DEAD, or DIAD, and PPh_3. As in the Steglich esterification, this is a one-step process to couple the carboxylic acid with vanillyl alcohol directly; additionally, the triphenylphosphineoxide byproduct can be removed by filtering the reaction mixture through a pad of Celite. This reaction occurs rapidly with most esterifications going to completion in as little time as one hour. Appendino used this method to prepare a few straight chain derivatives of capsiate (Scheme 2.11).[33] With a preferred method chosen, we set out to prepare a library of capsiate analogues.



Scheme 2.11

Until this study, only straight chain fatty acids had been coupled with vanillyl alcohol. We decided to prepare a few examples of these as well. We were able to prepare seven derivatives with side chains ranging from two to fourteen carbons in reasonable yield. Because only straight chain examples had been prepared previously, we decided to focus on changing the functionality of the side chains. Forty-four examples were prepared in yields ranging from 3 to 76%.

With the esters in hand we sought to test the anti-oxidant activity *in vitro* of these compounds in the hope of narrowing down which functionalities are the most active. All

of the compounds were tested via an ORAC assay. This assay measures the fluorescent decay of a fluorescent molecule, most commonly fluorescein. The change in the decay can be attributed to the oxygen radical absorbing capacity of the compounds being tested.[35] The decay curves are compared to a known anti-oxidant, in this case Trolox. The results are reported as μmol Trolox activity per gram of starting material. The results are summarized in Table 2.1. For example the acetate derivative has an ORAC value of 349. This means that 1g of the acetate reacts with as many molecules of AAPH, the radical source, as 349 μmol of Trolox.

Table 2.1

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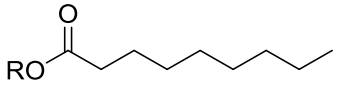
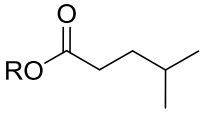
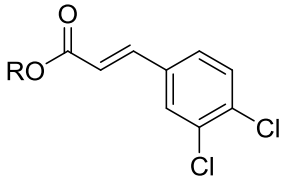
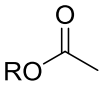
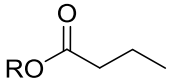
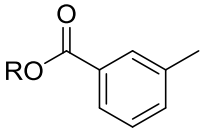
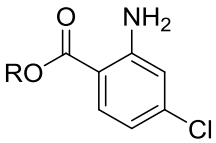
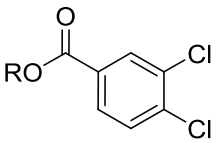
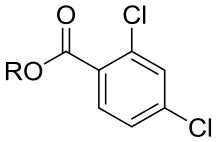
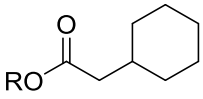
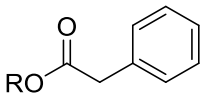
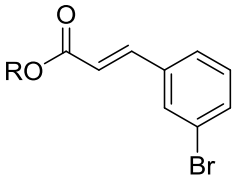
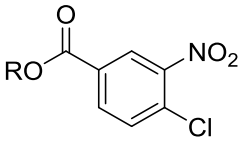
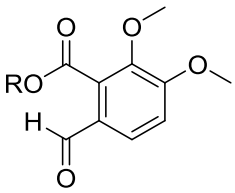
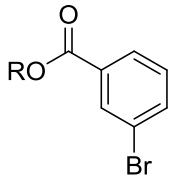
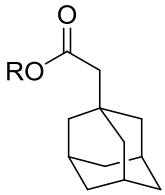
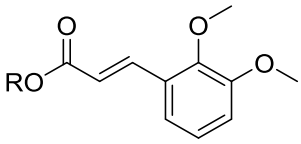
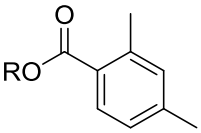
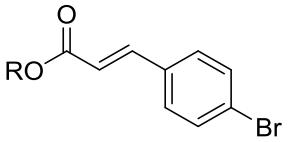
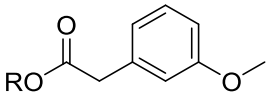
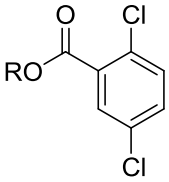
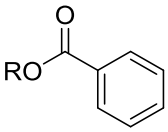
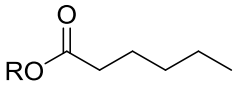
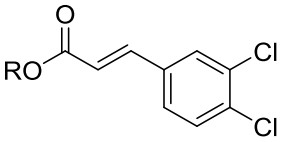
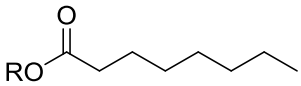
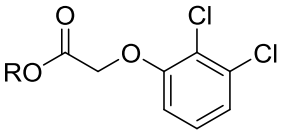
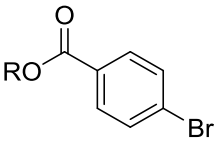
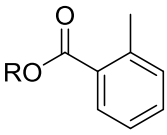
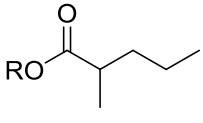
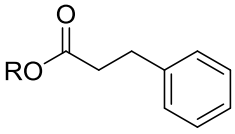
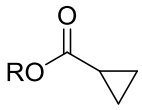
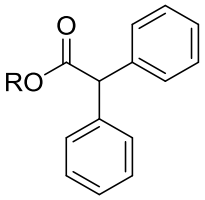
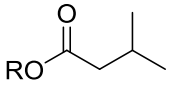
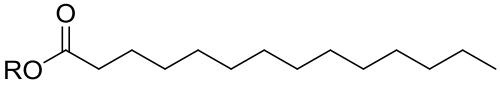
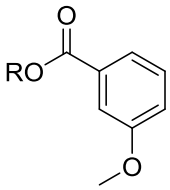
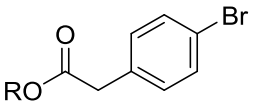
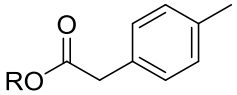
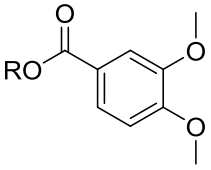
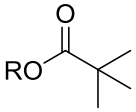
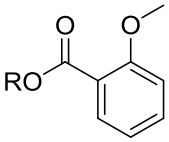
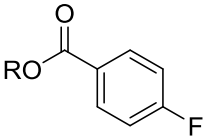
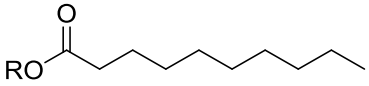
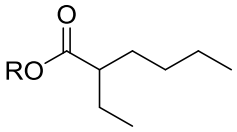
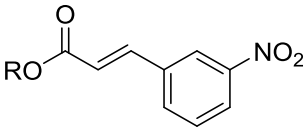
	1818		1448
	4876		349
	5897		14828
	1303		1483
	6420		3637

	548		1137
	3266		4017
	1527		1386
	653		1094
	542		1003
	3261		1980
	3369		799
	548		409
	464		2364
	3703		6677

	9078		1396
	2388		1484
	8259		2289
	2088		6087
	31054		377
	2347		584
	1608		1822

R= CH_2(3-MeO,4-OH)Ph

While there does not appear to be any correlation between the size or functionality of the side chain and the ORAC value, this observation is in agreement with previous studies.[30,36,37] Excitingly, 34 of the synthesized capsinoids exhibited ORAC values above 1,000 µmol Trolox per gram and 8 capsinoids exhibited values over 5,000 µmol Trolox per gram. The capsiate exhibiting the highest activity was the pivalate derivative (31,054 µmol Trolox per gram) and the capsiate with the lowest activity was the acetate derivate (349 µmol Trolox per gram). This study has provided a good foundation for investigation into the biological activity of capsiate analogues. Further

SAR work is needed to determine which functionalities will provide the best results. We have begun to collaborate with Dr. Jonathan Bernstein at the *University of Cincinnati School of Medicine*. These analogues are being investigated as part of a study on asthma and asthma treatments.

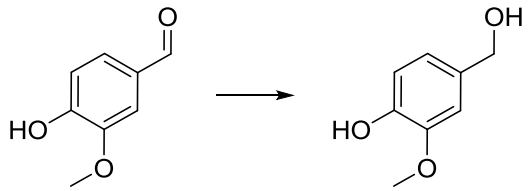
2.6 Summary and Conclusions

Forty-four different analogues of capsiate have been prepared in yields ranging from 3 to 76%. Additionally, these esters were tested via the ORAC assay to determine their anti-oxidant activity *in vitro* which ranged from 349 to 31,054 μmol Trolox per gram. These results are a harbinger of a more extensive investigation into the biological activity of these compounds.

2.7 Experimental Data and Procedures

General Procedures: All reactions were run under an argon atmosphere and monitored by TLC analysis. Unless otherwise noted all extractive workups consisted of the following procedure; the crude reaction mixture was diluted with diethyl ether and deionized water. The aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed twice with deionized water, once with brine and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the organic layers concentrated on a rotary evaporator. The crude residue was placed under vacuum at 1 torr until a constant weight was observed. The residue was subsequently purified by flash column chromatography using silica gel 60 (230-400 mesh ASTM) and distilled reagent grade hexanes and ethyl acetate. Melting points were

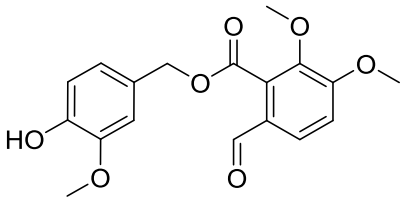
recorded on a DigiMelt MPA 160. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVB-400 MHz spectrometer with a ^{13}C operating frequency of 100 MHz. ^{1}H NMR spectra were obtained in $CDCl_3$ and normalized using trace $CHCl_3$ present (δ 7.27 ppm) as an internal reference. ^{13}C NMR spectra were obtained in $CDCl_3$ using trace $CHCl_3$ present (δ 77.23 ppm) as an internal reference. IR spectra were obtained on an Avatar 360FT-IR and are reported in frequency of absorption (cm^{-1}). Only selected IR frequencies are reported. High resolution MS were obtained on a Waters LCT Premier.



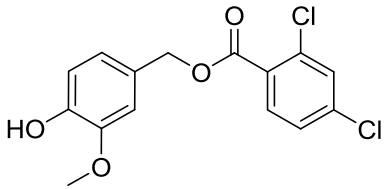
Reduction of Vanillin to Vanillyl alcohol: Vanillin (24.85 g, 163 mmol) was dissolved in 75 mL MeOH. 50 mL of 1M NaOH in MeOH was added to the solution. The mixture was cooled to 0 °C in an ice bath. $NaBH_4$ (6.19 g, 164 mmol) was added portion-wise to the flask. Once the vigorous fizzing subsided, the solution was stirred and warmed to room temperature over 1 hour. The solution was cooled back to 0 °C and acidified with conc. HCl until a white precipitate formed. The crystals were collected by vacuum filtration and the filter cake washed with deionized water until the washings were neutral to litmus. The product was dried under reduced pressure yielding vanillyl alcohol (18.09 g, 117 mmol, 72%).

General Esterification Procedure: Vanillyl alcohol (2.09 g, 13 mmol) was dissolved in 20 mL dry THF. *o*-Toluic acid (2.25 g, 16 mmol) was added to the solution. The solution was cooled to 0 °C. PPh_3 (4.32 g, 16 mmol) and diethyl azodicarboxylate (2.60 mL, 16 mmol) were subsequently added to the flask. The reaction was stirred at 0

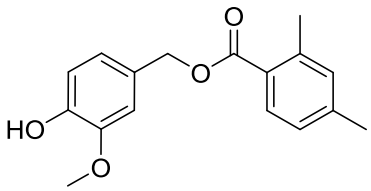
°C for 5 minutes then allowed to warm to room temperature over 1 hour. The THF was removed under reduced pressure on a rotary evaporator. The crude mixture was then taken up in 50 mL diethyl ether. This was then filtered through a pad of Celite to remove any solids. The filtrate was then concentrated and the mixture purified by column chromatography (hexanes/ethyl acetate, 4:1). This yielded 4-hydroxy-3-methoxybenzyl 2-methylbenzoate (882 mg, 3.2 mmol, 24 %) as a colorless viscous oil. [R_f = 0.58, 4:1 hexanes/ethyl acetate].



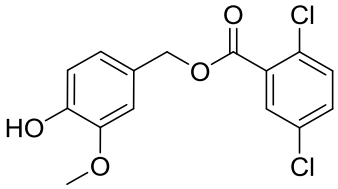
Preparation of 4-hydroxy-3-methoxybenzyl 6-formyl-2,3-dimethoxybenzoate: Yield 14% [R_f = 0.45, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.92 (s, 3H), 3.97 (s, 3H), 4.10 (s, 3H), 6.49 (s, 2H), 7.23 (m, 4H), 7.42 (m, 1H), 9.83 (s, 1H), 9.85 (s, 1H)



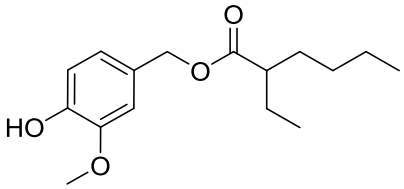
Preparation of 4-hydroxy-3-methoxybenzyl 2,4-dichlorobenzoate: Yield 11%, [R_f = 0.52, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.98 (s, 3H), 5.29 (s, 2H), 7.05 (d J= 12Hz, 1H), 7.44-7.46 (m, 3H), 7.48 (s, 1H), 7.80 (d J= 8Hz, 1H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 56.4, 68.0, 109.0, 114.6, 122.5, 126.8, 127.4, 127.9, 131.2, 131.7, 132.8, 133.7, 136.2, 139.7, 169.4.



Preparation of 4-hydroxy-3-methoxybenzyl 2,4-dimethylbenzoate: Yield 29%; [R_f = 0.55, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 2.38 (s, 3H), 2.64 (s, 3H), 3.91 (s, 3H), 5.25 (s, 2H), 6.97-7.05 (m, 3H), 7.43-7.45 (m, 1H), 7.85 (d J= 8Hz, 1H), 7.99 (d J= 8Hz, 1H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 21.7, 22.3, 56.2, 66.7, 108.9, 111.4, 114.5, 122.2, 126.8, 131.1, 132.0, 132.9, 141.7, 143.8, 145.9, 146.7, 169.9.

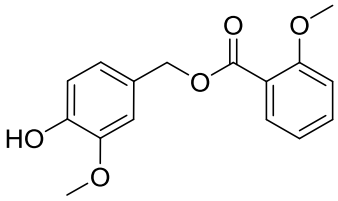


Preparation of 4-hydroxy-3-methoxybenzyl 2,5-dichlorobenzoate: Yield 20%; [R_f = 0.53, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.92 (s, 3H), 5.30 (s, 2H), 6.98-7.00 (m, 3H), 7.38-7.40 (m, 2H), 7.80 (s, 1H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 56.2, 68.2, 111.7, 114.7, 122.6, 127.3, 129.8, 131.5, 132.5, 132.8, 132.9, 133.0, 133.3, 133.7, 169.1.

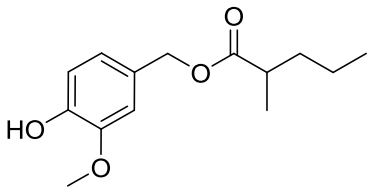


Preparation of 4-hydroxy-3-methoxybenzyl 2-ethylhexanoate: Yield 76%; [R_f = 0.62, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.92-0.96 (m, 6H),

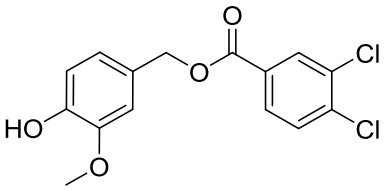
1.30-1.33 (m, 8H), 2.28 (pentet, 1H), 3.90 (s, 3H), 5.04 (s, 2H), 6.88-6.70 (m, 3H), 9.83 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ



Preparation of 4-hydroxy-3-methoxybenzyl 2-methoxybenzoate: Yield 15%; [R_f = 0.57, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.90 (s, 3H), 4.10 (s, 3H), 5.26 (s, 2H), 6.96-7.00 (m, 3H), 7.08 (d J= 8Hz, 1H), 7.16 (t, 1H), 7.59 (t, 1H), 8.20 (d J= 12Hz, 1H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 56.2, 56.9, 66.9, 111.5, 111.8, 112.2, 114.5, 117.8, 120.3, 122.1, 122.5, 131.9, 133.8, 134.1, 135.3, 165.5.

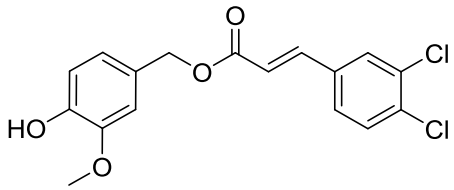


Preparation of 4-hydroxy-3-methoxybenzyl 2-methylpentanoate: Yield 10%; [R_f = 0.68, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.93 (t, 3H), 1.18 (d J= 8Hz, 3H), 1.38 (m, 4H), 2.48 (m, 1H), 3.90 (3H), 5.04 (s, 2H), 6.90 (m, 3H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ

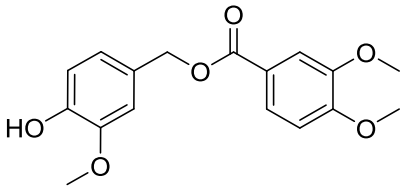


Preparation of 4-hydroxy-3-methoxybenzyl 3,4-dichlorobenzoate: Yield 26%; [R_f = 0.50, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.93 (s, 3H), 5.28 (s, 2H), 6.95-6.98 (m, 3H), 7.57 (d J= 8Hz, 1H), 7.93 (s, 1H), 8.14 (d J= 8Hz, 1H)

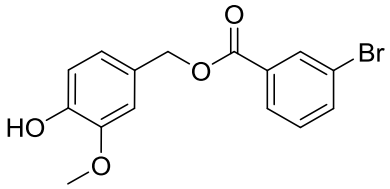
9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 56.2, 67.8, 109.5, 111.7, 114.7, 122.6, 129.0, 129.3, 129.4, 130.9, 131.8, 132.0, 132.3, 133.4, 169.9.



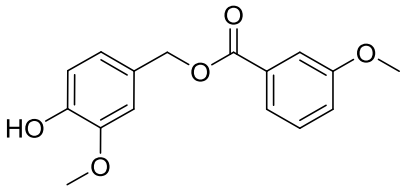
Preparation of 4-hydroxy-3-methoxybenzyl 3,4-dichlorocinnamate: Yield 31%; [R_f = 0.49, 4:1 hexanes/ethylacetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.93 (s, 3H), 5.19 (s, 2H), 6.43 (d J= 12Hz, 1H), 6.92-6.96 (m, 3H), 7.26 (d J= 8Hz, 1H), 7.44 (s, 1H), 7.54 (d J= 8Hz, 1H), 8.08 (d J= 12Hz, 1H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 56.2, 67.1, 111.6, 114.6, 121.3, 122.4, 127.8, 127.9, 128.6, 130.2, 131.4, 136.2, 136.8 139.9, 146.1, 146.8, 166.4,.



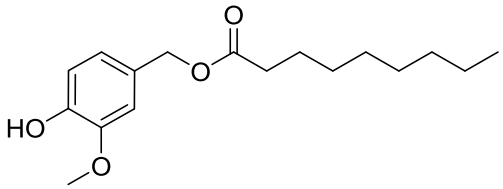
Preparation of 4-hydroxy-3-methoxybenzyl 3,4-dimethoxybenzoate: Yield 36%; [R_f = 0.52, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.91 (s, 3H), 3.92 (s, 3H), 3.95 (s, 3H), 5.26 (s, 2H), 6.91-6.95 (m, 3H), 7.58-7.60 (m, 2H), 7.78 (d J= 4Hz, 1H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 56.2, 56.2 [Note: overlapping signals], 56.3, 67.0, 110.4, 110.5, 111.5, 112.2, 112.5, 114.6, 122.2, 123.9, 124.7, 148.8, 153.2, 153.7, 166.6.



Preparation of 4-hydroxy-3-methoxybenzyl 3-bromobenzoate: Yield 40%; [R_f = 0.53, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.93 (s, 3H), 5.28 (s, 2H), 6.94-6.98 (m, 3H), 7.44 (t, 1H), 7.69 (d J= 8Hz, 1H), 7.99 (d J= 8Hz, 1H), 8.18 (s, 1H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 56.2, 67.6, 111.7, 114.6, 122.5, 122.8, 128.5, 129.0, 130.1, 131.3, 132.8, 133.4, 136.2, 137.0, 169.9

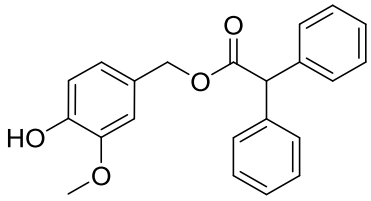


Preparation of 4-hydroxy-3-methoxybenzyl 3-methoxybenzoate: Yield 41%; [R_f = 0.52, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.85 (s, 3H), 3.92 (s, 3H), 5.28 (s, 2H), 6.97-7.00 (m, 3H), 7.19 (dd J= 8Hz, 1H), 7.40 (t, 1H), 7.64 (s, 1H), 7.72 (d J= 8Hz, 1H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 55.7, 56.2, 67.3, 111.5, 114.6, 119.7, 120.7, 122.3, 122.9, 128.1, 129.7, 130.7, 146.0, 146.7, 159.8, 166.6.

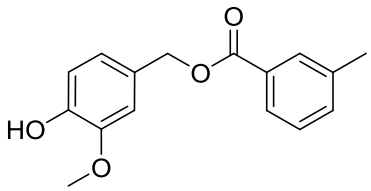


Preparation of 4-hydroxy-3-methoxybenzyl nonanoate: Yield 8%; [R_f = 0.66, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.88 (t, 3H), 1.28-1.40 (m, 12H), 2.34 (t, 2H), 3.91 (s, 3H), 5.03 (s, 2H), 6.88-6.90 (m, 3H), 9.84 (s, 1H); ^{13}C NMR

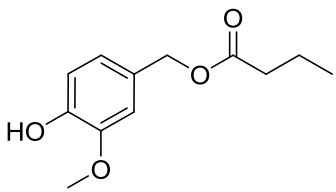
(100 MHz, $CHCl_3$) δ 14.3, 22.9, 24.9, 25.2, 29.3, 29.4, 32.0, 34.6, 56.1, 66.4, 111.4, 114.5, 122.2, 128.2, 145.9, 146.6, 169.9.



Preparation of 4-hydroxy-3-methoxybenzyl 2,2-diphenylacetate: Yield 13%; [R_f = 0.48, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 2.06 (s, 1H), 3.97 (s, 3H), 5.12 (s, 2H), 6.84-6.88 (m, 3H), 7.28-7.32 (m, 10 H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 57.1, 67.0, 111.1, 114.6, 122.0, 127.3, 127.7, 128.9, 138.1, 138.7, 169.8.

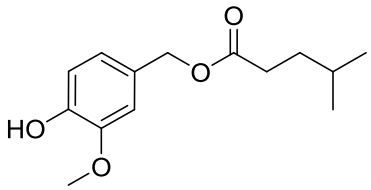


Preparation of 4-hydroxy-3-methoxybenzyl 3-methylbenzoate: Yield 9%; [R_f = 0.52, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 2.40 (s, 3H), 3.92 (s, 3H), 5.28 (s, 2H), 6.98-7.00 (m, 3H), 7.30-7.40 (m, 3H), 7.88 (s, 1H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 21.5, 56.2, 67.1, 111.5, 114.6, 122.3, 127.0, 127.6, 128.5, 129.4, 130.4, 134.0, 138.3, 146.0, 146.6, 167.0.

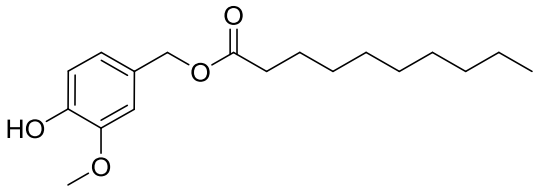


Preparation of 4-hydroxy-3-methoxybenzyl butanoate: Yield 3%; [R_f = 0.65, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.20 (m, 5H), 2.59 (t, 2H), 3.91

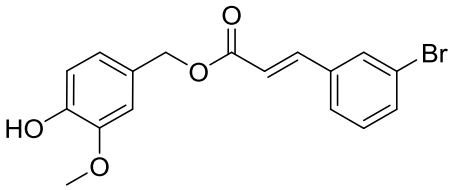
(s, 3H), 5.04 (s, 2H), 6.88-6.92 (m, 3H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 19.0, 33.7, 34.2, 56.1, 66.5, 111.2, 114.5, 122.0, 128.4, 145.8, 147.0, 170.0.



Preparation of 4-hydroxy-3-methoxybenzyl 4-methylpentanoate: Yield 25%; [R_f = 0.64, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.93 (d J= 8Hz, 6H), 1.54-1.58 (m, 3H), 2.35 (d J= 8Hz, 2H), 3.91 (s, 3H), 5.03 (s, 2H), 6.88-6.92 (m, 3H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 22.4, 22.4 [Note: overlapping signals], 27.8, 32.1, 33.7, 56.1, 66.6, 111.3, 114.5, 122.2, 128.2, 145.8, 146.6, 169.8.

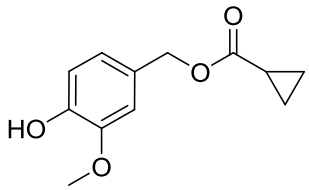


Preparation of 4-hydroxy-3-methoxybenzyl decanoate: Yield 65%, [R_f = 0.58, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.88 (t, 3H), 1.27-1.40 (m, 14H), 2.35 (t, 2H), 3.91 (s, 3H), 5.03 (s, 2H), 6.87-6.90 (m, 3H), 9.84 (s, 1H)

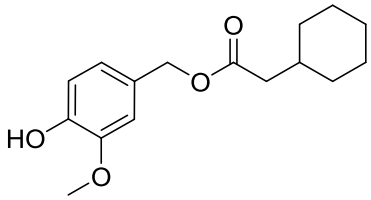


Preparation of 4-hydroxy-3-methoxybenzyl (E)-3-(3-bromophenyl)acrylate: Yield 22%; [R_f = 0.51, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.91 (s, 3H), 5.14 (s, 2H), 6.44 (d J= 16Hz, 1H), 6.92-6.94 (m, 3H), 7.52-7.54 (m, 2H), 7.68-7.70

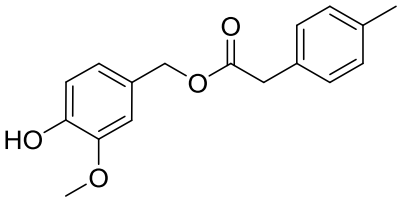
(m, 3H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 56.1, 67.0, 114.6, 119.0, 122.3, 122.4, 123.3, 127.0, 127.1, 130.6, 130.9, 131.2, 133.3, 133.7, 136.4, 145.4, 171.3.



Preparation of 4-hydroxy-3-methoxybenzyl cyclopropanecarboxylate: Yield 9%; [R_f = 0.64, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.88-0.90 (m, 1H), 0.94-0.96 (m, 1H), 1.00-1.02 (m, 1H), 1.07-1.09 (m, 1H), 1.60-1.64 (m, 1H), 3.91 (s, 3H), 5.04 (s, 2H), 6.90-6.92 (m, 3H), 9.85 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 8.7, 9.5, 13.0, 56.1, 66.8, 111.4, 114.5, 122.2, 128.1, 146.0, 146.6, 169.8.

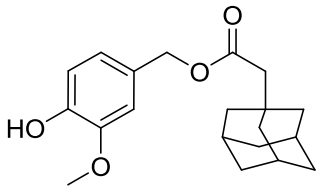


Preparation of 4-hydroxy-3-methoxybenzyl 2-cyclohexylacetate: Yield 22%; [R_f = 0.63, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.98-1.03 (m, 2H), 1.25-1.29 (m, 3H), 1.71-1.75 (m, 5H), 2.23 (d J= 4Hz, 2H), 3.90 (s, 3H), 5.03 (s, 2H), 6.87-6.91 (m, 3H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 26.2, 26.3, 33.2, 34.9, 56.1, 66.4, 111.4, 114.6, 122.2, 128.2, 145.8, 146.6, 169.9.

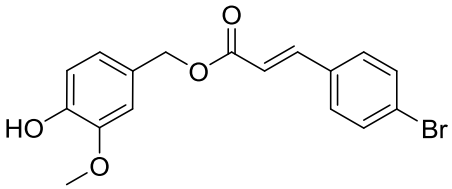


Preparation of 4-hydroxy-3-methoxybenzyl 2-(*p*-tolyl)acetate: Yield 60%; [R_f = 0.53, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 2.34 (s, 3H), 3.85 (s,

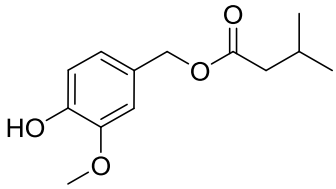
3H), 3.98 (s, 2H), 5.05 (s, 2H), 6.86-6.90 (m, 3H), 7.14 (d J= 8Hz, 2H), 7.18 (d J= 8Hz, 2H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 22.1, 40.7, 52.0, 66.9, 110.0, 111.2, 114.4, 121.9, 129.4, 129.4, 129.4 [Note: Overlapping signals], 129.6, 145.8, 146.6, 169.9.



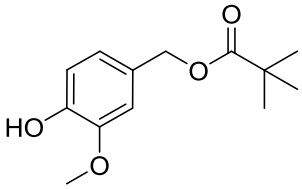
Preparation of 4-hydroxy-3-methoxybenzyl 2-adamantylacetate: Yield 24%; [R_f = 0.60, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.61-1.64 (m, 12H), 1.96-2.00 (m, 3H), 2.11 (s, 2H), 3.90 (s, 3H), 5.03 (s, 2H), 6.89-6.91 (m, 3H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 28.8, 33.1, 36.9, 42.6, 49.2, 56.1, 66.2, 111.3, 114.3, 122.3, 128.3, 145.7, 146.7, 169.9.



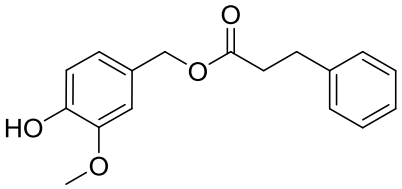
Preparation of 4-hydroxy-3-methoxybenzyl (E)-3-(4-bromophenyl)acrylate: Yield 22%; [R_f = 0.52, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.92, (s, 3H), 5.17 (s, 2H), 6.46 (d J= 16Hz, 1H), 6.91-6.95 (m, 3H), 7.38 (d J= 8Hz, 2H), 7.52 (d J= 8Hz, 2H), 7.64 (d J= 16Hz, 1H), 9.83 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 56.2, 67.0, 111.6, 114.5, 118.9, 122.4, 124.7, 127.9, 129.7, 132.3, 133.4, 143.9, 146.1, 146.7, 166.8.



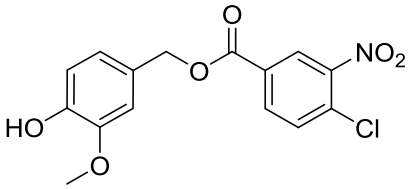
Preparation of 4-hydroxy-3-methoxybenzyl 3-methylbutanoate: Yield 33%; [R_f = 0.61, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.95 (d J= 8Hz, 6H), 1.48-1.54 (m, 1H), 2.24 (d J= 8Hz, 2H), 3.90 (s, 3H), 5.06 (d, 2H), 6.87-6.90 (m, 3H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 22.6, 25.7, 43.7, 56.1, 66.4, 111.4, 114.6, 122.3, 128.2, 146.0, 146.5, 169.9.



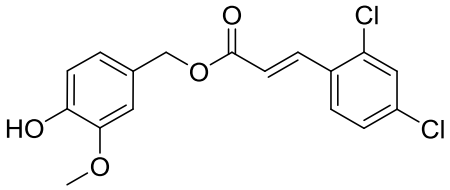
Preparation of 4-hydroxy-3-methoxybenzyl pivalate: Yield 25%; [R_f 0.65, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.22 (s, 9H), 3.90 (s, 3H), 5.03 (s, 2H), 6.87-6.91 (m, 3H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 27.2, 39.0, 56.2, 66.4, 110.9, 114.5, 121.6, 128.6, 145.7, 146.6, 170.0.



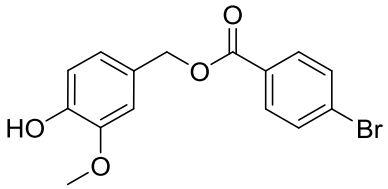
Preparation of 4-hydroxy-3-methoxybenzyl 3-phenylpropanoate: Yield 21%; [R_f = 0.51, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 2.70 (t, 2H), 2.98 (t, 2H), 3.89 (s, 3H), 5.03 (s, 2H), 6.89-6.91 (m, 3H), 7.29-7.35 (m, 5H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 30.8, 35.6, 56.2, 66.8, 111.5, 114.5, 122.2, 126.6, 128.4, 128.7, 128.8, 140.3, 145.8, 146.2, 169.9.



Preparation of 4-hydroxy-3-methoxybenzyl 4-chloro-3-nitrobenzoate: Yield 22%; [R_f = 0.50, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.93 (s, 3H), 5.32 (s, 2H), 6.94-6.98 (m, 3H), 7.64 (d J= 8Hz, 1H), 8.17 (d J=8Hz, 1H), 8.51 (s, 1H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 56.2, 68.4, 111.8, 114.7, 122.8, 126.9, 127.1, 130.5, 131.9, 132.3, 134.0, 146.4, 146.8, 163.8, 169.9.

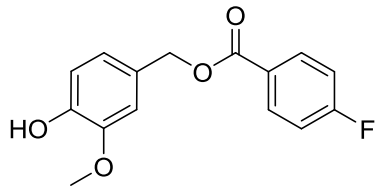


Preparation of 4-hydroxy-3-methoxybenzyl (E)-3-(2,4-dichlorophenyl)acrylate: Yield 8%; [R_f = 0.49, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.93 (s, 3H), 5.19 (s, 2H), 6.45 (d J= 16Hz, 1H), 6.92-6.96 (m, 3H), 7.26 (d J= 8Hz, 1H), 7.44 (s, 1H), 7.54 (d J= 8Hz, 1H), 8.05 (d, J= 16Hz, 1H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 56.2, 67.1, 111.5, 114.6, 121.3, 122.5, 127.7, 128.6, 130.2, 131.4, 135.7, 139.8, 146.1, 146.9, 166.4, 169.9.

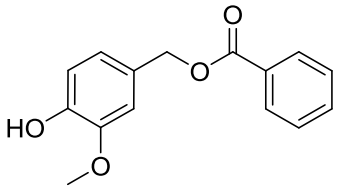


Preparation of 4-hydroxy-3-methoxybenzyl 4-bromobenzoate: Yield 7%; [R_f = 0.55, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.86 (s, 3H), 5.05 (s, 2H), 6.88-6.90 (m, 3H), 7.17 (d J= 8Hz, 2H), 7.47 (d J= 8Hz, 2H), 9.83 (s, 1H);

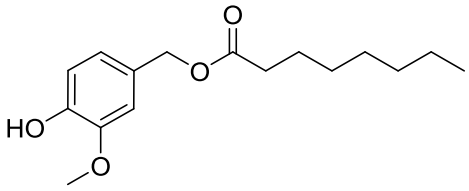
^{13}C NMR (100 MHz, $CHCl_3$) δ 56.1, 67.2, 111.4, 114.5, 121.6, 122.1, 127.7, 131.3, 131.9, 132.5, 145.9, 146.6, 169.9.



Preparation of 4-hydroxy-3-methoxybenzyl 4-fluorobenzoate: Yield 15%, [R_f = 0.55, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.97 (s, 3H), 5.27 (s, 2H), 6.96 (m, 3H), 7.16 (m, 4H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 56.3, 67.3, 111.6, 114.6, 115.8, 116.0, 122.4, 127.8, 132.5, 133.1, 146.1, 146.6, 169.9.

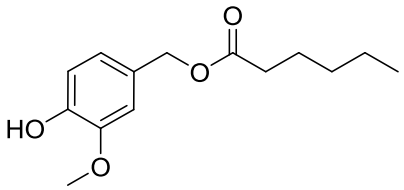


Preparation of 4-hydroxy-3-methoxybenzyl benzoate: Yield 17%; [R_f = 0.54, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.92 (s, 3H), 5.29 (s, 2H), 6.98-7.00 (m, 3H), 7.44-7.57 (m, 4H), 8.07 (d J= 8Hz, 1H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 56.2, 67.2, 111.4, 114.6, 122.2, 128.1, 128.6, 129.9, 130.4, 133.2, 133.9, 146.0, 146.7, 170.0.

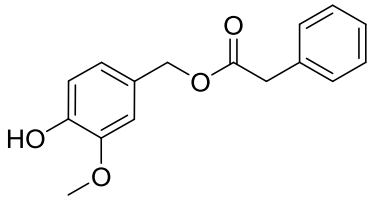


Preparation of 4-hydroxy-3-methoxybenzyl octanoate: Yield 24%; [R_f = 0.63, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.88 (t, 3H), 1.29-1.40 (m, 10H), 2.36 (t, 2H0, 3.91 (s, 3H), 5.04 (s, 2H), 6.88-6.90 (m, 3H), 9.84 (s, 1H); ^{13}C NMR

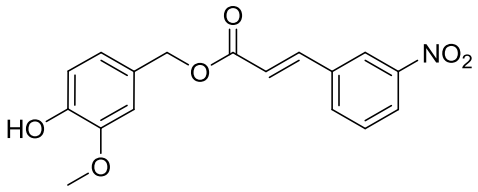
(100 MHz, $CHCl_3$) δ 14.3, 22.8, 25.2, 29.1, 29.3, 31.8, 34.6, 56.1, 66.5, 111.4, 114.5, 122.2, 128.2, 145.9, 146.8, 170.0.



Preparation of 4-hydroxy-3-methoxybenzyl hexanoate: Yield 30%; [R_f = 0.62, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.91 (t, 3H), 1.29-1.33 (m, 8H), 2.36 (t, 2H), 3.91 (s, 3H), 5.03 (s, 2H), 6.88-6.90 (m, 3H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 14.1, 22.5, 24.6, 31.4, 34.0, 34.6, 56.1, 66.7, 111.4, 114.5, 122.2, 128.2, 145.9, 146.7, 170.0.

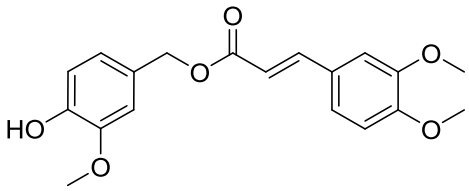


Preparation of 4-hydroxy-3-methoxybenzyl 2-phenylacetate: Yield 20%; [R_f = 0.56, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.83 (s, 3H), 5.06 (s, 2H), 6.86-6.90 (m, 3H), 7.28-7.34 (m, 5H), 9.82 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 41.2, 56.1, 67.0, 111.2, 114.3, 122.2, 127.4, 127.5, 128.8, 129.6, 133.5, 146.0, 146.6, 169.8.

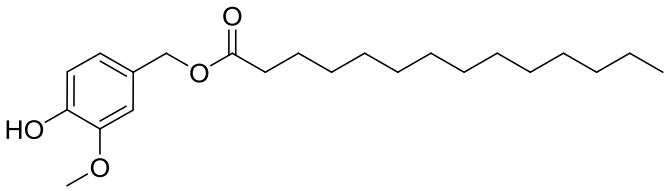


Preparation of 4-hydroxy-3-methoxybenzyl (E)-3-(3-nitrophenyl)acrylate: Yield 66%; [R_f = 0.50, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.98 (s,

3H), 5.19 (s, 2H), 6.94-6.98 (m, 3H), 7.62 (s, 1H), 7.84 (d J= 12Hz, 1H), 8.25 (t, 1H), 8.39 (d, J= 12Hz, 1H), 9.84 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 56.2, 68.6, 111.6, 114.6, 120.7, 122.5, 123.0, 124.8, 125.1, 130.2, 134.0, 140.3, 143.9, 146.4, 146.8, 150.0, 169.9.



Preparation of 4-hydroxy-3-methoxybenzyl (E)-3-(3,4-dimethoxyphenyl)acrylate: Yield 44%; [R_f = 0.51, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 3.91 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 5.14 (s, 2H), 6.33 (d J=16Hz, 1H), 6.86-6.90 (m, 3H), 7.06-7.18 (m, 3H), 7.71 (d J= 16Hz, 1H), 9.85 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 56.1, 56.2, 56.3, 66.1, 107.4, 110.2, 111.4, 115.2, 121.3, 123.1, 131.5, 134.9, 135.9, 136.8, 145.2, 146.6, 149.4, 156.6, 169.9.



Preparation of 4-hydroxy-3-methoxybenzyl tetradecanoate: Yield 19%; [R_f = 0.62, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.89 (t, 3H), 1.26-1.40 (m, 22H), 2.33 (t, 2H), 3.91 (s, 3H), 5.03 (s, 2H), 6.87-6.90 (m, 3H), 9.81 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 14.3, 22.9, 24.9, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 29.9, 29.9 [Note: Overlapping signals], 32.1, 34.6, 56.1, 66.6, 111.4, 114.5, 122.2, 128.2, 145.9, 146.6, 169.9.

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CHAPTER 3

PROGRESS TOWARDS THE TOTAL SYNTHESIS OF SALVIMULTINE, (+)-ROSMARIDIPHENOL, (+)-PEROVSKONE B and HYDRANGENONE

3.1: Introduction

Over the last forty years, a number of structurally and biologically interesting compounds have been isolated from several members of the genus *Salvia*. This genus is the largest in the Lamiaceae family with nearly 1000 species known worldwide. The vast majority are found in Central and South America while a significant number have been discovered in the Mediterranean and Central Asia.[1] A large number of the compounds isolated are diterpenoids, compounds containing 20 carbon atoms, possessing the abietane framework. The common structural element of the abietanes is the 6-6-6 tricyclic core (Figure 3.1). It has been hypothesized that the icetexanes, containing a 6-7-6 core, are biosynthetically related to the abietanes through a skeletal rearrangement.

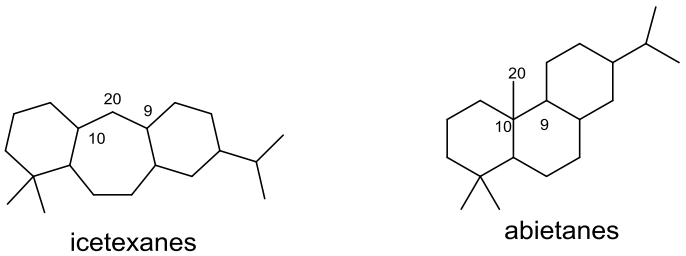
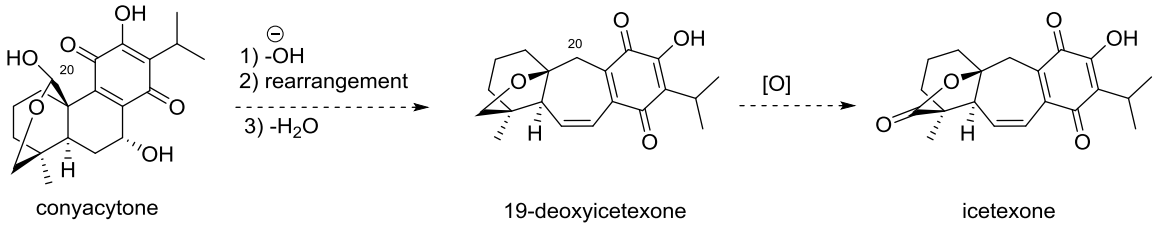


Figure 3.1

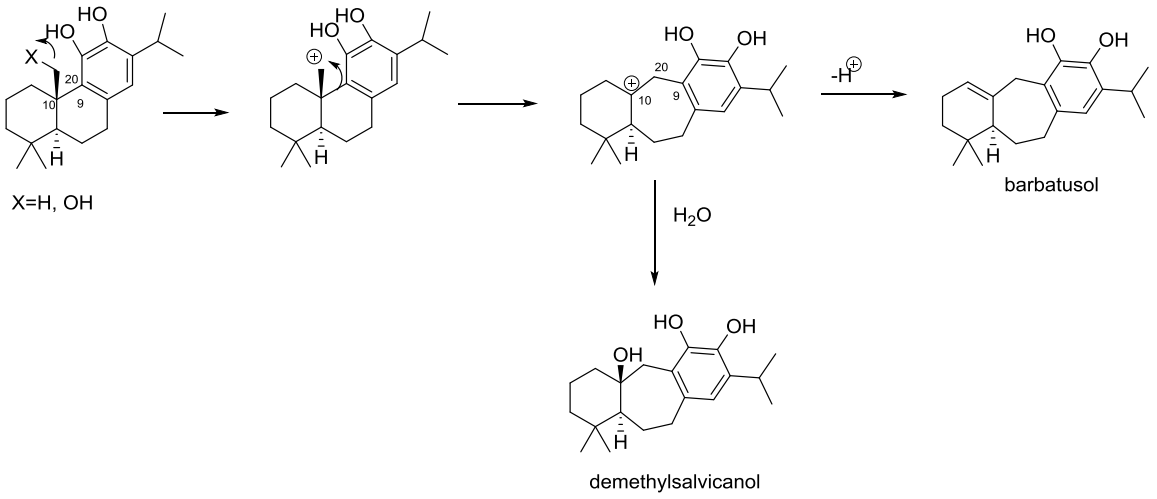
The first icetexane isolated was icetexone in 1976 from *Salvia ballotaeflorae*.[2] In addition to icetexone, conyacytone was also isolated. Conyacytone is an abietane diterpenoid and Taira suggested that icetexone could be a biosynthetic derivative of conyacytone. They posited that icetexone could result from loss of the C-20 hydroxide, ring expansion and a dehydration to create the cycloheptadiene D-ring (Scheme 3.1). This pathway would yield 19-deoxyicetexone and further oxidation of the tetrahydrofuran ring would result in icetexone.



conyacytone 19-deoxyicetexone icetexone

Scheme 3.1

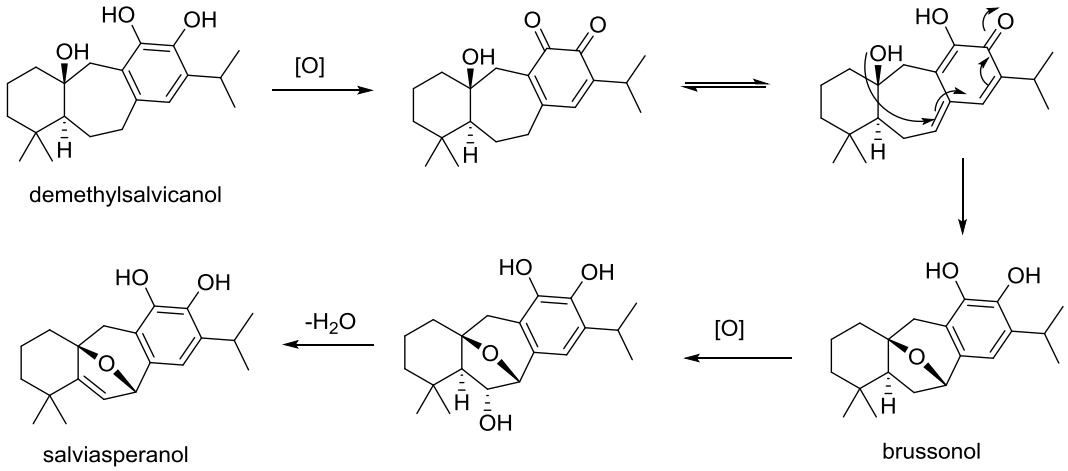
Since the icetexanes are synthetically named as 9(10→20)-*abeo*-abietane, this suggests that they arise as a rearrangement from the corresponding abietane. It has been posited that the rearrangement to the barbatusol family of icetexanes occurs from an abietane precursor via the mechanism shown in (Scheme 3.2). The loss of a hydride or hydroxide yields a primary carbocation. A subsequent ring expansion would result in a tertiary carbocation having the icetexane skeleton. Elimination of an α proton would yield barbatusol, while addition of water to the carbocation produces demethylsalvicanol which possesses a hydroxyl group at C-10.[3]



Scheme 3.2

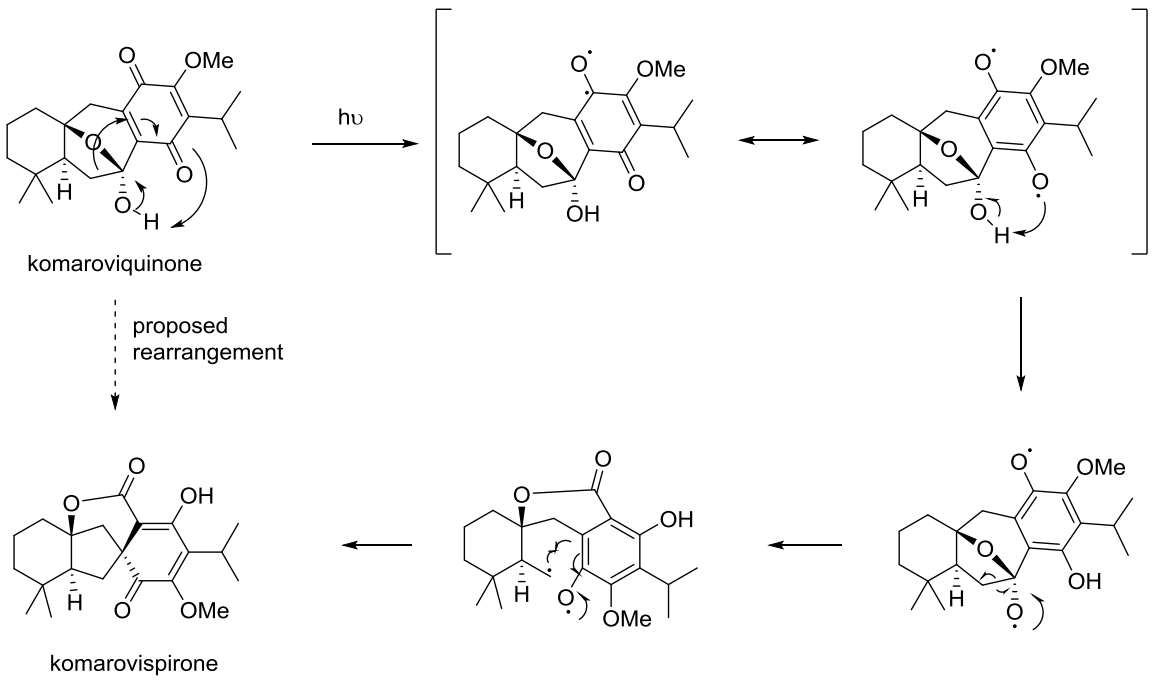
Interestingly, only the *trans* ring fusion has been observed in dimethylsalvicanol.[4] This suggests that the transformation may be enzymatically catalyzed because addition of water to the β-face of the carbocation would be sterically unfavorable.[4]

Demethylsalvicanol can undergo further oxidation to the *ortho*-quinone; which is then susceptible to nucleophilic attack from the C-10 hydroxyl in 1,6-fashion to yield brussonol. Subsequent oxidation and elimination results in salviasperanol (Scheme 3.3).[3]



Scheme 3.3

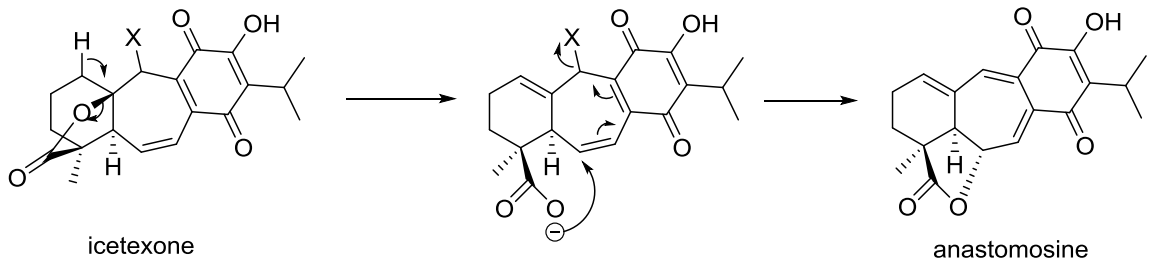
Komarovispirone has been shown to result from the rearrangement of komaroviquinone. This rearrangement was hypothesized to occur via a concerted mechanism.[5] However, Majetich and Yu disputed the proposed mechanism. When komaroviquinone was treated with acidic or basic conditions, no rearrangement to komarovispirone occurred[6] which suggested that the rearrangement proceeded via a different pathway. Indeed, when komaroviquinone was irradiated with 254 nm light the rearrangement rapidly occurred (Scheme 3.4). It has been postulated that komarovispirone is simply an artifact of the isolation procedure of komaroviquinone. Because the isomerization proceeds so quickly, if komarovispirone were produced naturally it should have been isolated as a major component. Because this compound was not observed, that lends support to the artifact hypothesis.[6]



Scheme 3.4

Anastomosine has also been linked biosynthetically to icetexone. Base-catalyzed fragmentation of the lactone would yield the intermediate carboxylate. This compound

can then undergo displacement of the leaving group at C-20 to result in anastomosine (Scheme 3.5).[7]



icetexone anastomosine

Scheme 3.5

3.2 Isolation of Icetexanes

In the last forty years, since the initial discovery of icetexone, several compounds containing the 6-7-6 core have been isolated. While no formal classification system exists for the icetexanes, Simmons and Sarpong suggested that they may be classified by the extent of oxidation to the core.[8] The major classes of icetexanes identified are compounds related to pisiferin, barbatusol, taxamairin, coulterone, and icetexone.

The unifying feature of the pisiferin class is a hydroxyl at C-12 in the C-ring (Figure 3.2). Pisiferin was the first compound isolated in this class in 1980 from the leaves of *Chamaecyparis pisifera*.[9] Interestingly, the structure of pisiferin was incorrectly assigned as having a 7-6-6 core but was subsequently revised to the typical 6-7-6 core following the isolation of isopisiferin from the seeds of *C. pisifera* in 1984.[10] In addition to isopisiferin, pisiferanol, 12-deoxypisiferanol and 1β-hydroxyisopisiferin were also isolated from the seeds of *C. pisifera*.[11] Pisiferdiol was isolated independently by two different groups and the structure determined by X-ray crystallography.[11,12] In 1999, both 12-*O*-methylpisiferanol and 1β-hydroxypisiferanol were isolated from *C.*

formosensis.[13] Interestingly, these two compounds were the first to be isolated from something other than *C. pisifera*. Sawaradienone, the only pisiferin oxidized at the B,C ring fusion, was isolated from the leaves of *C. pisifera* in 2001.[14]

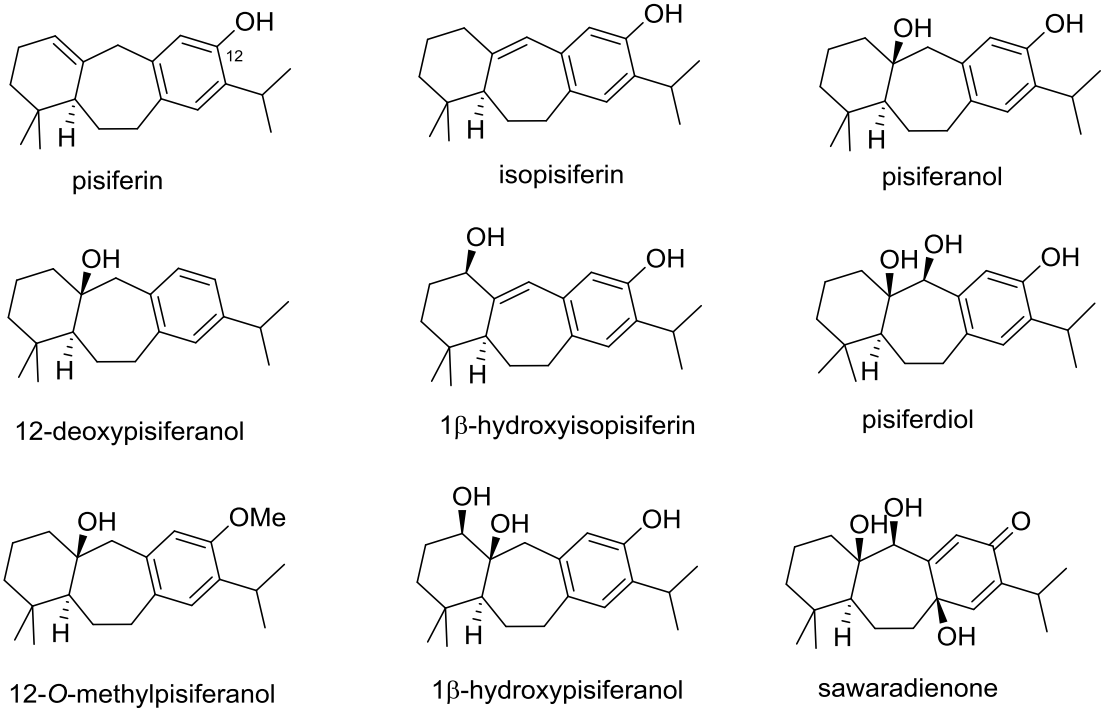


Figure 3.2

A related class to the pisiferins is the barbatusols. In addition to the C-12 hydroxyl group the barbatusols possess an additional hydroxyl at C-11 giving the C-ring a catechol nature (Figure 3.3). The parent compound, barbatusol, was first isolated from the bark and heartwood of *Coleus barbatus* in 1983.[15] A related compound, rosmaridiphenol, was first isolated in 1984 from the leaves of *Rosmarinus officinalis*.[16] However, like pisiferin, the structure of rosmaridiphenol was incorrectly assigned. In 2012 it was determined that the carbonyl in rosmaridiphenol was at C-1 rather than C-20 as had been initially postulated.[17] The first total synthesis of rosmaridiphenol is presented in this chapter. Salvicanol was isolated from the roots of both *Salvia*

canariensis and *S. mellifera*.[4,18] Two closely related compounds, demethylsalvicanol and isosalvicanol, were isolated from *C. barbatus* and *Lepechinia meyeni* respectively.[19,20] Extraction of the roots of *Salvia aspera* yielded salviasperanol and 5,6-dihydro-6α-hydroxysalviasperanol.[21] Brussonol was named for the species from which it was first isolated in 1995, *Salvia broussonetii*.[3] Przewalskins C and D were isolated in 2005 from *S. przewalskii*.[22] Finally in 2009, the *ortho*-quinone of brussonol, przewalskin E, was isolated from *S. przewalskii*.[23]

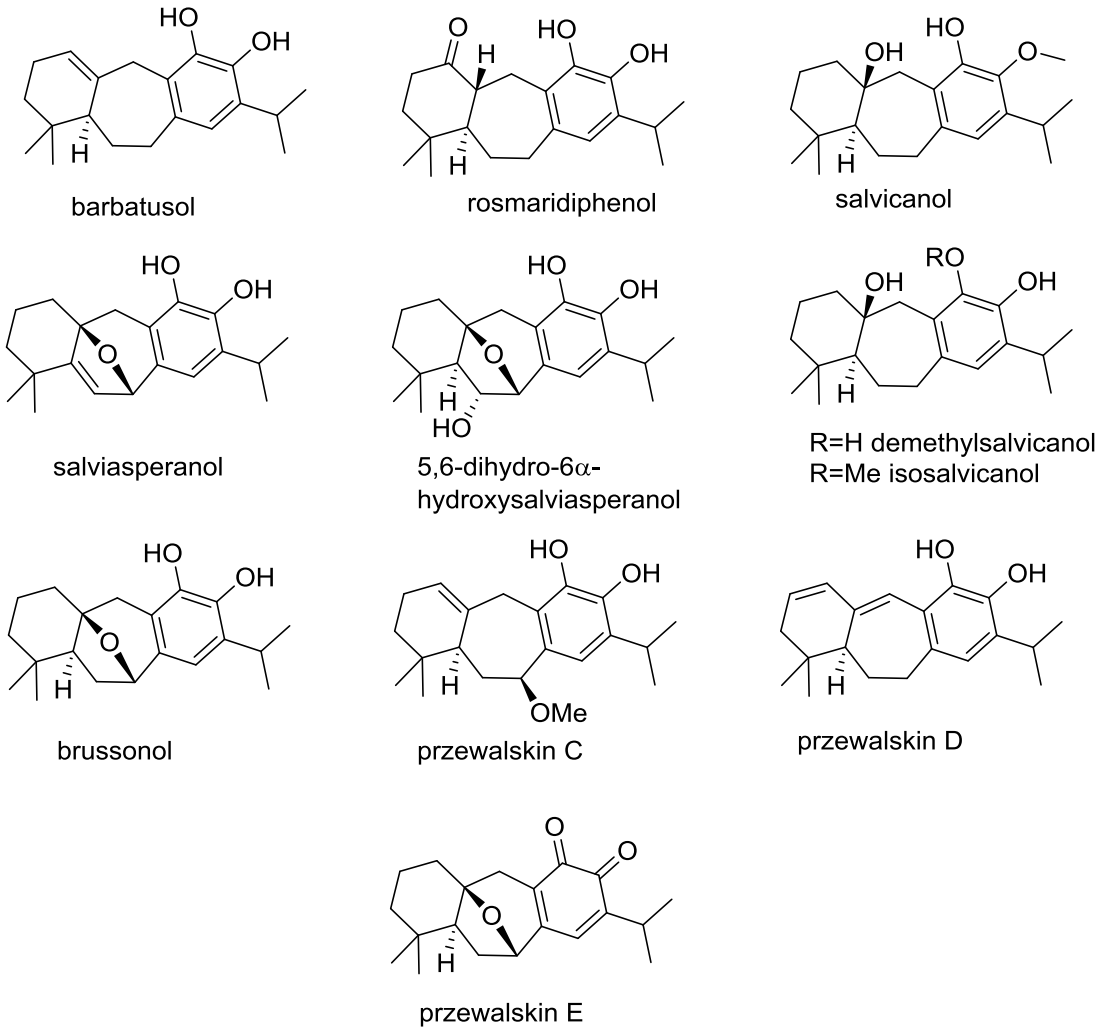


Figure 3.3

The taximairins are related to the barbatusols in that they are oxygenated at C-11 and C-12 and they are oxygenated at C-3 as well (Figure 3.4). The first taximairins to be isolated in 1987 were taxamairins A and B from *Taxus mairei*.[24] Eleven years later, taxamairins D-H were isolated from the twigs of *T. mairei*.[25] Finally, in 2005 two yet to be named taximairins were isolated from callus cell cultures from *T. cuspidate*.[26]

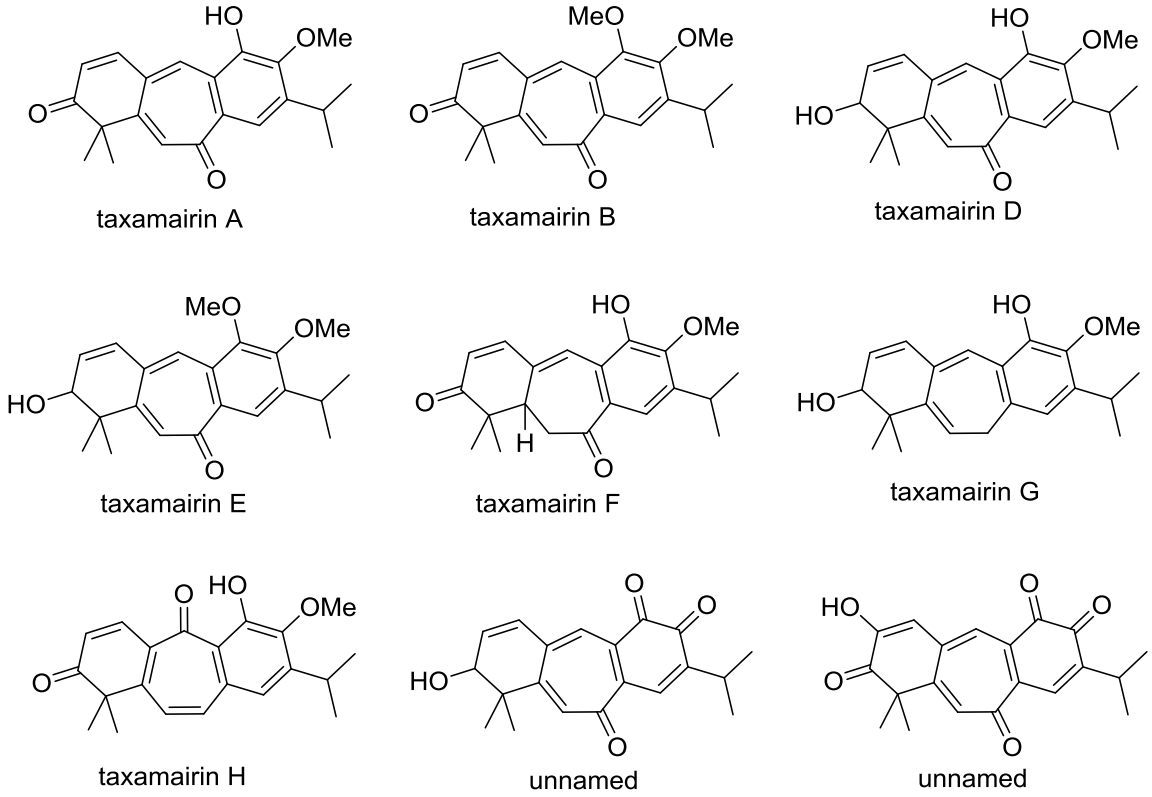


Figure 3.4

The coulterones possess the oxygenations of C-11 and C-12 like barbatusol but also contain an oxygen at C-14 (Figure 3.5). The namesake, coulterone, was first isolated in 1994 from *Salvia coulteri* and was later found in the roots of *Hyptis platanifolia* in 2005.[27,28] Cyclocoulterone and komaroviquinone were isolated in 2003 from *Dracocephalum komarovi*.[29] Abrotanone was isolated from *Perovskia abrotanoides* and

the structure was initially incorrectly determined.[30] Following chemical synthesis the stereochemistry at C-5 was reversed and determined to be the correct structure.[31]

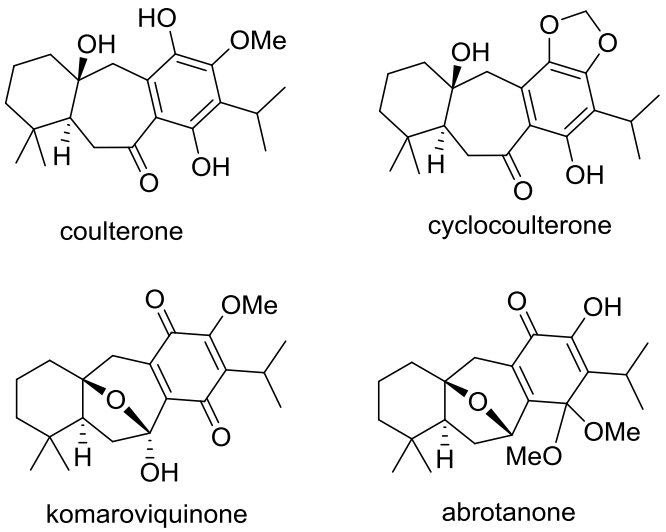


Figure 3.5

The final set of icetexanes, the icetexones, are oxygenated at C-19 (Figure 3.6). Icetexone and romulogarzone were both found in *Salvia ballotaeflora*.[32] Extraction of the aerial parts of *Saliva anastomosans* resulted in the isolation of anastomosine.[7] Two yet to be named icetexanes were isolated from *Salvia candicans* in 1995. However, the *bis*-acetlyated compound is not a natural product. This was obtained following reductive acetylation. It can be inferred, however, that the metabolite precursor is either the *para*-quinol or the *para*-quinone.[33] 19-Deoxyicetexone, 19-deoxyisoicetexone and 7,20-dihydroanastomosine were extracted from *S. ballotaeflora* twenty-one years after the initial isolation of icetexone.[34] 19(*R*)-Acetoxy-19-deoxoicetexone was isolated from *Salvia pubescens* in 1997.[35]

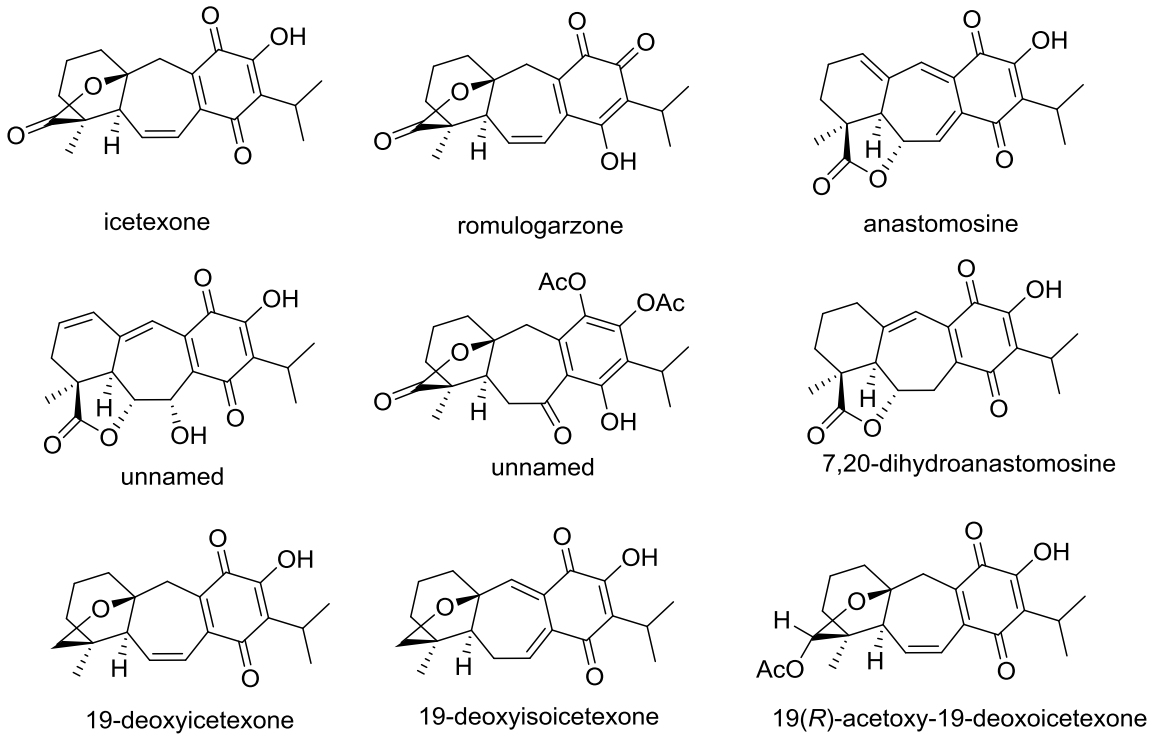


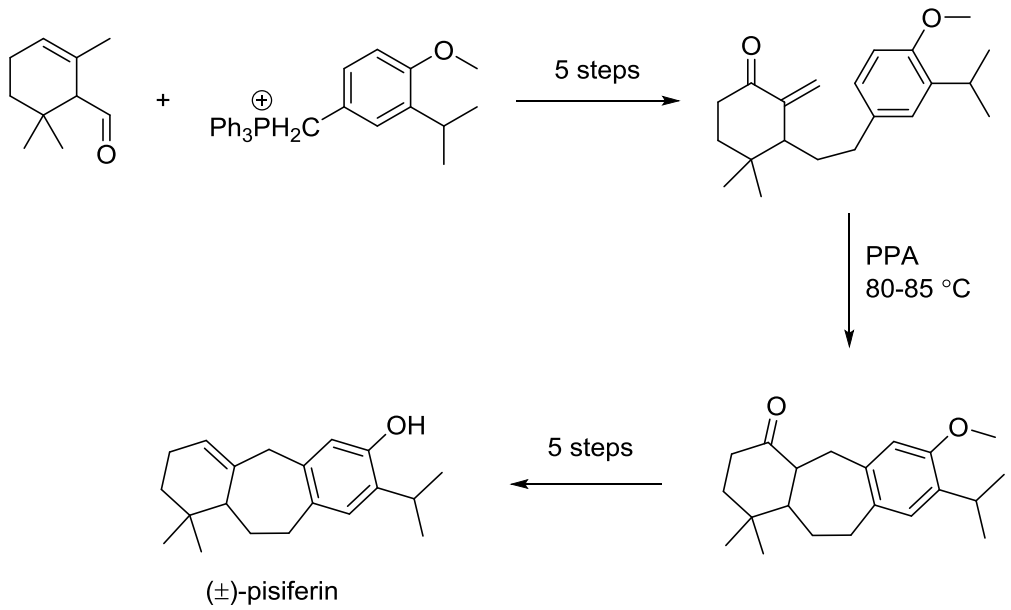
Figure 3.6

3.3 Synthetic Approaches to Icetexanes

Ever since icetexone was isolated in 1976, the icetexanes have been an attractive target for total synthesis.[8] Clearly, the impetus for synthesizing these molecules lies in their complex structural features and their significant biological activity. The challenge lies in creating methods to introduce the various oxygen functionalities and the specific stereochemistries of the icetexanes. In particular, creation of the seven-membered B-ring requires careful planning and execution. Several different strategies have been developed for the creation of the B-ring and will be discussed in this section.

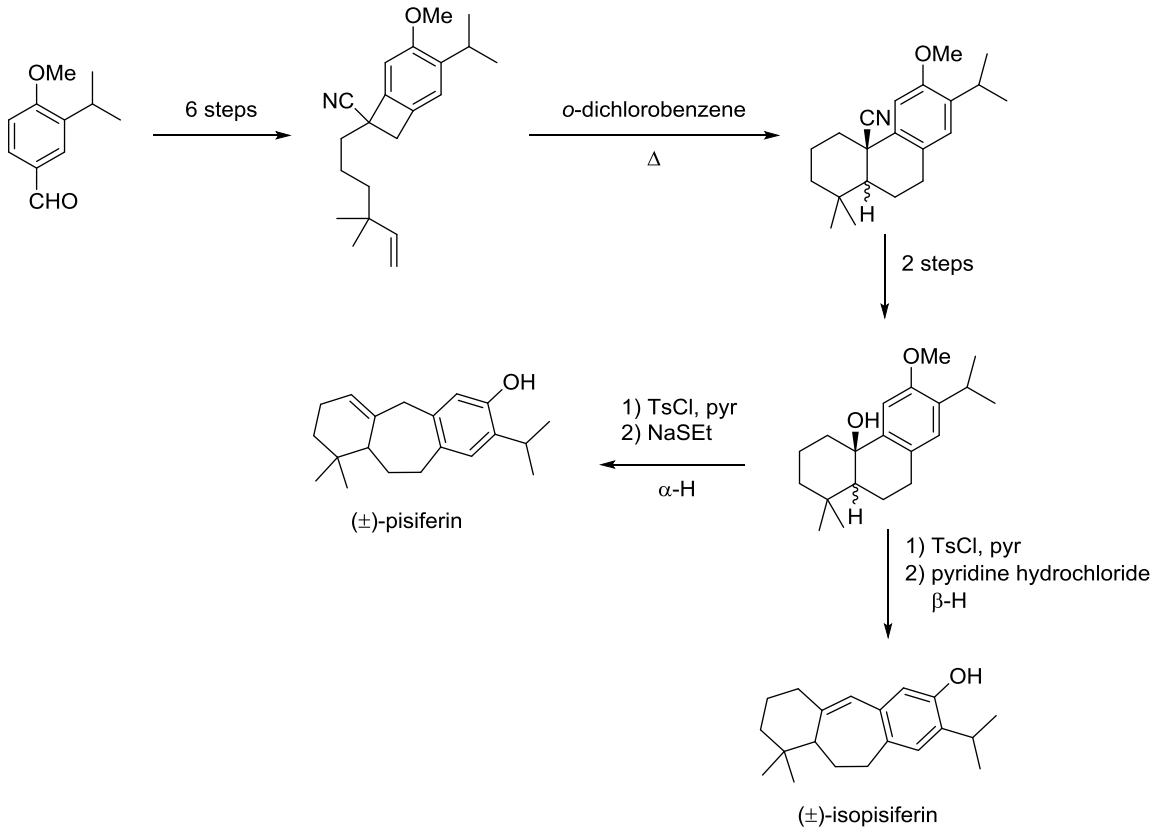
The first class of icetexanes to be synthesized was the pisiferins. In 1986, Matsumoto combined racemic α-cyclocitral and an aryl phosphonium salt under Wittig conditions to prepare the A and C rings of (±)-pisiferin. Heating of the exocyclic enone

with polyphosphoric acid afforded the cyclized Michael addition product in reasonable yield. Five additional steps afforded (±)-pisiferin (Scheme 3.6).[36]



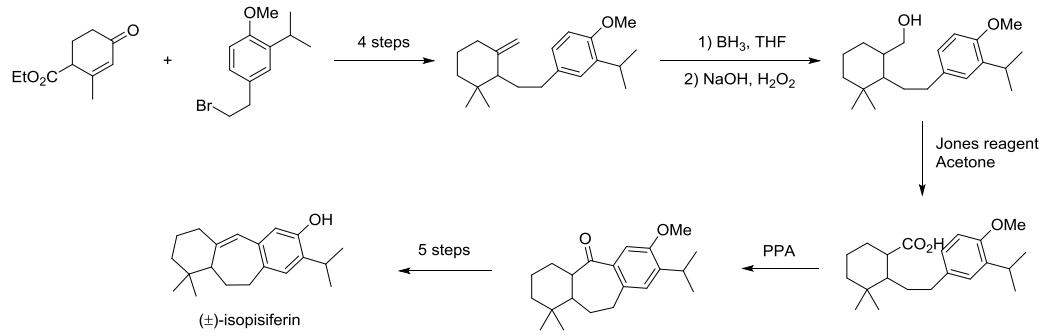
Scheme 3.6

Honda and co-workers published the first total synthesis of (±)-isopisiferin and the second synthesis of (±)-pisiferin in 1990.[37] They first prepared the 6-6-6 abietane framework through a 4π-electrocyclic ring opening/intramolecular Diels–Alder cascade. Upon conversion of the nitrile to the primary alcohol, a biomimetic ring expansion resulted in the 6-7-6 icetexane framework of both (±)-isopisiferin and (±)-pisiferin when the C-5 hydrogen was on the β- or α-face respectively (Scheme 3.7).



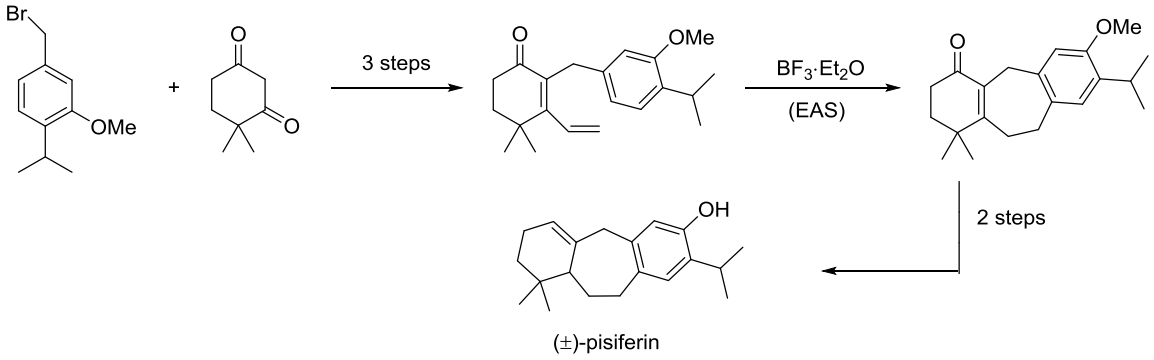
Scheme 3.7

Ghatak and co-workers prepared (±)-isopisiferin in 1990.[38] Like Matsumoto, they prepared the linked A and C rings with the exocyclic olefin. Hydroboration–oxidation, followed by Jones oxidation, resulted in the carboxylic acid. Heating the carboxylic acid with polyphosphoric acid achieved the cyclization resulting in the icetexane skeleton with a ketone at C-20. A further five steps resulted in (±)-isopisiferin (Scheme 3.8).



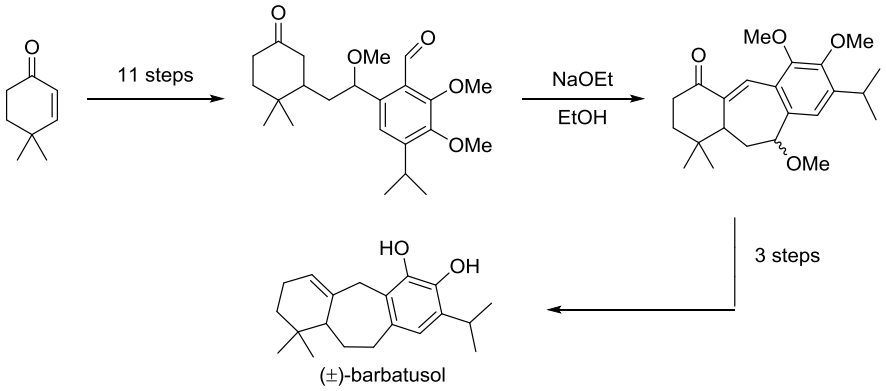
Scheme 3.8

In 1996, Majetich and co-workers prepared (±)-pisiferin via a new strategy.[39] Instead of preparing the B-ring by linking the A and C-rings through C-6 and C-7, they linked the rings through C-20. The B ring was cyclized using a Lewis Acid catalyzed EAS reaction. This strategy shortened the preparation of the icetexane skeleton to four steps from 4,4-dimethylcyclohexane-1,3-dione. A further two steps resulted in (±)-pisiferin (Scheme 3.9).



Scheme 3.9

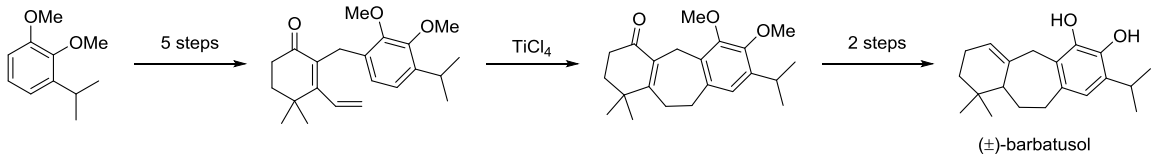
In addition to the pisiferins, the barbatusols have also received great synthetic interest. In 1987, Koft reported the first total synthesis of (±)-barbatusol.[40] He prepared the skeleton in a manner similar to Matsumoto and Ghatak in their syntheses of (±)-pisiferin and (±)-isopisiferin.



Scheme 3.10

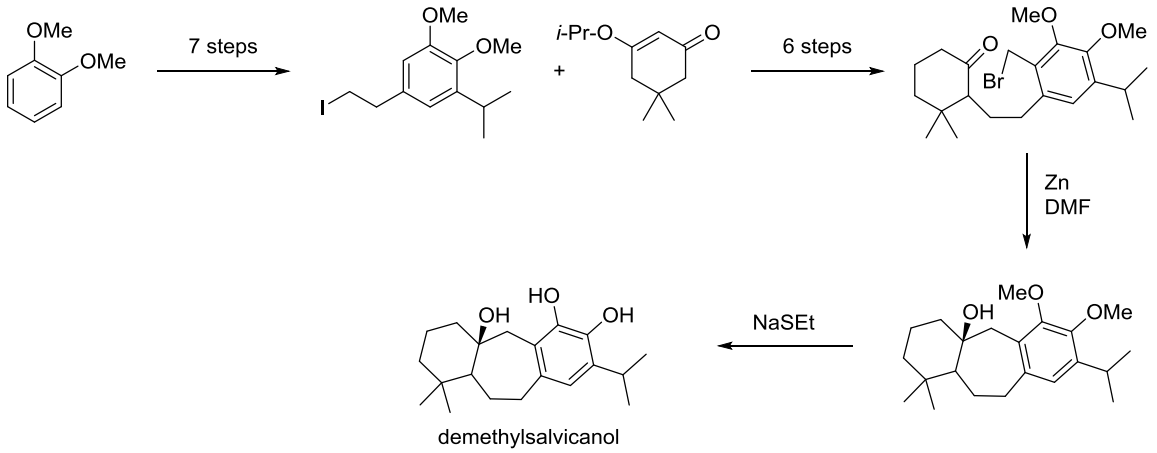
The cyclization precursor was prepared in eleven steps from 4,4-dimethylcyclohex-2-en-1-one. The cyclization was achieved via an intramolecular aldol condensation resulting in a C-10,C-20 enone. A further three transformations yielded (±)-barbatusol (Scheme 3.10).

In 1993, Majetich and co-workers published their preparation of (±)-barbatusol.[41] In a similar manner to the preparation of (±)-pisiferin, they utilized a cyclialkylation strategy (Scheme 3.11). The key dienone was prepared in five steps from 3-isopropylveratrole. In this case a much stronger Lewis acid, $TiCl_4$, was required to achieve the cyclization. The synthesis of (±)-barbatusol was completed by a Wolff–Kishner reduction to remove the carbonyl and isomerize the alkene and subsequent deprotection of the methyl aryl ethers with NaSEt. When the deprotection was attempted with acidic reagents, isomerization of the trisubstituted alkene occurred.



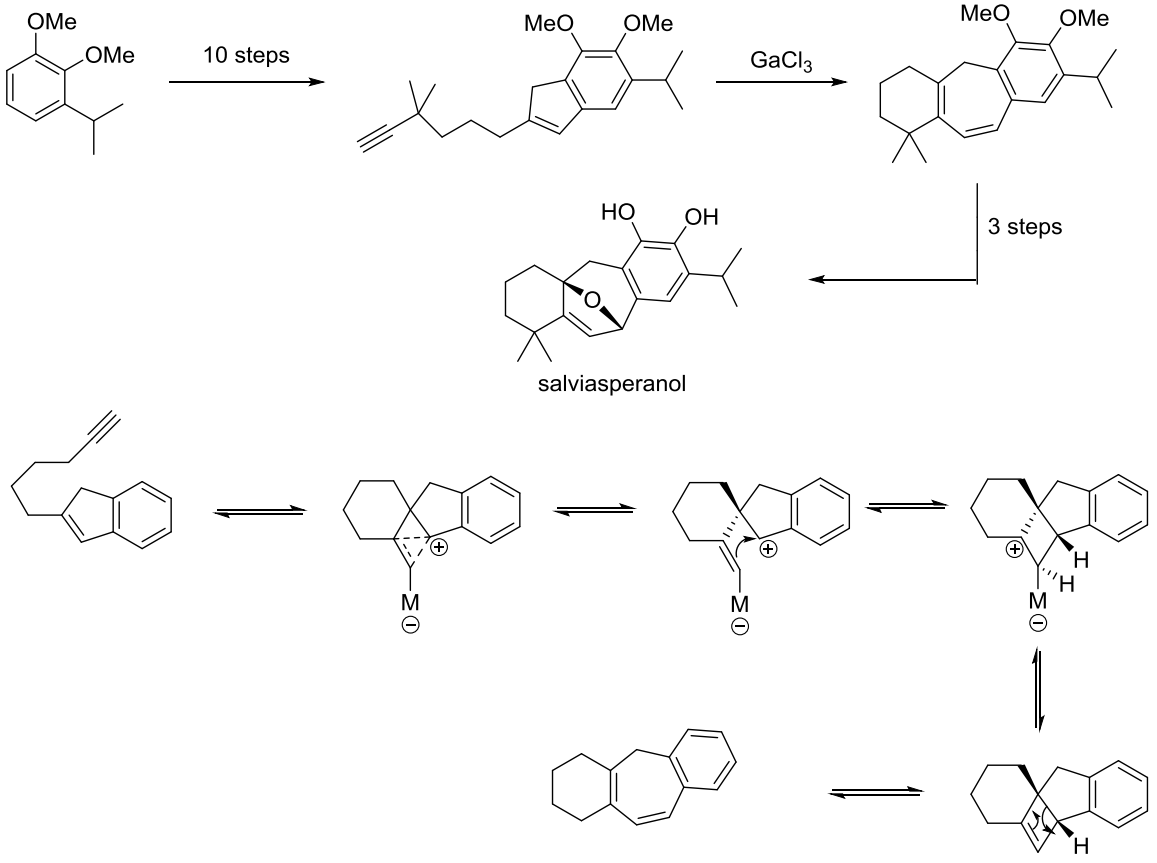
Scheme 3.11

In their preparation of (±)-demethylsalvicanol, Pan and co-workers employed a slightly different cyclization strategy. In a similar manner to Koft, they linked the A and C rings via C-6 and C-7. This adduct was prepared convergently in thirteen steps from veratrole and 5,5-dimethyl-1,3-cyclohexandione. An intramolecular Barbier reaction was used to cyclize the B-ring and to install the C-10 hydroxide. Subsequent deprotection with NaSEt yielded demethylsalvicanol (Scheme 3.12).[42]



Scheme 3.12

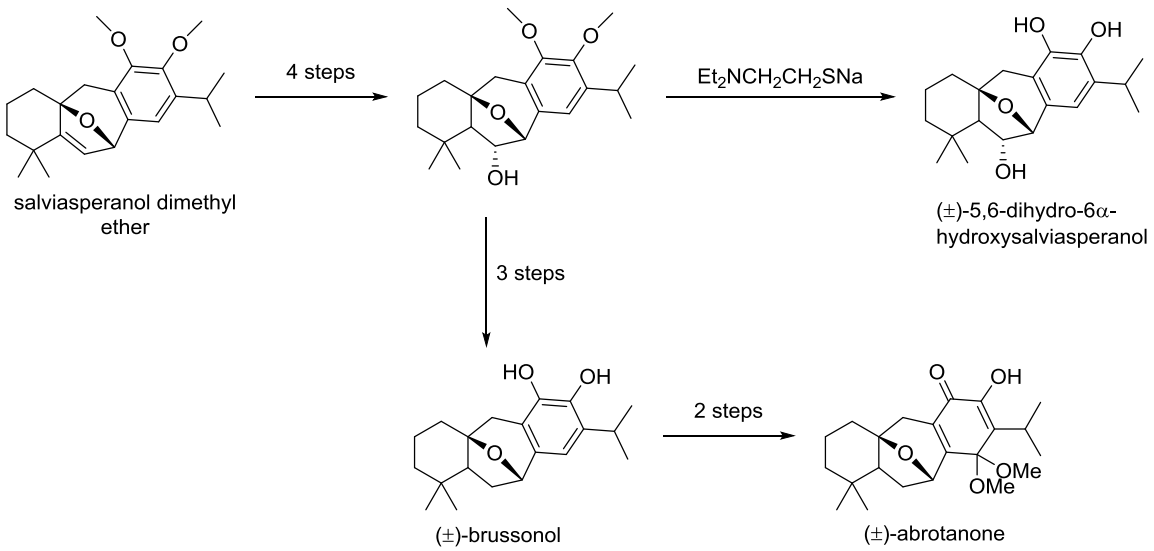
In 2006, Simmons and Sarpong completed the first total synthesis of (±)-salviasperanol (Scheme 3.13).[43] In this synthesis, the key indene intermediate was prepared in ten steps from 3-isopropylveratrole.



Scheme 3.13

The cyclization step was achieved using $GaCl_3$ in an enyne cycloisomerization. The proposed mechanism for the cyclization is presented in Scheme 3.13. Once the cyclized product was obtained, a further three steps resulted in salviasperanol.

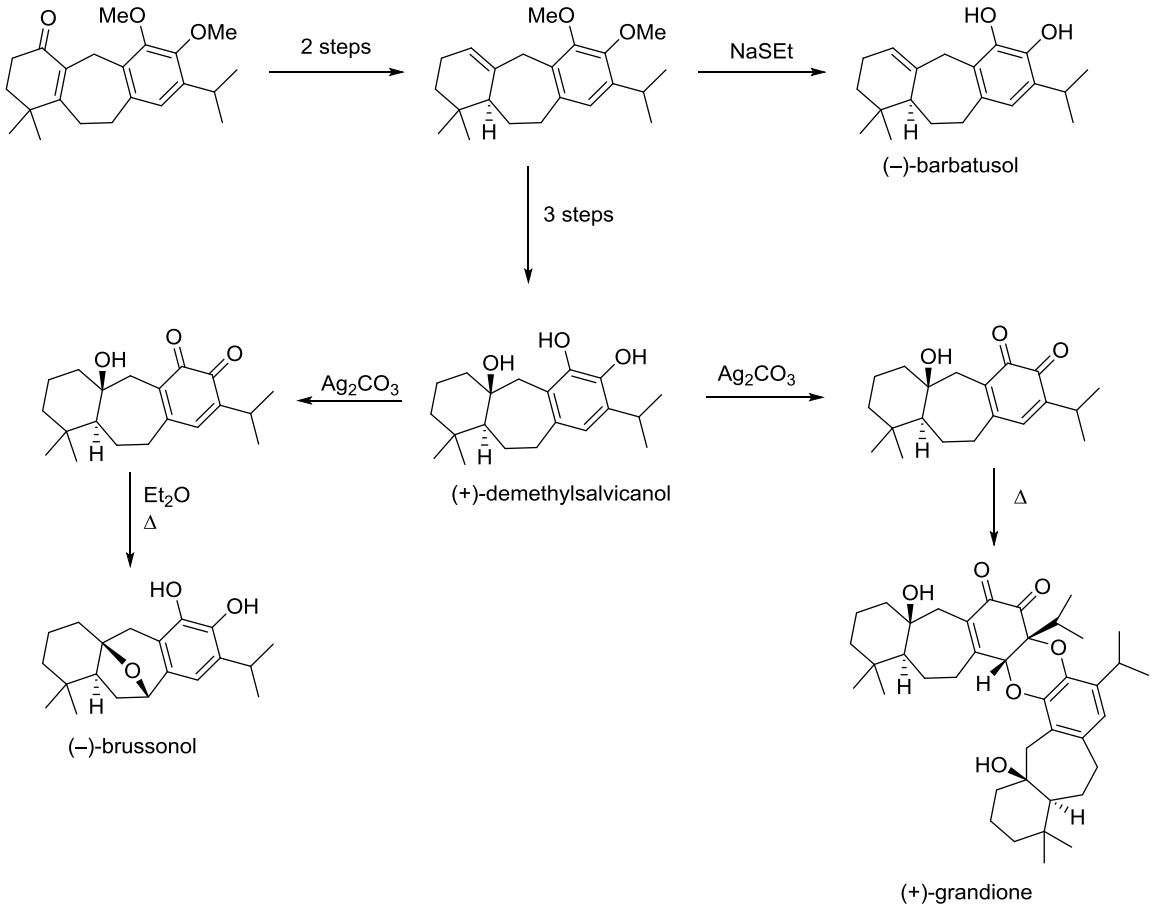
Simmons and Sarpong followed up their preparation of salviasperanol with the synthesis of (±)-5,6-dihydro-6α-hydroxysalviasperanol, (±)-brussonol and (±)-abrotanone.[31] Starting with salviasperanol dimethyl ether, four transformations led to an intermediate alcohol. Deprotection of the methyl ethers yielded (±)-5,6-dihydro-6α-hydroxysalviasperanol. Alternatively, this alcohol served as an intermediate in the preparation of (±)-brussonol and (±)-abrotanone (Scheme 3.14).



Scheme 3.14

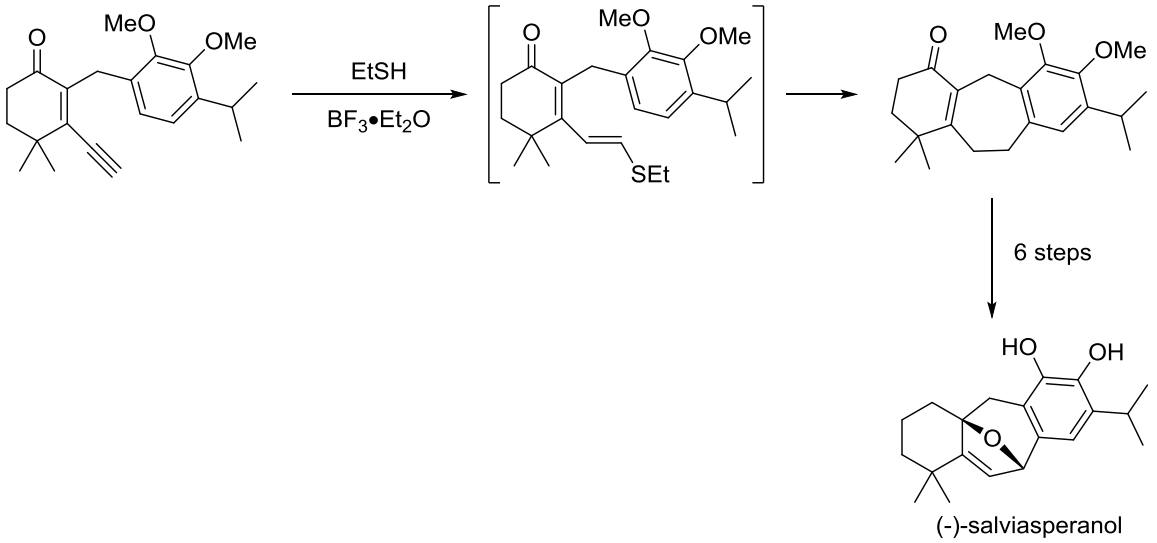
While many racemic preparations of brussonol derivatives had been reported, it was not until 2007 that Majetich and Zou published the first asymmetric preparations of (-)-barbatusol, (+)-demethylsalvicanol, (-)-brussonol and (+)-grandione.[44] Starting with a tricyclic enone, a late stage intermediate in the racemic synthesis of barbatusol, a stereospecific reduction led to (–)-barbatusol dimethyl ether. Deprotection of this intermediate led to (–)-barbatusol. Alternatively, three further steps yielded (+)-

demethylsalvicanol. Oxidation of this with Ag_2CO_3 led to the orthoquinone. This intermediate was then converted into either (–)-brussonol by heating in Et_2O or dimerized via a Diels–Alder to (+)-grandione (Scheme 3.15).



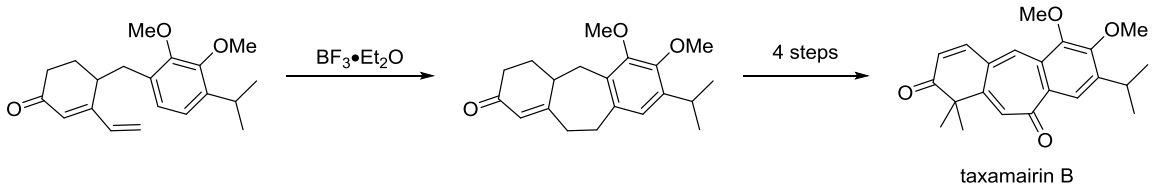
Scheme 3.15

The Majetich group continued to report asymmetric preparations of icetexanes with their synthesis of (–)-salviasperanol.[45] In their modified strategy, the cyclialkylation did not occur when the enynone was treated with strong Lewis acids. Instead, treatment of an enynone with EtSH and $BF_3 \cdot Et_2O$ resulted in 1,6-addition of the thiol and further reaction allowed the cyclization to occur. Six transformations, including a stereospecific reduction, yielded (–)-salviasperanol (Scheme 3.16).



Scheme 3.16

Only one group has reported the total synthesis of a taxamairin. In 1995 Pan and co-workers published the first total synthesis of taxamirin B.[46] They employed a similar cyclialkylation strategy to those employed by Majetich in previous syntheses. With the tricyclic skeleton complete, a further four steps furnished taxamairin B (Scheme 3.17).

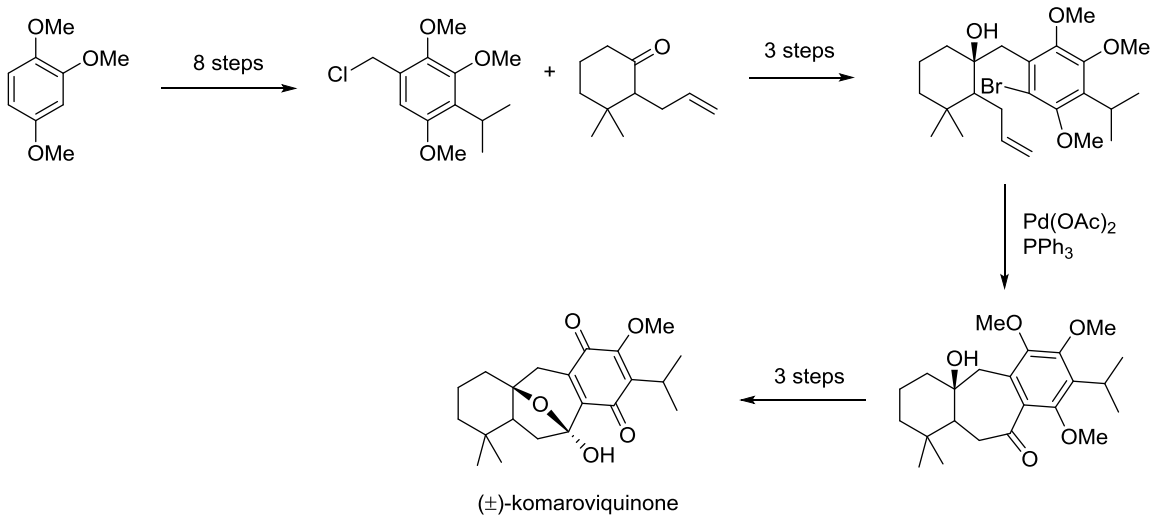


Scheme 3.17

The coulterones have received much greater synthetic attention than the taxamairins. However, very few total syntheses have been published. The difficulty in preparing the coulterones is the aromatic C-ring which is hexasubstituted. Also preparing the correct aromatic precursor has proven to be quite difficult.

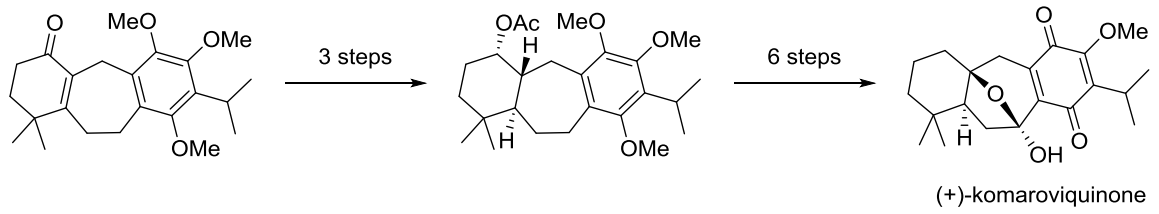
In 2005 Banerjee and co-workers published the first preparation of (±)-komaroviquinone.[47] They prepared the C-ring precursor in eight steps starting from 1,2,4-trimethoxybenzene. Coupling of the C-ring with the previously prepared allyl

ketone led to the cyclization precursor. An intramolecular Heck reaction was used to cyclize the B-ring and to install the exocyclic olefin. The olefin was then converted to the ketone and subsequently to (±)-komaroviquinone (Scheme 3.18).



Scheme 3.18

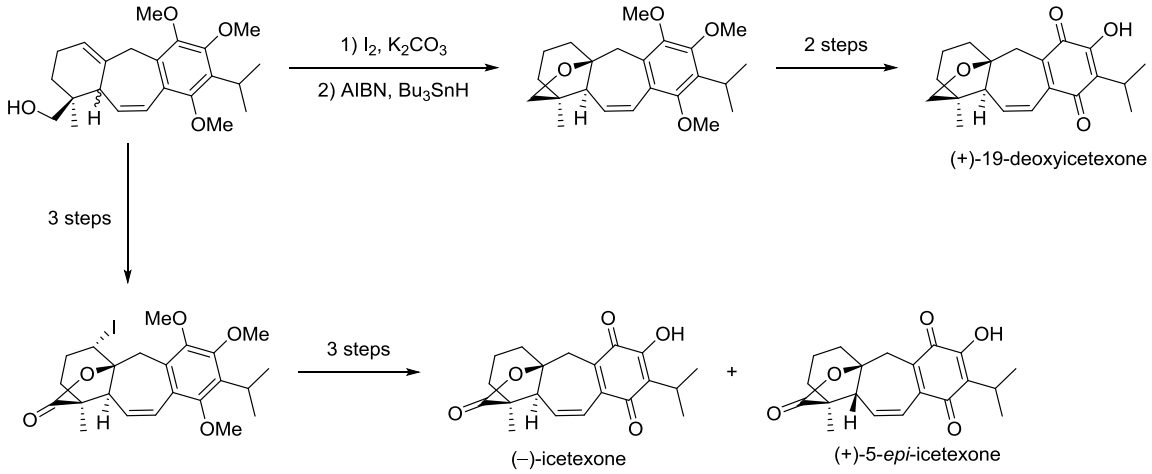
In 2007, Majetich and co-workers published both a racemic synthesis and an asymmetric preparation of (+)-komaroviquinone.[48,49] The icetexane framework was obtained via the cyclialkylation strategy previously employed. An asymmetric reduction, followed by a Myers allylic transposition installed the C-5 proton on the α-face. Three additional transformations resulted in (+)-komaroviquinone (Scheme 3.19).



Scheme 3.19

The most recent syntheses of icetexanes have centered on the preparation of icetexone derivatives. In 2009, Majetich and Grove published asymmetric syntheses of (+)-19-deoxyicetexone, (-)-icetexone and (+)-5-*epi*-icetexone.[50] The key intermediate

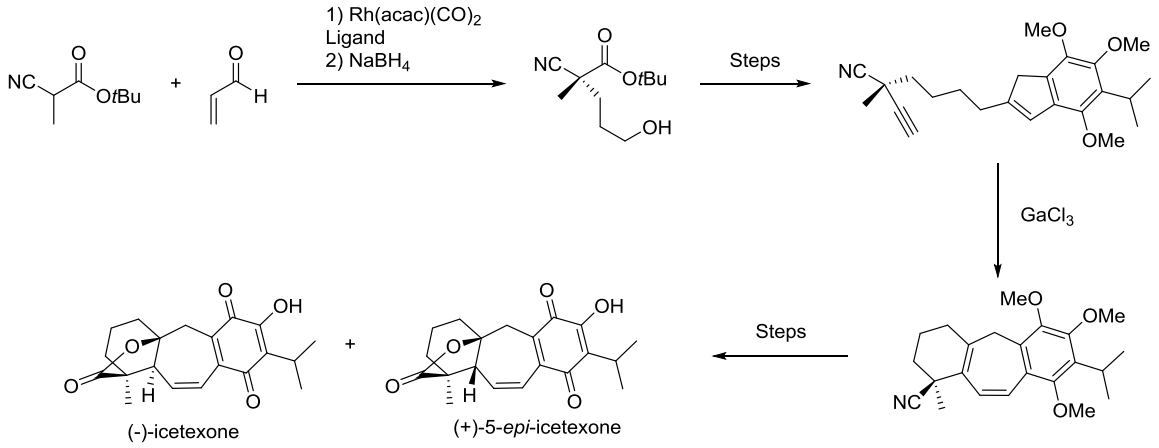
diene underwent iodo-etherification and radical halogen elimination to give a tetrahydrofuran ring. Subsequent methyl ether cleavage with NaSEt, followed by CAN oxidation, resulted in (+)-19-deoxyicetexone. Alternatively, consecutive oxidations of the primary alcohol gave the carboxylic acid which readily underwent iodolactonization. Removal of the iodide followed by BBr_3 deprotection and CAN oxidation gave two diastereomers (Scheme 3.20). These were determined to be (–)-icetexone and (+)-5-*epi*-icetexone. Surprisingly, it was determined by comparing physical and spectral data that the initial structures for icetexone and 5-*epi*-icetexone were reversed.



Scheme 3.20

In 2010, Sarpong and Cortez published a racemic preparation of icetexone and *epi*-icetexone[51] and in 2013 they published an asymmetric formal synthesis.[52] These syntheses utilized the $GaCl_3$–catalyzed cylcoisomerization previously developed by the Sarpong group. The enantioselectivity depended completely on the stereochemistry of the propargylic nitrile. Rhodium catalyzed asymmetric conjugate addition of cyanopropionates to acrolein yielded a precursor to the alkyne in high stereoselectivity. Further transformations led to the cyclization precursor. $GaCl_3$-catalyzed

cycloisomerization led to an enantio-enriched intermediate used in their racemic preparation (Scheme 3.21).



Scheme 3.21

3.4 Total Synthesis of Rosmaridiphenol

Rosmaridiphenol was first isolated in 1984 from *Rosmarinus officinalis*, rosemary.[16] Owing to the phenols present at C-11 and C-12, rosmaridiphenol is a barbatusol derivative. Interestingly, the carbonyl was originally assigned to C-20. It was not until 2012, however, that that structure was definitively proven. Muñoz and co-workers isolated a sample of rosmaridiphenol and protected the phenols as the acetates. A crystal was grown and the crystal structure unambiguously assigned the carbonyl to C-1 (Figure 3.7).[17] The crystal structure also elucidated the previously unknown stereochemistry of the hydrogens at C-5 and C-10.

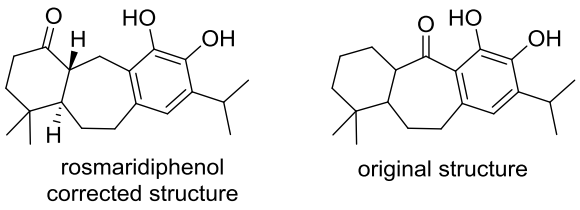
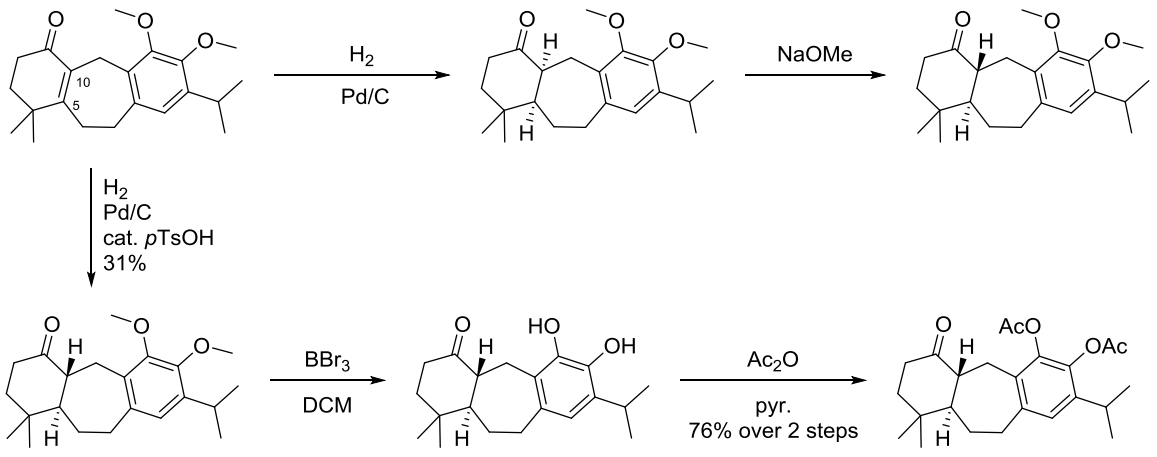


Figure 3.7

The first synthesis of racemic rosmaridiphenol was achieved in 2014. Starting with an advanced intermediate from the synthesis of barbatusol[41] a catalytic hydrogenation removed the C-5,C-10 olefin (Scheme 3.22). Subsequent epimerization at C-10 to the required *trans* ring fusion with NaOMe proceeded cleanly. However, we discovered that if the hydrogenation was performed with a catalytic amount of *p*-TsOH the epimerization occurred *in situ*. Deprotection of the methyl ethers was achieved with BBr_3 to yield (±)-rosmaridiphenol. In a similar observation to Muñoz, the resulting compound was not stable and significant decomposition was observed.[17] To remedy this, immediately after deprotection, the catechol was treated with Ac_2O and pyridine to give the diacetate in good yield. The spectra of the diacetate was identical to that reported by Muñoz.[17] Thus, the first total synthesis of rosmaridiphenol was complete.



Scheme 3.22

3.5 Total Synthesis of Salvimultine

Salvimultine was isolated in 2000 by Ulubelen and Topcu from *Salvia multicaulis*.[53] Salvimultine is related to pisiferin in that there is a phenol at C-12.

However, salvimultine is a noricetexane diterpenoid due to there being one fewer carbon in the A-ring (Figure 3.8).

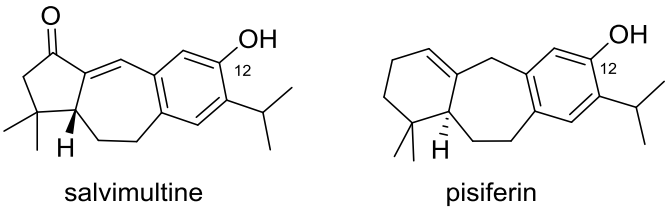
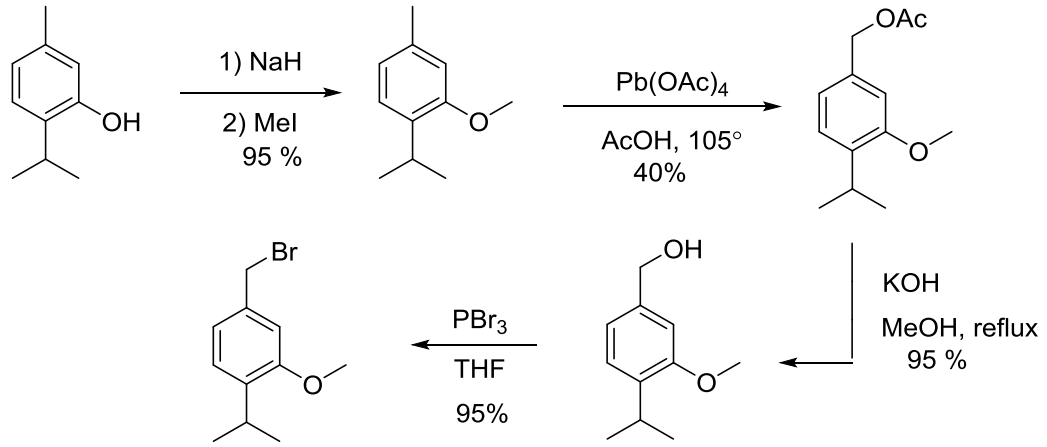


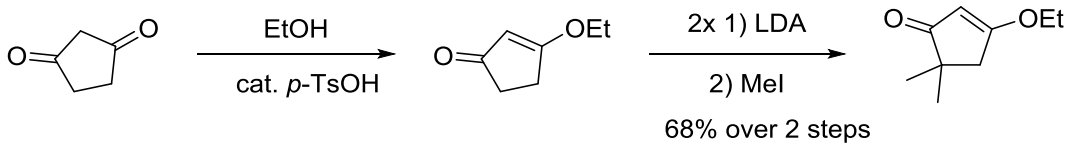
Figure 3.8

We envisioned an A+C→ABC cyclialkylation strategy to synthesize salvimultine. To prepare the C-ring, the natural product thymol was first protected as the methyl ether (Scheme 3.23). Treatment with $Pb(OAc)_4$ introduced a benzylic acetate in reasonable yield.[54] The crude acetate was then saponified with KOH in MeOH to yield the benzyl alcohol. Subsequent treatment with PBr_3 produced the desired benzylic bromide.



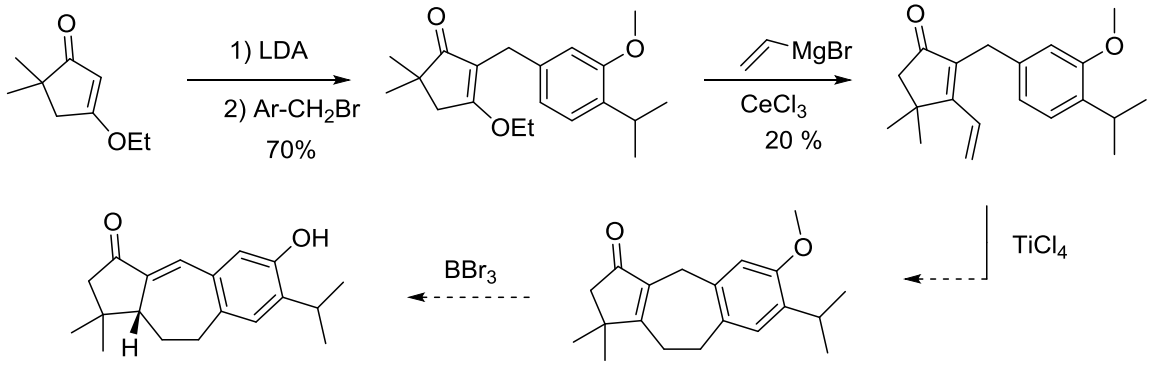
Scheme 3.23

The A-ring was prepared from 1,3-cyclopentanedione (Scheme 3.24). Refluxing the dione with EtOH and catalytic *p*TsOH resulted in the vinylogous ester.[55] Two consecutive α methylations with LDA and MeI yielded the A-ring in reasonable yield.



Scheme 3.24

By treating the 3-ethoxy enone with two equivalents of LDA overnight resulted in the anion and quenching with the C-ring gave the A+C product in moderate yield. Introducing the vinyl group to create the cyclization precursor was not trivial. Treatment of the enone with three equivalents of vinylmagnesium bromide and 0.3 equivalents of $CeCl_3$, followed by acid hydrolysis gave the dienone in moderate yield (Scheme 3.25). This cyclialkylation will be achieved by treatment with 2.5 equivalents of 1 M $TiCl_4$. Finally, simultaneous deprotection of the methyl ether and olefin isomerization with BBr_3 will cleanly yield racemic salvimultine.



Scheme 3.25

3.6 Progress Towards the Total Synthesis of Perovskone B and Hydrangenone

Perovskone B was first isolated from *Salvia hydrangea* in 2011 by Farimani and co-workers.[56] The core of perovskone B is based on the coulterone framework due to the presence of oxygens at C-11, C-12 and C-14. Hydrangenone was also isolated from *S.*

hydrangea in 2011.[57] The main difference between the two natural products is the carbon framework configuration. Perovskone B is a heptacyclic natural product with a 6-7-6-6-5 skeleton and hydrangenone has a 6-7-6-5-5 skeleton (Figure 3.9). Each of these compounds also possess two tetrahydrofuran rings.

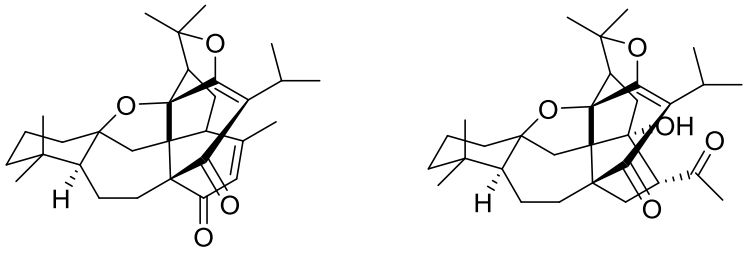


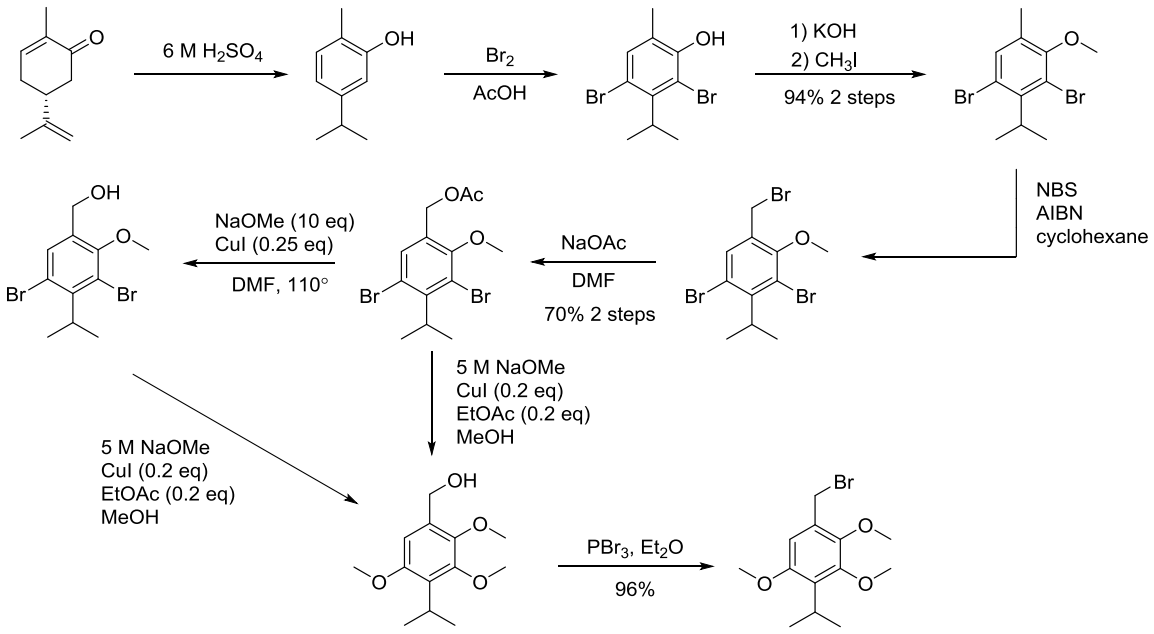
Figure 3.9

We believe that both perovskone B and hydrangenone are biosynthetically related to perovskone, another heptacyclic coulterone derivative and have hypothesized that both can be prepared from perovskone and/or *iso*-perovskone respectively.

Previous work in the Majetich lab has resulted in both a racemic and asymmetric preparation of perovskone.[58] While this synthesis was quite elegant, there was room for improvement in the preparation of the coulterone core. Once again we employed an A+C→ABC cyclialkylation strategy during this synthesis.

The C-ring of perovskone could be prepared from the inexpensive, commercially available (*R*)-carvone. An acid-catalyzed isomerization proceeded cleanly to generate carvacrol (Scheme 3.26). This isomerization is also possible starting from (*S*)-carvone but this enantiomer is far more expensive. With carvacrol in hand, the next step was to protect the phenol as the methyl ether. This reaction proceeded smoothly and could be done on a large scale. Treatment of carvacrol methyl ether with Br_2 led to the *bis*–bromide. Radical benzylic bromination with NBS gave the benzylic bromide in good

yield. Bromination occurred only at the primary carbon due to an electronic effect from the *ortho* methoxy group. Substitution with NaOAc resulted in the benzylic acetate. Unfortunately, treatment with NaOMe and CuI in DMF only resulted in the saponification of the ester. However, I discovered that treatment of the benzyl alcohol with 5 M NaOMe, 0.2 equivalents of CuI, 0.2 equivalents of EtOAc in MeOH cleanly yielded the trimethoxy benzyl alcohol.[59] When the acetate was resubmitted to the improved substitution conditions, the cuprate addition to the bromides and saponification of the acetate gave the trimethoxy benzyl alcohol in moderate yield. Addition of PBr_3 completed the preparation of the benzylic bromide (96% yield).

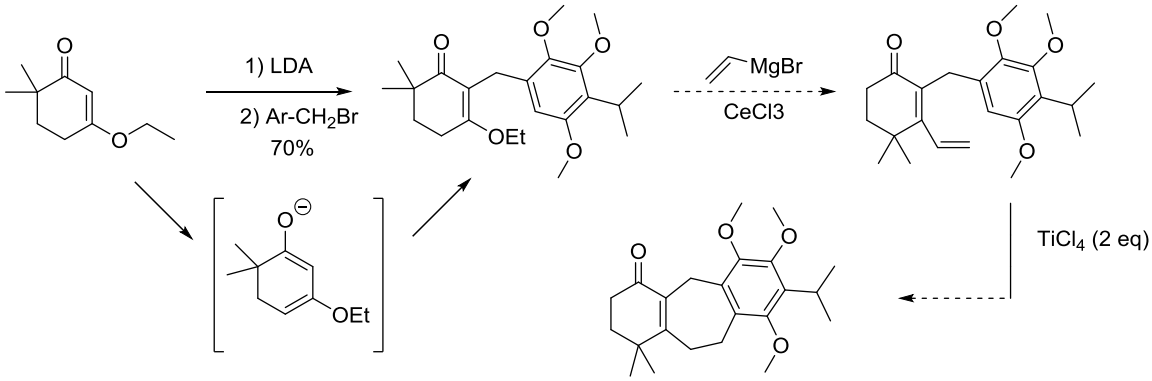


Scheme 3.26

The preparation of the A-ring began with the conversion of 1,3-cyclohexanedione to a vinylogous ester by refluxing in benzene with a catalytic amount of *p*-TsOH in EtOH (Scheme 3.27).[55] Consecutive α-methylations with LDA and MeI gave the A-ring in moderate yield.

Scheme 3.27

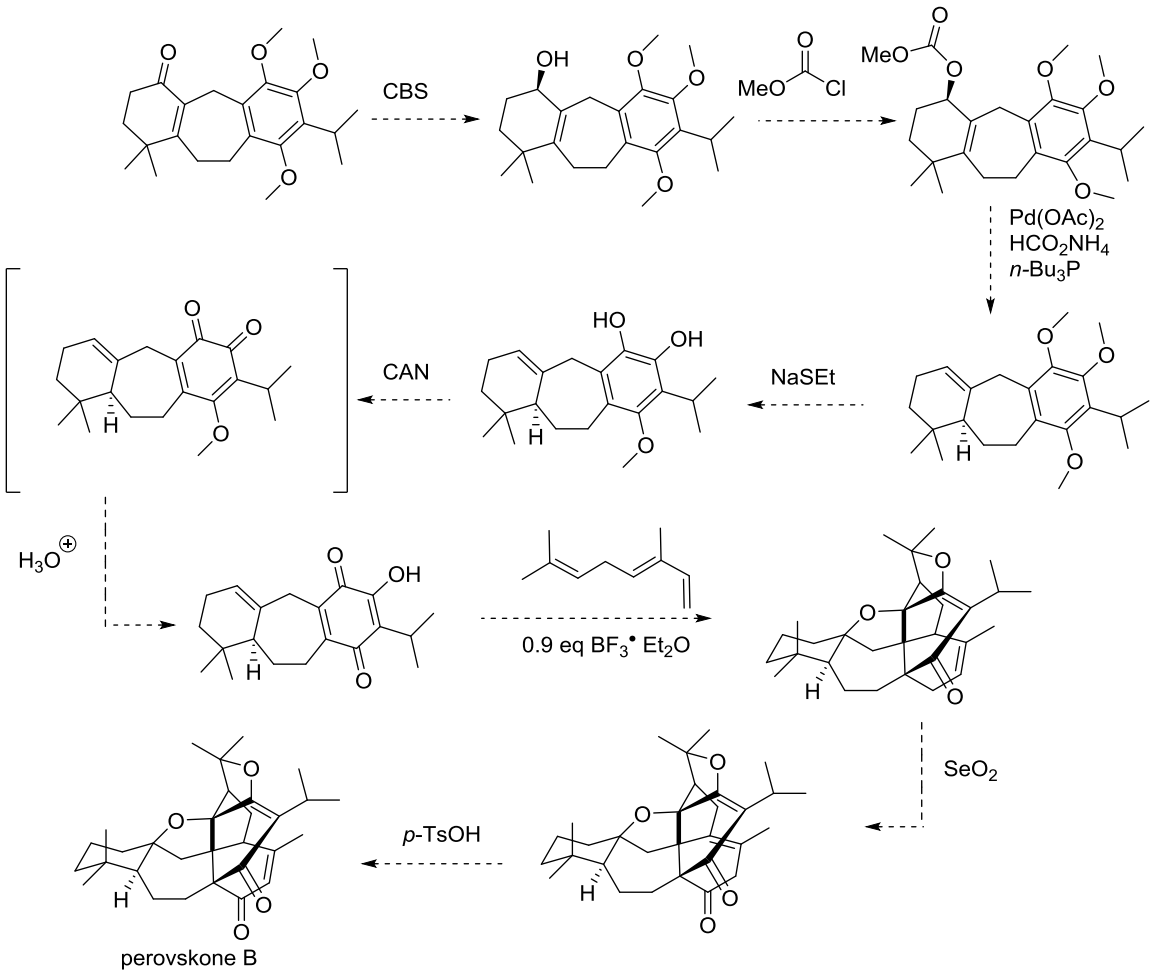
Treatment of the A-ring with two equivalents of LDA created the anion shown and alkylation of the enolate with the benzylic bromide gave the A+C precursor (Scheme 3.28). Addition of vinylmagnesium bromide, and subsequent acid hydrolysis, will lead to the dienone cyclization precursor. Two equivalents of 1 M $TiCl_4$ will give the ABC product.



Scheme 3.28

To complete the synthesis, a CBS-reduction will asymmetrically reduce the ketone present in the A-ring (Scheme 3.29). Formation of a carbonate, followed by $Pd(OAc)_2$ catalyzed conjugate addition, will introduce the hydrogen on the α-face. Deprotection of two of the methyl ethers with NaSEt will give a catechol which will then be oxidized to the *ortho*-quinone with CAN. Acid-catalyzed isomerization to the *para*-quinone will give the precursor needed for the key Diels–Alder reaction. Treatment of the *para*-quinone with (*E*)-β-ocimene and 0.9 equivalents $BF_3{\cdot}Et_2O$ will result in a cascade reaction culminating in (+)-perovskone. Allylic oxidation with SeO_2 will install

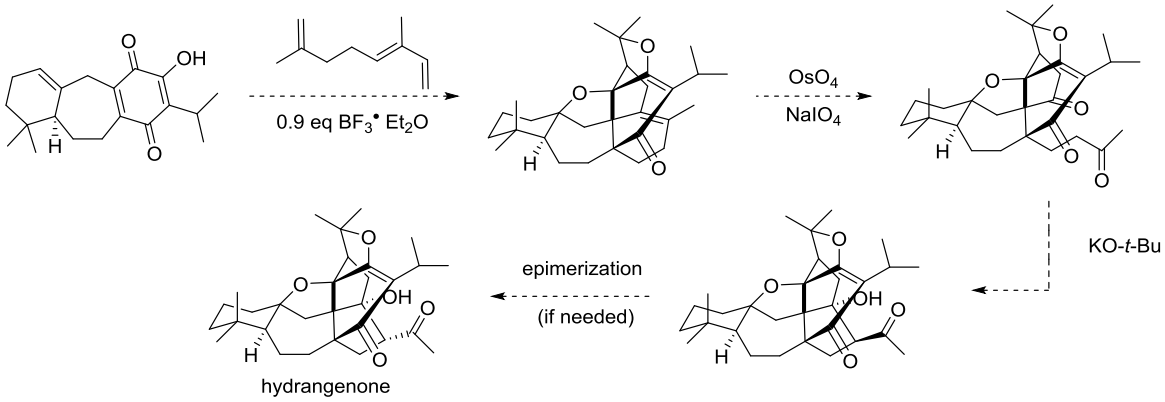
the final carbonyl group and isomerization of the olefin to create the enone will complete the synthesis of perovskone B.



Scheme 3.29

To achieve a synthesis of hydrangenone, instead of (*E*)-β-ocimene being used in the Diels–Alder cascade, (*E*)-α-ocimene will be used instead (Scheme 3.30). This will produce isoperovskone. Lemieux–Johnson cleavage will result in the diketone. A base-catalyzed aldol condensation of the diketone shown will form the final five-membered ring and isomerize the ketone to the α-face. The product of an aldol reaction is often an enone. However, dehydration of hydrangenone would violate Bredt's rule by introducing

a double bond in a five-membered ring. This dehydration produces a highly-strained double bond. Thus, we predict this undesired elimination will not occur.



Scheme 3.30

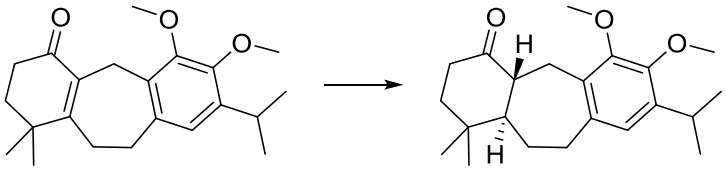
3.7 Summary and Conclusions

In summary, the first total synthesis of rosmaridiphenol has been completed. In addition, significant progress has been made towards the first total syntheses of salvimultine, perovskone B and hydrangenone. These syntheses should be completed in the near future.

3.8 Experimental Data and Procedures

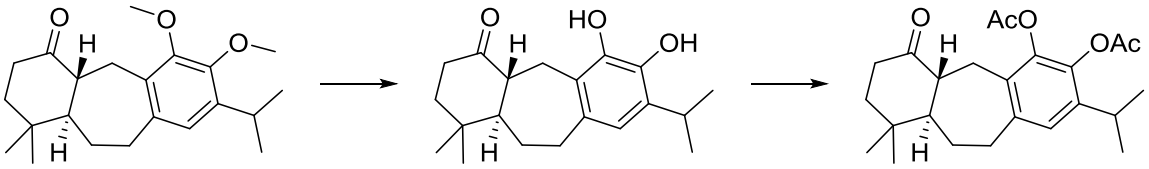
General Procedures: All reactions were run under an argon atmosphere and monitored by TLC analysis. Unless otherwise noted all extractive workups consisted of the following procedure: the crude reaction mixture was diluted with diethyl ether and deionized water. The aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed twice with deionized water, once with brine and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration

and the organic layers concentrated on a rotary evaporator. The crude residue was placed under vacuum at 1 torr until a constant weight was observed. The residue was subsequently purified by flash column chromatography using silica gel 60 (230-400 mesh ASTM) and distilled reagent grade hexanes and ethyl acetate. Melting points were recorded on a DigiMelt MPA 160. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVB-400 MHz spectrometer with a ^{13}C operating frequency of 100 MHz. ^{1}H NMR spectra were obtained in $CDCl_3$ and normalized using trace $CHCl_3$ present (δ 7.27 ppm) as an internal reference. ^{13}C NMR spectra were obtained in $CDCl_3$ using trace $CHCl_3$ present (δ 77.23 ppm) as an internal reference. IR spectra were obtained on an Avatar 360FT-IR and are reported in frequency of absorption (cm^{-1}). Only selected IR frequencies are reported. High resolution MS were obtained on a Waters LCT Premier.



Hydrogenation/ Epimerization of Enone: The enone (46 mg, 0.13 mmol), 10% Pd/C (8 mg), and *p*TsOH (4 mg) were dissolved in dry MeOH (10 mL). The solution was placed under 1 atm of H_2 and allowed to stir for 4 hours. The solution was filtered through Celite to remove the catalyst and the solvent was evaporated. Column chromatography (6:1 hexanes/ethyl acetate) gave rosmaridiphenol dimethyl ether (13 mg, 0.04 mmol, 31% yield) as a colorless oil. [R_f = 0.52, 6:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.99 (s, 3H) 1.03 (s, 3H), 1.19 (d, J= 8Hz, 3H), 1.23 (d J= 8Hz, 3H) 1.70 (m, 4H), 2.16 (m, 3H), 2.35 (d, J= 16Hz, 1H), 2.52 (m, 1H), 2.73 (m, 1H), 3.28 (heptet, 1H), 3.78 (s, 3H), 3.84 (s, 3H), 3.98 (q, 1H), 6.71 (s, 1H); ^{13}C NMR (100 MHz,

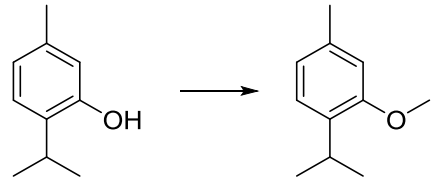
$CHCl_3$) δ 20.4, 23.7, 24.0, 24.7, 26.9, 29.6, 29.7, 34.5, 34.8, 38.9, 42.6, 51.1, 58.2, 61.0, 61.1, 120.8, 131.7, 140.0, 140.4, 148.8, 150.7, 212.5.



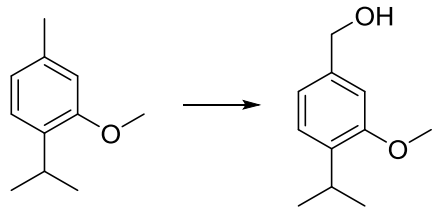
Preparation of rosmaridiphenol diacetate: The dimethyl ether (13 mg, 0.04 mmol) was dissolved in DCM (5 mL). The solution was cooled to -30 °C. To this was added 1M BBr_3 (0.15 mL, 0.15 mmol) dropwise. The solution was warmed to 0 °C and stirred for 20 minutes. The solution was diluted with Et_2O (10 mL) and deionized water (5 mL) and stirred for an additional 5 minutes. Standard ethereal workup followed by column chromatography (4:1 hexanes/ethyl acetate) gave rosmaridiphenol (9 mg, 0.03 mmol, 76% yield) which was homogeneous by TLC [R_f = 0.25, 4:1 hexanes/ethyl acetate]. The rosmaridiphenol was immediately used in the next step without further characterization.

Rosmaridiphenol (9 mg, 0.03 mmol) was dissolved in pyridine (2 mL). To this solution was added acetic anhydride (2 mL, 21 mmol) dropwise. The solution was stirred at room temperature overnight. The solvent was removed under reduced pressure and column chromatography (4:1 hexanes/ethyl acetate) gave rosmaridiphenol diacetate (4 mg, 0.01 mmol, 30% yield) as off-white crystals. [R_f = 0.38, 4:1 hexanes/ethyl acetate]: ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.99 (s, 3H), 1.03 (s, 3H), 1.17 (d J = 6Hz, 3H), 1.22 (d J = 6Hz, 3H), 1.31 (m, 1H), 1.61-1.71 (m, 3H), 2.14-2.18 (m, 3H), 2.29 (s, 3H), 2.30 (m, 1H), 2.31 (s, 3H), 2.48-2.54 (m, 1H), 2.79 (t, 2H), 2.94 (heptet, 1H), 3.56 (d J = 16Hz, 1 H), 6.93 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 20.3, 20.6, 20.7, 23.1, 23.3, 25.8, 27.7,

29.2, 29.7, 34.3, 34.9, 38.5, 42.1, 50.0, 57.7, 123.4, 131.6, 138.3, 139.1, 140.2, 142.8, 169.0, 169.1, 211.8; HRMS (ESI) calculated for M+Na = *m/z* 423.2147, found 423.2140.

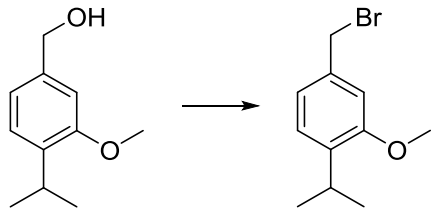


Preparation of thymol methyl ether: Thymol (11.41 g, 76 mmol) was dissolved in dry THF (200 mL). To this solution was added KOH (5.07 g, 90 mmol). The solution was heated to reflux for 1 hour. After cooling the solution to room temperature, methyl iodide (5.2 mL, 83 mmol) was added dropwise. The solution was stirred for an additional 30 minutes. Standard ethereal workup followed by column chromatography (30:1 hexanes/ethyl acetate) gave thymol methyl ether (8.48 g, 52 mmol, 68% yield) as a colorless oil. [R_f = 0.80, 30:1 hexanes/ethyl acetate]; ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.21 (d J= 8Hz, 6H), 2.35 (s, 3H), 3.29 (heptet, 1H), 3.83 (s, 3H), 6.69 (s, 1H), 6.76 (d J = 8Hz, 1H), 7.11 (d J = 8Hz, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 25.2, 23.0, 26.6, 55.5, 111.6, 121.3, 126.0, 134.2, 136.5, 156.8.



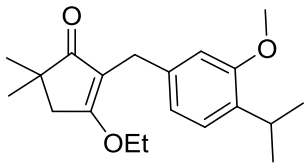
Preparation of 4-(hydroxymethyl)-1-isopropyl-2-methoxybenzene: Thymol methyl ether (8.48 g, 52 mmol) was dissolved in glacial acetic acid (100 mL). To this solution was added $Pb(OAc)_4$ (35.96 g, 81 mmol). The solution was heated at 105 °C for 3.5 hours. After cooling to room temperature, ethylene glycol (10 mL) was added to quench any remaining $Pb(OAc)_4$. The solution was diluted with deionized water (100

mL). Standard ethereal workup yielded a brown oil which was immediately used without any further purification. This oil was dissolved in dry methanol (150 mL). To this solution was added KOH (6.27 g, 111 mmol). The solution was refluxed overnight. After cooling to 0 °C the solution was acidified with 6M HCl. Standard ethereal workup followed by column chromatography (4:1 hexanes/ethyl acetate) gave 4-(hydroxymethyl)-1-isopropyl-2-methoxybenzene (2.21 g, 12 mmol, 23% yield) as a colorless oil. [R_f = 0.20, 4:1 hexanes/ethyl acetate]; ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.21 (d J = 8Hz, 6H), 3.32 (heptet, 1H), 3.86 (s, 3H), 4.67 (s, 2H), 6.91-6.94 (m, 2H), 7.20 (d J = 8Hz, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 22.9, 26.8, 55.6, 65.8, 109.4, 119.3, 126.3, 136.8, 139.6, 157.2.

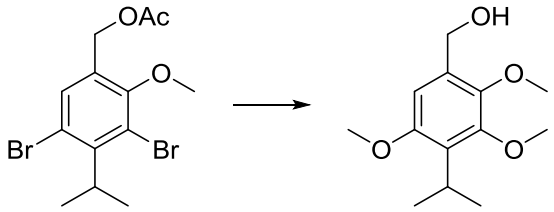


Preparation of 4-(bromomethyl)-1-isopropyl-2-methoxybenzene: The benzyl alcohol (2.21 g, 12 mmol) was dissolved in diethyl ether (200 mL). The solution was cooled to 0 °C and PBr_3 (0.7 mL, 7 mmol) was added dropwise. The solution was warmed to room temperature and stirred for 30 minutes. The solution was then diluted with deionized water (100 mL). Standard ethereal workup followed by column chromatography (9:1 hexanes/ethyl acetate) gave 4-(bromomethyl)-1-isopropyl-2-methoxybenzene (2.77 g, 11 mmol, 96% yield) as a colorless oil. [R_f = 0.88, 9:1 hexanes/ethyl acetate]; ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.21 (d J = 8Hz, 6H), 3.30 (heptet, 1H), 3.85 (s, 3H), 4.51 (s, 2H), 6.88 (s, 1H), 6.96 (d J = 8Hz, 1H), 7.17 (d J = 8Hz, 1H);

^{13}C NMR (100 MHz, $CHCl_3$) δ 22.8, 26.9, 34.4, 55.6, 111.1, 121.4, 126.5, 136.2, 137.9, 157.1.



Preparation of 3-ethoxy-2-(4-isopropyl-3-methoxybenzyl)-5,5-dimethylcyclopent-2-en-1-one: Diisopropylamine (0.18 mL, 1.2 mmol) was dissolved in dry THF (0.25 mL). The solution was cooled to -78 °C and 1.8M *n*-BuLi (0.80 mL, 1.44 mmol) was added dropwise. The solution was stirred for 30 minutes and then 3-ethoxy-5,5-dimethylcyclopent-2-en-1-one (90 mg, 0.6 mmol) dissolved in THF (0.25 mL) was added via cannula. This solution was warmed to room temperature and stirred overnight. The solution was cooled back to -78 °C and 4-(bromomethyl)-1-isopropyl-2-methoxybenzene (141 mg, 0.6 mmol) dissolved in THF (0.25 mL) was added via cannula. This solution was then allowed to stir for 2 hours. The solution was quenched with crushed ice. Standard ethereal workup followed by column chromatography gave 3-ethoxy-2-(4-isopropyl-3-methoxybenzyl)-5,5-dimethylcyclopent-2-en-1-one (50 mg, 0.15 mmol, 25% yield) as a white solid. [R_f = 0.48, 2:1 hexanes/ethyl acetate]; ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.15-1.19 (m, 12H), 1.38 (t, 3H), 2.52 (s, 2H), 3.24 (heptet, 1H), 3.43 (s, 2H), 3.79 (s, 3H), 4.17 (q J = 8Hz, 2H), 6.77-6.79 (m, 2H), 7.06 (d J = 8Hz, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 15.5, 23.0, 25.6, 26.7, 27.4, 41.7, 43.4, 55.5, 65.3, 111.1, 117.1, 120.5, 125.8, 134.4, 139.1, 156.8, 181.7, 209.4.



Preparation of 1-(hydroxymethyl)-4-isopropyl-2,3,5-trimethoxybenzene: To a solution of 5M NaOMe (20 mL) was added the benzyl acetate (1.03 g, 2.7 mmol), CuI (110 mg, 0.6 mmol), and EtOAc (0.2 mL, 2 mmol). The solution was refluxed overnight. After cooling to room temperature the solution was filtered through a pad of Celite. Standard ethereal workup followed by column chromatography (0-1% DCM in MeOH) gave 1-(hydroxymethyl)-4-isopropyl-2,3,5-trimethoxybenzene (455 mg, 1.9 mmol, 70%) as a yellow oil. [R_f = 0.48, 1:1 hexanes/ethyl acetate]; ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.31 (d J = 8Hz, 6H), 3.50 (heptet, 1H), 3.79 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 4.67 (s, 2H), 6.60 (s, 1H); ^{13}C NMR (100 MHz, $CHCl_3$) δ 21.4, 25.4, 56.0, 61.0, 61.0, 61.8, 106.6, 130.4, 131.8, 145.3, 151.8, 154.9.

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