# University of Alberta

Selenium-stabilized Carbanions and Synthetic Studies on the Marinopyrroles

by

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*DEDICATED TO*

*MY FAMILY*

## ABSTRACT

The first chapter of this thesis describes the development of a general route for the generation of selenium stabilized carbanions via a method that bypasses acid catalyzed formation of selenoacetals. Aldehydes are first converted into α-hydroxystannanes by nucleophilic addition of $Bu_3SnLi$. The resulting hydroxyl is then converted to the corresponding phenyl selenide by treatment with PhSeCN and $Bu_3P$ to give the α-(phenylseleno)stannane. Upon treatment with BuLi, the α-(phenylseleno)stannane undergoes preferential Sn/Li exchange to give a selenium stabilized carbanion. This carbanion is condensed with an aldehyde to give a β-hydroxy selenide, which can be converted into an allylic alcohol upon oxidation and selenoxide fragmentation. The formation of α-(phenylseleno)stannanes has been applied to aldehydes containing straight and branched alkyl chains, aromatic substituents, and acid sensitive functional groups. The selenium stabilized carbanions have been condensed with aldehydes containing straight and branched alkyl chains, aromatic substituents, and α,β-unsaturation.

The second chapter describes synthetic studies towards two marine natural products, marinopyrrole A and B. The synthesis began with the preparation of the unprecedented *N,C*2 linked bispyrrole core through a Paal-Knorr condensation onto the amino group of ethyl 3-aminopyrrole-2-carboxylate. Preparation of the densely halogenated core of the marinopyrroles through selective chlorination of the bispyrrole seems to be impossible and was not pursued. Due to unexpected alterations to the electronic structure of the pyrrole ring in the presence of electron withdrawing substituents, preparation of a fully functionalized top ring was unsuccessful. Blocking

the 3' position of the bispyrrole with a removable blocking group was also unsuccessful by an *ortho* metallation approach.

Preparation of the halogenated bispyrrole starting with the fully functionalized bottom pyrrole seems promising after a model intramolecular conjugate displacement reaction had shown that it is possible to mount the precursor to the top pyrrole on top of the bottom pyrrole. Work is in progress to prepare the mountable precursor to the top ring.

## ACKNOWLEDGEMENTS

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Finally, I would like to thank my wife Nishara and my other family members for their constant support and encouragement, especially during the course of my graduate studies and during the preparation of this thesis.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| Ac | acetyl |
| AcOH | acetic acid |
| ADD | azodicarbonyldipiperidide |
| AIBN | 2,2'-azobisisobutyronitrile |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene |
| BINAL-H | 2,2'-dihydroxy-1,1'-binaphthyl lithium aluminum hydride |
| Bn | benzyl |
| Bu | butyl |
| *t*-Bu | *tert*-butyl |
| Bz | benzoyl |
| Cbz | benzyloxycarbonyl |
| COSY | correlation spectroscopy |
| DCE | dichloroethane |
| DEAD | diethyl azodicarboxylate |
| DIBAL-H | diisobutylaluminum hydride |
| DMAP | 4-(dimethylamino)pyridine |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethylsulfoxide |
| Et | ethyl |
| h | hour |
| HMBC | heteronuclear multiple bond coherence |
| HMPT | hexamethylphosphoric triamide |

| | |
|---|---|
| HPLC | high performance liquid chromatography |
| HRMS | high resolution mass spectrometry |
| HSQC | heteronuclear single quantum coherence |
| IBX | 2-iodoxybenzoic acid |
| ICD | intermolecular conjugate displacement |
| Im | imidazole |
| KHMDS | potassium hexamethyldisilazide |
| LHMDS | lithium hexamethyldisilazide |
| LDA | lithium diisopropylamide |
| LDBB | lithium di-*tert*-butylbiphenylide |
| Lys | lysine |
| Me | methyl |
| min | minute(s) |
| MOM | (methoxymethoxy)methyl |
| Ms | methanesulfonyl |
| NBS | *N*-bromosuccinimide |
| NCS | *N*-chlorosuccinimide |
| NIS | *N*-iodosuccinimide |
| NMO | 4-methylmorpholine *N*-oxide |
| NMR | nuclear magnetic resonance |
| Pg | protecting group |
| Ph | phenyl |
| PPTS | pyridinium *p*-toluenesulfonic acid |

| | |
|---|---|
| *i*-Pr | *iso*-propyl |
| PSP | (phenylseleno)phthalimide |
| Pyr | pyridine |
| rt | room temperature |
| TBDMS | *tert*-butyldimethylsilyl |
| TBS | *tert*-butyldimethylsilyl |
| TCIA | trichloroisocyanuric acid |
| TLC | thin layer chromatography |
| TEMPO | 2,2,6,6-tetramethylpiperidine-1-oxyl |
| Tf | trifluoromethanesulfonyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TIPS | tri-*iso*-propylsilyl |
| TMEDA | tetramethylethylenediamine |
| TMS | trimethylsilyl |
| Tol | *p*-toluene- |
| Ts | *p*-toluenesulfonyl |
| TsOH | *p*-toluenesulfonic acid |

# CHAPTER 1

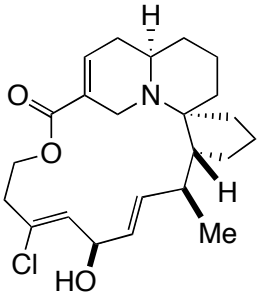
# Selenium-stabilized Carbanions

# 1. INTRODUCTION

## 1.1 General

A great number of synthetic methods involving organoselenium reagents have been developed during the past few decades.[1] Among these reagents, selenium-stabilized carbanions have proven to be useful synthons because the presence of the selenium moiety allows a number of selenium-based modifications[2] to be performed later in a synthesis. Selenium is known to increase the acidity of hydrogen atoms on $\alpha$ carbons by 10 to 15 pKa units[3] relative to the all-carbon counterparts and this enables carbanions adjacent to selenium to be used as stable nucleophiles in carbon-carbon bond forming reactions. Once a carbon-carbon bond is formed the selenium can be removed reductively[4] (by a radical process) or oxidatively[5] (by selenoxide fragmentation).

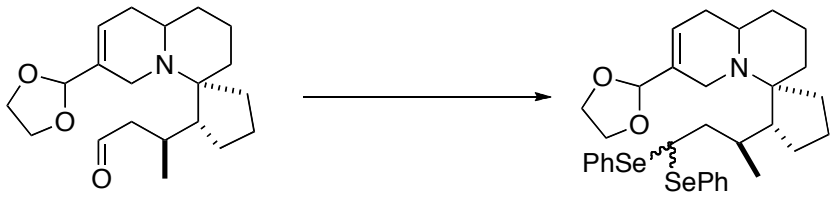
The most widely employed method for the formation of selenium-stabilized carbanions is to start with selenoacetals which are prepared via acid catalyzed reactions. A previous problem[6] met in this laboratory during the synthesis of halichlorine (**1**), required the generation of a selenium-stabilized carbanion, and it so happened that the selenoacetal route could not be used because an additional requirement imposed by the properties of the halichlorine substrate, was that acidic reagents be avoided.




**1**

The most effective route to selenoacetals involves the use of Brønsted or Lewis acids,[7] and so an alternative approach had to be developed in order to gain access to the required selenium-stabilized carbanion from the parent aldehyde.

In the original halichlorine synthesis the aldehyde was compound **1.1** (Scheme 1), and conversion into the selenoacetal **1.2** would have been an ideal route to the derived carbanion, by subsequent treatment with BuLi.

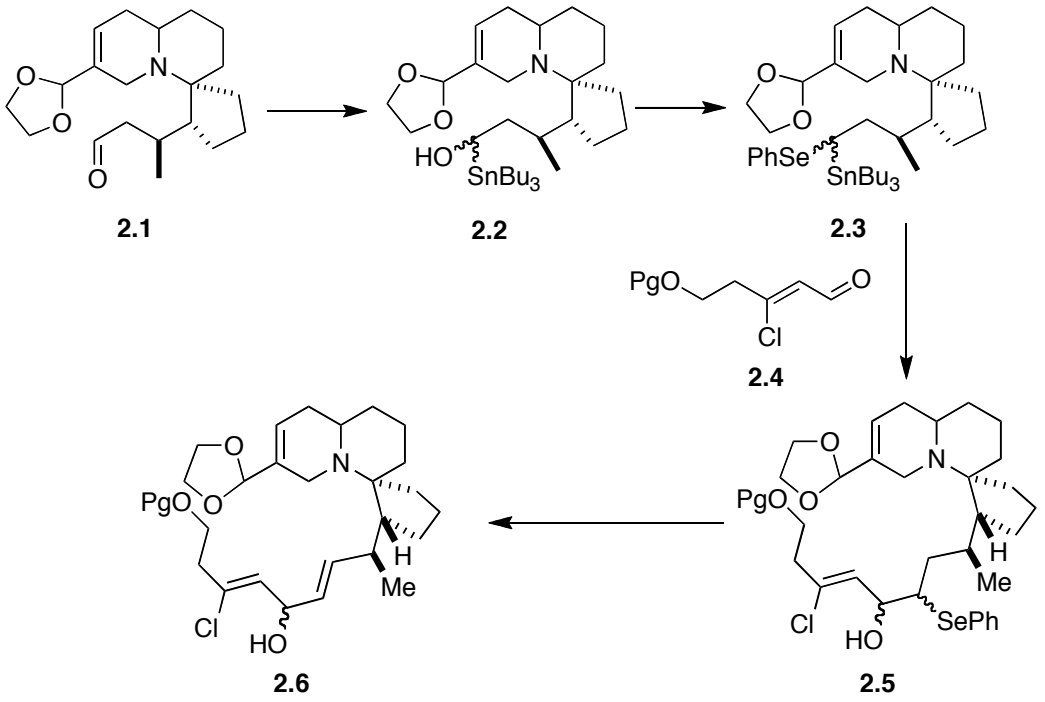



**1.1** **1.2**

**Scheme 1**

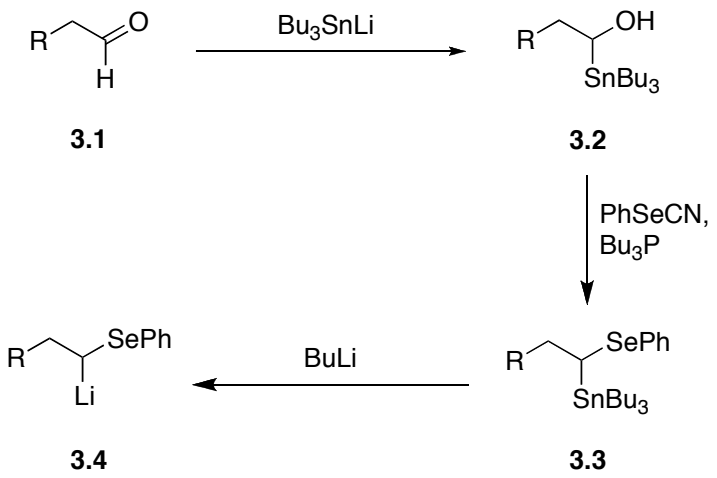
However, the use of acids was prohibited since **1.1** decomposed in their presence, and so an equivalent route to the carbanion was examined along the lines summarized in Scheme 2. As indicated in the Scheme, the approach involves addition of a tin anion to the aldehyde **2.1** so as to generate the stannyl

alcohol **2.2**. If the hydroxyl could be replaced by a PhSe group to give the stannyl selenide **2.3** then preferential Sn/Li exchange would deliver the desired carbanion which could be condensed with aldehyde **2.4** to give the desired hydroxyselenide **2.5**.




**Scheme 2**

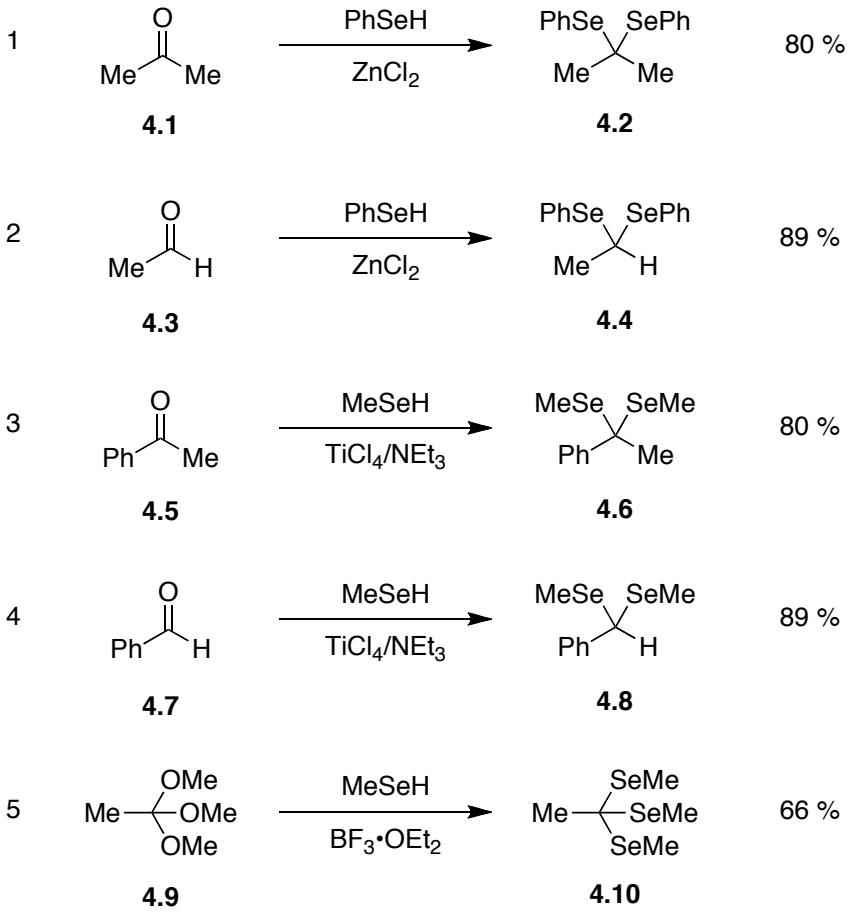
There was some precedent in the literature for the formation of stannyl selenides,[8,9] and it was also known[10] that the rate of Sn/Li exchange is about 15 times as fast as the rate of Se/Li exchange at -70 °C. On this basis, the proposed route of Scheme 3 appeared very worthy of examination, as I describe below, after presenting short reviews of the individual components of this Scheme.




**Scheme 3**

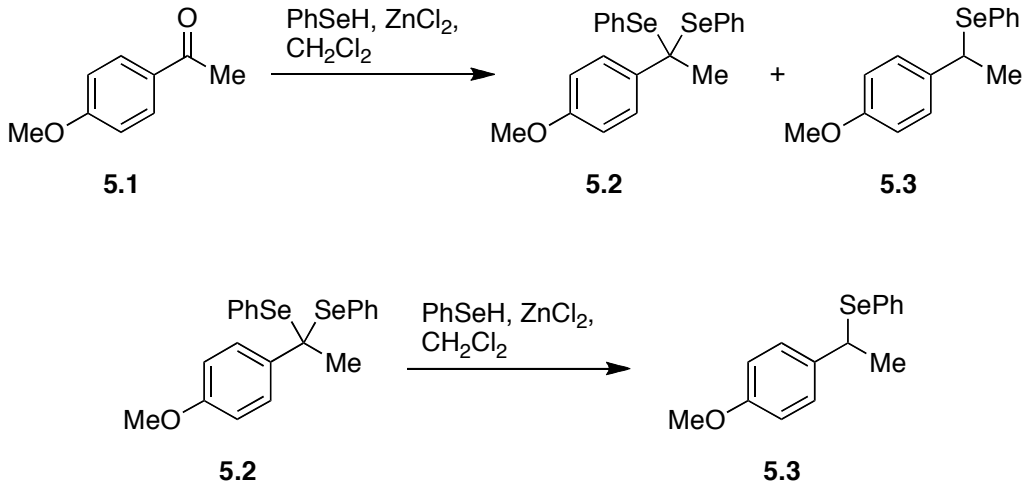
## 1.2 Routes to selenoacetals

Selenoacetals are important functional groups in organoselenium chemistry.[11] Their stability to basic conditions, mild acidic conditions, and nucleophilic reagents such as Grignard reagents has allowed functional group manipulations to be carried out smoothly in the presence of selenoacetals. Selenoacetals/selenoketals can be readily prepared using aldehydes/ketones[7] or acetals[12] and selenols at room temperature under Brønsted or Lewis acidic conditions.[7] In the case of aliphatic ketones and aldehydes (Scheme 4, Entries 1 and 2), $ZnCl_2$[7] is commonly used as the Lewis acid and in the case of aromatic ketones and aldehydes (Scheme 4, Entries 3 and 4), $TiCl_4$[13] is the Lewis acid of choice. If an orthoester is used in place of an acetal then the result will be an orthoselenoester[14] (Scheme 4, Entry 5).



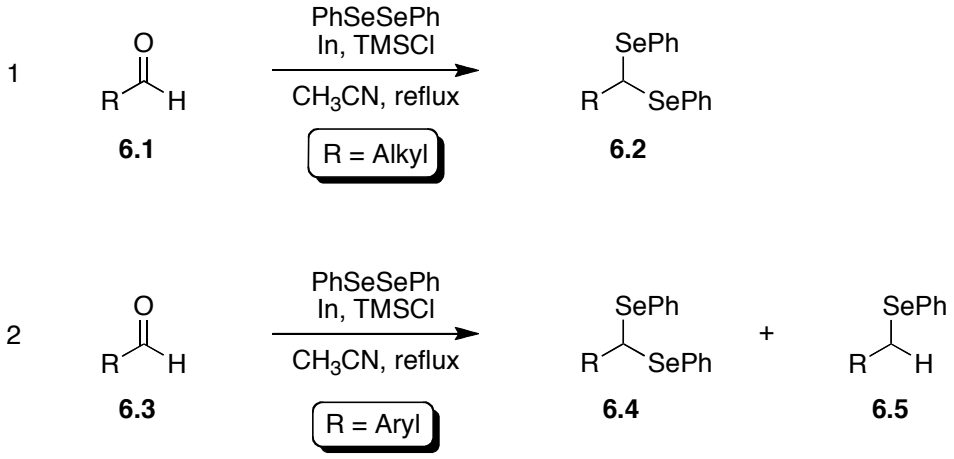

**Scheme 4**

A major difficulty encountered in the preparation of selenoacetals and selenoketals from aldehydes and ketones, using PhSeH and $ZnCl_2$ as the Lewis acid, is that the selenoacetal and selenoketals (**5.2**) undergo over reduction to give the corresponding selenide (**5.3**) exclusively or in significant quantity (Scheme 5).[13] In order to test the hypothesis that it is indeed an over reduction of the selenoketal (**5.2**) that gives the corresponding selenide (**5.3**), a sample of a selenoketal prepared via a different route was treated with a selenol in the presence of $ZnCl_2$, and the corresponding selenide that was expected was obtained in 95% yield along with some diselenide, proving that the hypothesis is valid.




**Scheme 5**

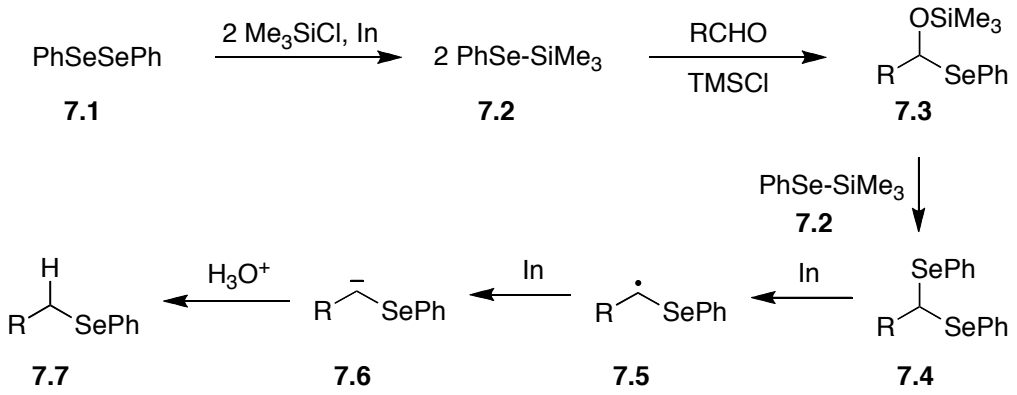
A novel route to the formation of selenoacetals starting with aldehydes and PhSeSePh through the mediation of In metal and $Me_3SiCl$ (TMSCl) was reported by Ranu and Mandal in 2006.[11] However, the scope of this method was limited: the method applies only to aldehydes and not to ketones. Moreover, when heated at reflux in MeCN, aliphatic aldehydes and PhSeSePh in the presence of In-TMSCl gave the desired selenoacetal (Scheme 6, Entry 1) while, under the same conditions aromatic aldehydes gave either exclusively the corresponding selenide or a mixture of the selenoacetal and the selenide (Scheme 6, Entry 2).




**Scheme 6**

Similar to the over reduction of selenoacetals to selenides in the $ZnCl_2$ catalyzed reactions mentioned above, over reduction was observed in the case of In-TMSCl mediated reactions upon prolonged reaction times when aryl aldehydes were used as the substrate. This problem was encountered only with aryl aldehydes, and aliphatic aldehydes were unaffected. Suspecting that the selenoacetal was the intermediate in the route to the selenide, a pure sample of the selenoacetal of 3-bromobenzaldehyde was subjected to the same reaction conditions and most of the selenoacetal, even though not 100%, was converted into the corresponding selenide in 6 h. The same experiment was repeated using an aliphatic selenoacetal and no conversion to the corresponding selenide was observed, even after longer reaction times. The exact reason for this over reduction of aryl selenoacetals was not identified, but it was observed that in the case of 2-methoxybenzaldehyde, adding 4-hydroxy TEMPO, which is a radical quencher, to the reaction medium suppressed the over reduction considerably. A 1:1 mixture of the selenoacetal and the selenide was obtained in the presence of

the radical quencher in 5 h, while under the same reaction conditions in the absence of the radical quencher the selenide was obtained exclusively in 3 h. The same reaction was done using an aliphatic aldehyde and there was no conversion of the aliphatic selenoacetal to the corresponding selenide. These observations and previous knowledge of In metal as a radical initiator[15] led the authors to speculate that a free radical process is involved in the conversion of the selenoacetal to the selenide. This is favored only by an aromatic substituent and the following pathway was proposed (Scheme 7).

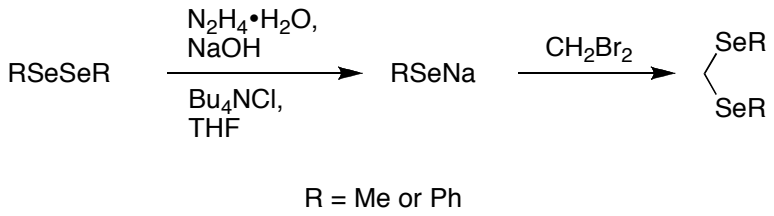



**Scheme 7**

It was discovered that the reaction did not proceed in the absence of either In metal or TMSCl. The absolute necessity of these two reagents was further proven when the reaction failed to proceed if $BF_3 \bullet Et_2O$ was used in place of $Me_3SiCl$ and when InI was used in place of In metal.

In 1984 Syper and Mlochowski reported[16] that a simple preparation of selenoacetals is by the alkylation of alkyl or arylseleno anions. Treatment of sodium selenolates with 1,1-dihalo compounds gave alkyl or arylselenoacetals in

good yields. The sodium selenolates were prepared by treating dialkyl or diaryl selenides with $N_2H_4 \bullet H_2O$ and NaOH in THF in the presence of catalytic $Bu_4NCl$ (Scheme 8).



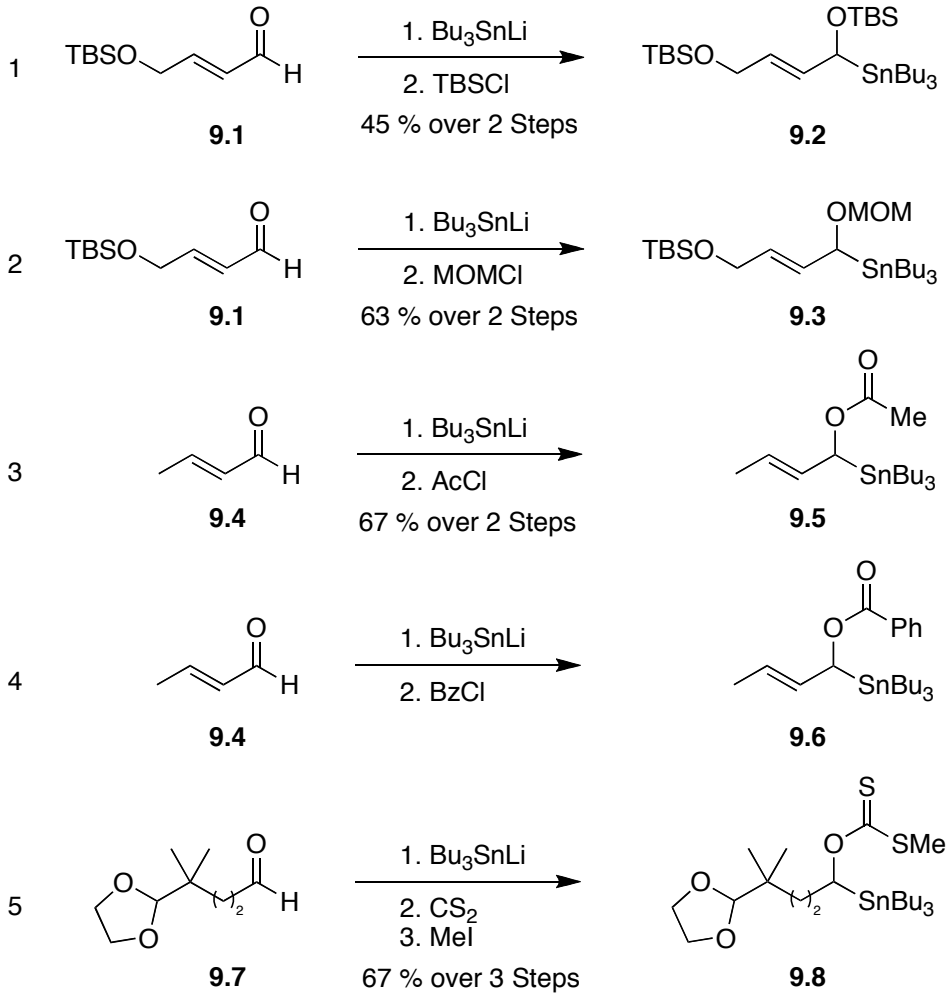

**Scheme 8**

## 1.3 Formation of α-hydroxystannanes

α-Hydroxyorganostannanes have gained considerable attention in organic chemistry as precursors to α-alkoxy organostannanes, which are increasingly popular for their ability to undergo Sn-metal exchange to give α-alkoxy organolithium and α-alkoxy organocopper reagents.[17] The major difficulty encountered in handling α-hydroxy organostannanes is that these compounds are labile and are known to decompose during chromatography, upon contact with acid, and on prolonged standing.[18] There are several well-known methods of preparing α-hydroxystannanes: addition of trialkylstannyl anions to carbonyls, reduction of acyl stannanes, and reaction of trialkylstannyl halides with α-alkoxy organolithium reagents.

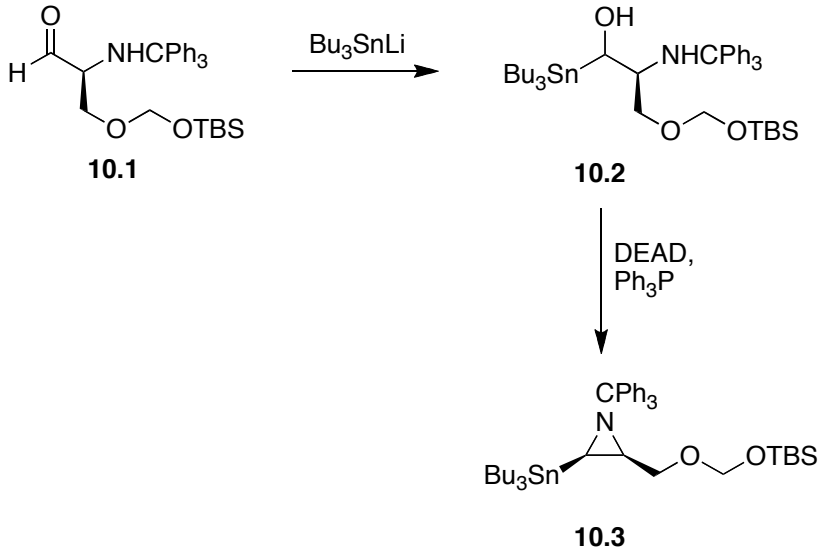
*1.3.1 Addition of trialkylstannyl anions to carbonyls:*

Trialkylstannyl anions add to carbonyls resulting in α-hydroxystannanes. These alcohols are highly unstable[19] and in most cases they are immediately silylated,[20] alkylated,[20] or acylated,[19] or converted into xanthates[21] before extensive purification (Scheme 9). Unprotected hydroxy stannanes are highly sensitive to acidic conditions. Acidic workup or chromatography using silica gel is often detrimental and leads to loss of product.



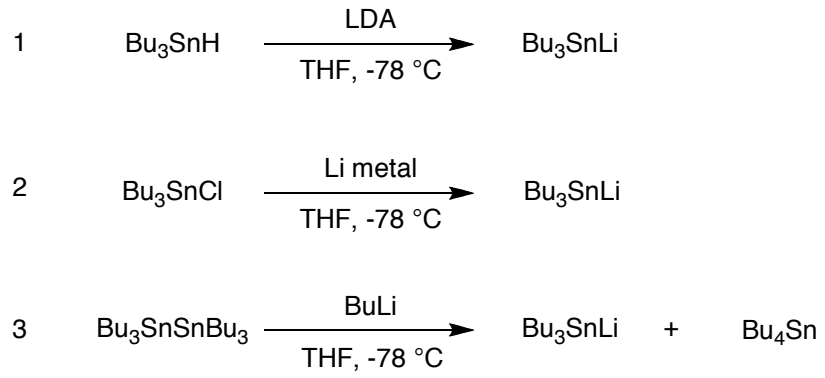

**Scheme 9**

Vedejs and coworkers reported[22] that α-hydroxystannanes can undergo intramolecular Mitsunobu reactions upon treatment with DEAD and $Ph_3P$ (Scheme 10). In this particular case α-hydroxystannane **10.2** was converted to stannylaziridine **10.3** by displacing the hydroxyl group by a neighboring amine.



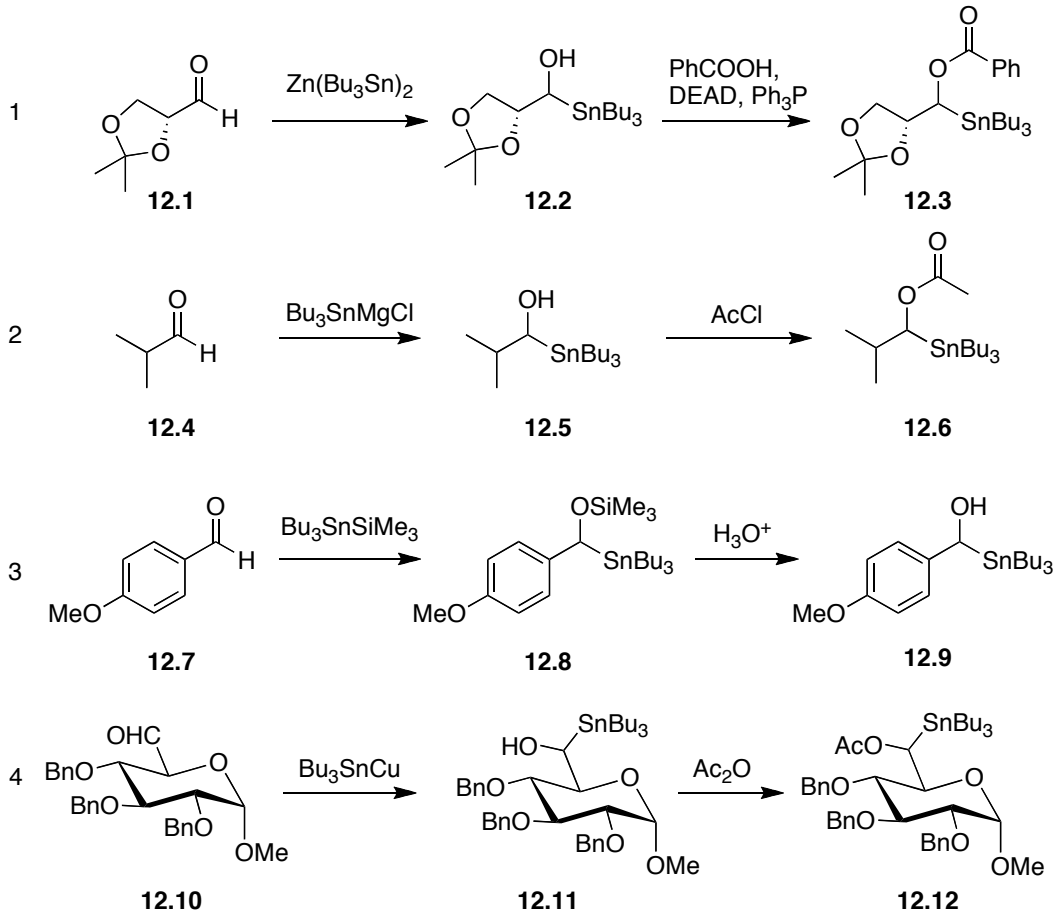

**Scheme 10**

There are several different forms of trialkylstannyl anions reported in the literature (Scheme 11). Out of these, trialkylstannyllithiums seem to be the most commonly used trialkylstannyl anions and these are prepared in a few different ways. $Bu_3SnH$ can be deprotonated using a strong base such as LDA in THF at -78 °C.[22] Also, $Bu_3SnCl$ with Li metal in THF at -78 °C gives $Bu_3SnLi$.[23] $Bu_3SnSnBu_3$ reacts with BuLi in THF at -78 °C to give inactive $Bu_4Sn$ and $Bu_3SnLi$.[24]




**Scheme 11**

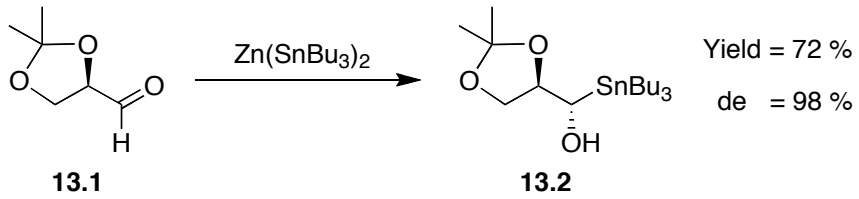
Nucleophilic trialkylstannyl anions are also available in other forms besides their Li salts (Scheme 12). They are accessible from tin-zinc,[25,26] tin-magnesium,[27] tin-copper[28] and tin-silicon,[29,30] reagents.




**Scheme 12**

Falck and coworkers reported[26] that when an α-alkoxystannane with a defined stereochemistry is needed, the tin-zinc reagents give very high diastereoselectivity compared to the Sn-Li and Sn-Mg compounds (Scheme 13). When Sn-Li and Sn-Mg were added to prochiral aldehydes under different reaction conditions a mixture of *syn* and *anti* products was obtained. When the same aldehyde **13.1** was treated with the Sn-Zn reagent good yields (72%) and excellent diastereoselectivity (de = 98%) were obtained, favoring the *anti* product **13.2**. The authors propose that the carbonyl addition of the trialkylstannyl anion

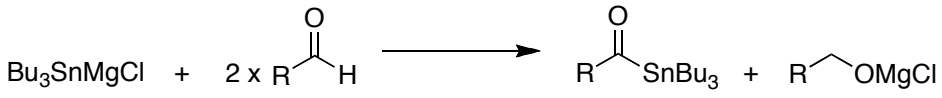
in the presence of Zn metal follows a nonchelating Felkin model. It is not clear why, in the presence of chelating metals such as Li and Mg, the selectivity is lost yielding a mixture of *syn* and *anti* products.




**13.1** **13.2**

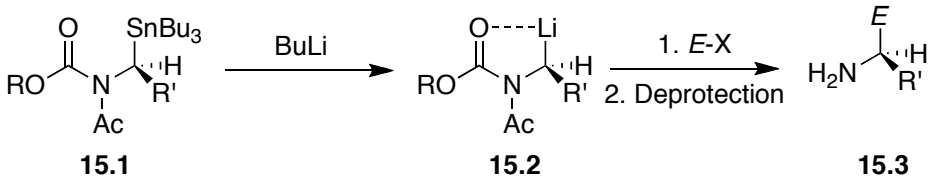
**Scheme 13**

Trialkylstannylmagnesium halides have been used as a source of nucleophilic trialkylstannyl anions.[27] In 1987 Kosugi and coworkers reported[31] the use of $Bu_3SnMgCl$ in Cannizzaro type reactions of aldehydes to prepare acyltin compounds (Scheme 14). For this purpose, an excess of aldehyde was treated with $Bu_3SnMgCl$ which was prepared by reacting *i*-PrMgCl with $Bu_3SnH$. This Cannizzaro type reaction was attempted using other tributylstannyl metal reagents such as $Bu_3SnLi$, $Bu_3SnZnCl$, $Bu_3SnZnSnBu_3$, $Bu_3SnSiMe_3$, and $Bu_3SnSnBu_3$ but in all these cases the required reaction did not occur.




**Scheme 14**

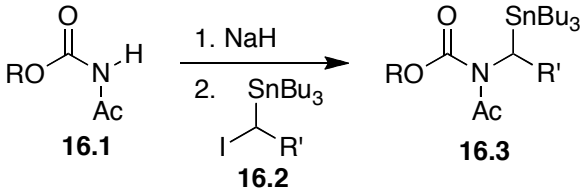
In 1993 Pearson and coworkers reported[32] a route to α-substituted primary amines via *N*-acylated α-aminostannanes (Scheme 15). A Sn/Li exchange on the *N*-acylated α-aminostannanes (**15.1**) gave an organolithium species (**15.2**) that reacted stereospecifically with electrophiles. Upon reaction with an electrophile and deprotection of the nitrogen an α-substituted primary amine was released (**15.3**).




**15.1** **15.2** **15.3**

**Scheme 15**

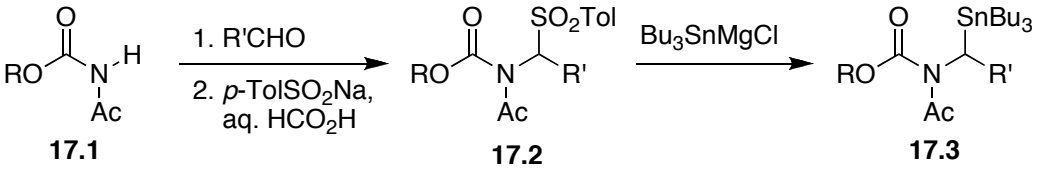
In previous cases[33] the *N*-acylated α-aminostannanes (**16.3**) were prepared by reacting the sodium salt of a carbamate (**16.1**) with an α-iodoalkylstannane (**16.2**) (Scheme 16). However this method has always been somewhat problematic since, except for (iodomethyl)trialkylstannanes and (1-iodoethyl)trialkylstannanes, α-iodo-alkyl-stannanes are not readily available and the elimination of the iodide has often been a problem.




**16.1** **16.2** **16.3**

**Scheme 16**

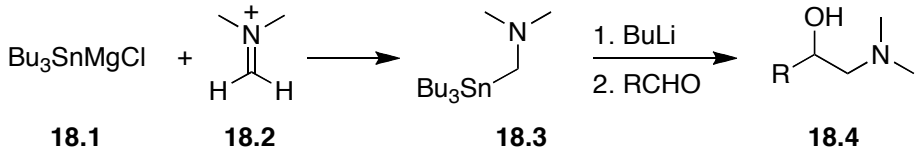
In order to overcome the difficulties in preparing the *N*-acylated α-aminostannanes a novel synthetic route was developed starting with an *N*-acylated amine (Scheme 17). The carbamate **17.1** was first condensed with an aldehyde and the newly formed secondary alcohol was converted into the sulfone **17.2** by reaction with sodium *p*-toluenesulfinate and HCOOH. Displacement of the sulfone with tributyltin anions gave the desired *N*-acylated α-aminostannanes **17.3**. Besides $Bu_3SnMgCl$, the corresponding Zn and Li salts were also effective, although $Bu_3SnMgCl$ gave only moderate yields (~30%).




**Scheme 17**

In 1988 Quintard and coworkers reported[34] a regiospecific route to β-aminoalcohols (Scheme 18). In this novel methodology $Bu_3SnMgCl$ was used as trialkylstannyl anion equivalent. $Bu_3SnMgCl$, which was prepared by treating $Bu_3SnH$ with *i*-PrMgCl, reacts with immonium salts (**18.2**) and gives nonsubstituted, α-substituted, or α,α-disubstituted aminomethyltributylstannanes (**18.3**). These reactions are not affected by the nature of the counter anion of the immonium salt. Aminomethyltributylstannanes undergo Sn/Li exchange upon treatment with BuLi. The organolithium species can then be condensed with

carbonyl compounds such as aldehydes or ketones to give a route to β-aminoalcohols (**18.4**).



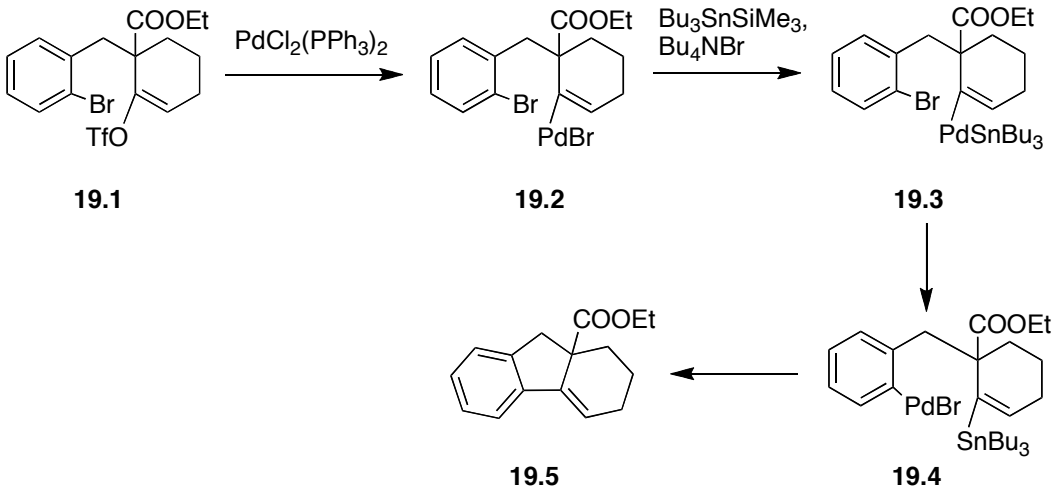

**18.1** **18.2** **18.3** **18.4**

**Scheme 18**

Trialkylstannylsilanes are used commonly with base-sensitive or highly functionalized substrates as they are known to be mild reagents. Bhatt and coworkers reported[30] that using $Bu_3Sn\text{-}SiMe_3$ and $Bu_4N^+CN^-$ with aliphatic aldehydes gave the silyl protected hydroxy stannane, which was purified on a silica gel column and both protected and deprotected hydroxystannanes were obtained in excellent yield. Since protected hydroxystannanes have relatively higher stability on silica gel, silyl protected hydroxystannanes undergo minimum or no loss of product during purification. The silyl protected hydroxystannane was conveniently deprotected through an aqueous work-up with dilute acid (Scheme 12, Entry 3).

Mori and coworkers reported[29] the use of $Bu_3Sn\text{-}SiMe_3$ as a source of tributylstannyl anion in transmetallation reactions (Scheme 19). The silylated stannane was treated with $Bu_4NBr$ to generate the stannyl anion. In this experiment $Bu_3Sn\text{-}SiMe_3$ was used to transmetallate a stannane onto Pd that had been inserted into a C-OTf bond. First Pd(0) was oxidatively added to the vinyl triflate **19.1** and the triflate was converted to the bromide **19.2**. Then, by

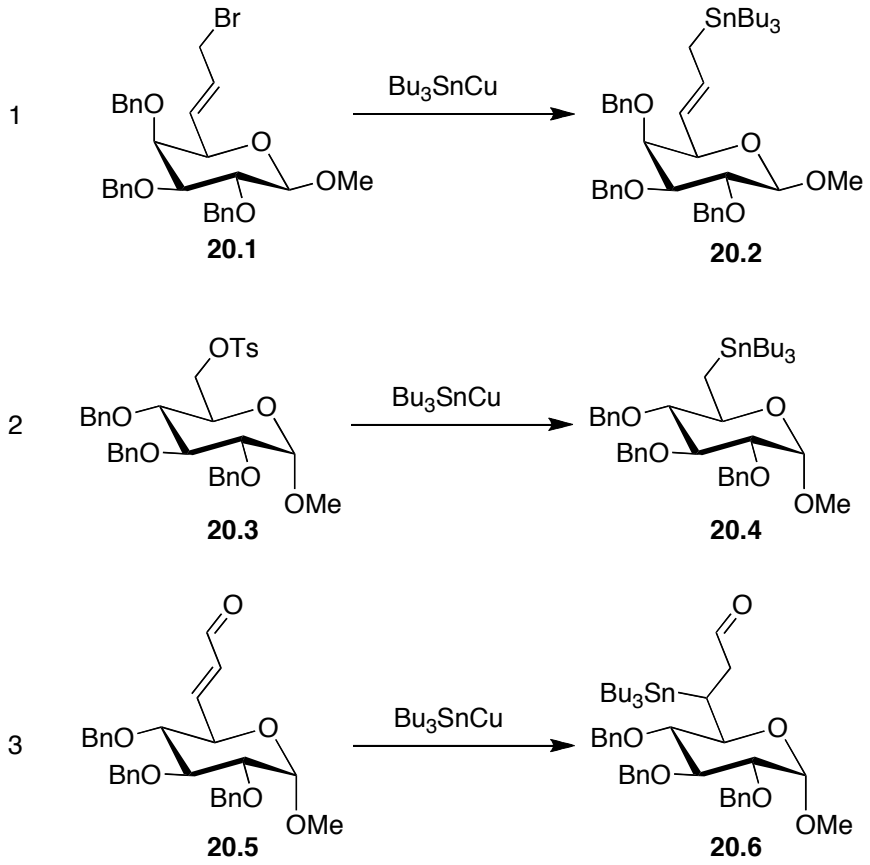
transmetallation of the stannyl group onto the Pd, the vinylpalladium stannane **19.3** was generated. Reductive elimination of the vinyl stannane and oxidative addition of the palladium to the aryl bromine bond (**19.3→19.4**) set the stage for an intramolecular transmetallation; finally, reductive elimination of the palladium gave the desired cyclized product **19.5**.




**Scheme 19**

In 1996 Jarosz reported[28] the application of trialkylstannylcuprates as trialkylstannyl anion equivalents (Scheme 20). Among several uses of trialkylstannylcuprates, one was used to displace bromides from allyl bromides mounted onto a sugar moiety with retention of the double bond geometry (**20.1→20.2**). This same reaction had been attempted previously with $Bu_3SnLi$ and complete destruction of the starting material was observed. Less reactive substrates such as tosylated sugars that are known to give poor yields with $Bu_3SnLi$ were converted smoothly in good yields into stannylated sugars with the

Cu reagent (**20.3→20.4**). Addition of $Bu_3SnLi$ to conjugated aldehydes gives a mixture of 1,4- and 1,2-addition products. Complete decomposition of starting material occurred when $Bu_3SnLi$ was added to sugar **20.5** containing a conjugated aldehyde. However, the addition of $Bu_3SnCu$ to sugar **20.5** gave the 1,4-addition product cleanly (**20.5→20.6**).



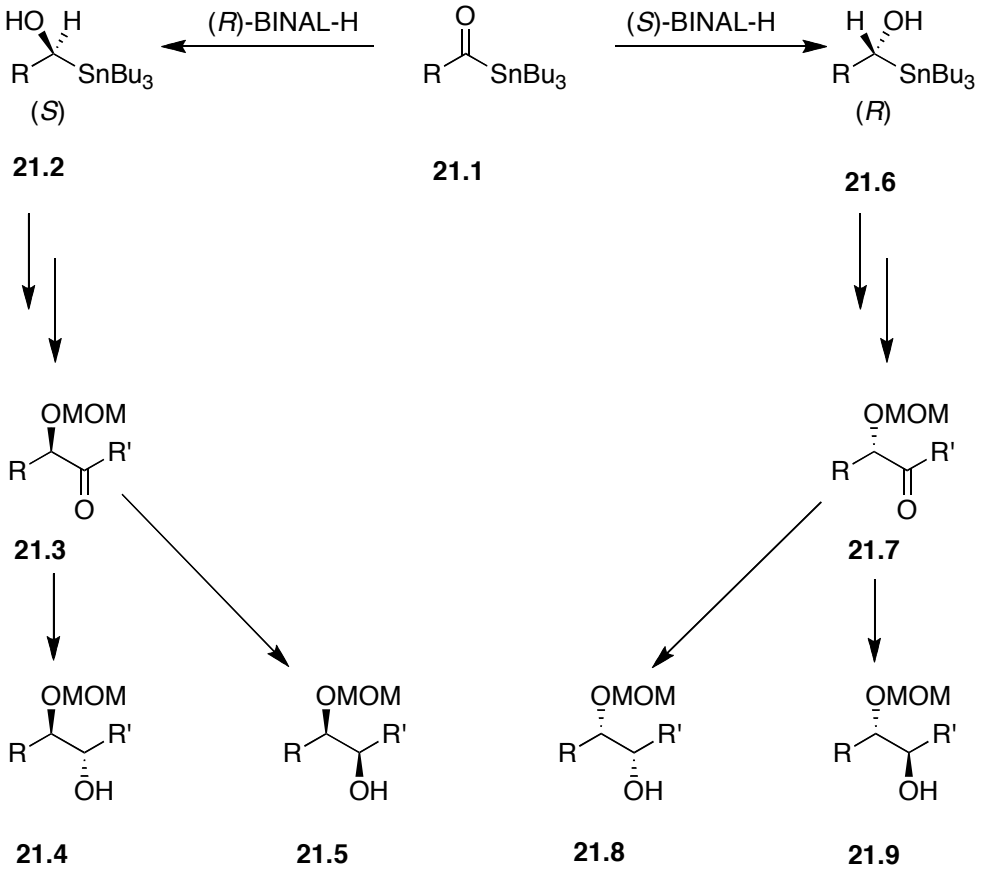

**Scheme 20**

*1.3.2 Reduction of acyl stannanes:*

α-Hydroxystannanes have also been prepared by reduction of the carbonyl group of acylated stannanes. The acylated stannanes themselves have been

prepared by addition of a trialkylstannyl anion to an aldehyde and then carrying out an in situ oxidation using the Mukaiyama protocol[35] with azodicarbonyldipiperidide (ADD) which acts as a hydride acceptor.[36] α-Hydroxystannanes prepared by adding a trialkylstannyl anion to an aldehyde results in very poor or no stereoselectivity. Therefore, by oxidizing the α-hydroxystannane to the corresponding acylstannane and stereoselectively reducing the carbonyl, enantiomerically enriched α-hydroxystannanes can be prepared.

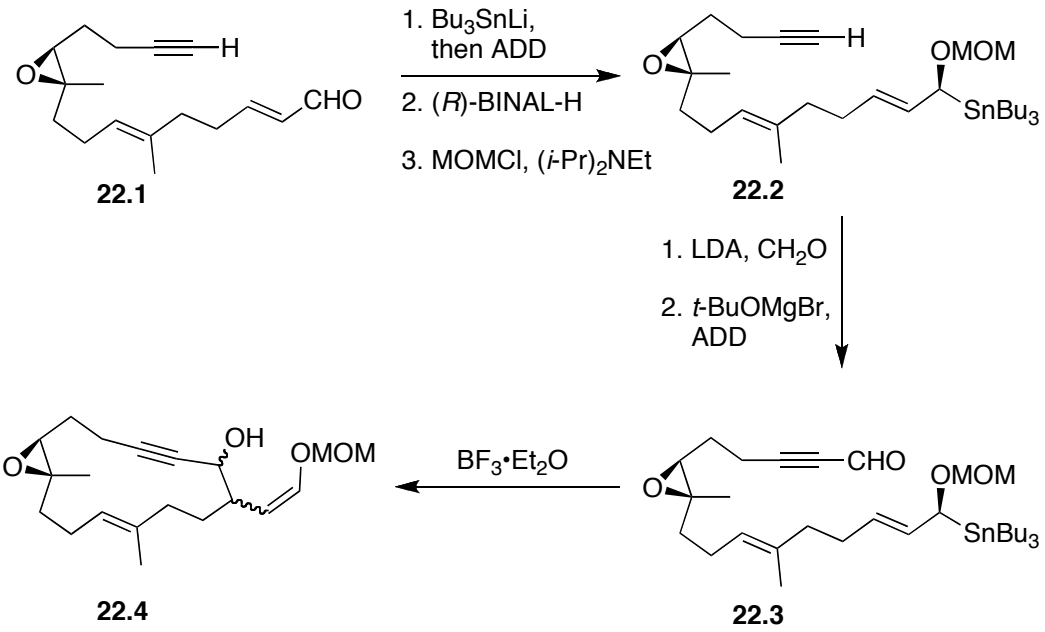
Chong and Mar showed that once prepared, the carbonyl of the acyl stannane can be reduced asymmetrically to get an α-hydroxystannane in excellent enantiomeric purity (>98%), using 2,2'-dihydroxy-1,1'-binaphthyl-modified lithium aluminum hydride (BINAL-H).[37] By converting an α-alkoxystannane with a defined stereochemistry into an α-alkoxyketone (via an α-alkoxylithium obtained by Sn/Li exchange) (**21.2→21.3** and **21.6→21.7**) followed by a selective chelation-controlled reduction, it is possible to selectively obtain enantiomerically enriched *syn*- or *anti*-diols (Scheme 21).




**Scheme 21**

Marshall and coworkers showed the application of allylic α-alkoxystannanes as precursors for cyclization reactions in the synthesis of macrocycles.[36,38,39] (Scheme 22) Following the protocol reported by Chong and Mar mentioned[37] above, $Bu_3SnLi$ was added to an unsaturated aldehyde followed by in situ oxidation with ADD. Then stereoselective reduction with (*R*)-BINAL-H and MOM protection of the α-hydroxystannane gave the allylic α-alkoxystannanes in excellent enantiomeric purity (**22.1→22.2**). This allylic α-alkoxystannane was used as the precursor in a cyclization reaction (**22.3→22.4**) to

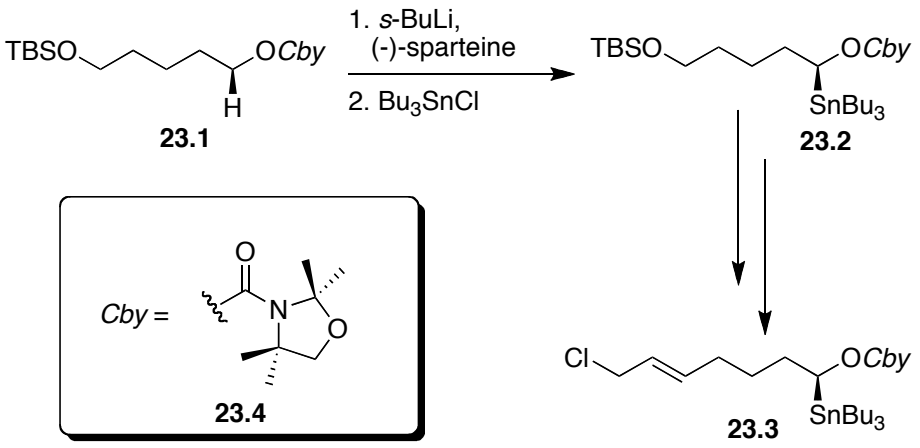
form a macrocyclic intermediate towards the total synthesis of macrocyclic natural products cembranolides I and II.[39]




**Scheme 22**

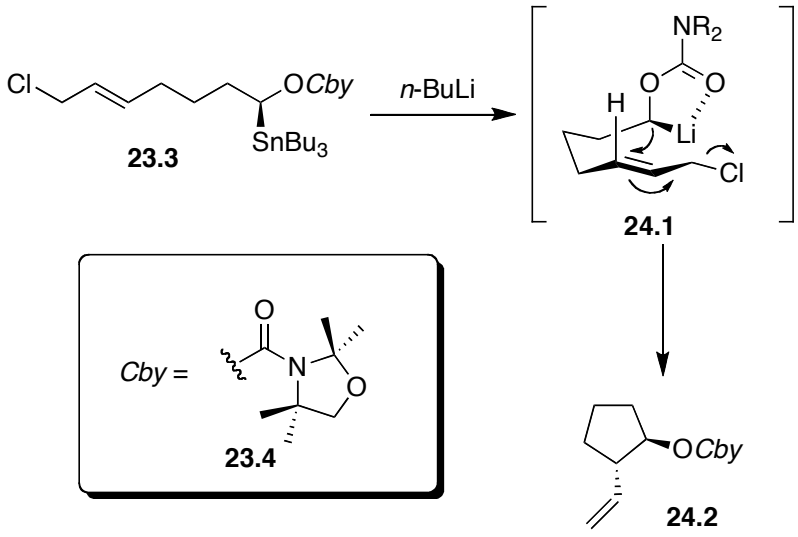
*1.3.3 Addition of trialkylstannylhalides to α-alkoxyorganolithium:*

Hoppe and coworkers reported[40,41] that α-alkoxyorganolithiums react with trialkylstannyl halides to give α-alkoxystannanes (Scheme 23). Alkyl carbamates (**23.1**) were deprotonated using *s*-BuLi in the presence of (-)-sparteine and subsequently treated with trialkylstannyl halides to give highly enantioenriched protected α-alkoxystannanes (**23.2**). These α-alkoxystannanes can be viewed as stable carbanion equivalents since they can be prepared at an earlier stage of the synthesis and carried forward until conveniently converted to α-alkoxyorganolithiums by reaction with BuLi.



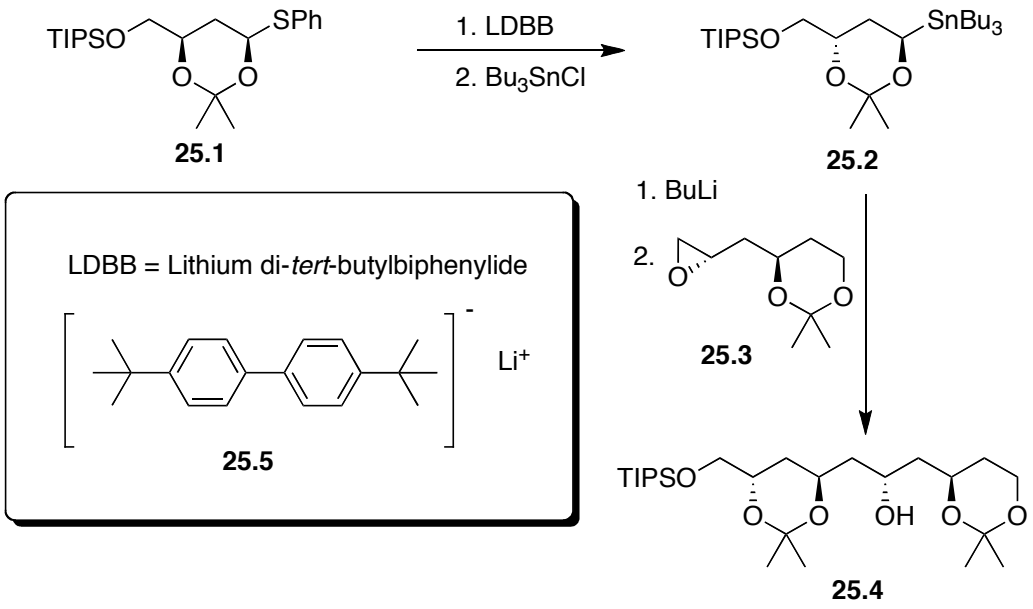

**Scheme 23**

Upon destannylation with BuLi, the resulting α-alkoxyorganolithiums (**24.1**) undergo stereoselective cycloalkylation to give cyclopentanes (**24.2**) in very good yields (96%) and high enantiomeric purity (> 95% ee) (Scheme 24).




**Scheme 24**

Similar to the work done by Hoppe, Rychnovsky reported[42] the formation of α-alkoxystannanes via α-alkoxyorganolithiums and trialkylstannyl halides (Scheme 25). However, in this case the α-alkoxyorganolithium was prepared by reduction of a hemithioacetal (**25.1**) with lithium di-*tert*-butylbiphenylide (LDBB) (**25.5**) instead of by deprotonation. At low temperatures (-78 °C) the kinetic axial alkyllithium is obtained as the major product and upon warming to higher temperatures (-20 °C) the axial alkyllithium epimerizes to the thermodynamically more stable equatorial alkyllithium. Using this information this methodology was applied towards the synthesis of polyol chains (**25.4**) with defined stereocentres.

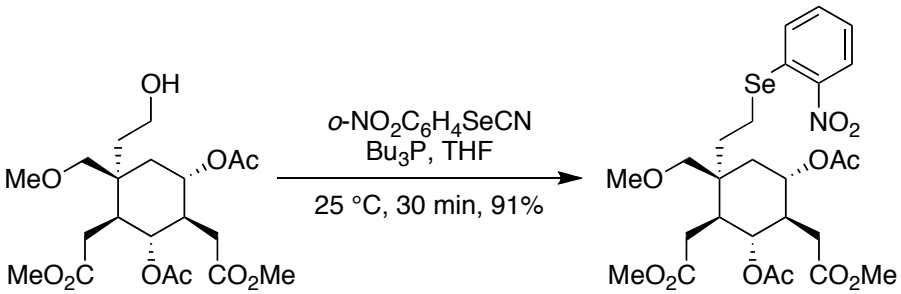



**Scheme 25**

## 1.4 Conversion of alcohols into selenides

Grieco and coworkers reported[43] that treatment of a variety of primary alcohols with *o*-nitrophenylselenocyanate and $Bu_3P$ in THF or pyridine at room

temperature resulted in a very high yield ( >90%) of primary alkyl selenides (Scheme 26). Prior to this one-step procedure, primary alcohols were converted into alkyl selenides in two steps by first converting the alcohols to the corresponding mesylate or tosylate and then displacing the leaving group with a selenide anion. This two-step procedure resulted in lower yields than the method developed by Grieco.



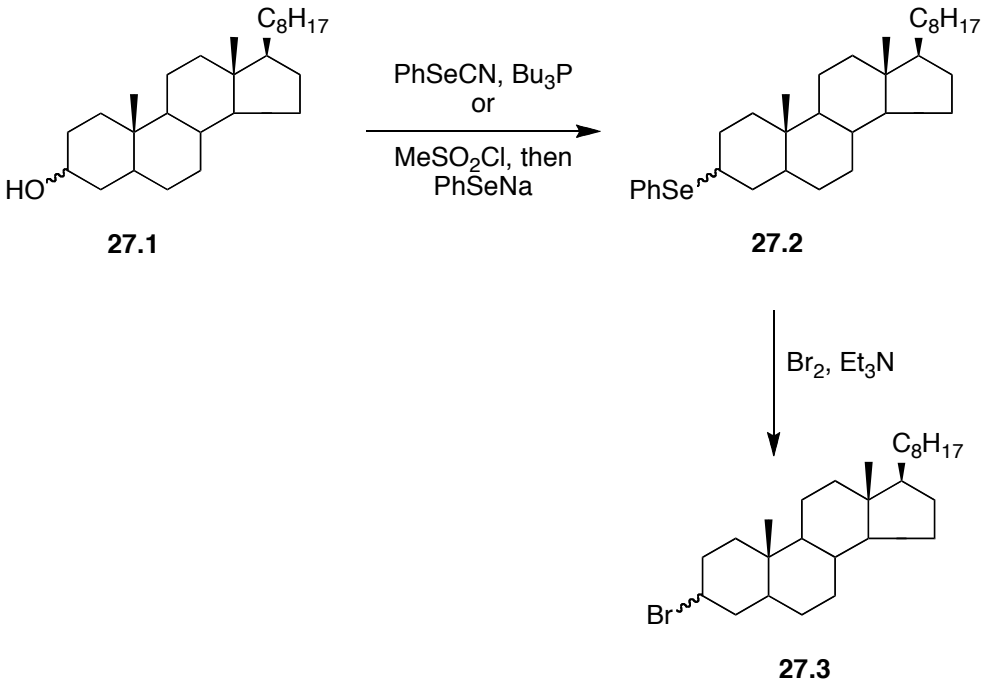

**26.1** **26.2**

**Scheme 26**

The highly functionalized primary alcohol **26.1** (Scheme 26) was converted to the alkyl selenide (**26.2**) using *o*-nitrophenylselenocyanate and $Bu_3P$ in 91% yield; the same alcohol was converted to the alkyl selenide using the two step procedure in only 77% yield. This one-step conversion of alcohols to selenides can also be performed using PhSeCN but does not proceed with di-*o*-nitrophenyl diselenide, PhSeSePh, or PhSeCl. Similar to primary alcohols, secondary alcohols can also be converted into secondary alkyl selenides using either *o*-nitrophenylselenocyanate or PhSeCN in similar yields. For example, *i*-

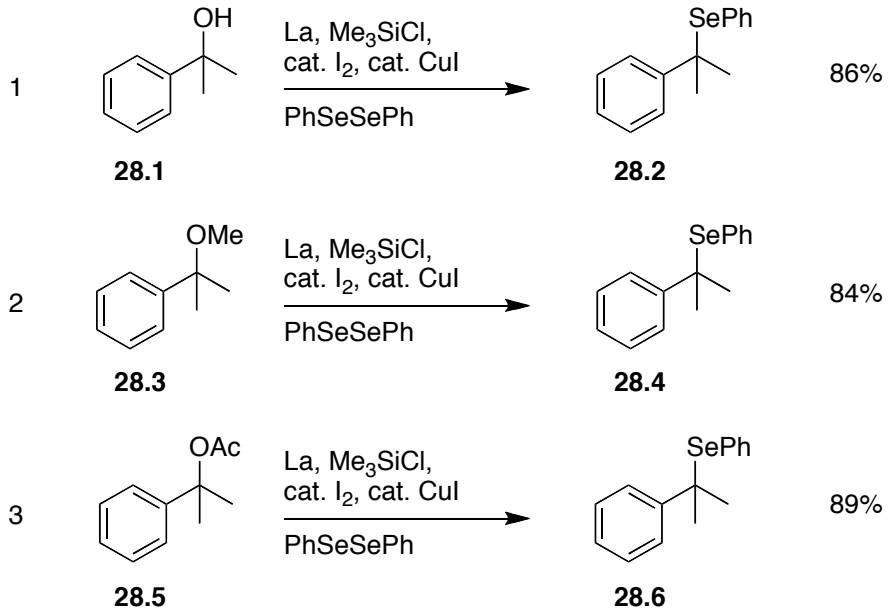
PrOH was converted to the corresponding isopropyl selenide using *o*-nitrophenylselenocyanate in 93% yield, using PhSeCN the yield was 85%.

Krief and Sevrin reported[44] the use of alkyl selenides as intermediates in a novel route to alkyl bromides from secondary alcohols (Scheme 27). In this two-step process the secondary alcohol **27.1** was first converted to the corresponding selenide **27.2** and the selenide was then converted to the bromide **27.3**. Conversion of the alcohol to the selenide was achieved through two different methods, with either PhSeCN with $Bu_3P$ or by protecting the alcohol with $MeSO_2Cl$ and then displacing the mesylate with PhSeNa. Once the selenide was prepared it was converted to the bromide using $Br_2$ and $Et_3N$. The functional group manipulation occurred with a high degree of retention of configuration (>92%) and in reasonable yield (60%). The methodology was applied to prepare 2-bromooctane, cyclohexyl bromide, and 3β-bromocholestane.



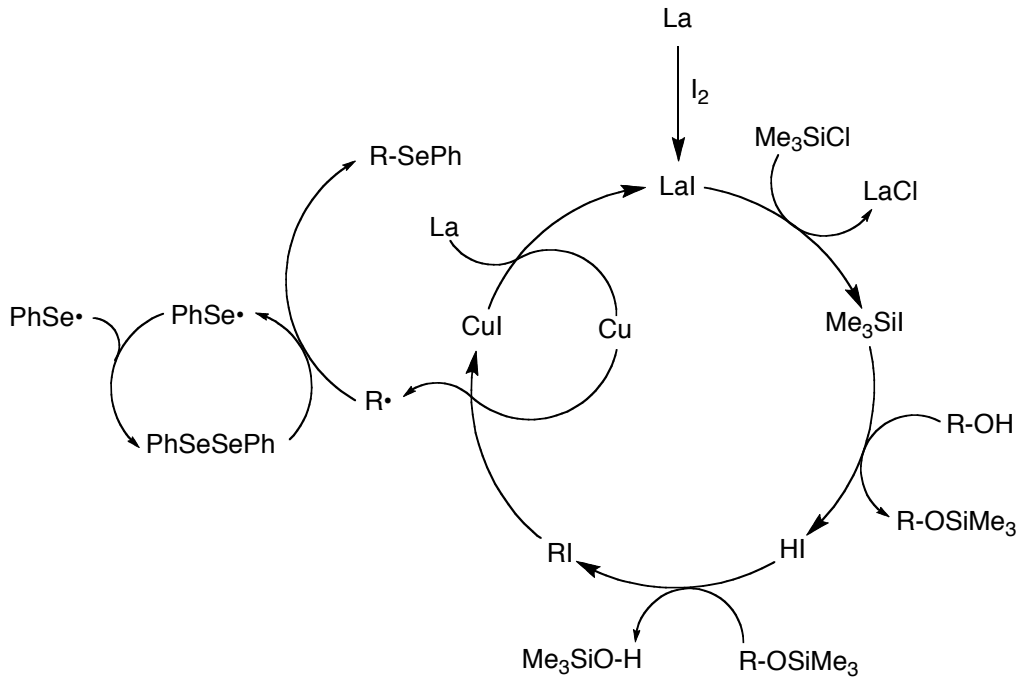

**Scheme 27**

In 2003 Sonoda and coworkers reported[45] that alcohols can be converted to alkyl selenides by the use of La, $Me_3SiCl$, and catalytic amounts of $I_2$ and CuI, along with PhSeSePh as the source of Se. This methodology can be applied successfully for the conversion of tertiary alcohols to tertiary alkyl selenides in good yields. Besides alcohols, the method has been applied successfully to ethers and esters to give high yields (Scheme 28).



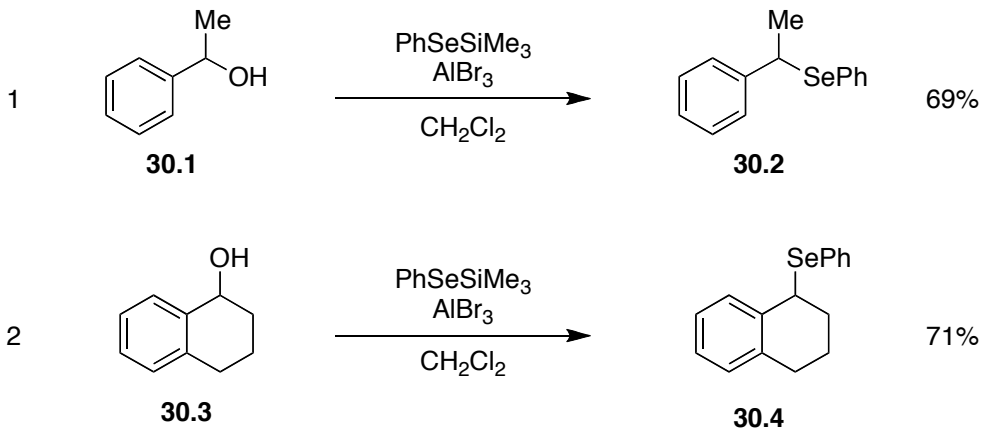

**Scheme 28**

Sonoda and coworkers have proposed that the conversion of the alcohols to the corresponding selenides occurs via a radical process. First the La, $Me_3SiCl$, $I_2$, and CuI reduces the alcohol to an alkyl radical and then the alkyl radical is captured by the PhSeSePh, which is an efficient radical scavenger, to give an alkyl phenyl selenide (Scheme 29).



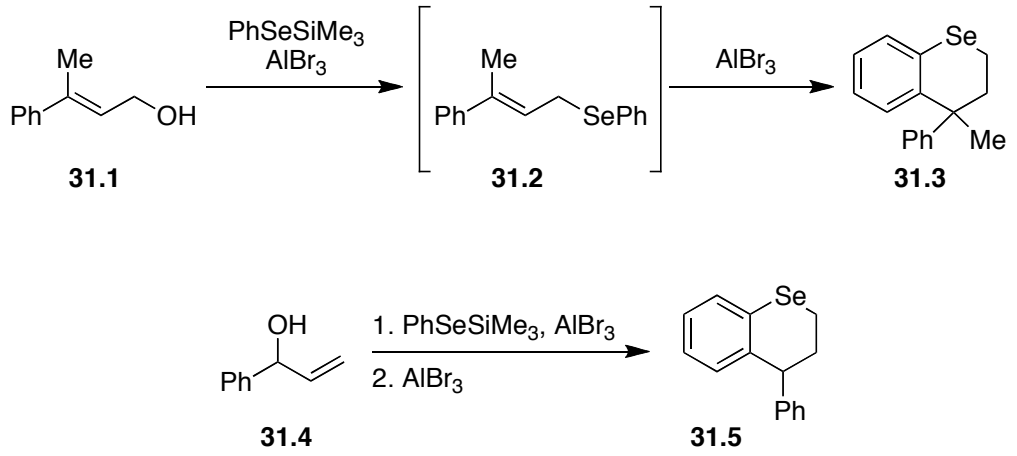

**Scheme 29**

In 1998 Yarayama and coworkers reported[46] that benzylic alcohols can be converted to the corresponding selenides using a combination of $PhSeSiMe_3$ and $AlBr_3$ (Scheme 30). Formerly, $PhCH_2OH$ were converted to selenides (**30.1→30.2** and **30.3→30.4**) by treating the alcohol with a selenolate anion generated by the reductive cleavage of PhSeSePh in the presence of $AlCl_3$ at high temperatures. The $PhSeSiMe_3$ and $AlBr_3$ combination is considered to be much milder than the selenolate and $AlCl_3$ since the former does not require high temperatures and harsh reductive conditions.



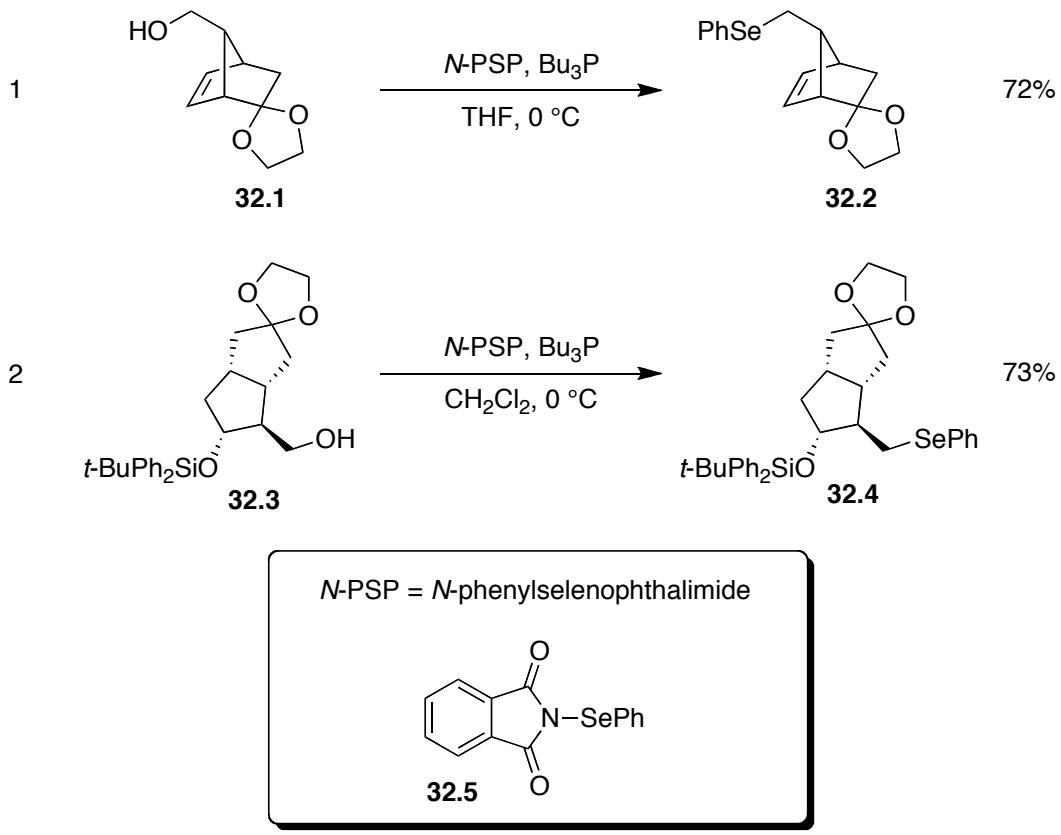

**Scheme 30**

As a follow up to their 1998 work, in 2001 Yarayama and coworkers reported[47] a one-pot conversion of allylic alcohols into selenium containing heterocycles (selenochromans) through an allylic selenide intermediate that is formed in situ (Scheme 31). $Me_3SiSePh$ and $AlBr_3$ were used to convert the allylic alcohols into the selenides and an extra portion of $AlBr_3$ was used as a Lewis acid to prepare the selenochroman. To test the hypothesis that the reaction proceeds via an allylic selenide the reaction was performed using substrate **31.4** under the same reaction conditions as for the other substrates. The expected selenochroman **31.5** was obtained in moderate yield (41%), proving that the hypothesis is valid and the allylic selenide is indeed an intermediate in the selenochrome formation reaction.



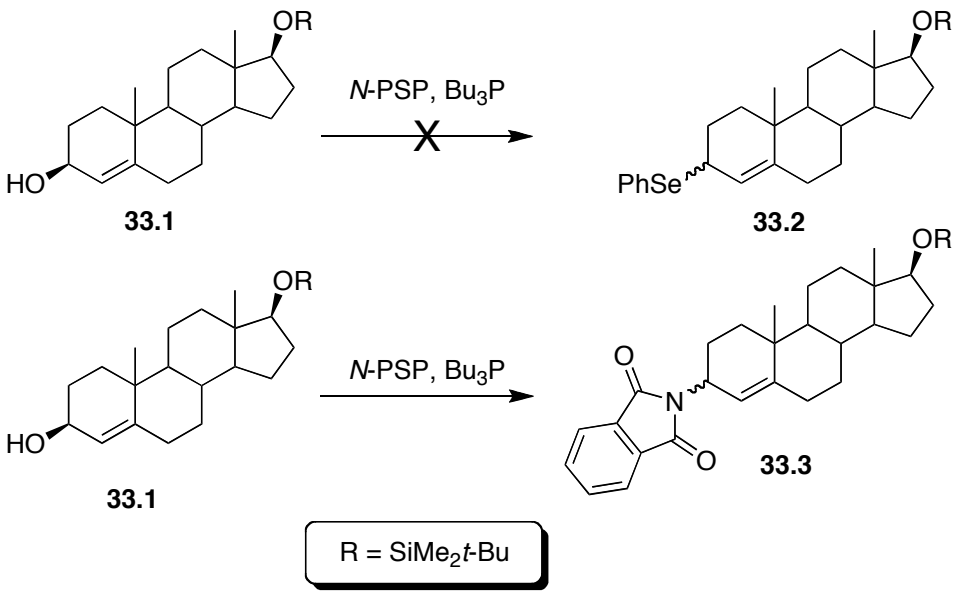

**Scheme 31**

In 1981 Grieco and coworkers reported[48] the use of *N*-phenylselenophthalimide (*N*-PSP) **32.5** as a convenient alternative for PhSeCN in the conversion of primary alcohols into primary alkyl selenides (Scheme 32). PhSeCN is an extremely sensitive, unpleasant smelling liquid which slowly decomposes during storage. In contrast, *N*-PSP is a stable, crystalline, relatively odorless substance that is much easier to handle. Alcohols are converted in high yield into the corresponding alkyl selenides using *N*-PSP and $Bu_3P$ either in THF or in $CH_2Cl_2$. Another advantage in using *N*-PSP is that it is inert towards other functional groups such as acetals, ketals, silyl ethers, olefins, acetylenes, and aromatic residues.



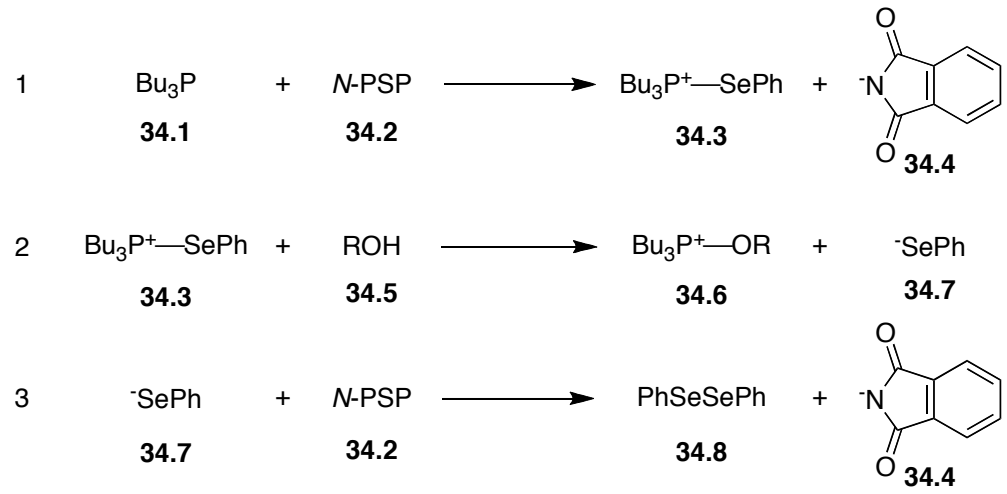

**Scheme 32**

In 1984 Back and McPhee further investigated[49] the applicability of *N*-PSP towards the conversion of secondary allylic alcohols into the corresponding selenides (Scheme 33). It was found that changing either the number of molar equivalents or the rate of addition of *N*-PSP to the reaction mixture did not convert the allylic secondary alcohol into the corresponding selenide. Instead of the expected selenide the alcohol was replaced by the phthalimido group, giving compound **33.3,** and a significant amount of PhSeSePh was produced as a byproduct. This study by Back and McPhee shows that *N*-PSP can only be applied to the conversion of primary alcohols into alkyl selenides.




**Scheme 33**

According to Back, the mechanism of the initial steps of the reaction of *N*-PSP with secondary allylic alcohols is the same as that which was proposed by Grieco[48] for primary alcohols. *N*-PSP, $Bu_3P$, and the alcohol together generate the phosphine intermediates **34.3** and **34.6**. However, at this stage, instead of attacking the phosphine **34.6,** the phenylselenide anion **34.7** attacks another molecule of *N*-PSP generating PhSeSePh that was recovered as the byproduct (Scheme 34).




**Scheme 34**

## 1.5 Formation of selenium-stabilized carbanions

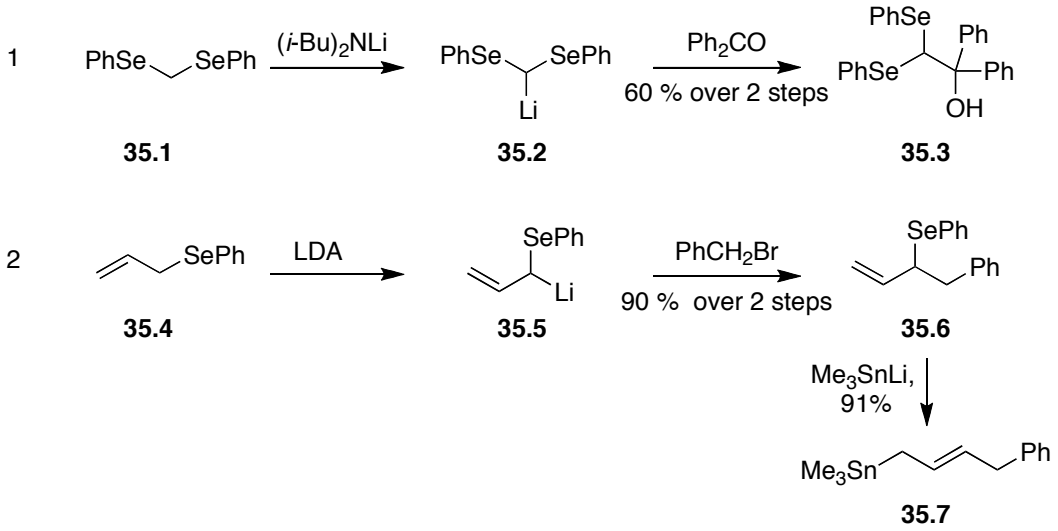
The normal way of generating a selenium-stabilized carbanion is to start with a selenoacetal.[50] This is by far the most common method, but selenium-stabilized carbanions are also available by alternate methods[51] as illustrated in Scheme 35. These selenium-stabilized carbanions are highly nucleophilic and this high nucleophilicity allows them to be added to alkyl halides,[52] epoxides,[5] ketones,[53] aldehydes,[54] esters,[54] and silyl halides.[55] Several ways for the formation of selenium-stabilized carbanions are: (i) deprotonation α to a selenide using a strong base,[56,8] (ii) Se/Li exchange of selenoacetals or selenoketals,[9] and (iii) conjugate addition of nucleophiles to vinyl selenides or selenoxides.[57]

### *1.5.1 Selenium-stabilized carbanions by deprotonation α to selenium:*

As mentioned earlier, the acidity of hydrogen atoms on carbon α to selenium is increased by 10 to 15 pKa units[3] relative to the all-carbon

counterparts. This enables deprotonation α to selenium using a strong base. In 1969 Seebach and Peleties reported[56] that selenoacetals (**35.1**) can be deprotonated on the α carbon using (*i*-Bu)$_2$NLi to give a selenium-stabilized carbanion (**35.2**) which was condensed with $Ph_2CO$ to give a β-hydroxy selenide (**35.3**) in a good yield (Scheme 35).

In 1988 Reich and Ringer prepared[8] selenium-stabilized carbanions which were condensed with $PhCH_2Br$ to prepare the intermediate **35.6** en route to the synthesis of allyl stannyl compounds (**35.7**). Deprotonation was done using LDA in THF and the methodology was applied to deprotonate α to selenium in allylic, propargylic, and benzylic selenides (Scheme 35).

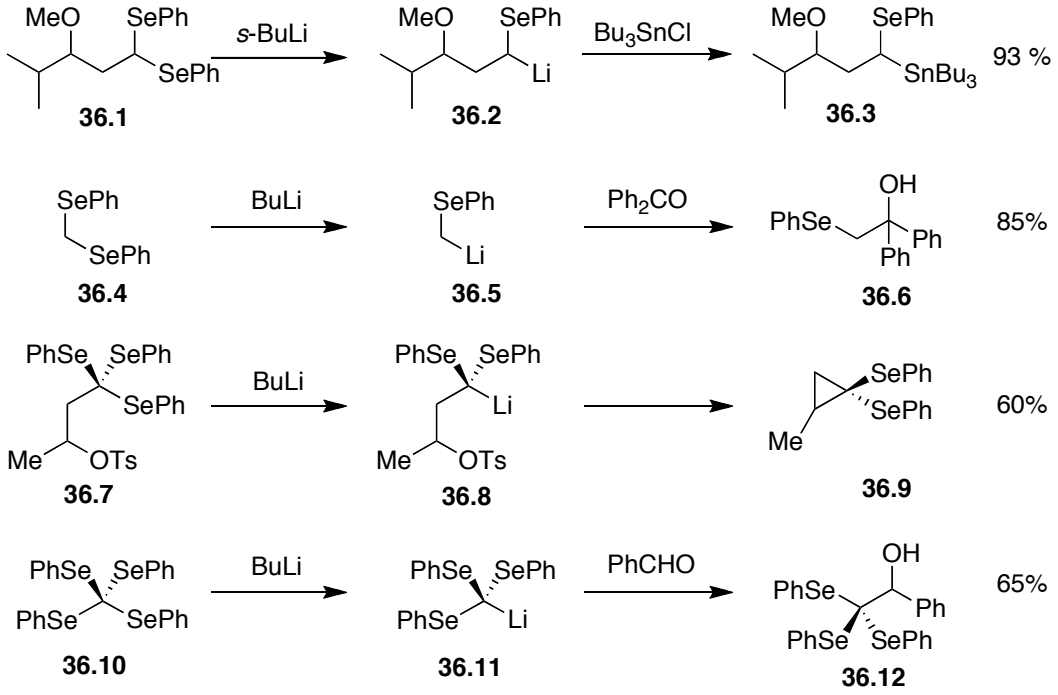



**Scheme 35**

*1.5.2 Selenium-stabilized carbanions by Se-Li exchange:*

The alkyllithium-promoted cleavage of the C-Se bond in MeSe- and PhSe- acetals and ketals is a well established reaction[50] which occurs rapidly and

in high yield in THF (>95% yield). Hoffman and coworkers reported[9] that selenium-stabilized carbanions can be generated by a Se/Li exchange on a selenoacetal by treating the selenoacetal with an alkyllithium at very low temperatures (-105°C) and then trapping with an electrophile. Seebach and Peleties reported[56] that both selenoacetals and orthoselenoesters undergo Se-Li exchange with alkyllithiums to give selenium-stabilized carbanions that can be trapped with electrophiles (Scheme 36).

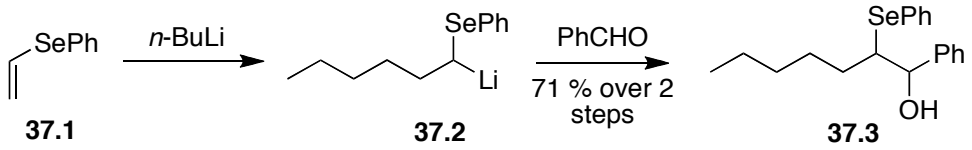



**Scheme 36**

*1.5.3 Selenium-stabilized carbanions by conjugate addition of nucleophiles to vinyl selenides:*

Raucher and Koolpe reported[57] that vinyl phenyl selenides such as **37.1** can be used as a $^{+}CH{=}CH^{-}$ synthon because they can be reacted with an

alkyllithium and the resulting α-lithioalkyl phenyl selenide **37.2**, which is a selenium-stabilized carbanion, can be trapped with an electrophile to give compounds of type **37.3** (Scheme 37). Even though vinyl phenyl selenides react readily with alkyllithiums, they are unreactive towards $Bu_2CuLi$ and BuMgBr. One of the major disadvantages of this methodology is that selenium-stabilized carbanions prepared in this manner might cause unnecessary deprotonations or C-Se bond cleavages. However, these side reactions can be minimized by careful manipulation of the reaction conditions. Best results were obtained when the reaction was done at 0 °C using either dimethoxymethane or $Et_2O$ as the solvent.

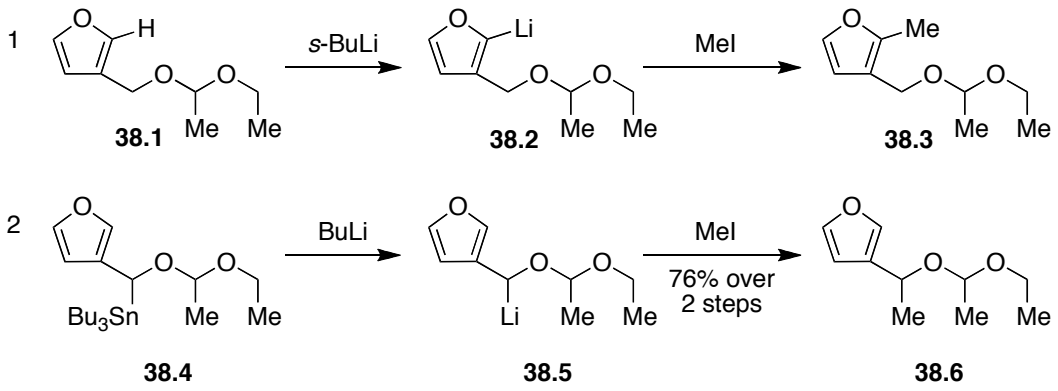



**Scheme 37**

## 1.6 Tin-metal exchange

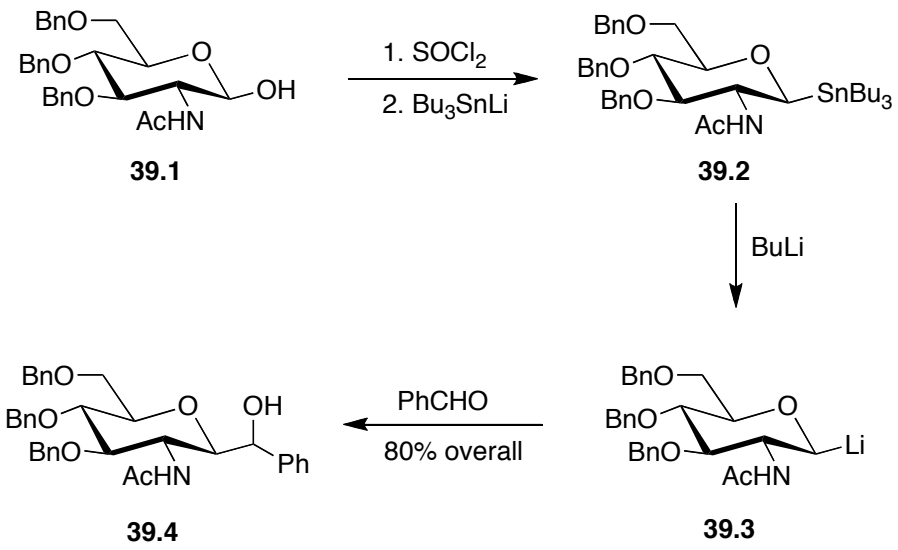
Organostannanes can be considered as carbanion equivalents since they readily undergo Sn/Li exchange when treated with organolithium reagents.[18] Preparation of carbanions by Sn/Li exchange has become exceedingly popular in cases where generation of a carbanion by deprotonation leads to undesired byproducts. Such a case was reported by Still[18] where an attempted metallation on the side chain of the furan ring in compound **38.1** in an attempt to prepare the methylated compound **38.6** led mainly to metallation on the furan ring and gave

the undesired product **38.3**. The side chain metallated furan was readily prepared by a Sn/Li exchange on the alkoxystannane **38.4** in good yield (Scheme 38).




**Scheme 38**

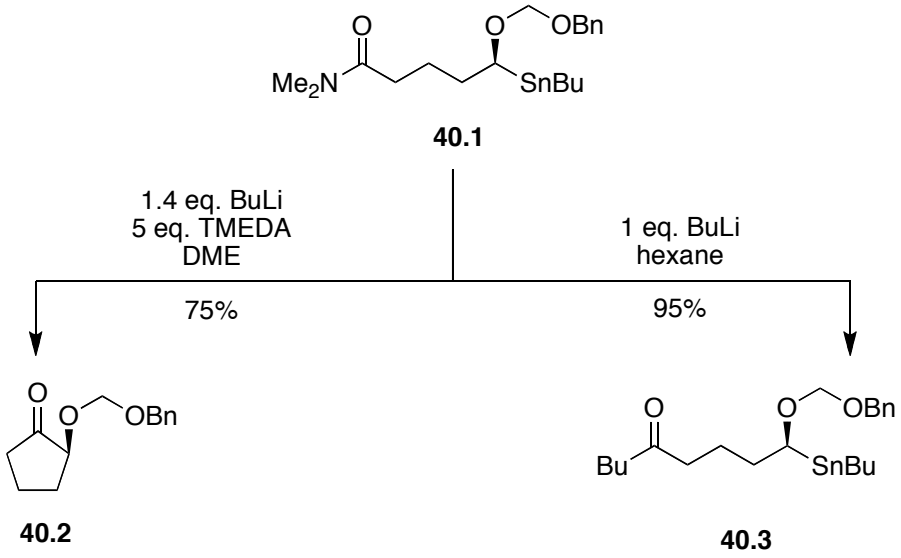
In 1994 Hoffman and Kessler reported[58] the application of Sn/Li exchange as a synthetic tool in carbohydrate chemistry, primarily in the synthesis of *C*-glycosides from D-glucosamine (Scheme 39). *C*-Glycosides are considered stable analogs of *O*- and *N*-glycosides. The conventional way of preparing *C*-glycosides is by Lewis acid catalyzed addition of carbon nucleophiles to carbohydrate derivatives. The novel method reported by the authors uses an anion, generated by Sn/Li exchange, which is captured by a carbon electrophile to give the *C*-glycosides (**39.4**) in high yield.




**Scheme 39**

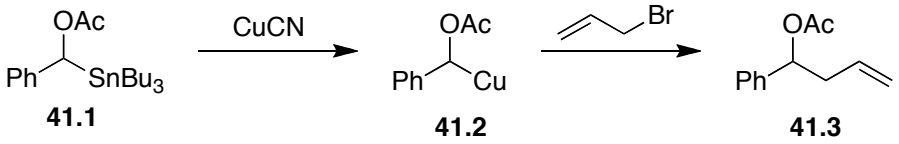
In 1985 McGarvey and Kimura reported[59] a new carbon-carbon bond forming cyclization (Scheme 40) where a carbanion generated via Sn/Li exchange is condensed intramolecularly with a *N*,*N*-dimethyl amide (**40.1**). Since the organostannane used in the Sn/Li exchange is an α-alkoxy organostannane, this method is also useful in the preparation of α-alkoxy carbonyl products (**40.2**). It was postulated that conducting the Sn/Li exchange by reacting the trialkylorganostannane with BuLi in the presence of the electrophilic *N*,*N*-dimethyl amide was possible due to the kinetic preference of BuLi to undergo Sn/Li exchange instead of addition to the amide. However initial reactions in the study gave a mixture of products indicating competing reactions at the stannane and the amide. Further investigations gave the desired cyclized product cleanly when the reaction was done with a slight excess of BuLi in the presence of TMEDA using DME as the solvent. Sn/Li exchange was completely suppressed

and exclusive addition of BuLi to the amide occurred (**40.1→40.3**) when the reaction was done in hexane with an equimolar amount of BuLi.




**Scheme 40**

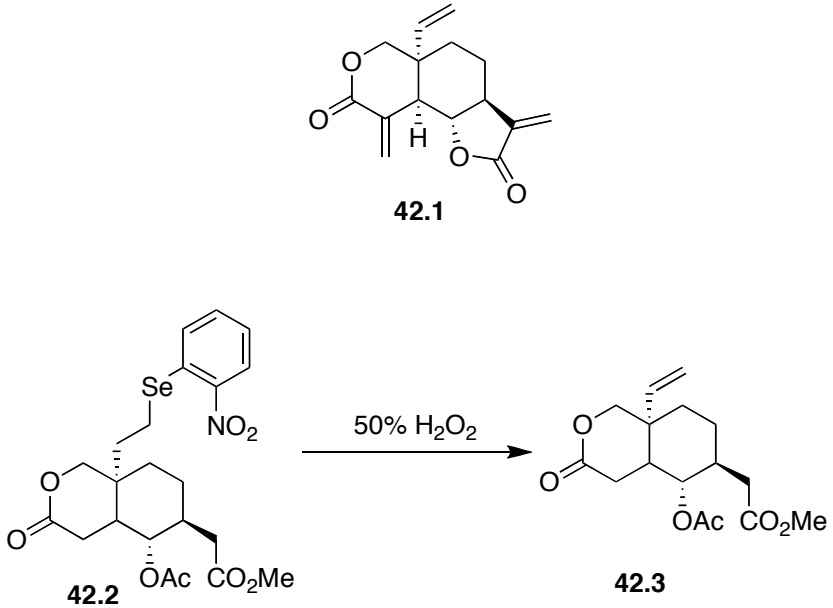
In 1995 Falck and coworkers reported[60] a method for the cross coupling of α-alkoxy organostannanes with organohalides (Scheme 41). In this method, in contrast to methods seen before in which a Sn/Li exchange was used to generate the carbanion, a trialkylstannane (**41.1**) underwent transmetallation readily with a catalytic amount of Cu in situ to give an α-alkoxy organocuprate (**41.2**) prior to the coupling with the organohalide. Best results were obtained when the reactions were done in solvents such as THF, PhMe, and PhH, using CuCN as the source of Cu.




**Scheme 41**

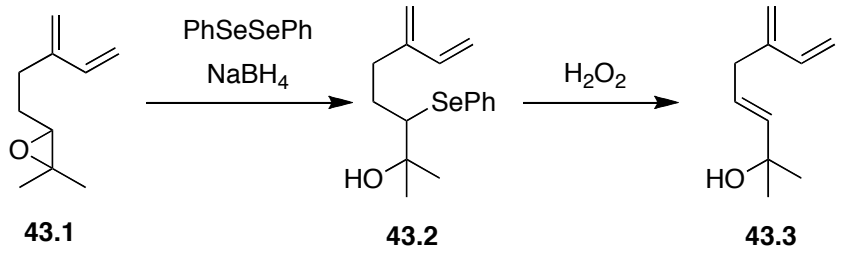
## 1.7 Oxidation and elimination of selenides to give allylic alcohols

In 1975 Grieco and coworkers reported[61] the use of oxidation and elimination of alkyl selenides to give terminal alkenes to prepare an advanced intermediate in the total synthesis of deoxyvernolepin (**42.1**). The *o*-nitrophenyl alkyl selenide **42.2** was treated with $H_2O_2$ to oxidize the selenium to the corresponding selenoxide, and the selenoxide elimination then gave the terminal alkene **42.3** (Scheme 42).




**Scheme 42**

In a case where the alkyl selenide that is oxidized and eliminated is a β-hydroxyselenide, then the result is an allylic alcohol. An example of such a process was reported by Sharpless and Lauer in 1973.[5] As reported, the conversion of epoxides to allylic alcohols was carried out via a β-hydroxyselenide intermediate. The epoxide **43.1** was first treated with PhSeNa, which was prepared by the reaction of PhSeSePh with $NaBH_4$, to give the β-hydroxyselenide **43.2**. This was then oxidized by treatment with $H_2O_2$ and elimination gave the corresponding allylic alcohol **43.3** (Scheme 43).




**43.1** **43.2** **43.3**

**Scheme 43**

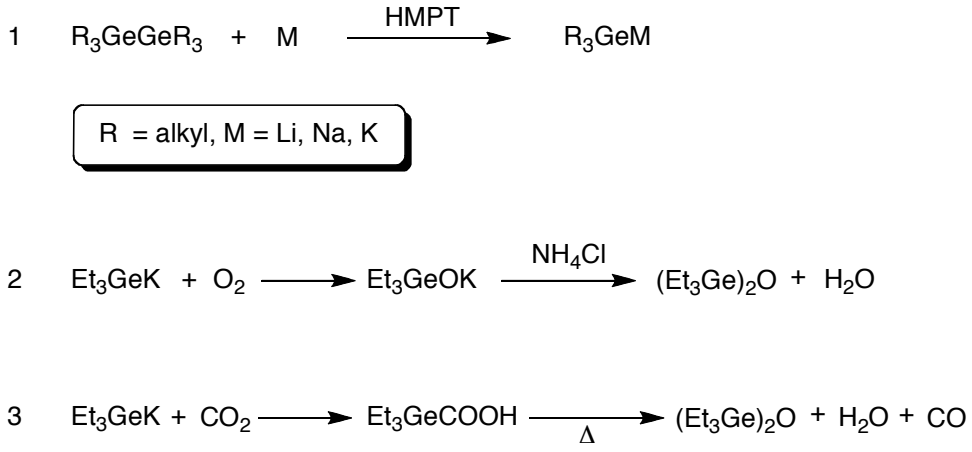
## 1.8 Germanium as an alternative to tin

Germanium, an element in group 4, is in the same group as C, Si, and Sn and has received some attention in the past to investigate its resemblance to these other elements. Compared to Sn, Ge is a metalloid and has less metallic character.[62] Anions of Ge and other elements of group 4 have been appearing recently in the literature as synthetic tools.[63]

In 1971 Noltes and Bulten reported[64] a series of reactions involving trialkylgermyl alkali metal derivatives to demonstrate the versatility of germyl

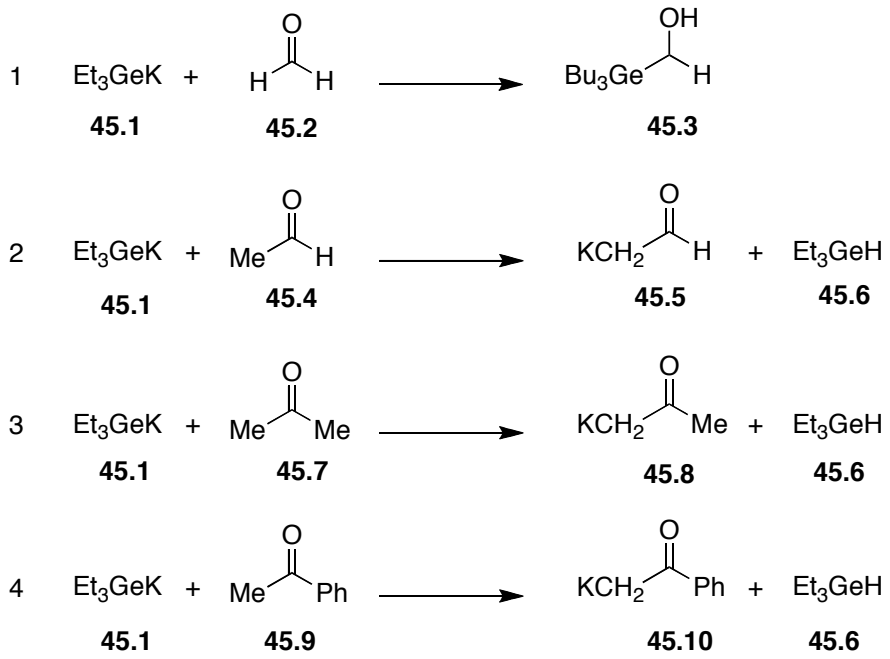
anions as reactive nucleophiles. These trialkylgermyl alkali metal compounds, in hexamethylphosphoric triamide (HMPT), have been found to be highly reactive nucleophiles and some reactions with inorganic compounds such as $O_2$ and $CO_2$, along with organic compounds such as alkyl halides, aldehydes, ketones, epoxides, and lactones were reported.

Trialkylgermyl alkali metal compounds were prepared by the cleavage of hexaalkyldigermanes with alkali metals in HMPT at room temperature (Scheme 44, Entry 1). Solutions of triethylgermylpotassium in HMPT reacts rapidly with $O_2$ at room temperature, and decomposition of the reaction mixture with $NH_4Cl$ gives quantitatively the corresponding germanium oxides (Scheme 44, Entry 2). Similarly when reacted with $CO_2$, $Et_3GeK$ gives $Et_3GeCOOH$, which decomposes to give the corresponding germanium oxide upon heating above 100 °C (Scheme 44, Entry 3).




**Scheme 44**

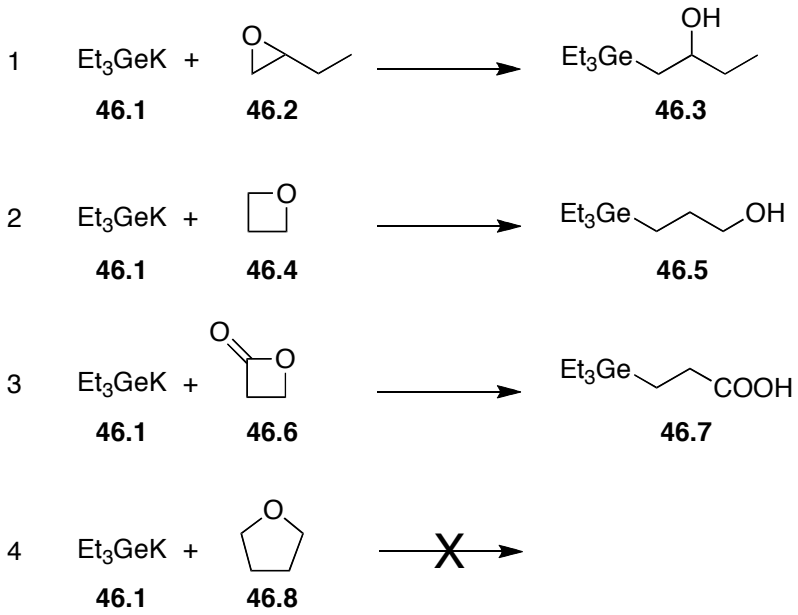
Trialkylgermyl alkali metals react rapidly with organic compounds containing carbonyl groups such as aldehydes or ketones and with small ring ethers. When reacted with HCHO the desired monoaddition product was formed (Scheme 45, Entry 1). However, reactions of the trialkylgermyl alkali metal compounds with acetaldehyde, acetone, and acetophenone gave exclusively trialkylgermane, suggesting that metallation predominates in these cases over addition (Scheme 45, Entry 2-4). There was no addition or metallation reaction observed between $Et_3GeK$ and cyclohexanone in HMPT.




**Scheme 45**

Small cyclic ethers such as epoxides (**46.2**), trimethylene oxide (**46.4**), and propiolactone (**46.6**) reacted instantaneously at room temperature to give the expected trialkylgermyl addition products (Scheme 46). The five-membered

ether, THF, did not undergo ring cleavage at room temperature and the low thermal stability of the germanium reagent did not allow this reaction to be tried at higher temperatures.




**Scheme 46**

# 2. RESULTS AND DISCUSSION

## 2.1 Research objectives

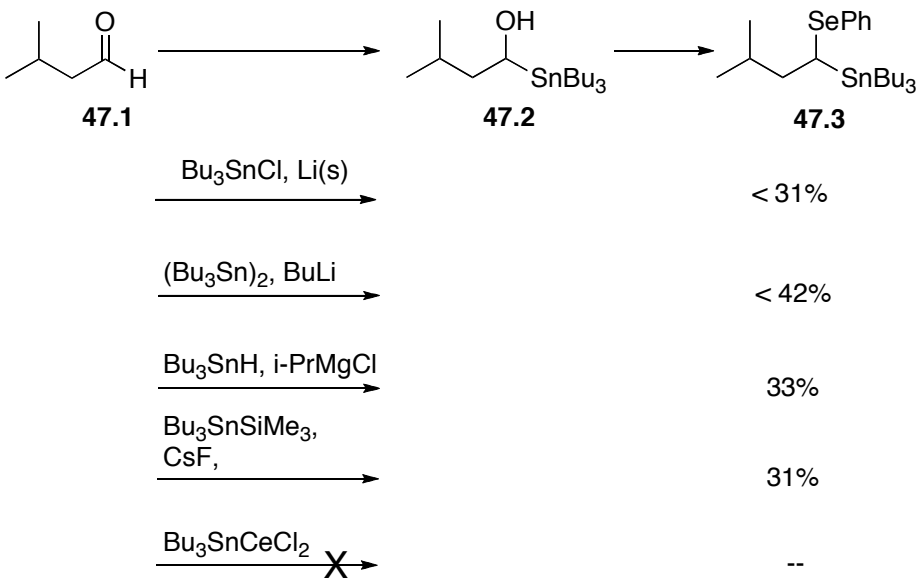
As mentioned earlier, the present route to carbanions was first developed in the synthesis of halichlorine in order to bypass the need for acid-catalyzed preparation of selenoacetals. The complex aldehyde **2.1** (Scheme 2) which was an advanced intermediate in the halichlorine synthesis was unstable under the acidic conditions needed to form a selenoacetal. Therefore the starting aldehyde was first treated with $Bu_3SnLi$ which was prepared from $Bu_3SnH$ and LDA at -78°C in THF, to get the α-hydroxystannane **2.2** (Scheme 2), and the hydroxyl of the α-hydroxystannane was converted to the corresponding phenyl selenide using PhSeCN and $Bu_3P$ to give the mixed Sn-Se acetal **2.3** (Scheme 2). Next, upon treatment with BuLi, the Sn-Se acetal underwent preferential Sn/Li exchange, and the selenium-stabilized carbanion produced was condensed with the aldehyde **2.4** to give the β-hydroxyselenide **2.5** (Scheme 2). Upon oxidation and selenoxide fragmentation the required allylic alcohol **2.6** (Scheme 2) was obtained from the β-hydroxyselenide.

The success of the Sn-Se route in the demanding context of the halichlorine synthesis indicated that the method might be of general utility and so a detailed investigation was undertaken by me.[65]

## 2.2 Detailed study of the Sn-Se route to carbanions

### *2.2.1 Formation of stannyl alcohols:*

The first intermediate in the route towards selenium-stabilized carbanions was the stannyl alcohol and the formation of this species was studied first. As a test substrate, isovaleraldehyde (**47.1**) was used and $Bu_3SnLi$ was added to the aldehyde at -78°C in THF. The $Bu_3SnLi$ was generated by deprotonating $Bu_3SnH$ with LDA at 0°C. The success of the $Bu_3SnLi$ addition was determined based on the yield of the (phenylseleno)stannane **47.3** obtained from the crude stannyl alcohol **47.2** over two steps. Several other methods, such as $Bu_3SnCl$ with Li metal, $Bu_3SnSnBu_3$ with BuLi, $Bu_3SnH$ with *i*-PrMgCl, and $Bu_3SnCeCl_2$, for generating the tributylstannyl anion were also investigated in order to increase the yield of the reaction. However, none of the alternative methods made any significant improvement to the isolated yield of the (phenylseleno)stannane and therefore deprotonation of $Bu_3SnH$ with LDA was chosen as the optimum method for generating $Bu_3SnLi$.

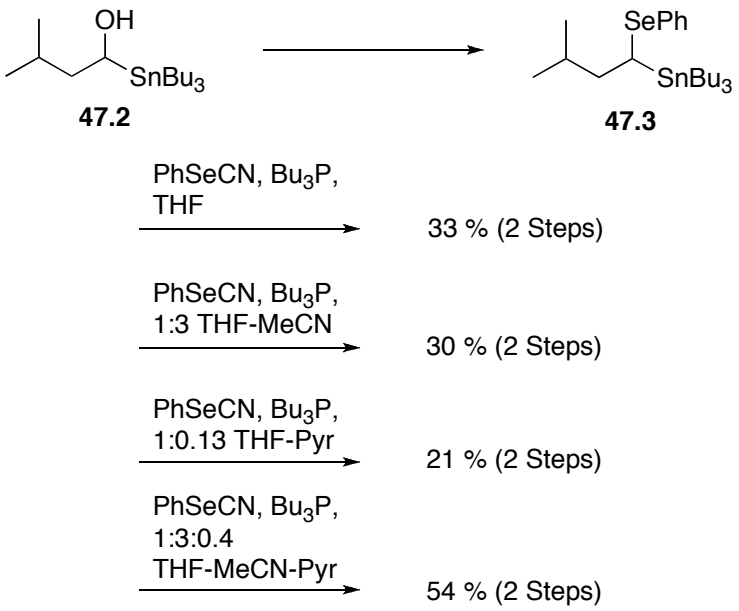



**Scheme 47**

Literature sources[18] suggested that stannyl alcohols are highly sensitive to acidic conditions and were known to decompose during storage or chromatography on silica gel. These facts regarding the stannyl alcohol were tested using compound **47.2**. Attempts to chromatograph **47.2** on silica gel resulted in significant (at least 20%) loss of the compound and TLC analysis of the compound using a square TLC plate developed in two orthogonal directions confirmed that extensive decomposition of the stannyl alcohol occurs upon contact with silica gel. In order to minimize the loss of product during the handling of the stannyl alcohol after an aqueous workup and drying, the crude product was used directly in the next step where the stannyl alcohol was converted into the corresponding stannyl selenide.

*2.2.2 Conversion of stannyl alcohols into stannyl selenides:*

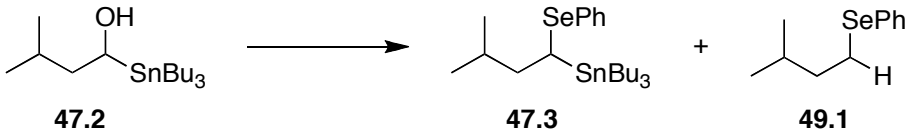
As mentioned earlier, the conversion of the stannyl alcohol into the stannyl selenide was carried out using the crude stannyl alcohol. Initially, conversion of the alcohol to the selenide was done in THF and resulted in a low yield (33%). Therefore different solvents and solvent combinations had to be tested to find the optimum solvents. To this end the transformation was carried out in different combinations of THF, MeCN, and pyridine, keeping all other reaction conditions and reagents constant. Finally a mixture of 1:3:0.4 THF-MeCN-pyridine was found to be the optimum mixture that gave the highest overall yield (aldehyde to stannyl selenide).




**Scheme 48**

When we made the selenide in THF in the absence of pyridine or MeCN, we usually isolated some alkylselenide corresponding to the desired α-

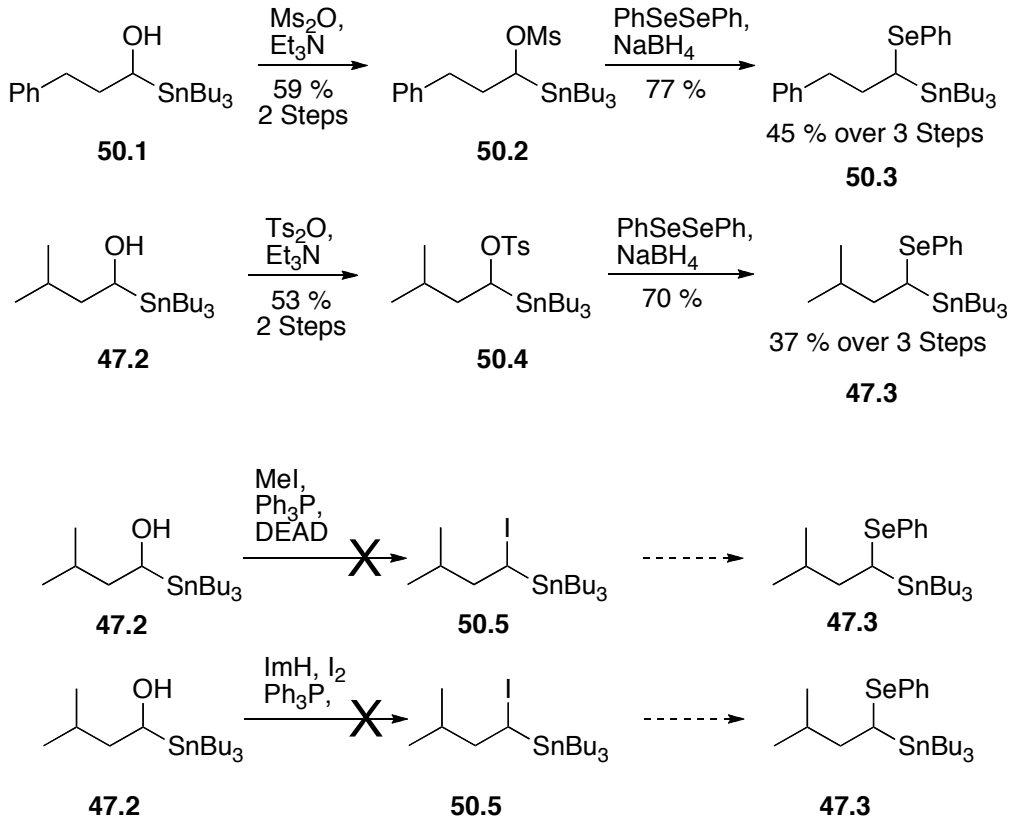
(phenylseleno)stannane but having the $Bu_3Sn$ unit replaced by a hydrogen (**49.1**, Scheme 49). However, under the optimum solvent conditions of THF-MeCN-pyridine, the formation of this byproduct was usually insignificant.




**47.2** **47.3** **49.1**

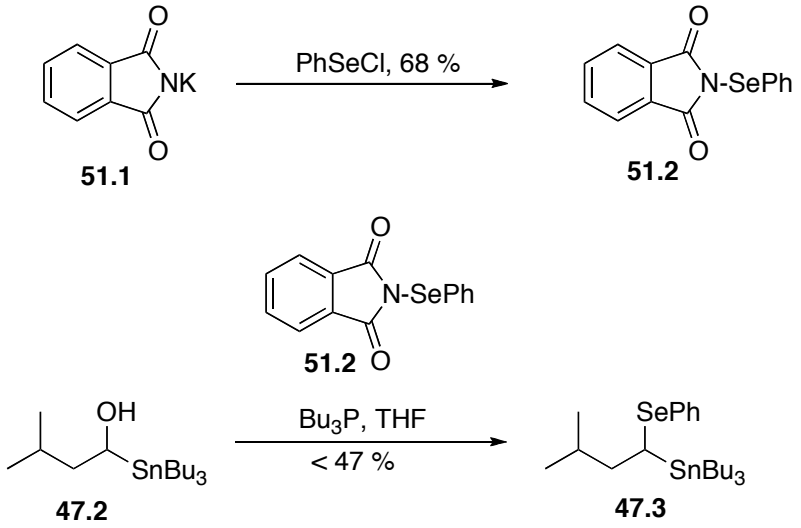
**Scheme 49**

Several alternate routes for the conversion of the stannyl alcohol to the stannyl selenide were attempted in place of the $PhSeCN/Bu_3P$ method. Displacement of the hydroxyl by a PhSe group was attempted by first converting the alcohol to the corresponding mesylate **50.2,** tosylate **50.4**, and iodide **50.5**. However, none of these alternate routes made any improvement to the yields over the use of $PhSeCN/Bu_3P$.




**Scheme 50**

Instead of PhSeCN/$Bu_3P$, we also tried the reagents *N*-(phenylseleno)-phthalimide/$Bu_3P$ as the source of PhSe for the displacement of the hydroxyl of the stannyl alcohol. *N*-(Phenylseleno)phthalimide was prepared following a literature procedure[66] using potassium phthalimide and PhSeCl. However, this new reagent combination of *N*-(phenylseleno)phthalimide/$Bu_3P$ did not improve the yield above the PhSeCN/$Bu_3P$ combination (Scheme 51).

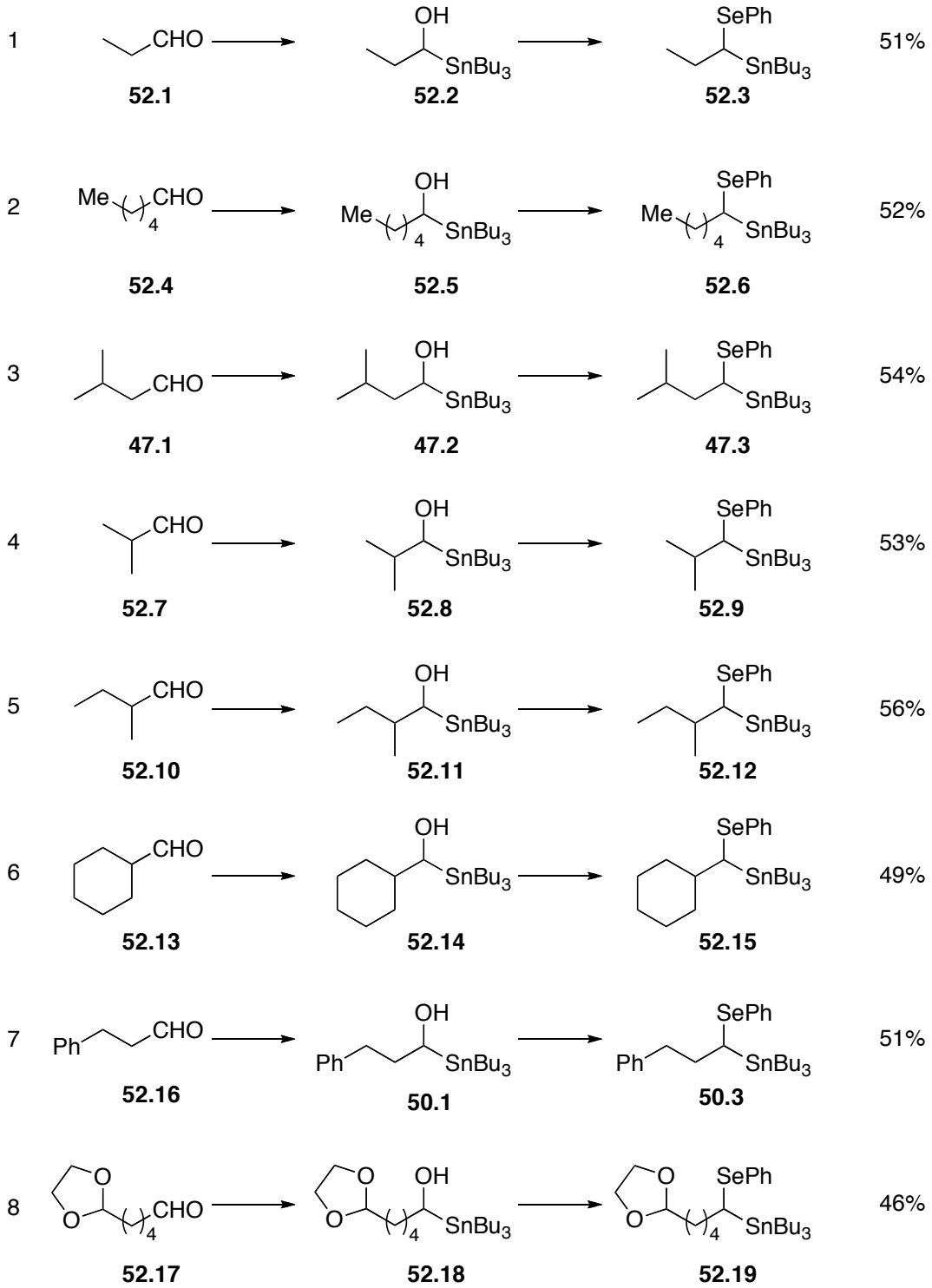



**Scheme 51**

One of the major byproducts in the stannyl alcohol→stannyl selenide conversion is PhSeSePh. Since both the desired product (phenylseleno)stannane and the undesired product PhSeSePh are highly nonpolar, the desired product could not be isolated free of any PhSeSePh by using flash chromatography on silica gel. However, PhSeSePh was most conveniently removed by reaction first with $NaBH_4$ and then capturing the resulting phenylselenide anion with $BrCH_2COOH$.

Our optimum conditions for the conversion of the stannyl alcohol to the stannyl selenide was using $PhSeCN/Bu_3P$ in a solvent combination of THF-MeCN-pyridine. Using the optimum conditions, different aldehydes were converted to stannyl selenides in two steps. As shown in Scheme 52 the methodology was applied to aldehydes with branched and straight alkyl chains (Entries 1-5), aldehydes with cyclic side chains (Entry 6), aldehydes containing

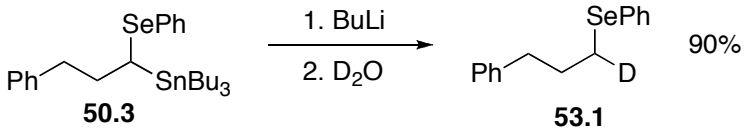
aromatic substituents (Entry 7), and aldehydes containing acid sensitive functional groups (Entry 8).




**Scheme 52**

*2.2.3 Preferential tin/lithium exchange:*

Generation of selenium-stabilized carbanions from the stannyl selenide proceeded without incident and only a few experiments were required to establish satisfactory conditions. These involved treatment of the α-(phenylseleno)stannane with an excess of BuLi (2 equiv) in THF at -78°C, usually for no longer than 15 min, followed by the addition of the aldehyde (3 equiv). Yields are generally well above 70%, based on the α-(phenylseleno)stannane. In one case the intermediate selenium-stabilized carbanion was quenched with $D_2O$ to afford the expected monodeuterated product (**53.1**) in 90% yield, indicating that selective cleavage of the C-Sn bond occurs efficiently, at least in this case (Scheme 53).

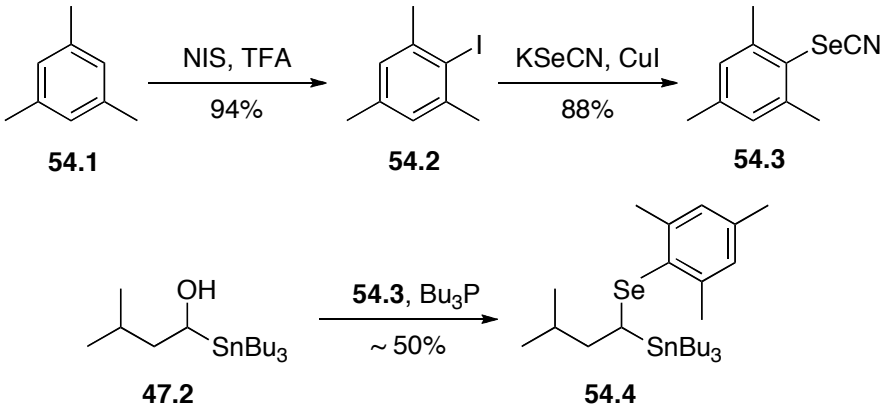



**50.3** **53.1**

**Scheme 53**

In a few cases the condensation yields were below 70% and it was hypothesized that instead of the C-Sn bond, cleavage of the C-Se bond could be responsible. In order to increase the selectivity in favor of the C-Sn bond, the ArSe unit had to be made more hindered, thus blocking attack by BuLi on the Se. To this end it was decided to prepare an α-(mesitylseleno)stannane **54.4**. This was made by using mesitylselenocyanate **54.3** with $Bu_3P$ instead of the PhSeCN/$Bu_3P$ in the conversion of the stannyl alcohol to the stannyl selenide.

Mesitylselenocyanate **54.3** was prepared following a literature procedure[67] using mesityl iodide (**54.1**) with KSeCN and CuI in HMPT. However, under the optimized conditions the replacement of the hydroxyl group by the hindered mesitylselenide gave an impure product in low yield and the matter was not pursued any further.

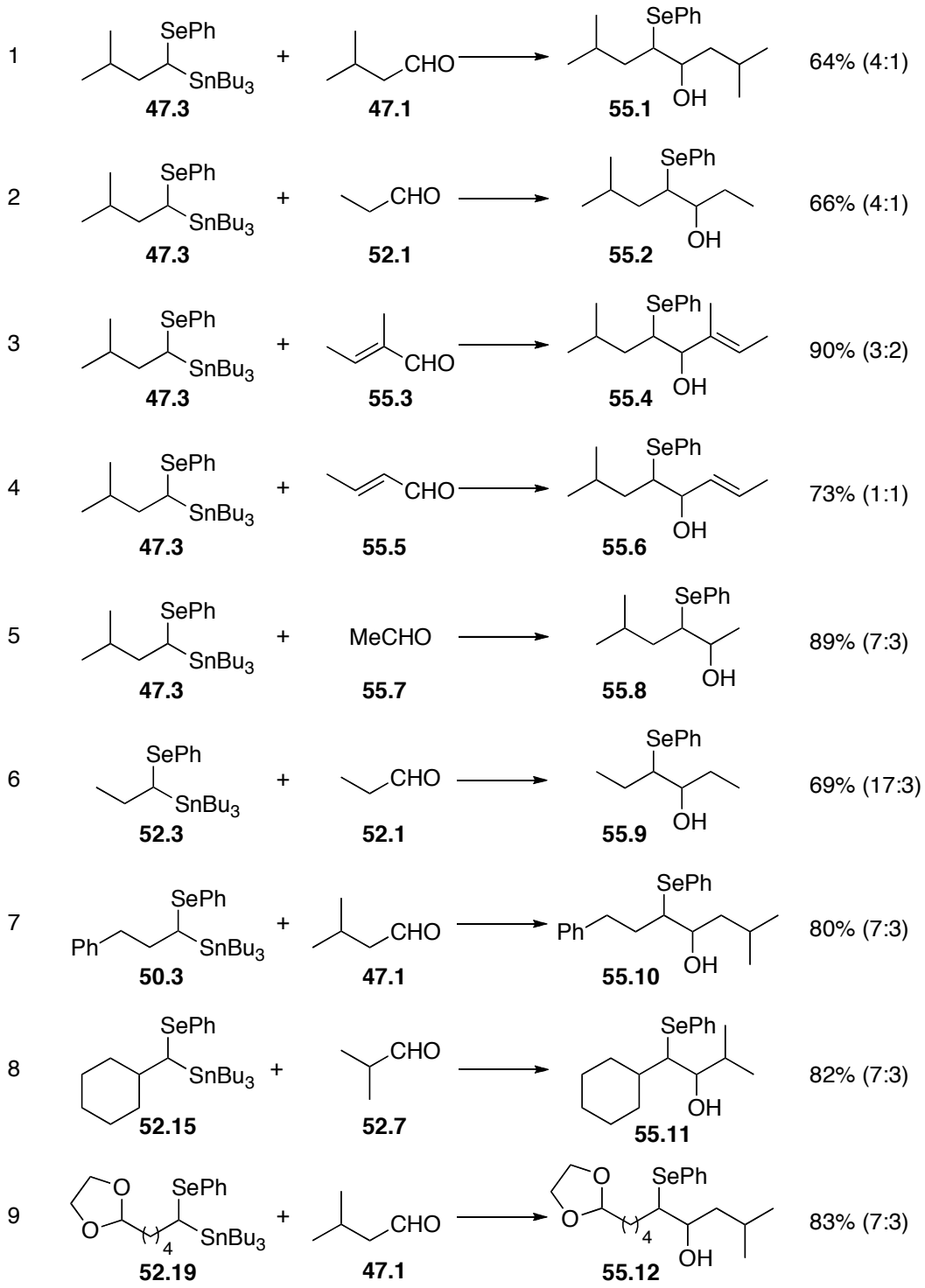



**Scheme 54**

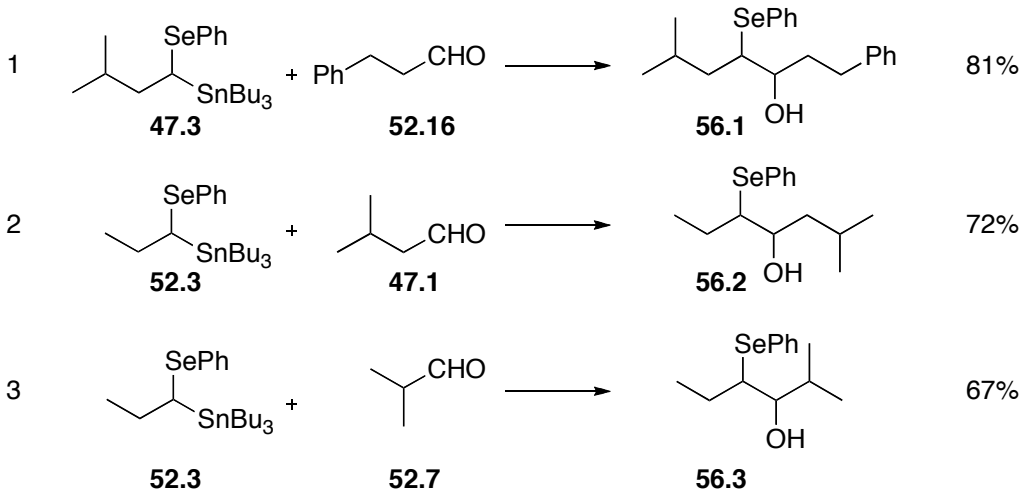
*2.2.4 Condensation with aldehydes:*

Once the selenium-stabilized carbanions were generated from the stannyl selenides they were condensed with aldehydes to give β-hydroxyselenides as expected. These β-hydroxyselenides were generally obtained as a mixture of *syn* and *anti* diastereomers (Scheme 55), but in three cases (Scheme 56), based on their $^{1}$H-NMR and $^{13}$C-NMR, they were clearly obtained as single isomers. The aldehydes that were condensed with the selenium-stabilized carbanions included examples with straight chains, branched chains, aromatic substituents, and α,β-unsaturation (Scheme 55, Entries 3,4). The stannyl selenide containing the acid

sensitive cyclic acetal (Scheme 55, Entry 9) condensed smoothly in excellent yield (83%) to give the corresponding β-hydroxyselenide **55.12** without incident.



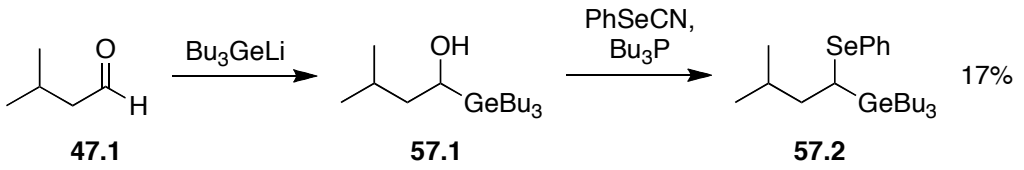

**Scheme 55**




**Scheme 56**

*2.2.5 Attempted extension to germanium:*

Once we had gained some experience in making the (phenylseleno)stannanes, we attempted to extend the methodology by preparing the Ge analogs of the stannyl selenides (Scheme 57). To this end, $Bu_3GeH$ was deprotonated with LDA and added to isovaleraldehyde to obtain the desired α-germyl alcohol, which was converted to the corresponding α-germyl selenide in a low overall yield (17% in two steps). A few examples have been reported[64] for the formation of germyl alcohols by addition of trialkylgermyl alkali metals to carbonyl compounds and the process has often been problematic.




**Scheme 57**

The methodology could not be extended in the case of the Ge series since Ge/Li exchange did not appear to take place when the germyl selenide was treated with BuLi under standard conditions. Attempts were made to trap the resulting selenium-stabilized carbanion with $D_2O$ and isovaleraldehyde, in case a Ge/Li exchange had occurred. However in both cases only the starting germyl selenide was isolated and there was no evidence for the presence of the desired product. It is reasonable to believe that the expected Ge/Li exchange failed to take place due to the lower metallic character of Ge (since it is a metalloid) relative to Sn.

## 3. CONCLUSION

Selenium containing synthons are extremely useful tools in organic chemistry due to the feasibility of smooth conversion of selenides to various functional groups. Selenium stabilized carbanions are widely used in carbon-carbon bond forming reactions and the anions are generally prepared via Se/metal exchange reactions of (phenylseleno)acetals. (Phenylseleno)acetals are prepared under acid catalysis and these conditions are detrimental to substrates containing acid sensitive moieties. We have introduced a route to selenium-stabilized carbanions, prepared via preferential Sn/Li exchange of α-stannylselenides. α-Stannylselenides can be prepared in the absence of acid and provide a route that can be applied to the formation of selenium-stabilized carbanions for acid sensitive substrates. Selenium-stabilized carbanions prepared in this fashion can be condensed with different types of aldehydes to give β-hydroxyselenides. Formation of allylic alcohols from β-hydroxyselenides is a well established

reaction and so the present route provides access to these alcohols through a route that bypasses the need to generate (phenylseleno)acetals. The methodology cannot be applied to Ge analogs due to the inability of the α-germylselenides to undergo Ge/Li exchange.

# 4. EXPERIMENTAL

Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar or $N_2$ that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven (140 °C) for at least 3 h before use and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar or $N_2$. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane and ethyl acetate used for chromatography were distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at, or below, room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Air was then drawn through for 1 min and the syringe was stored under vacuum. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar or $N_2$), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F–254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid, followed by charring with a heat gun, or by examination

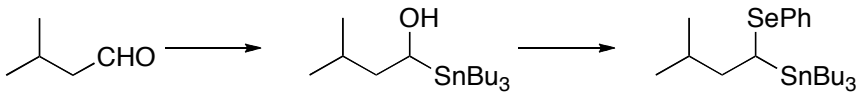
under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry THF, $Et_2O$, PhH, PhMe and dioxane were distilled from sodium and benzophenone ketyl. Dry $CH_2Cl_2$, $Et_3N$, *i*-$Pr_2NEt$ and pyridine were distilled from $CaH_2$. Dry MeOH was distilled from $Mg(OMe)_2$. Acetone was distilled from $KMnO_4$ and dried over 4Å molecular sieves. FT-IR measurements were made from the specified solvent using KBr plates.

The symbols s, d, t, and q used for $^{13}C$ NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, as based on the APT experiment.

Mass spectra were recorded with Agilent Technologies 6220 Accurate-Mass TOF LC/MS, Perseptive Biosystems Mariner Biospectrometry Workstation, Kratos MS50 or Micromass ZabSpec Hybrid Sector-TOF mass spectrometers. Compounds isolated by flash chromatography were pure by TLC and, unless otherwise stated, also as judged by high field $^1H$ and $^{13}C$ NMR spectra.

**Tributyl[3-methyl-1-(phenylseleno)butyl]stannane (47.3).**




**47.1** **47.2** **47.3**

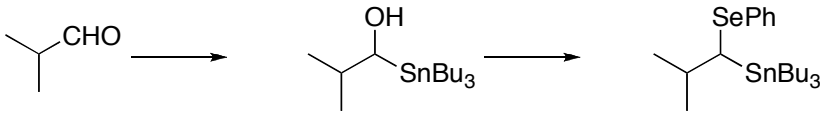
BuLi (1.6 M in hexane, 0.63 mL, 1.00 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-$Pr_2NH$ (0.15 mL, 1.1 mmol) in THF (3 mL). Stirring

was continued at -78 °C for 30 min, and the flask was transferred to an ice bath. $Bu_3SnH$ (0.30 mL, 1.1 mmol) was added and stirring was continued for 15 min. The flask was then transferred back to a cold bath at -78 °C and aldehyde **47.1** (0.055 mL, 0.50 mmol) was added dropwise. Stirring was continued at -78 °C for 30 min, and the mixture was quenched with saturated aqueous $NH_4Cl$. The cold bath was removed and the mixture was allowed to reach room temperature (ca 30 min). The aqueous phase was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. The crude product (**47.2**) was left under oilpump vacuum for 15 min and used directly in the next step.

The above crude hydroxystannane (**47.2**) was dissolved in 3:1 MeCN-THF (4 mL), and pyridine (0.4 mL, 5.0 mmol) was added. The mixture was cooled to 0 °C and PhSeCN (0.12 mL, 1.0 mmol) and $Bu_3P$ (0.25 mL, 1.0 mmol) were added successively at a fast dropwise rate. The ice bath was removed and stirring was continued for 4 h. The solvent was evaporated and the residue was dissolved in 4:1 THF-MeOH (5 mL). The stirred solution was cooled to 0 °C and an excess of $NaBH_4$ (100 mg) was added. Stirring was continued for 20 min, an excess of $BrCH_2CO_2H$ (400 mg) was added and the ice bath was removed. Stirring was continued for 30 min, the mixture was diluted with EtOAc and saturated aqueous $NaHCO_3$ was added. The mixture was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 25 cm), using hexane, gave **47.3** (138 mg, 54%) as a colorless oil: FTIR ($CH_2Cl_2$, cast) 3071, 2956, 2926, 2870, 2854 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 0.76-1.07 (m, 21 H), 1.25-1.40 (sextet, $J$ = 7.1 Hz, 6 H), 1.45-1.68 (m, 7 H), 1.77-1.83 (m, 2 H),

3.05 (dd, *J* = 8.4, 7.5 Hz, 1 H), 7.2-7.29 (m, 3 H), 7.5 (dd, *J* = 8.1, 1.5 Hz, 2 H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 9.9 (t), 13.7 (q), 22.0 (q), 22.7 (q), 23.0 (d), 27.4 (t), 28.8 (d), 29.2 (t), 45.6 (t), 126.4 (d), 128.8 (d), 132.3 (d), 132.6 (s); exact mass *m*/*z* calcd for $C_{23}H_{42}{}^{80}Se^{118}Sn$ 516.14679, found 516.14617.

**Tributyl[2-methyl-1-(phenylseleno)propyl]stannane (52.9).**



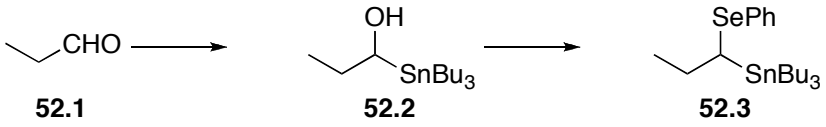

**52.7** **52.8** **52.9**

BuLi (1.6 M in hexane, 0.63 mL, 1.0 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-$Pr_2NH$ (0.15 mL, 1.1 mmol) in THF (3 mL). Stirring was continued at -78 °C for 30 min, and the flask was transferred to an ice bath. $Bu_3SnH$ (0.30 mL, 1.1 mmol) was added and stirring was continued for 15 min. The flask was then transferred back to a cold bath at -78 °C and aldehyde **52.7** (0.045 mL, 0.5 mmol) was added dropwise. Stirring was continued at -78 °C for 30 min, and the mixture was quenched with saturated aqueous $NH_4Cl$. The cold bath was removed and the mixture was allowed to reach room temperature (ca 30 min). The aqueous phase was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. The crude product (**52.8**) was left under oilpump vacuum for 15 min and used directly in the next step.

The above crude hydroxystannane (**52.8**) was dissolved in 3:1 MeCN-THF (4 mL), and pyridine (0.4 mL, 5.0 mmol) was added. The mixture was cooled to

0 °C and PhSeCN (0.12 mL, 1.0 mmol) and $Bu_3P$ (0.25 mL, 1.0 mmol) were added successively at a fast dropwise rate. The ice bath was removed and stirring was continued for 4 h. The solvent was evaporated and the residue was dissolved in 4:1 THF-MeOH (5 mL). The stirred solution was cooled to 0 °C and an excess of $NaBH_4$ (100 mg) was added. Stirring was continued for 20 min, an excess of $BrCH_2CO_2H$ (400 mg) was added and the ice bath was removed. Stirring was continued for 30 min, the mixture was diluted with EtOAc and saturated aqueous $NaHCO_3$ was added. The mixture was extracted with EtOAc, dried ($Na_2SO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 25 cm), using hexane, gave **52.9** (134 mg, 53%) as a colorless oil: FTIR (neat, film) 3071, 2956, 2926, 2870 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 0.87-1.12 (m, 21 H), 1.30-1.42 (sextet, $J$ = 7.4 Hz, 6 H), 1.46-1.66 (m, 6 H), 2.12-2.24 (m, 1 H), 3.10 (d, $J$ = 24 Hz, 1 H), 7.18-7.28 (m, 3 H), 7.50 (d, $J$ = 6.4 Hz, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 10.8 (t), 13.6 (q), 22.9 (q), 23.7 (q), 27.4 (t), 29.1 (t), 33.0 (d), 36.9 (d), 126.2 (d), 128.7 (d), 131.8 (d), 133.4 (s); exact mass *m/z* calcd for $C_{18}H_{31}{}^{78}Se^{120}Sn$ (M-Bu) 445.06207, found 445.06288.

**Tributyl[1-(phenylseleno)propyl]stannane (52.3).**



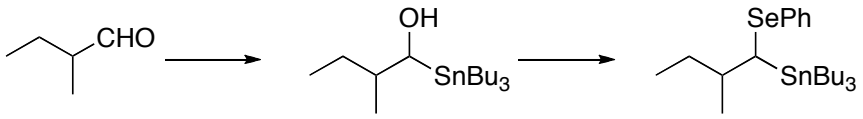

**52.1** **52.2** **52.3**

BuLi (1.6 M in hexane, 0.63 mL, 1.0 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-$Pr_2NH$ (0.15 mL, 1.1 mmol) in THF (3 mL). Stirring was continued at -78 °C for 30 min, and the flask was transferred to an ice bath. $Bu_3SnH$ (0.30 mL, 1.1 mmol) was added and stirring was continued for 15 min. The flask was then transferred back to a cold bath at -78 °C and aldehyde **52.1** (0.036 mL, 0.5 mmol) was added dropwise. Stirring was continued at -78 °C for 30 min, and the mixture was quenched with saturated aqueous $NH_4Cl$. The cold bath was removed and the mixture was allowed to reach room temperature (ca 30 min). The aqueous phase was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. The crude product (**52.2**) was left under oilpump vacuum for 15 min and used directly in the next step.

The above crude hydroxystannane (**52.2**) was dissolved in 3:1 MeCN-THF (4 mL), and pyridine (0.4 mL, 5.0 mmol) was added. The mixture was cooled to 0 °C and PhSeCN (0.12 mL, 1.0 mmol) and $Bu_3P$ (0.25 mL, 1.0 mmol) were added successively at a fast dropwise rate. The ice bath was removed and stirring was continued for 4 h. The solvent was evaporated and the residue was dissolved in 4:1 THF-MeOH (5 mL). The stirred solution was cooled to 0 °C and an excess of $NaBH_4$ (100 mg) was added. Stirring was continued for 20 min, an excess of $BrCH_2CO_2H$ (400 mg) was added and the ice bath was removed. Stirring was continued for 30 min, the mixture was diluted with EtOAc and saturated aqueous $NaHCO_3$ was added. The mixture was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 25 cm), using hexane, gave **52.3** (124 mg, 51%) as a colorless oil: FTIR ($CH_2Cl_2$, cast)

3070, 2956, 2927, 2871, 2853 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 0.87-1.06 (m, 18 H), 1.35 (sextet, $J$ = 7.3 Hz, 6 H), 1.45-1.64 (m, 6 H), 1.86-2.02 (m, 2 H), 3.06 (dd, $J$ = 6.4, 5.4 Hz, 1 H), 7.17-7.29 (m, 3 H), 7.46-7.53 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 9.9 (t), 13.7 (q), 15.2 (d), 27.5 (t), 27.7 (t), 27.8 (d), 29.2 (t), 126.3 (d), 128.8 (d), 132.1 (d), 132.5 (s); exact mass *m/z* calcd for $C_{21}H_{38}{}^{78}Se^{120}Sn$ 488.11685, found 488.11779.

**Tributyl[2-methyl-1-(phenylseleno)butyl]stannane (52.12).**

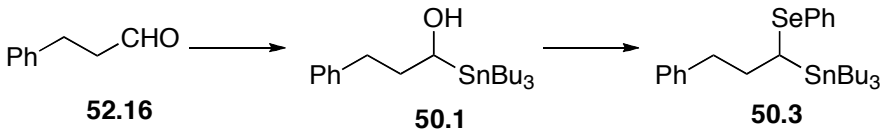



**52.10** **52.11** **52.12**

BuLi (1.6 M in hexane, 0.63 mL, 1.0 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-$Pr_2NH$ (0.15 mL, 1.1 mmol) in THF (3 mL). Stirring was continued at -78 °C for 30 min, and the flask was transferred to an ice bath. $Bu_3SnH$ (0.30 mL, 1.1 mmol) was added and stirring was continued for 15 min. The flask was then transferred back to a cold bath at -78 °C and aldehyde **52.10** (0.055 mL, 0.5 mmol) was added dropwise. Stirring was continued at -78 °C for 30 min, and the mixture was quenched with saturated aqueous $NH_4Cl$. The cold bath was removed and the mixture was allowed to reach room temperature (ca 30 min). The aqueous phase was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. The crude product (**52.11**) was left under oilpump vacuum for 15 min and used directly in the next step.

The above crude hydroxystannane (**52.11**) was dissolved in 3:1 MeCN-THF (4 mL), and pyridine (0.4 mL, 5.0 mmol) was added. The mixture was cooled to 0 °C and PhSeCN (0.12 mL, 1.0 mmol) and $Bu_3P$ (0.25 mL, 1.0 mmol) were added successively at a fast dropwise rate. The ice bath was removed and stirring was continued for 4 h. The solvent was evaporated and the residue was dissolved in 4:1 THF-MeOH (5 mL). The stirred solution was cooled to 0 °C and an excess of $NaBH_4$ (100 mg) was added. Stirring was continued for 20 min, an excess of $BrCH_2CO_2H$ (400 mg) was added and the ice bath was removed. Stirring was continued for 30 min, the mixture was diluted with EtOAc and saturated aqueous $NaHCO_3$ was added. The mixture was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 25 cm), using hexane, gave **52.12** (144 mg, 56%) as a colorless oil: FTIR ($CH_2Cl_2$, microscope) 3071, 2957, 2926, 2871, 2854 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) (3:2 mixture of stereoisomers) δ 0.80-1.09 (m, 21 H), 1.25-1.42 (m, 7 H), 1.45-1.65 (m, 6.4 H), 1.70-1.80 (m, 0.6 H), 1.81-1.91 (m, 1 H), 3.14 (d, $J$ = 3.0 Hz, 0.4 H), 3.20 (d, $J$ = 3.1 Hz, 0.6 H), 7.18-7.28 (m, 3 H), 7.47-7.55 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 10.8 (t), 11.0 (t), 12.4 (q), 12.5 (q), 13.7 (q), 20.4 (q), 20.6 (q), 27.2 (t), 27.5 (t), 27.8 (t), 29.1 (t), 29.2 (t), 29.3 (t), 29.8 (t), 30.7 (t), 35.4 (d), 36.1 (d), 40.2 (d), 126.2 (d), 126.3 (d), 128.7 (d), 128.8 (d), 131.8 (d), 132.3 (d), 133.3 (s), 133.5 (s); exact mass $m/z$ calcd for $C_{19}H_{33}{}^{78}Se^{120}Sn$ (M-Bu) 459.07773 found 459.07753.

**Tributyl[3-phenyl-1-(phenylseleno)propyl]stannane (50.3).**

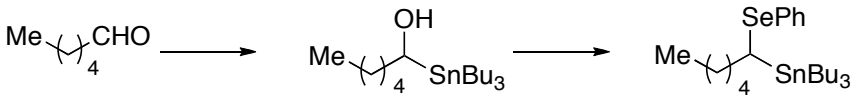



BuLi (1.6 M in hexane, 0.63 mL, 1.0 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-$Pr_2NH$ (0.15 mL, 1.1 mmol) in THF (3 mL). Stirring was continued at -78 °C for 30 min, and the flask was transferred to an ice bath. $Bu_3SnH$ (0.30 mL, 1.1 mmol) was added and stirring was continued for 15 min. The flask was then transferred back to a cold bath at -78 °C and aldehyde **52.16** (0.065 mL, 0.5 mmol) was added dropwise. Stirring was continued at -78 °C for 30 min, and the mixture was quenched with saturated aqueous $NH_4Cl$. The cold bath was removed and the mixture was allowed to reach room temperature (ca 30 min). The aqueous phase was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. The crude product (**50.1**) was left under oilpump vacuum for 15 min and used directly in the next step.

The above crude hydroxystannane (**50.1**) was dissolved in 3:1 MeCN-THF (4 mL), and pyridine (0.4 mL, 5.0 mmol) was added. The mixture was cooled to 0 °C and PhSeCN (0.12 mL, 1.0 mmol) and $Bu_3P$ (0.25 mL, 1.0 mmol) were added successively at a fast dropwise rate. The ice bath was removed and stirring was continued for 4 h. The solvent was evaporated and the residue was dissolved in 4:1 THF-MeOH (5 mL). The stirred solution was cooled to 0 °C and an excess of $NaBH_4$ (100 mg) was added. Stirring was continued for 20 min, an excess of

$BrCH_2CO_2H$ (400 mg) was added and the ice bath was removed. Stirring was continued for 30 min, the mixture was diluted with EtOAc and saturated aqueous $NaHCO_3$ was added. The mixture was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 25 cm), using hexane, gave **50.3** (143 mg, 51%) as a colorless oil: FTIR ($CH_2Cl_2$, cast) 3062, 3027, 2956, 2925, 2871, 2852 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 0.88-1.15 (m, 15 H), 1.35 (sextet, $J$ = 7.3 Hz, 6 H), 1.50-1.62 (m, 6 H), 2.15-2.25 (m, 2 H), 2.49-2.63 (m, 1 H), 2.76-2.90 (m, 1 H), 3.07 (t, $J$ = 6.1 Hz, 1 H), 7.05-7.11 (m, 2 H), 7.13-7.29 (m, 6 H), 7.43-7.52 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 10.0 (t), 13.7 (q), 25.2 (d), 27.4 (t), 29.2 (t), 36.9 (t), 37.1 (t), 125.8 (d), 126.5 (d), 128.3 (d), 128.4 (d), 128.9 (d), 132.3 (d), 132.4 (s), 141.8 (s); exact mass $m/z$ calcd for $C_{27}H_{42}{}^{80}Se^{118}Sn$ 564.14679, found 564.14814.

**Tributyl[(1-phenylseleno)hexyl]stannane (52.6).**




**52.4** **52.5** **52.6**

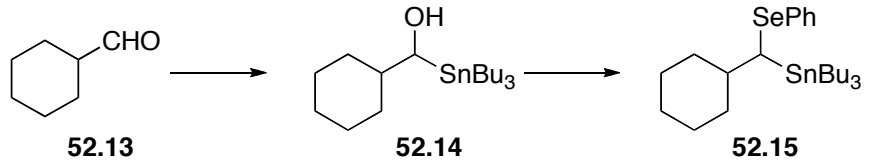
BuLi (1.6 M in hexane, 0.63 mL, 1.0 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-$Pr_2NH$ (0.15 mL, 1.1 mmol) in THF (3 mL). Stirring was continued at -78 °C for 30 min, and the flask was transferred to an ice bath. $Bu_3SnH$ (0.30 mL, 1.1 mmol) was added and stirring was continued for 15 min. The flask was then transferred back to a cold bath at -78 °C and aldehyde **52.4**

(0.06 mL, 0.5 mmol) was added dropwise. Stirring was continued at -78 °C for 30 min, and the mixture was quenched with saturated aqueous $NH_4Cl$. The cold bath was removed and the mixture was allowed to reach room temperature (ca 30 min). The aqueous phase was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. The crude product (**52.5**) was left under oilpump vacuum for 15 min and used directly in the next step.

The above crude hydroxystannane (**52.5**) was dissolved in 3:1 MeCN-THF (4 mL), and pyridine (0.4 mL, 5.0 mmol) was added. The mixture was cooled to 0 °C and PhSeCN (0.12 mL, 1.0 mmol) and $Bu_3P$ (0.25 mL, 1.0 mmol) were added successively at a fast dropwise rate. The ice bath was removed and stirring was continued for 4 h. The solvent was evaporated and the residue was dissolved in 4:1 THF-MeOH (5 mL). The stirred solution was cooled to 0 °C and an excess of $NaBH_4$ (100 mg) was added. Stirring was continued for 20 min, an excess of $BrCH_2CO_2H$ (400 mg) was added and the ice bath was removed. Stirring was continued for 30 min, the mixture was diluted with EtOAc and saturated aqueous $NaHCO_3$ was added. The mixture was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 25 cm), using hexane, gave **52.6** (136 mg, 52%) as a colorless oil: FTIR ($CH_2Cl_2$, cast) 3070, 2956, 2925, 2871, 2853 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 0.82-1.08 (m, 18 H), 1.20-1.41 (m, 12 H), 1.48-1.60 (m, 6 H), 1.84-1.95 (m, 2 H), 3.05 (t, $J$ = 6.0 Hz, 1 H), 7.18-7.28 (m, 3 H), 7.46-7.52 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 9.9 (t), 13.6 (q), 13.9 (q), 22.5 (t), 25.7 (d), 27.3 (t), 29.1 (t), 30.4 (t), 31.5

(t), 35.1 (t), 126.2 (d), 128.7 (d), 132.0 (d), 132.5 (s); exact mass *m*/*z* calcd for $C_{24}H_{44}{}^{80}Se^{118}Sn$ 530.16241, found 530.16209.

**Tributyl[cyclohexyl(phenylseleno)methyl]stannane (52.15).**



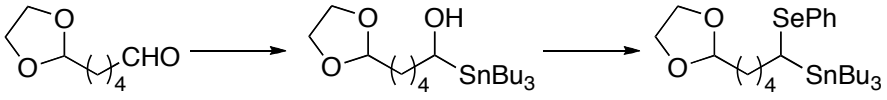

**52.13** **52.14** **52.15**

BuLi (1.6 M in hexane, 0.63 mL, 1.0 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-$Pr_2NH$ (0.15 mL, 1.1 mmol) in THF (3 mL). Stirring was continued at -78 °C for 30 min, and the flask was transferred to an ice bath. $Bu_3SnH$ (0.30 mL, 1.1 mmol) was added and stirring was continued for 15 min. The flask was then transferred back to a cold bath at -78 °C and aldehyde **52.13** (0.06 mL, 0.5 mmol) was added dropwise. Stirring was continued at -78 °C for 30 min, and the mixture was quenched with saturated aqueous $NH_4Cl$. The cold bath was removed and the mixture was allowed to reach room temperature (ca 30 min). The aqueous phase was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. The crude product (**52.14**) was left under oilpump vacuum for 15 min and used directly in the next step.

The above crude hydroxystannane (**52.14**) was dissolved in 3:1 MeCN-THF (4 mL), and pyridine (0.4 mL, 5.0 mmol) was added. The mixture was cooled to 0 °C and PhSeCN (0.12 mL, 1.0 mmol) and $Bu_3P$ (0.25 mL, 1.0 mmol) were added successively at a fast dropwise rate. The ice bath was removed and

stirring was continued for 4 h. The solvent was evaporated and the residue was dissolved in 4:1 THF-MeOH (5 mL). The stirred solution was cooled to 0 °C and an excess of $NaBH_4$ (100 mg) was added. Stirring was continued for 20 min, an excess of $BrCH_2CO_2H$ (400 mg) was added and the ice bath was removed. Stirring was continued for 30 min, the mixture was diluted with EtOAc and saturated aqueous $NaHCO_3$ was added. The mixture was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 25 cm), using hexane, gave **52.15** (132 mg, 49%) as a pale yellow oil: FTIR (microscope) 3070, 2955, 2923, 2870, 2851 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 0.88-1.01 (m, 16 H), 1.08-1.24 (m, 4 H), 1.35 (sextet, *J* = 7.6 Hz, 6 H), 1.43-1.80 (m, 11 H), 1.96 (d, *J* = 12.5 Hz, 1 H), 3.02 (d, *J* = 3.6 Hz, 1 H), 7.16-7.27 (m, 3 H), 7.45-7.50 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 11.1 (t), 13.7 (q), 26.3 (t), 26.5 (t), 26.7 (t), 27.5 (t), 29.3 (t), 34.2 (t), 34.5 (t), 35.4 (d), 43.5 (d), 126.1 (d), 128.9 (d), 131.6 (d), 134.0 (s); exact mass *m/z* calcd for $C_{25}H_{44}{}^{78}Se^{120}Sn$ 542.16382, found 542.16374.

**Tributyl[5-[[1,3]dioxolan-2-yl-1-(phenylseleno)pentyl]]stannane (52.19).**



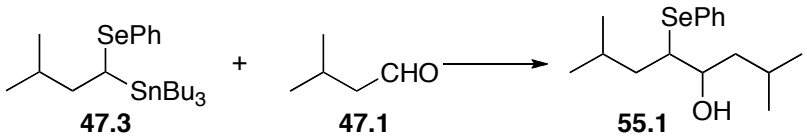

**52.17** **52.18** **52.19**

BuLi (2.5 M in hexane, 0.30 mL, 0.75 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-$Pr_2NH$ (0.12 mL, 0.83 mmol) in THF (3 mL). Stirring was continued at -78 °C for 30 min, and the flask was then transferred to an ice bath. $Bu_3SnH$ (0.23 mL, 0.83 mmol) was added and stirring was continued for 15 min. The flask was then transferred back to a cold bath at -78 °C and a solution of aldehyde **52.17** (50 mg, 0.32 mmol) in THF (1 mL) was added dropwise. Stirring was continued at -78 °C for 30 min, and the mixture was quenched with saturated aqueous $NH_4Cl$. The cold bath was removed and the mixture was allowed to reach room temperature (ca 30 min). The aqueous phase was extracted with EtOAc and the combined organic extracts were dried ($Na_2SO_4$) and evaporated. The crude product (**52.18**) was left under oilpump vacuum for 15 min and used directly in the next step.

The above crude **52.18** was dissolved in 3:1 MeCN-THF (4 mL), and pyridine (0.4 mL, 5.0 mmol) was added. The mixture was cooled to 0 °C and PhSeCN (0.12 mL, 1.0 mmol) and $Bu_3P$ (0.25 mL, 1.0 mmol) were added successively at a fast dropwise rate. The ice bath was removed and stirring was continued for 4 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 25 cm), using hexane, gave **52.19** (86 mg, 46%) as a pale yellow oil: FTIR (neat film) 3070, 3057, 2925 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 0.86-0.99 (m, 15 H), 1.26-1.43 (m, 8 H), 1.46-1.65 (m, 10 H), 1.85-1.96 (m, 2 H), 3.03 (t, *J* = 6.4 Hz, 1 H), 3.77-4.00 (m, 4 H), 4.80 (t, *J* = 4.8 Hz, 1 H), 7.17-7.28 (m, 3 H), 7.45-7.51 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 9.9 (t), 13.6 (q), 23.8 (t), 25.5 (d), 27.3 (t), 29.1 (t), 30.6 (t), 33.7 (t), 35.0 (t), 64.7 (t),

104.4 (d), 126.3 (d), 128.7 (d), 132.1 (d), 132.4 (s); exact mass *m*/*z* calcd for $C_{26}H_{46}Na^{78}O_2{}^{80}Se^{120}Sn$ 613.15772, found 613.15818.

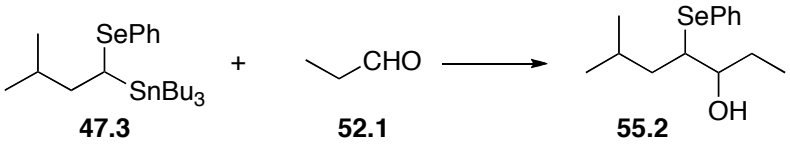
**2,7-Dimethyl-5-(phenylseleno)octan-4-ol (55.1).**




BuLi (1.6 M in hexane, 0.12 mL, 0.19 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **47.3** (49 mg, 0.095 mmol) in THF (3 mL) (Ar atmosphere). Stirring was continued for 15 min at -78 °C, and a solution of isovaleraldehyde (**47.1**) (0.03 mL, 0.29 mmol) in THF (1 mL) was added dropwise (ca 1 min). Stirring was continued for 30 min and the mixture was quenched with saturated aqueous $NH_4Cl$. The cooling bath was removed and stirring was continued for 30 min. The aqueous phase was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 x 10 cm), using 5:95 *t*-BuOMe-$CH_2Cl_2$, gave **55.1** (19 mg, 64%) as a colorless oil: FTIR ($CH_2Cl_2$, cast) 3455, 3072, 2956, 2931, 2869 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) (4:1 mixture of stereoisomers) δ 0.81-0.98 (m, 12 H), 1.17-1.25 (m, 1 H), 1.33-1.53 (m, 2 H), 1.54-1.65 (m, 1 H), 1.70-1.82 (m, 1 H), 1.85-1.96 (m, 0.8 H), 1.98-2.08 (m, 0.2 H), 2.24 (d, *J* = 5.6 Hz, 0.8 H), 2.30 (d, *J* = 5.3 Hz, 0.2 H), 3.13-3.20 (m, 0.2 H), 3.32-3.39 (m, 0.8 H), 3.55-3.63 (m, 0.2 H), 3.67-3.75 (m, 0.8), 7.25-7.30 (m, 3 H), 7.56-7.60 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100

MHz) δ 21.4 (q), 21.6 (q), 21.8 (q), 21.9 (q), 23.1 (q), 23.3 (q), 23.3 (q), 23.5 (q), 24.8 (d), 24.9 (d), 26.2 (d), 26.3 (d), 39.0 (t), 41.2 (t), 42.5 (t), 44.0 (t), 54.7 (d), 70.7 (d), 71.5 (d), 127.5 (d), 127.6 (d), 128.7 (s), 128.9 (d), 129.0 (d), 129.3 (s), 134.5 (d), 134.9 (d); exact mass *m/z* calcd for $C_{16}H_{26}O^{80}Se$ 314.11490, found 314.11466.

**7-Methyl-4-(phenylseleno)heptan-3-ol (55.2).**

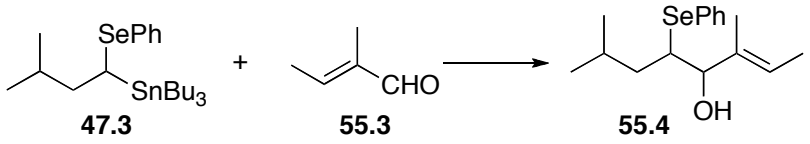



**47.3** **52.1** **55.2**

BuLi (1.6 M in hexane, 0.40 mL, 0.62 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **47.3** (160 mg, 0.31 mmol) in THF (4 mL) (Ar atmosphere). Stirring was continued for 15 min at -78 °C, and a solution of propionaldehyde (**52.1**) (54 mg, 0.93 mmol) in THF (2 mL) was added dropwise (ca 1 min). Stirring was continued for 30 min and the mixture was quenched with saturated aqueous $NH_4Cl$. The cooling bath was removed and stirring was continued for 30 min. The aqueous phase was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 25 cm), using 0-10% EtOAc-hexane, gave **55.2** (59 mg, 66%) as a colorless oil: FTIR ($CH_2Cl_2$, cast) 3454, 3071, 2958, 2931, 2869 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) (4:1 mixture of stereoisomers) δ 0.85-0.99 (m, 9 H), 1.40-1.71 (m, 4 H), 1.84-2.10 (m, 1 H), 2.31 (d, *J* = 5.4 Hz, 0.8 H), 2.44 (d, *J* = 4.6 Hz, 0.2 H),

3.15-3.23 (m, 0.2 H), 3.33-3.47 (m, 1 H), 3.48-3.58 (m, 0.8 H),7.22-7.31 (m, 3 H), 7.54-7.62 (m, 2 H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 10.0 (q), 10.7 (q), 21.4 (q), 21.6 (q), 23.1 (q), 23.4 (q), 26.3 (d), 26.4 (d), 26.4 (t), 27.7 (t), 38.7 (t), 41.3 (t), 53.9 (d), 54.0 (d), 74.4 (d), 74.6 (d), 127.6 (d), 127.7 (d), 128.4 (s), 129.0 (d), 129.1 (d), 129.3 (s), 134.5 (d), 135.2 (d); exact mass *m*/*z* calcd for $C_{14}H_{22}O^{80}Se$ 286.08359, found 286.08346.

**3,7-Dimethyl-5-(phenylseleno)oct-2-en-4-ol (55.4).**

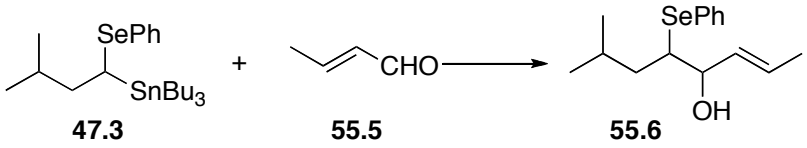



**47.3** **55.3** **55.4**

BuLi (1.6 M in hexane, 0.13 mL, 0.21 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **47.3** (54 mg, 0.11 mmol) in THF (3 mL) (Ar atmosphere). Stirring was continued for 15 min at -78 °C, and a solution of (*E*)-2-methyl-2-butenal (**55.3**) (27 mg, 0.32 mmol) in THF (1 mL) was added dropwise (ca 1 min). Stirring was continued for 30 min and the mixture was quenched with saturated aqueous $NH_4Cl$. The cooling bath was removed and stirring was continued for 30 min. The aqueous phase was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 20 cm), using 0-10% EtOAc-hexane, gave **55.4** (29.5 mg, 90%) as a pale yellow oil: FTIR (microscope) 3458, 3057, 2956, 2927, 2868 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) (3:2 mixture of stereoisomers) δ 0.82-0.95 (m, 6 H), 1.08-1.17

(m, 0.5 H), 1.21-1.30 (m, 0.5 H), 1.39-1.47 (m, 3 H), 1.52-1.56 (m, 1 H), 1.57-1.64 (m, 3 H), 1.82-1.95 (m, 0.6 H), 2.00-2.18 (m, 0.4), 2.41 (d, *J* = 5.8 Hz, 0.6 H), 3.12-3.24 (m, 0.8 H), 3.36-3.45 (m, 0.6 H), 3.68 (dd, *J* = 9.2, 1.6 Hz, 0.4 H), 4.03 (s, 0.6 H), 5.43 (qm, *J* = 6.8 Hz, 0.4 H), 5.61 (q of quintets, *J* = 6.8, 1.2 Hz, 0.6 H), 7.24-7.35 (m, 3 H), 7.55-7.65 (m, 2 H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 10.5 (q), 12.9 (q), 13.0 (q), 13.1 (q), 21.0 (q), 21.2 (q), 23.4 (q), 23.5 (q), 25.9 (d), 26.3 (d), 37.3 (t), 40.2 (t), 50.5 (d), 52.7 (d), 76.8 (d), 78.8 (d), 120.7 (d), 124.1 (d), 126.2 (s), 127.6 (d), 128.1 (d), 128.8 (d), 129.0 (d), 133.8 (s), 134.2 (s), 134.8 (d), 136.2 (d); exact mass *m*/*z* calcd for $C_{16}H_{24}O^{80}Se$ 312.09924, found 312.09919.

**7-Methyl-5-(phenylseleno)oct-2-en-4-ol (55.6).**

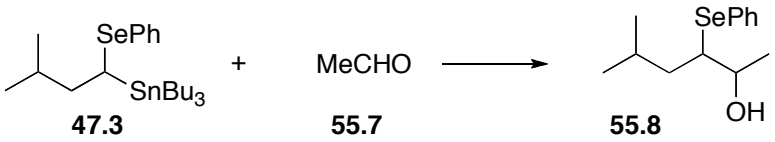



**47.3** **55.5** **55.6**

BuLi (1.6 M in hexane, 0.11 mL, 0.18 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **47.3** (46 mg, 0.09 mmol) in THF (3 mL) (Ar atmosphere). Stirring was continued for 15 min at -78 °C, and a solution of crotonaldehyde (**55.5**) (19 mg, 0.27 mmol) in THF (1 mL) was added dropwise (ca 1 min). Stirring was continued for 30 min and the mixture was quenched with saturated aqueous $NH_4Cl$. The cooling bath was removed and stirring was continued for 30 min. The aqueous phase was extracted with EtOAc, dried

($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 20 cm), using 0-10% EtOAc-hexane, gave **55.6** (19.4 mg, 73%) as a pale yellow oil: FTIR (microscope) 3443, 3071, 3057, 2956, 2868 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) (1:1 mixture of stereoisomers) δ 0.85 (dd, *J* = 6.6, 4.2 Hz, 3 H), 0.92 (t, *J* = 6.0 Hz, 3 H), 1.36-1.44 (m, 1 H), 1.49-1.58 (m, 1 H), 1.66-1.73 (m, 3 H), 1.83-2.13 (m, 1 H), 2.44 (d, *J* = 5.1 Hz, 0.5 H), 2.76 (s, 0.5 H), 3.05-3.18 (m, 0.5 H), 3.32-3.43 (m, 0.5 H), 3.88 (t, *J* = 6.9 Hz, 0.5 H), 4.12 (s, 0.5 H), 5.40-5.54 (m, 1 H), 5.62-5.78 (m, 1 H), 7.22-7.34 (m, 3 H), 7.54-7.64 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 17.7 (q), 17.8 (q), 21.4 (q), 21.6 (q), 23.2 (q), 23.3 (q), 26.2 (d), 26.2 (d), 40.2 (t), 40.5 (t), 53.9 (d), 54.4 (d), 73.7 (d), 74.4 (d), 127.5 (d), 127.6 (s), 127.9 (d), 128.5 (d), 129.0 (d), 129.1 (d), 129.3 (d), 129.5 (s), 130.4 (d), 131.2 (d), 134.5 (d), 135.5 (d); exact mass *m/z* calcd for $C_{15}H_{22}O^{80}Se$ 298.08359, found 298.08406.

**5-Methyl-3-(phenylseleno)heptan-2-ol (55.8).**

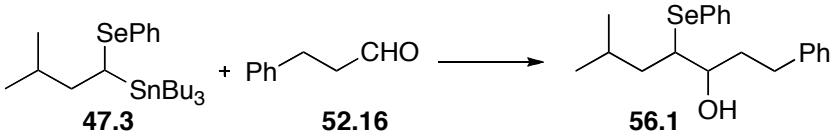



**47.3** **55.7** **55.8**

BuLi (1.6 M in hexane, 0.06 mL, 0.094 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **47.3** (24 mg, 0.047 mmol) in THF (1 mL) (Ar atmosphere). Stirring was continued for 15 min at -78 °C, and a solution of acetaldehyde (**55.7**) (0.008 mL, 0.14 mmol) in THF (0.5 mL) was added dropwise

(ca 1 min). Stirring was continued for 30 min and the mixture was quenched with saturated aqueous $NH_4Cl$. The cooling bath was removed and stirring was continued for 30 min. The aqueous phase was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 x 10 cm), using 0-10% EtOAc-hexane, gave **55.8** (11.4 mg, 89%) as a pale yellow oil: FTIR (microscope) 3428, 3071, 3058, 2956, 2931, 2868 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) (7:3 mixture of stereoisomers) δ 0.85-0.98 (m, 6 H), 1.19 (d, $J$ = 6.3 Hz, 2.1 H), 1.27 (d, $J$ = 6.0 Hz, 0.9 H), 1.37-1.65 (m, 2 H), 1.84-2.15 (m, 1 H), 2.35 (d, $J$ = 6.3 Hz, 0.7 H), 2.60 (s, 0.3 H), 3.02-3.11 (m, 0.3), 3.29-3.40 (m, 0.7 H), 3.67 (t, $J$ = 5.7 Hz, 0.3 H), 3.77-3.90 (m, 0.7 H), 7.22-7.34 (m, 3 H), 7.53-7.65 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 19.6 (q), 20.5 (q), 21.4 (q), 21.5 (q), 23.3 (q), 23.4 (q), 26.3 (d), 26.4 (d), 39.7 (t), 40.7 (t), 55.7 (d), 55.8 (d), 68.8 (d), 69.3 (d), 127.6 (d), 127.8 (d), 128.0 (s), 129.0 (d), 129.1 (d), 129.3 (s), 134.5 (d), 135.3 (d); exact mass $m/z$ calcd for $C_{13}H_{20}O^{80}Se$ 272.06793, found 272.06780.

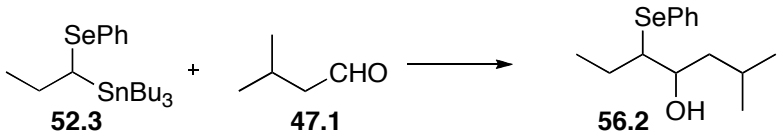
**6-Methyl-1-phenyl-4-(phenylseleno)heptane-3-ol (56.1).**




BuLi (1.6 M in hexane, 0.13 mL, 0.20 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **47.3** (52 mg, 0.10 mmol) in THF (3 mL)

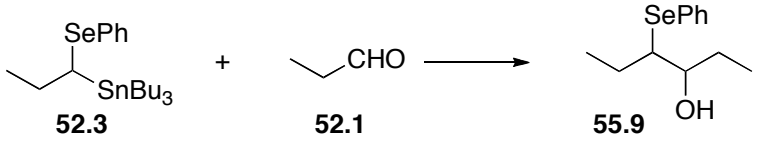
(Ar atmosphere). Stirring was continued for 15 min at -78 °C, and a solution of hydrocinnamaldehyde (**52.16**) (0.04 mL, 0.30 mmol) in THF (1 mL) was added dropwise (ca 1 min). Stirring was continued for 30 min and the mixture was quenched with saturated aqueous $NH_4Cl$. The cooling bath was removed and stirring was continued for 30 min. The aqueous phase was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 25 cm), using 0-20% EtOAc-hexane, gave **56.1** (29.4 mg, 81%) as a colorless oil containing minor impurities ($^1$H NMR): FTIR (neat, microscope) 3450, 3061, 3027, 2955, 2928, 2867 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) δ 0.86 (d, *J* = 6.5 Hz, 3 H), 0.93 (d, *J* = 6.7 Hz, 3 H), 1.39-1.48 (m, 1 H), 1.52-1.64 (m, 1 H), 1.68-1.94 (m, 3 H), 2.36 (br s, 1 H), 2.56-2.66 (m, 1 H), 2.78-2.88 (m, 1 H), 3.32-3.40 (m, 1 H), 3.59-3.68 (m, 1 H), 7.12-7.20 (m, 3 H), 7.22-7.31 (m, 5 H), 7.51-7.57 (m, 2 H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 21.3 (q), 23.3 (q), 26.3 (d), 32.4 (t), 35.3 (t), 38.8 (t), 54.2 (d), 72.0 (d), 125.7 (d), 127.6 (d), 128.3 (d), 128.3 (d), 129.0 (s), 129.1 (d), 134.5 (d), 141.7 (s); exact mass *m*/*z* calcd for $C_{20}H_{26}O^{80}Se$ 362.11490, found 362.11548.

**1-Methyl-5-(phenylseleno)heptan-4-ol (56.2).**



BuLi (1.6 M in hexane, 0.20 mL, 0.32 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **11b** (76 mg, 0.16 mmol) in THF (3 mL) (Ar atmosphere). Stirring was continued for 15 min at -78 °C, and a solution of isovaleraldehyde (**47.1**) (0.05 mL, 0.48 mmol) in THF (1 mL) was added dropwise (ca 1 min). Stirring was continued for 30 min and the mixture was quenched with saturated aqueous $NH_4Cl$. The cooling bath was removed and stirring was continued for 30 min. The aqueous phase was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 x 10 cm), using 2:98 *t*-BuOMe-hexane, gave **56.2** (33 mg, 72%) as a colorless oil: FTIR (microscope) 3447, 3058, 2957, 2932, 2870 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 0.86 (d, $J$ = 6.6 Hz, 3 H), 0.89 (d, $J$ = 6.7 Hz, 3 H), 1.11 (t, $J$ = 7.3 Hz, 3 H), 1.22-1.30 (m, 1 H), 1.39-1.47 (m, 1 H), 1.60-1.73 (m, 1 H), 1.74-1.88 (m, 2 H), 2.18 (d, $J$ = 6.6 Hz, 1 H), 3.23 (ddd, $J$ = 9.7, 4.7, 3.4 Hz, 1 H), 3.75 (ddd, $J$ = 13.3, 6.7, 3.6 Hz, 1 H) 7.24-7.30 (m, 3 H), 7.56-7.62 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 13.3 (q), 21.8 (q), 23.4 (q), 23.9 (t), 24.7 (d), 42.7 (t), 59.0 (d), 70.7 (d), 127.4 (d), 129.0 (d), 129.6 (s), 134.3 (d); exact mass *m*/*z* calcd for $C_{14}H_{22}O^{80}Se$ 286.08359, found 286.08360.

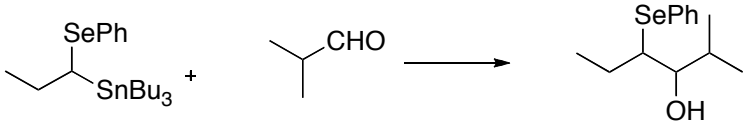
**4-(Phenylseleno)hexan-3-ol (55.9).**[23]




**52.3** **52.1** **55.9**

BuLi (1.6 M in hexane, 0.09 mL, 0.15 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **52.3** (20 mg, 0.04 mmol) in THF (2 mL) (Ar atmosphere). Stirring was continued for 15 min at -78 °C, and a solution of propionaldehyde (**52.1**) (0.014 mL, 0.20 mmol) in THF (1 mL) was added dropwise (ca 1 min). Stirring was continued for 30 min and the mixture was quenched with saturated aqueous $NH_4Cl$. The cooling bath was removed and stirring was continued for 30 min. The aqueous phase was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 x 10 cm), using 0-10% EtOAc-hexane, gave **55.9** (7.1 mg, 69%) as a colorless oil: FTIR ($CH_2Cl_2$, cast) 3440, 3071, 3058, 3015, 2962, 2930, 2874, 2854 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) (17:3 mixture of stereoisomers) δ 0.92-0.99 (m, 3 H), 1.07-1.15 (m, 3 H), 1.42-1.74 (m, 3 H), 1.77-1.90 (m, 1 H), 2.22 (d, $J$ = 6.1 Hz, 0.85 H), 2.34 (d, $J$ = 4.8 Hz, 0.15 H), 3.03-3.09 (m, 0.15 H), 3.21-3.27 (m, 0.85 H), 3.48-3.61 (m, 1 H), 7.23-7.31 (m, 3 H), 7.55-7.62 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 10.6 (q), 13.2 (q), 23.6 (t), 26.6 (t), 58.1 (d), 74.3 (d), 127.4 (d), 128.9 (d), 129.0 (d), 129.5 (s), 134.3 (d), 134.8 (d); exact mass $m/z$ calcd for $C_{12}H_{18}O^{80}Se$ 258.05228, found 258.05232.

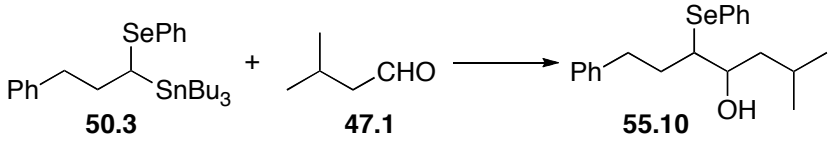
**2-Methyl-4-(phenylseleno)propan-3-ol (56.3).**




**52.3** **52.7** **56.3**

BuLi (1.6 M in hexane, 0.12 mL, 0.18 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **52.3** (45 mg, 0.09 mmol) in THF (1 mL) (Ar atmosphere). Stirring was continued for 15 min at -78 °C, and a solution of isobutyraldehyde (**52.7**) (0.025 mL, 0.28 mmol) in THF (1 mL) was added dropwise (ca 1 min). Stirring was continued for 30 min and the mixture was quenched with saturated aqueous $NH_4Cl$. The cooling bath was removed and stirring was continued for 30 min. The aqueous phase was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 20 cm), using 0-10% EtOAc-hexane, gave **56.3** (16.8 mg, 67%) as a pale yellow oil: FTIR (hexane, microscope) 3470, 3071, 2961, 2931, 2872 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) (7:3 mixture of stereoisomers) δ 0.82 (d, $J$ = 6.8 Hz, 3 H), 0.95 (d, $J$ = 6.6 Hz, 3 H), 1.14 (t, $J$ = 7.3 Hz, 3 H), 1.52-1.65 (m, 1 H), 1.79-1.98 (m, 2 H), 2.33 (br s, 1 H), 3.27 (dd, $J$ = 8.1, 3.5 Hz, 1 H), 3.34 (dt, $J$ = 10.2, 3.3 Hz, 1 H), 7.25-7.30 (m, 3 H), 7.53-7.58 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 13.3 (q), 19.1 (q), 19.2 (q), 21.4 (t), 30.3 (d), 55.0 (d), 78.0 (d), 127.5 (d), 129.0 (d), 134.4 (d); exact mass $m/z$ calcd for $C_{13}H_{20}O^{80}Se$ 272.06793, found 272.06781.

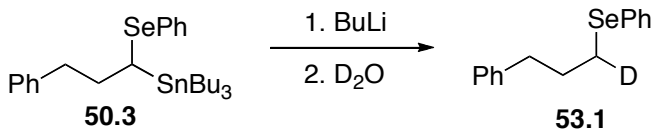
**2-Methyl-7-phenyl-5-(phenylseleno)heptane-4-ol (55.10).**




**50.3** **47.1** **55.10**

BuLi (1.6 M in hexane, 0.038 mL, 0.06 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **50.3** (17 mg, 0.03 mmol) in THF (1 mL) (Ar atmosphere). Stirring was continued for 1 h at -78 °C, and neat isovaleraldehyde (**47.1**) (0.010 mL, 0.09 mmol) was added. Stirring was continued for 30 min and the mixture was quenched with saturated aqueous $NH_4Cl$. The cooling bath was removed and stirring was continued for 30 min. The aqueous phase was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 x 10 cm), using 0-20% EtOAc-hexane, gave **55.10** (8.8 mg, 80%) as a colorless oil: FTIR ($CHCl_3$, microscope) 3450, 3061, 3026, 2954, 2930, 2867 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 0.79-0.93 (m, 6 H), 1.16-1.28 (m, 1 H), 1.33-1.51 (m, 1 H), 1.62-1.78 (m, 1 H), 1.86-2.15 (m, 2 H), 2.16-2.26 (m, 1 H), 2.66-2.84 (m, 1 H), 2.94-3.14 (m, 1.3 H), 3.21-3.30 (m, 0.7 H), 3.63-3.79 (m, 1 H), 7.12-7.32 (m, 8 H), 7.52-7.60 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 21.7 (q), 21.8 (q), 23.3 (q), 23.5 (q), 24.7 (d), 24.8 (d), 32.2 (t), 33.9 (t), 34.2 (t), 34.3 (t), 42.6 (t), 43.9 (t), 55.9 (d), 70.9 (d), 71.4 (d), 125.8 (d), 125.9 (d), 127.5 (d), 127.6 (d), 128.3 (d), 128.4 (d), 128.8 (d), 129.0 (s), 129.1 (d), 129.3 (s), 134.3 (d), 134.7 (d), 141.3 (s), 141.7 (s); exact mass *m*/*z* calcd for $C_{20}H_{26}O^{80}Se$ 362.11490, found 362.11483.

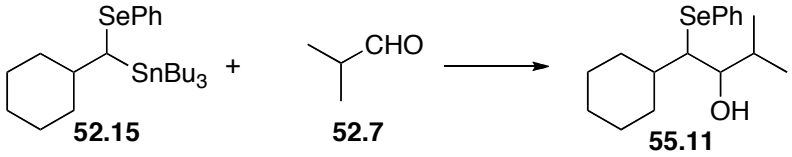
**3-Phenyl-1-deutero-1-(phenylseleno)propane (53.1).**




**50.3** **53.1**

BuLi (1.6 M in hexane, 0.065 mL, 0.10 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **50.3** (18 mg, 0.032 mmol) in THF (1 mL) (Ar atmosphere). Stirring was continued for 15 min at -78 °C, and $D_2O$ (0.20 mL, 10 mmol) was added rapidly. Stirring was continued for 30 min and the mixture was quenched with saturated aqueous $NH_4Cl$. The cooling bath was removed and stirring was continued for 30 min. The aqueous phase was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 x 10 cm), using hexane, gave **53.1** (8 mg, 90%) as a pale yellow oil: FTIR ($CH_2Cl_2$, microscope) 3061, 3026, 2925, 2853 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 2.02 (q, *J* = 7.2 Hz, 2 H), 2.74 (t, *J* = 7.3 Hz, 2 H), 2.89 (t, *J* = 7.2 Hz, 1 H), 7.10-7.32 (m, 8 H), 7.42-7.51 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 26.6, 26.9, 27.1 (1:1:1 t), 31.5 (t), 35.7 (t), 125.9 (d), 126.7 (d), 128.4 (d), 128.5 (d), 129.0 (d), 130.2 (s), 132.5 (d), 141.3 (s); exact mass *m*/*z* calcd for $C_{15}H_{15}D^{80}Se$ 277.04800, found 277.04770.

**2-Methyl-4-cyclohexyl-4-(phenylseleno)butane-3-ol (55.11).**

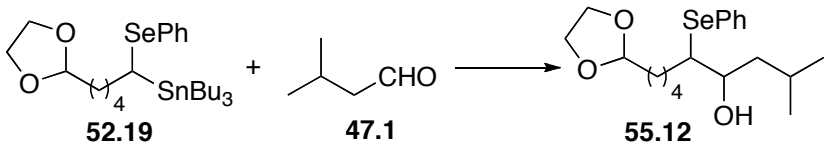



**52.15** **52.7** **55.11**

BuLi (1.6 M in hexane, 0.05 mL, 0.082 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **52.15** (22 mg, 0.041 mmol) in THF (1 mL)

(Ar atmosphere). Stirring was continued for 15 min at -78 °C, and a solution of isobutyraldehyde (**52.7**) (0.011 mL, 0.123 mmol) in THF (1 mL) was added dropwise (ca 1 min). Stirring was continued for 30 min and the mixture was quenched with saturated aqueous $NH_4Cl$. The cooling bath was removed and stirring was continued for 30 min. The aqueous phase was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 x 10 cm), using 0-10% EtOAc-hexane, gave **55.11** (11 mg, 82%) as a pale yellow oil: FTIR ($CHCl_3$, microscope) 3481, 3071, 2957, 2958, 2926, 2852 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) (7:3 mixture of stereoisomers) δ 0.79-0.88 (m, 5 H), 0.94 (d, *J* = 6.7 Hz, 1 H), 1.09-1.39 (m, 4 H), 1.58-1.83 (m, 6 H), 1.84-1.95 (m, 1 H), 2.02-2.14 (m, 1 H), 2.33 (br s, 1 H), 3.20-3.24 (m, 1 H), 3.40 (t, *J* = 5.6 Hz, 0.7 H), 3.47 (t, *J* = 5.8 Hz, 0.3 H), 7.21-7.29 (m, 3 H), 7.51-7.63 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 16.5 (q), 18.0 (q), 19.8 (q), 20.2 (q), 26.1 (t), 26.3 (t), 26.3 (t), 26.5 (t), 30.3 (d), 30.5 (t), 30.6 (t), 31.2 (d), 32.1 (t), 33.2 (t), 38.1 (d), 41.3 (d), 61.5 (d), 63.8 (d), 76.5 (d), 77.8 (d), 127.0 (d), 127.2 (d), 129.0 (d), 129.0 (d), 130.1 (s), 131.1 (s), 133.8 (d), 134.2 (d); exact mass *m*/*z* calcd for $C_{17}H_{26}O^{80}Se$ 326.11490, found 326.11527.

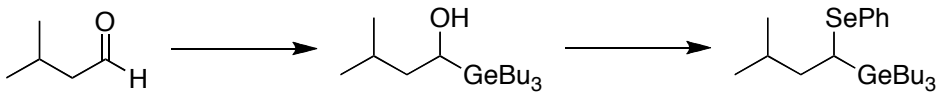
**9-[[1,3]Dioxolan-2-yl]-2-methyl-(5-phenylseleno)nonan-4-ol (55.12).**




**52.19** **47.1** **55.12**

BuLi (2.4 M in hexane, 0.054 mL, 0.13 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **52.19** (38 mg, 0.065 mmol) in THF (2 mL) (Ar atmosphere). Stirring was continued for 15 min at -78 °C, and isovaleraldehyde (**47.1**) (0.022 mL, 0.195 mmol) was added in one portion. Stirring was continued for 30 min and the mixture was quenched with saturated aqueous $NH_4Cl$. The cooling bath was removed and stirring was continued for 30 min. The aqueous phase was extracted with EtOAc and the combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 25 cm), using 0-50% EtOAc-hexane, gave **55.12** (21 mg, 83%) as a colorless oil: FTIR (neat film) 3377, 3059, 2955, 2958, 2871 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) (7:3 mixture of stereoisomers) δ 0.80-0.97 (m, 7 H), 1.18-1.29 (m, 1 H), 1.31-1.53 (m, 5 H), 1.60-1.85 (m, 6 H), 2.16-2.30 (m, 1 H), 3.04-3.18 (m, 0.3 H), 3.23 (m, 0.7 H), 3.59-3.68 (m, 0.3 H), 3.68-3.77 (m, 0.7 H), 3.79-4.01 (m, 4 H), 4.84 (t, *J*=4.7 Hz, 1 H), 7.21-7.31 (m, 3 H), 7.53-7.61 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 21.7 (q), 21.8 (q), 23.3 (q), 23.5 (q), 23.68 (t), 23.72 (t), 24.77 (d), 24.8 (d), 28.0 (t), 28.3 (t), 30.4 (t), 32.3 (t), 33.6 (t), 42.6 (t), 44.0 (t), 56.6 (d), 56.7 (d), 64.7 (t), 70.7 (d), 71.3 (d), 104.4 (d), 127.44 (d), 127.48 (d), 128.95 (d), 129.0 (d), 129.4 (s), 134.3 (d), 134.7 (d); exact mass *m*/*z* calcd for $C_{19}H_{30}NaO_3{}^{80}Se$ 409.12524, found 409.12543.

**Tributyl[3-methyl-1-(phenylseleno)butyl]germane (57.2).**




**47.1** **57.1** **57.2**

BuLi (1.6 M in hexane, 0.56 mL, 0.9 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-$Pr_2NH$ (0.12 mL, 0.9 mmol) in THF (3 mL). Stirring was continued at -78 °C for 30 min, and the flask was transferred to an ice bath. A solution of $Bu_3GeH$ (161 mg, 0.69 mmol) in THF (1 mL) was added, and stirring was continued for 15 min. The flask was then transferred back to a cold bath at -78 °C and isovaleraldehyde (**47.1**) (0.055 mL, 0.50 mmol) was added dropwise. Stirring was continued at -78 °C for 30 min, and the mixture was quenched with saturated aqueous $NH_4Cl$. The cold bath was removed and the mixture was allowed to reach room temperature (ca 30 min). The aqueous phase was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. The crude product [3-methyl-1-(tributylgermanyl)butan-1-ol] (**57.1**) was kept under oilpump vacuum for 15 min and used directly in the next step.

The above crude alcohol (**57.1**) was dissolved in 3:1 MeCN-THF (4 mL), and pyridine (0.4 mL, 5.0 mmol) was added. The mixture was cooled to 0 °C and PhSeCN (0.12 mL, 1.0 mmol) and $Bu_3P$ (0.25 mL, 1.0 mmol) were added successively at a fast dropwise rate. The ice bath was removed and stirring was continued for 4 h. The solvent was evaporated and the residue was dissolved in 4:1 THF-MeOH (5 mL). The stirred solution was cooled to 0 °C and an excess of

$NaBH_4$ (100 mg) was added. Stirring was continued for 20 min, an excess of $BrCH_2CO_2H$ (400 mg) was added and the ice bath was removed. Stirring was continued for 30 min, the mixture was diluted with EtOAc and saturated aqueous $NaHCO_3$ was added. The mixture was extracted with EtOAc, dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 25 cm), using hexane, gave tributyl[3-methyl-1-(phenylseleno)butyl]germane (**57.2**) (40 mg, 17%) as a colorless oil: FTIR (hexane, microscope) 3847, 2955, 2925, 2870, 2855 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) d 0.71 (d, *J* = 6.5 Hz, 3 H), 0.82-0.92 (m, 18 H), 1.24-1.42 (m, 12 H), 1.58-1.75 (m, 2 H), 1.76-1.87 (m, 1 H), 2.81 (dd, *J* = 9.9, 5.4 Hz, 1 H), 7.19-7.26 (m, 3 H), 7.51-7.57 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 12.5 (t), 13.7 (q), 21.5 (q), 23.1 (q), 26.6 (t), 27.0 (d), 27.5 (t), 28.5 (d), 44.1 (t), 126.4 (d), 128.8 (d), 132.3 (d), 132.6 (s); exact mass *m*/*z* calcd for $C_{19}H_{33}{}^{72}Ge^{80}Se$ (M - Bu) 413.09683, found 413.09768.

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# CHAPTER 2

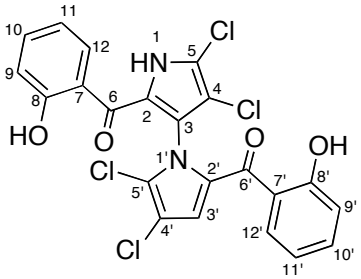
# Synthetic Studies on the Marinopyrroles

# 1. INTRODUCTION

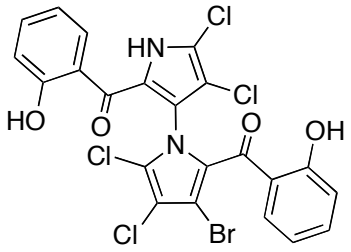
## 1.1 General

Historically, the majority of drugs have been discovered and developed from natural products, or their derivatives, metabolites, or mimics.[1] Natural product based drug discovery reached its peak during the 1970's and 1980s.[2] In the past 20 years over 50% of the small molecule drugs introduced to the market have been based on natural products, and synthetic or semisynthetic derivitaves.[2,3]

For over half a century, the cultivation of bacteria has become a source for obtaining structurally and functionally diverse secondary metabolites.[4] It has been discovered that some of these secondary metabolites posses remarkable biological activities which qualify them as drug candidates for treating diseases in humans. Traditionally, these bacteria were studied and obtained from soil habitats. Today, however, since a pressing need exists for the discovery of new antibiotics, the study of bacteria has been expanded from soil habitats to marine habitats.[5] A major difficulty in studying marine natural products in the past has been the limited access due to the limitations of the technology for collection. For many years scuba diving has been the only way to reach ocean bottoms and collect samples. Today, instead of scuba diving, marine sediments are collected using deep water sampling tools. With the improvement in the methods of sample collection, research in the field of marine natural products has become more active in both industrial and academic laboratories.




**marinopyrrole A (1.1)**




**marinopyrrole B (1.2)**

**Scheme 1**

In 2008 Fenical and coworkers reported[6] the findings of a study on actinomycetes that inhabit ocean sediments. Chemical studies of these bacteria, which include new species, have yielded a growing number of unique, bioactive natural products. Extracts of an actinomycetes strain, CNQ-418, which was obtained from a marine sediment sample, showed remarkable antibiotic activity. Further studies and isolation of the natural products from the extracts yielded two prominent metabolites, the marinopyrroles A (**1.1**) and B (**1.2**) (Scheme 1).

## 1.2 Isolation and structure elucidation of the marinopyrroles.

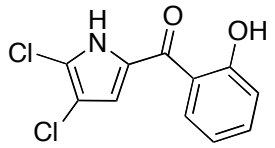
The actinomycetes strain CNQ-418 was cultivated in a seawater-based medium for 7 days with vigorous shaking. Solid phase extraction of the broth using Amberlite resin (XAD-16), filtration through cheesecloth, and elution of the resin with acetone afforded, after solvent removal under vacuum, a gummy extract that was subjected to fractionation on silica gel. Using C8 reverse phase HPLC, two prominent metabolites were isolated. These were identified as

marinopyrrole A, with the molecular formula $C_{22}H_{12}Cl_4N_2O_4$ and marinopyrrole B, with the molecular formula $C_{22}H_{11}BrCl_4N_2O_4$.

Initial progress towards the structure elucidation of the marinopyrroles began with 2D NMR analysis of marinopyrrole A. The presence of two benzoyl groups was identified through interpretation of COSY, HSQC, and HMBC spectral data. Analysis of the rest of the structure unambiguously, using simply NMR data was difficult, and alternate characterization techniques such as X-ray crystallography were required. To this end several derivatives of marinopyrrole A were prepared to obtain crystals suitable for crystallographic analysis. The phenolic groups were esterified to produce the corresponding *O,O'*-diacetyl-, di-*p*-bromobenzoyl-, and di-*p*-nitrobenzoyl esters. Also the *N*-methyl derivative was made by treating marinopyrrole A with $CH_2N_2$ in $Et_2O$. Even though all these derivatives of marinopyrrole were crystalline, none of them gave crystals that were suitable for X-ray analysis. However, suitable crystals of marinopyrrole B were obtained by slow evaporation from PhMe. Once the crystals of marinopyrrole B were obtained, its structure and absolute configuration were readily obtained by X-ray analysis. With that information in hand, the structure of marinopyrrole A was assigned by comparison of the spectral data of the two compounds.

Both marinopyrroles were isolated as single atropo-enantiomers with an M configuration. Isolation of single enantiomers suggests that the pyrrole-pyrrole coupling is an enzyme catalyzed process. Also isolated along with the marinopyrroles from the cultures of the actinomycete strain CNQ-418 was

monodeoxypyoluteorin **(2.1)**. This compound, which can be viewed as the precursor of marinopyrrole A, provides direct evidence for the biosynthetic route to marinopyrrole A. It further confirms the argument that marinopyrrole A is biosynthesized by the coupling of two pyrroles, a process which gives rise to the *N,C*2 linked bispyrrole core.




**monodeoxypyoluteorin (2.1)**

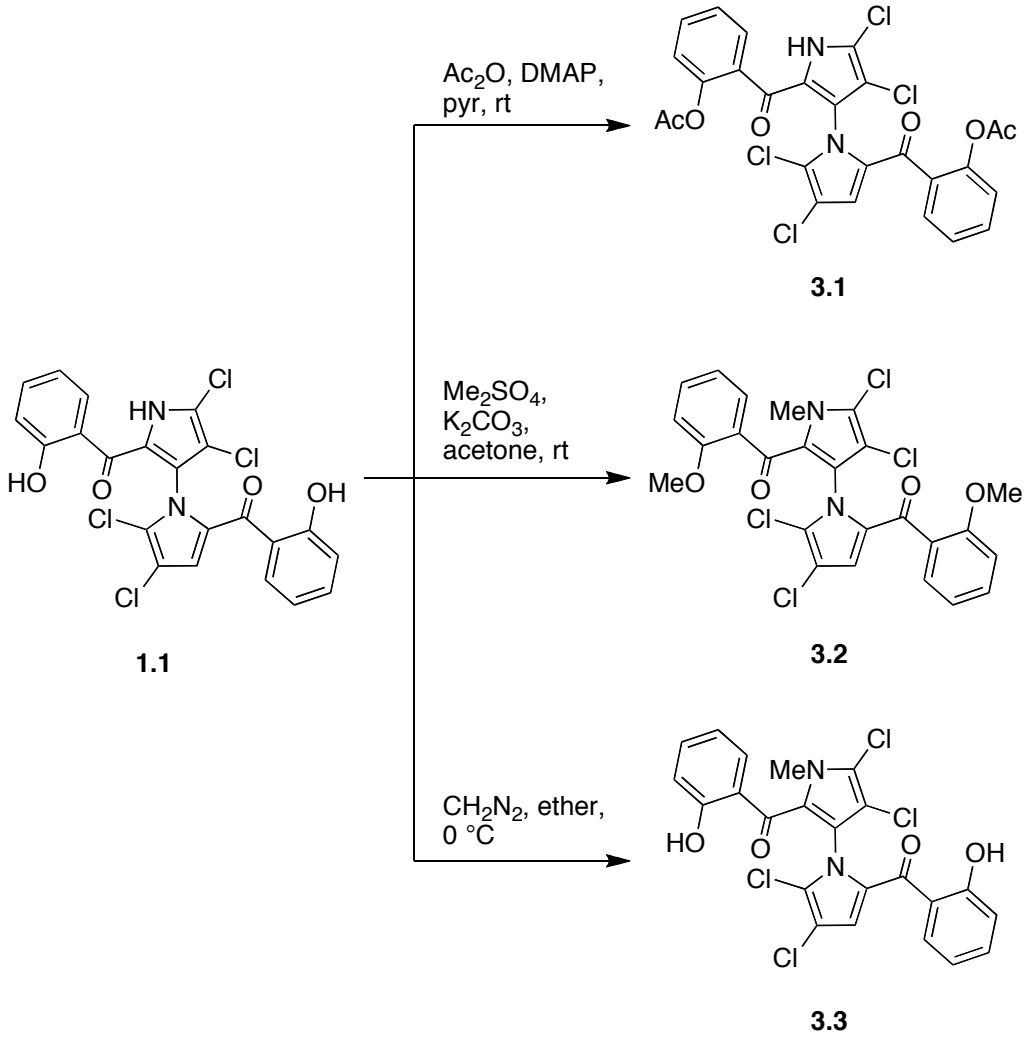
**Scheme 2**

Marinopyrroles are the first natural products with an *N,C*2 linked bispyrrole motif to be described in the natural products literature. Though these metabolites were configurationally stable at room temperature they tend to isomerize at elevated temperatures. The natural atropo-enantiomer of marinopyrrole A, which has an M configuration, was heated in PhMe at 120 °C and a racemate was obtained. The M and P atropo-enantiomers were isolated by converting them to the corresponding Mosher's esters, separating the diastereoisomers on a silica gel column, and saponifying the bis-esters. It was interesting to note that the configuration about the biaryl axis of the marinopyrroles appeared to be of little consequence since the non-natural atropo-enantiomer of marinopyrrole A showed potency similar to that of the natural product.

## 1.3 Reactivity of the marinopyrroles.

In 2010 Fenical and coworkers reported[7] the reactivity of marinopyrrole A with various electrophiles and nucleophiles under various conditions. Manipulation of the polar functional groups of marinopyrrole A was first examined. When the natural product was treated with $Ac_2O$ both of the phenolic hydroxyl groups were cleanly acetylated (**3.1**). When the natural product was treated with $Me_2SO_4$ both phenolic hydroxyl groups and the unprotected pyrrole nitrogen were methylated (**3.2**). It was interesting to discover that when the natural product was treated with $CH_2N_2$ in $Et_2O$ only the pyrrole nitrogen and not the phenolic hydroxyl groups was methylated (**3.3**). However, when the natural product was treated with $CH_2N_2$ in MeOH the *N*-methylated derivative of the natural product was obtained in low yield.

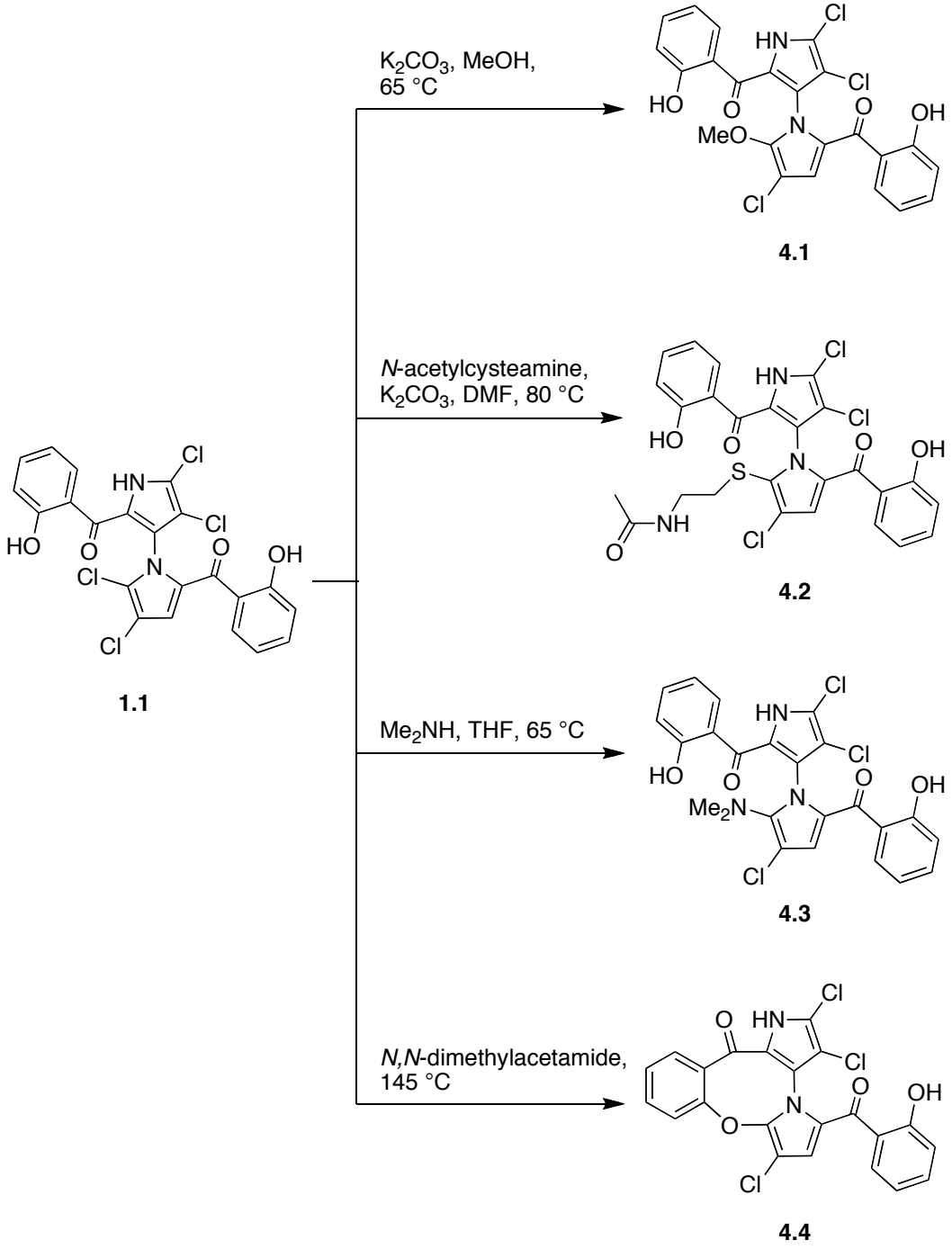
This variation of the products by variation of the solvent confirms the existence of a strong network of hydrogen bonds between the two phenolic hydroxyl groups and the benzoyl carbonyls. When MeOH was used as the solvent, the intramolecular hydrogen bonding was disrupted and the phenolic hydroxyl groups were then available for methylation.




**Scheme 3**

The densely halogenated nature of the core of the marinopyrroles suggests that the molecule might be electrophilic. To test this hypothesis, marinopyrrole A and its analogs were treated with several different nucleophiles containing oxygen, sulfur, and nitrogen (Scheme 4). When marinopyrrole A was treated with MeOH (**4.1**), *N*-acetylcysteamine (**4.2**), and $Me_2NH$ (**4.3**) at elevated temperatures the compound underwent nucleophilic aromatic substitution

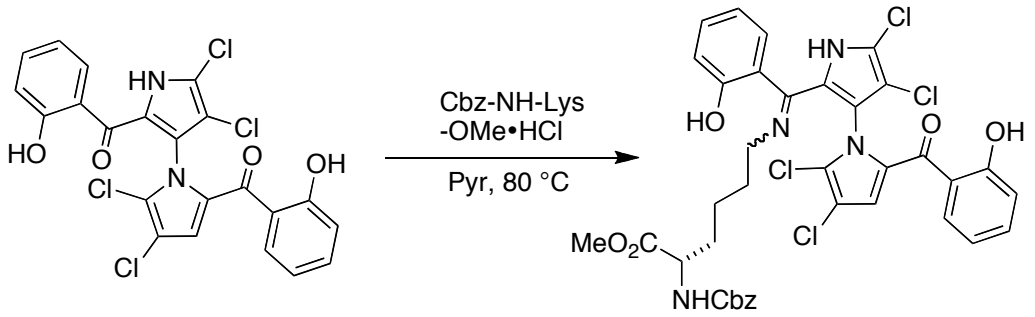
reactions. In all of these cases the chlorine at *C*5' was replaced exclusively by the nucleophile.




**Scheme 4**

Upon prolonged heating at 145 °C in *N,N*-dimethylacetamide, marinopyrrole A was converted into marinopyrrole F (**4.4**, Scheme 4), demonstrating again the tendency of aromatic substitution of the marinopyrroles. Unlike marinopyrrole A, monodeoxypyoluteorin, when subjected to the same reaction conditions, did not undergo any nucleophilic aromatic substitution.

At elevated temperatures (80 °C) in pyridine, marinopyrrole A reacted with the ε-amino group of *N*-α-benzyloxycarbonyllysine methyl ester hydrochloride to give exclusively the *C*6 imine (**5.1**). In a previous study, Fenical and coworkers had reported[8] that cytotoxicity in eukaryotic cells is observed when the marinopyrroles target the protein actin in muscles and undergo imine formation. The experimental observation of imine formation has been used to probe the mechanism by which the marinopyrroles cause cytotoxicity in eukaryotic cells.




**1.1** **5.1**

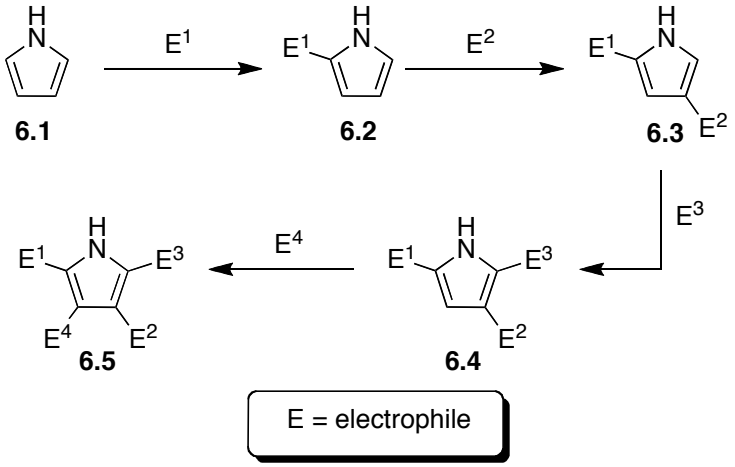
**Scheme 5**

Even though marinopyrrole A is susceptible to nucleophiles and electrophiles under mild conditions and is racemized above 100 °C, it is

configurationally stable to both strongly acidic conditions such as TFA in $CH_2Cl_2$, and to strongly basic conditions such as 6 N aqueous NaOH in MeOH. It is also interesting to note that when the optically pure natural product marinopyrrole A underwent the reactions shown in Schemes 3 and 4 the optical purity was maintained when the reaction took place distal to the biaryl bond as in the formation of **3.3** (Scheme 3), and was lost when the reaction took place *ortho* to the biaryl bond as in the formation of **4.1** (0% ee), **4.2** (76% ee), and **4.3** (0% ee) (Scheme 4).

## 1.4 Electrophilic substitution/Halogenation of pyrroles.

It is well known that pyrroles undergo predominantly or exclusively kinetic electrophilic substitution at the α (i. e. 2)-position with most electrophilic reagents.[9] The only exception to this rule is in the silylation of *N*-methyl- or *N*-benzylpyrrole with TMSOTf in $Et_3N$, where trimethylsilylation at the β (or 3-position) is the predominant result.[10,11] According to theoretical calculations pyrrole has the highest net negative charge density at the β-position and hard electrophiles such as TMSOTf are directed to the β-position[12] while soft electrophiles are directed towards the α-position. The preparation in a readily accessible manner of β-substituted pyrroles has been the object of numerous investigations in recent years.



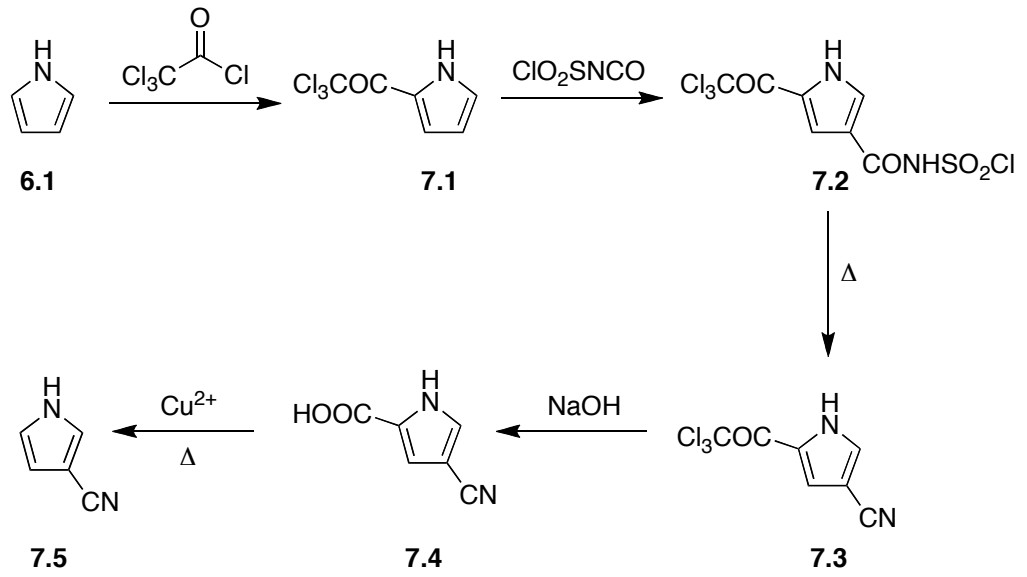

**Scheme 6**

Since the order of reactivity at each carbon of the pyrrole is 2(α)>4(γ)>5(δ)>3(β) (Scheme 6), a number of different approaches have been employed to prepare β-substituted pyrroles. Three of the most common methods are:

*1.4.1 Utilization of a removable group at the 2-position to direct an electrophile to the 4-position.*

In 1981 Anderson and Loader reported[13] that β-substituted pyrroles can be prepared by first placing a directing group at the 2-position and later removing the directing group once the 4-position is substituted. Using the preparation of pyrrole-3-carbonitrile as an example, the authors demonstrated that the reaction of 2-trichloroacetylpyrrole with chlorosulfonyl isocyanate gave compound **7.2** (Scheme 7), which was then converted to the corresponding nitrile **7.3** upon heating. After hydrolysis of the trichloroacetyl moiety to the corresponding

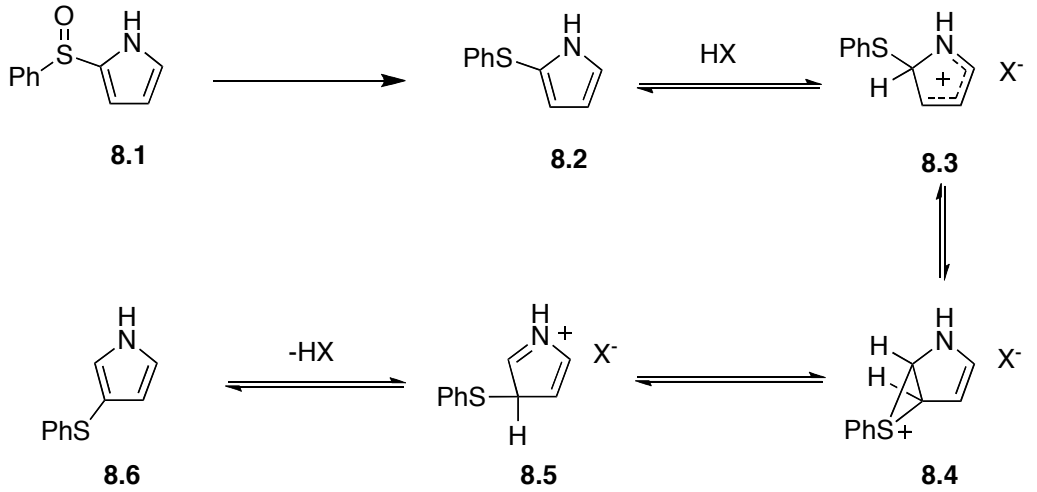
carboxylic acid **7.4** with NaOH, Cu catalyzed decarboxylation gave pyrrole-3-carbonitrile (**7.5**).

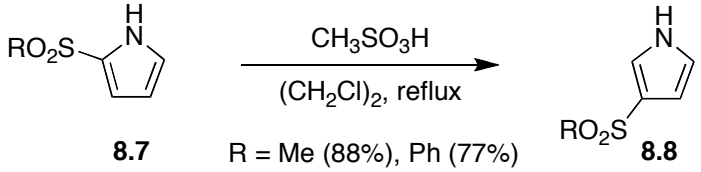



**Scheme 7**

*1.4.2 Acid mediated isomerization of the α isomers.*

In 1982 Muchowski and coworkers reported[14] that β-substituted pyrroles can be prepared by acid mediated isomerization of the α substituted pyrroles. As shown in Scheme 8, phenyl-2-pyrrolyl sulfide (**8.2**), which was obtained by the reduction of 2-(phenylsulfinyl) pyrrole (**8.1**), when treated with TsOH undergoes rearrangement to give phenyl-3-pyrrolyl sulfide (**8.6**). The acid mediated isomerizations are not limited to sulfides, and can also be applied to sulfones. 2-(Phenylsulfonyl)pyrrole, and 2-(methylsulfonyl)pyrrole, under the same acid mediated conditions, rearranged to the 3-(phenylsulfonyl)pyrrole and 3-(methylsulfonyl)pyrrole in good yield (77% and 88% respectively).



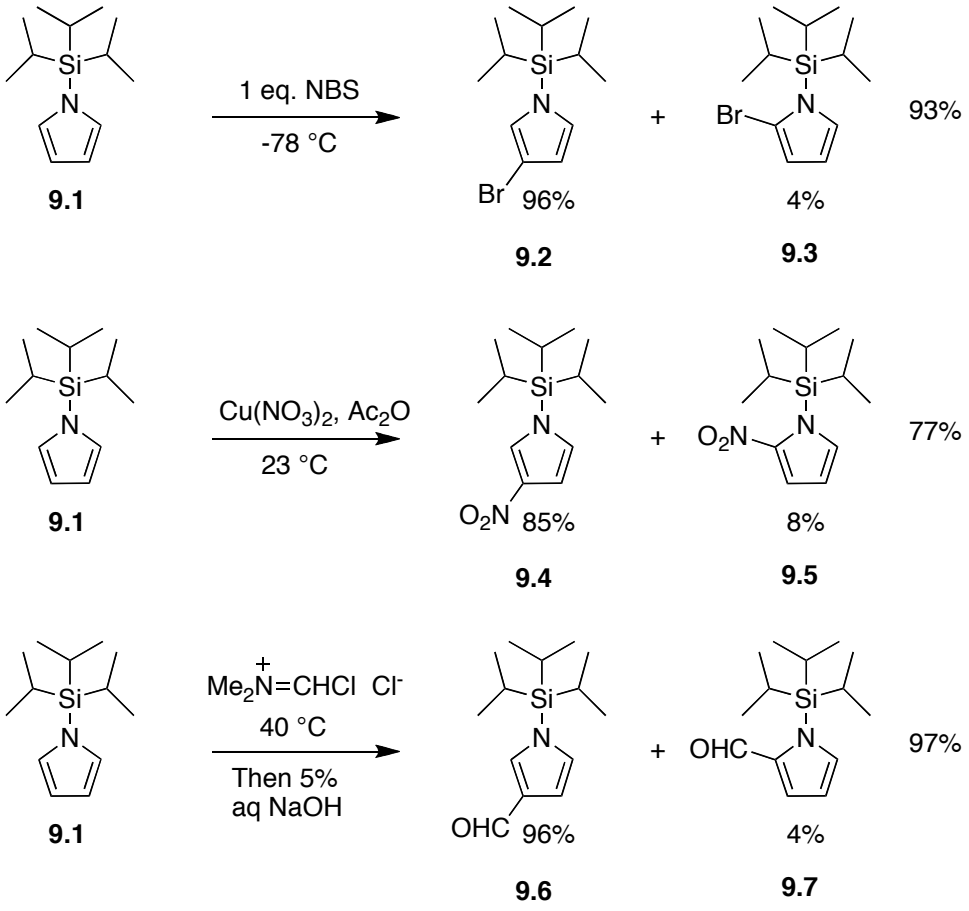




**Scheme 8**

*1.4.3 Placement of a bulky group on the nitrogen.*

In 1990 Muchowski and coworkers reported[15] that placement of a bulky group such as a *i*-$Pr_3Si$ moiety on the nitrogen creates a significant amount of steric hindrance that obstructs the α-position of pyrrole so that electrophilic substitution at the β-position predominates. Once the β-position is substituted, deprotection of the nitrogen gives the β-substituted pyrroles, making this sequence a facile route for the preparation of β-substituted pyrroles. Various different β substitutions including bromination, nitration, and formylation were done on nitrogen-protected pyrroles. Chlorination predominantly at the 2-position

under several different conditions was unsuccessful and gave significant amounts of undesired products such as the 2-chloro- and 2,3,5-trichloropyrroles. Formation of a minor amount of undesired substitution products was a major disadvantage of this methodology. However, by careful manipulation of the reaction conditions and the number of equivalents of electrophile, it proved possible to increase the yield of the desired β-substituted product.

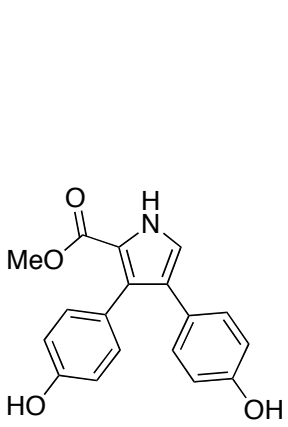



**Scheme 9**

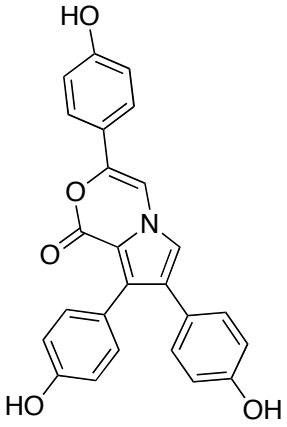
Halogens are a significant feature of many medicinal natural products.[16] Enzyme mediated halogenations during the biosynthesis of natural products

allows fine tuning of electronic and steric properties of a molecule so that it can effectively interact with its biological target. Of the many halogenated natural products, halogenated pyrroles play a significant role as antimicrobial agents, especially against Gram-positive bacteria.[17]

Preparation of halogenated pyrroles has been challenging due to the peculiar order of reactivity at each carbon of the pyrrole towards different electrophiles. In 2006, Smith and coworkers addressed[18] the challenges posed in the synthesis of aryl pyrroles. In the synthesis of natural products such as lamellarin Q (**10.1**) and lukinol A (**10.2**) (Scheme 10), which contain arylated pyrroles, the pyrrole-aryl bond can be put in place through the use of a Suzuki-Miyaura reaction.




**10.1**

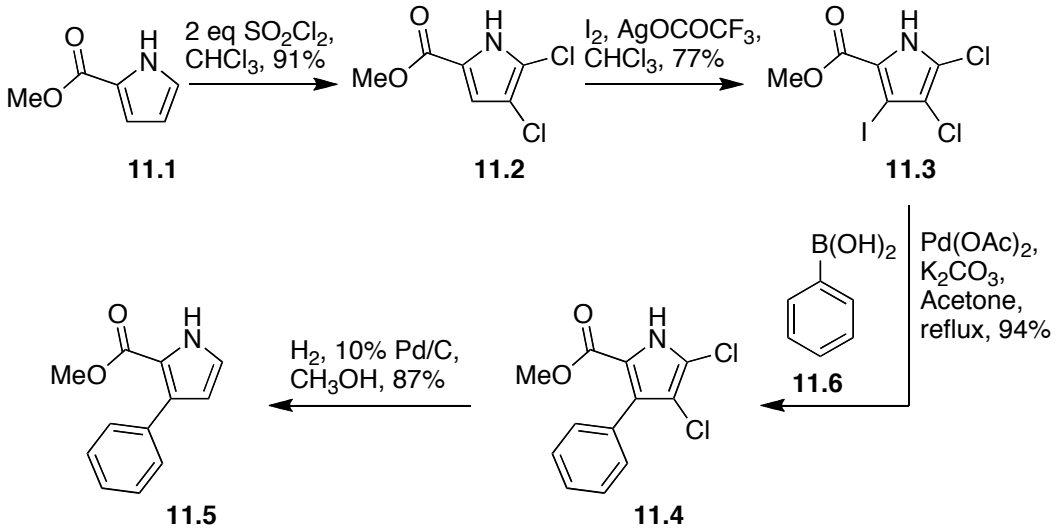



**10.2**

**Scheme 10**

Prior to carrying out the Suzuki-Miyaura reaction for the arylation, the pyrrole has to be selectively halogenated. The scope of the Suzuki-Miyaura

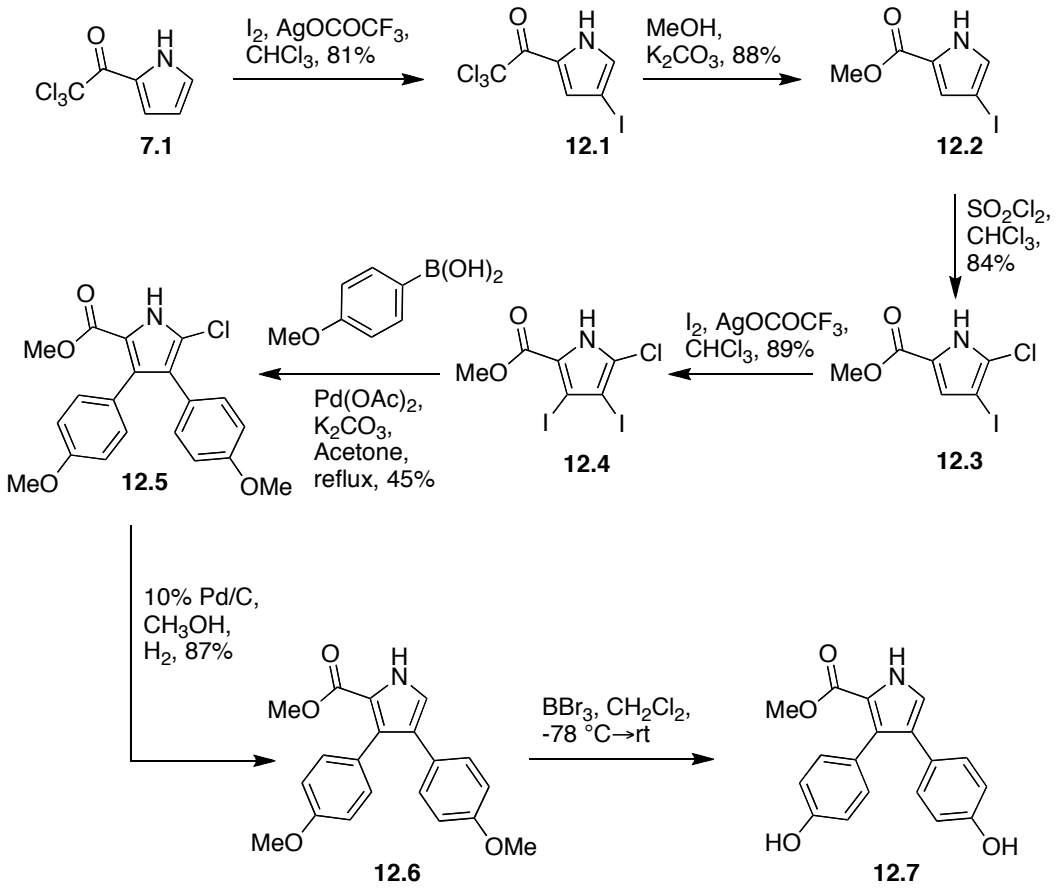
reaction is limited in this case due to the difficulty in regioselective introduction of the halides onto the pyrrole core. For example, in the case of a pyrrole with a substituent at the *C*2-*position* it is not possible to directly introduce a halide at *C*3 or *C*5 without any substitution also occurring at *C*4. The authors overcame this challenge by using iodides as the halogens of choice for the Suzuki-Miyaura reaction and using chlorides as removable blocking groups to allow selective direct iodination of the pyrrole core. The *C*3-position is the least reactive position on a *C*2-substituted pyrrole and arylation at *C*3 is achieved by first blocking the more reactive *C*4 and *C*5-positions by substitution by chlorine (**11.1→11.2**). Once the more reactive positions are blocked, the *C*5-position is iodinated (**11.3**) and arylated (**11.4**) through a Suzuki-Miyaura reaction. Removal of the chlorines




**Scheme 11**.

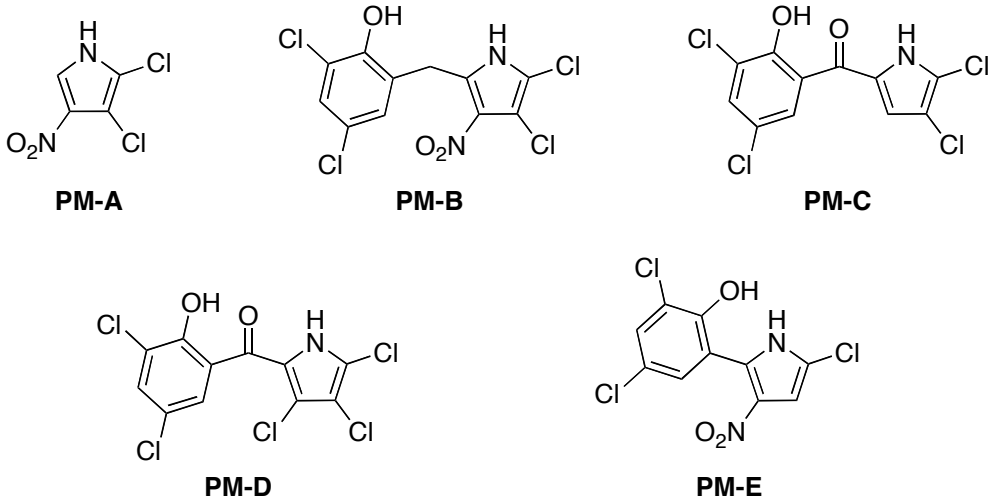
that had acted as blocking groups for *C*4 and *C*5 gives the *C*2-substituted, *C*3-arylated pyrrole **11.5** (Scheme 11).

Once the authors had prepared the *C*2 substituted monoarylated pyrrole, they extended the investigation to prepare bisarylated pyrroles towards the total synthesis of the natural product lukinol A (**10.1**) (Scheme 12). A new challenge then arose in the investigation since the bisarylation needs to be done at the most reactive *C*4-position and the least reactive *C*3-*position* while the moderately reactive C5-position is to be left unsubstituted in the already *C*2 substituted pyrrole core. Since two iodine atoms are required at the *C*3 and *C*4-*position*s to set stage for the Suzuki-Miyaura reaction, a single iodine was introduced at *C*4 first (**12.1**) and a chlorine was introduced at C5 as the removable blocking group (**12.3**). Next the iodine at *C*3 was put in place to get the precursor (**12.4**) for the Suzuki-Miyaura reaction. Once the halogens were in place, Pd mediated bisarylation was done using 4-methoxyphenyl boronic acid (**12.5**) and then the chlorine was removed (**12.6**). Deprotection of the methylated phenols gave the natural product lukinol A (**12.7**).



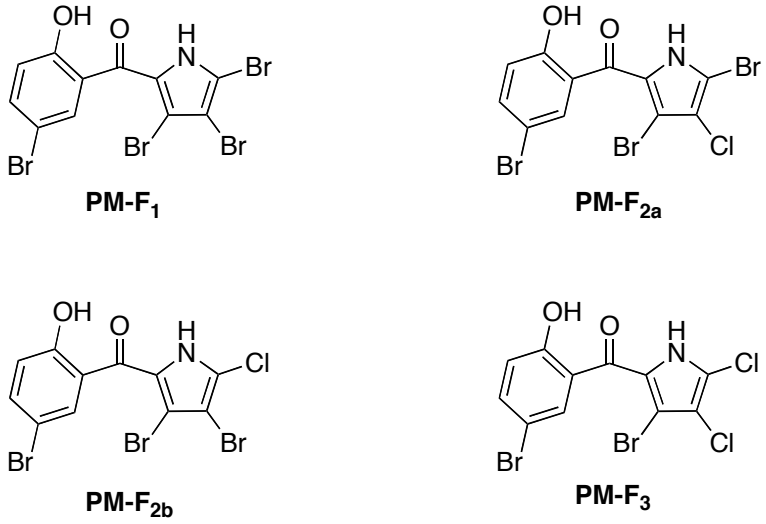

**Scheme 12**

A group of halogenated pyrrole natural products called pyrrolomycins (**PM-A** to **PM-E**, Scheme 13) have been isolated from the culture broth of *Actinosporangium vitaminophilum* SF-2080 and are significant drug candidates since they show good activity against Gram-positive bacteria. Among the group of pyrrolomycins (**PM-A** to **PM-E**) **PM-D** was found to be the most active component.



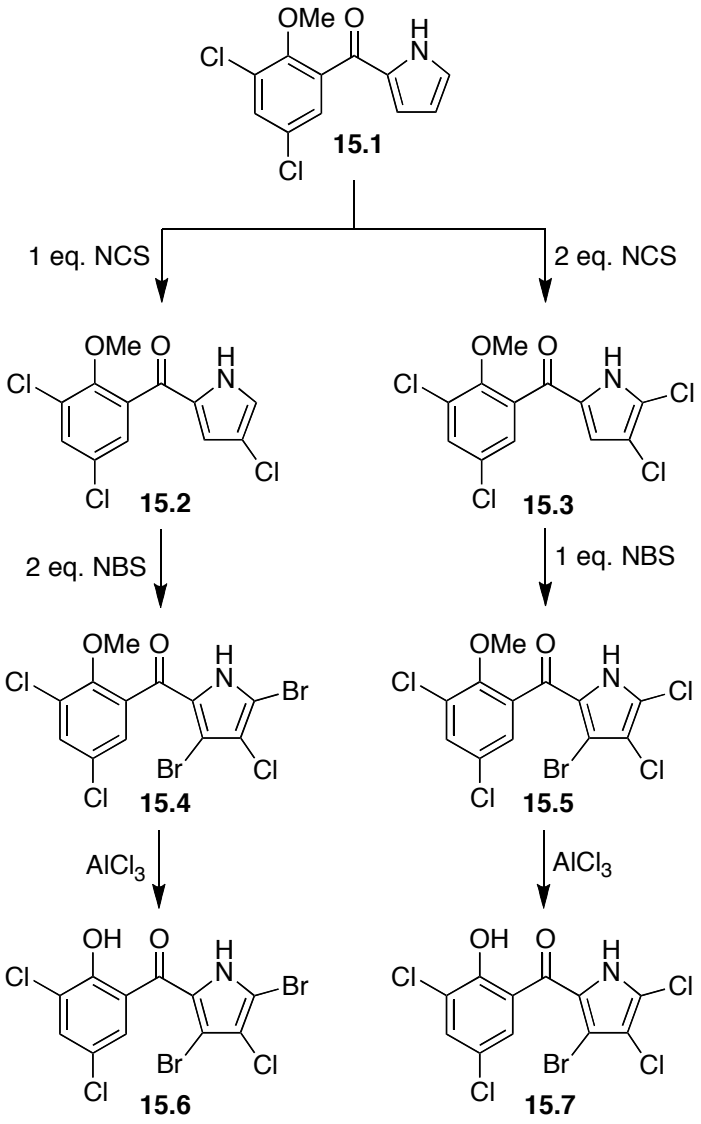

**Scheme 13**

A different group of brominated pyrrolomycins, generally named **PM-F** (Scheme 14), has been produced when bromide ions were introduced to a fermentation medium of *A. vitaminophilum* SF-2080. **PM-$F_{2a}$** was found to be the most active member of the naturally produced pyrrolomycins F. Since the **PM-F**'s are equally or more potent against some Gram-positive bacteria than even **PM-D** they are of synthetic importance.




**Scheme 14**

In 2007 Raimondi and coworkers published[19] their work on the synthesis of a class of compounds related to the pyrrolomycins F. The authors demonstrated that by manipulation of the number of equivalents of the electrophiles and by utilizing the distinct reactivities of each carbon on a pyrrole it is possible to selectively place the required halogens on the pyrrole core (Scheme 15). The synthetic analogs of the pyrrolomycins F were all found to be more active than **PM-F$_{2a}$** which is the most active component of the naturally produced pyrrolomycins F.

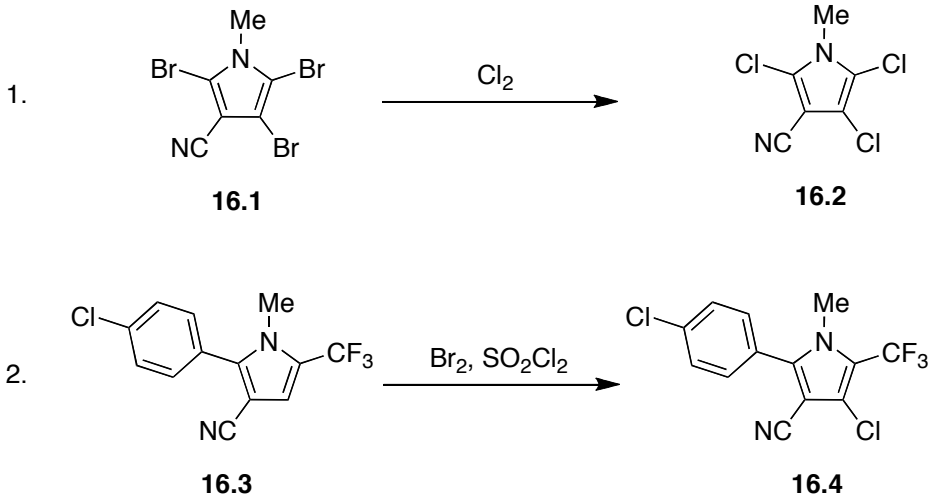



**Scheme 15**

In 1993 Kameswaran of the American Cyanamide Company reported[20] that pyrroles bearing electron withdrawing substituents can be chlorinated quantitatively via a process called debrominative chlorination, where bromine atoms on the pyrrole ring are replaced by chlorine atoms.

When the tribromopyrrole **16.1** was treated with $Cl_2$ the three bromine atoms were replaced by chlorine atoms to give the trichlorinated pyrrole **16.2**

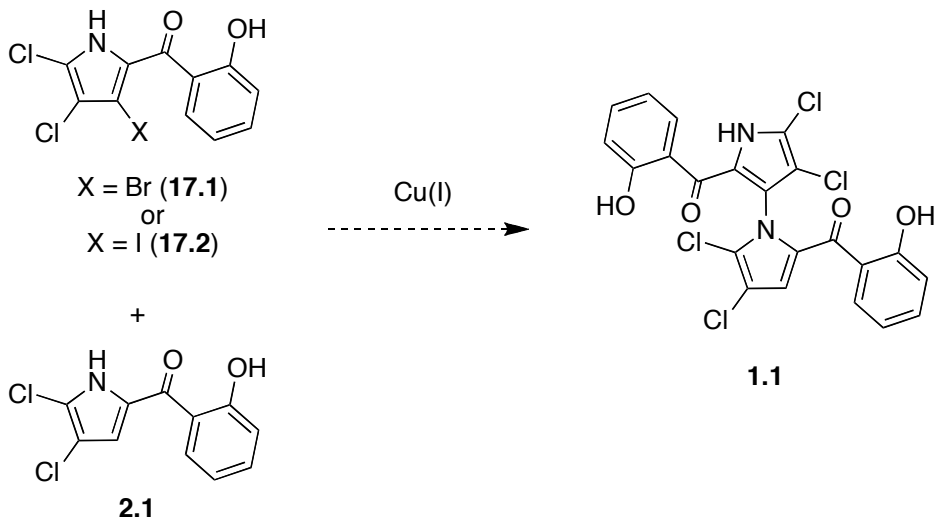
(Entry 1, Scheme 16). The process of debrominative chlorination is not limited to the chlorination of pyrroles that are already brominated. It can also be applied to the chlorination of nonhalogenated pyrroles if a catalytic amount of bromine is used such as in **16.3→16.4** (Entry 2, Scheme 16).




**Scheme 16**

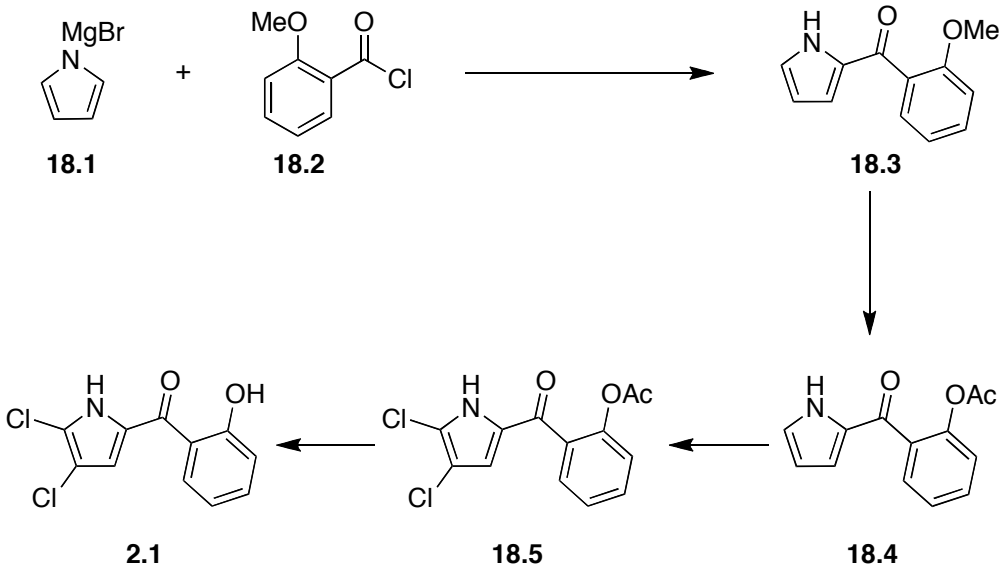
## 1.5 Attempted synthesis of the marinopyrroles in the Fenical laboratory.

In 2010 Fenical and coworkers reported[7] their synthetic studies towards the total synthesis of the marinopyrroles. The synthesis began by attempting to couple two pyrrole units, monodeoxypyoluteorin with either 3-bromomonodeoxypyoluteorin (**17.1**), or with 3-iodomonodeoxypyoluteorin (**17.2**) via a Cu catalyzed Ullmann coupling. Although the preparation of *N*-phenylazoles via Ullmann coupling is well documented, it has not been applied to the formation of *N,C*-linked bispyrroles.



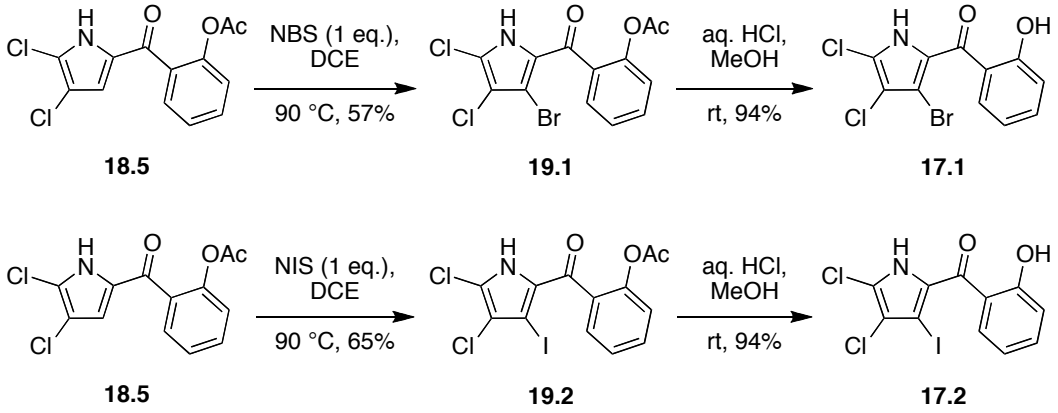

**Scheme 17**

First, the monodeoxypyoluteorin (**2.1**) was prepared following a literature procedure[21] using a short sequence (Scheme 18) starting with the reaction between pyrrylmagnesium bromide (**18.1**) and 2-methoxybenzoyl chloride (**18.2**) to give the intermediate **18.3**. Next, the methylated phenol was demethylated and acetylated (**18.4**). Selective chlorination at the *C*4 and the *C*5-positions of the acylated pyrrole gave *O*-acetyl monodeoxypyoluteorin (**18.5**). Finally, monodeoxypyoluteorin (**2.1**) was liberated upon deprotection of the phenolic acetyl group under acidic conditions. The synthetic monodeoxypyoluteorin was compared with the natural product isolated from the culture of the strain CNQ-418 and found to be in identical in all respects.




**Scheme 18**

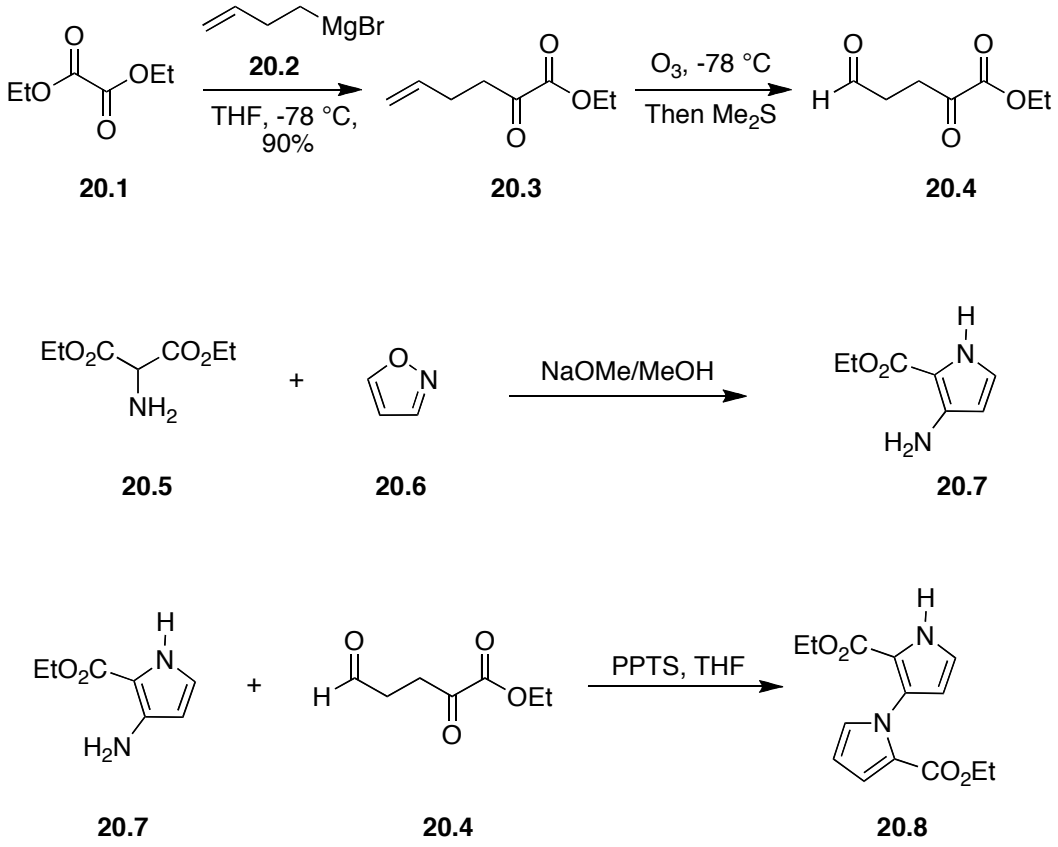
Once the monodeoxypyoluteorin (**2.1**) was in hand the coupling partners **17.1** and **17.2** for the Ullmann reaction were prepared by treating *O*-acetyl monodeoxypyoluteorin (**18.5**) with NBS and NIS respectively to get **19.1** and **19.2**. Deprotection of the acetyl groups of **19.1** and **19.2** gave **17.1** and **17.2** (Scheme 19).




**Scheme 19**

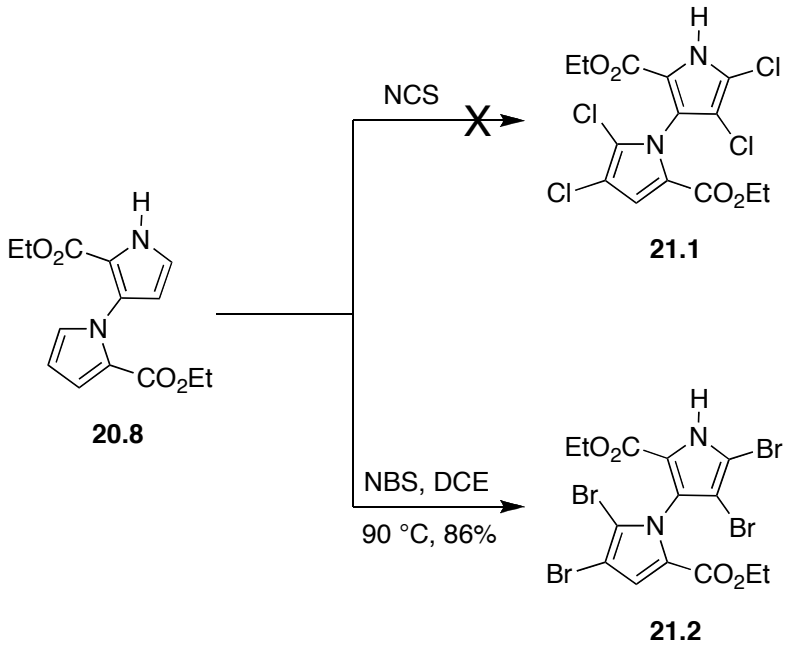
All attempts to couple two halopyrrole units through an Ullmann reaction and other coupling methods failed. The authors believe that the coupling of the pyrroles was not attainable due to unfavorable steric interactions between the substituents *ortho* to the site of the intended bond formation. According to reports in the literature[22] the efficiency of transition metal catalyzed Ullmann reactions is greatly reduced by the presence of one or more *ortho* substituents. Even the preparation of di-*ortho* substituted biaryl systems requires forcing conditions such as high concentrations and high catalyst loading. For these reasons attempts to prepare the tetra-*ortho* substituted biaryl systems of the marinopyrrole type via an Ullmann reaction were not pursued.

Once the Ullmann coupling approach had failed to yield the biaryl core of the marinopyrroles, the authors changed their strategy to use the Paal-Knorr reaction which had previously been successful for the synthesis of bispyrroles. The Paal-Knorr reaction generates bispyrroles by condensing a 1,4-dicarbonyl compound onto a 3-aminopyrrole. The synthesis of the bispyrrole core began by preparing the dicarbonyl compound (Scheme 20). First, the Grignard reagent **20.2** was added to $(CO_2Et)_2$ (**20.1**) at low temperature to obtain the monoaddition product **20.3**. Ozonolysis of the terminal alkene to the corresponding aldehyde gave the dicarbonyl compound **20.4**. The 3-aminopyrrole ethyl ester **20.7** was prepared according to the known literature procedure[23] using diethyl aminomalonate and isoxazole in NaOMe/MeOH. Next, **20.4** was condensed with **20.7** under acid catalysis to give the bispyrrole **20.8**.




**Scheme 20**

It was not possible to tetrachlorinate the bispyrrole **20.8** with NCS regioselectively to give **21.1**. However, it was possible to tetrabrominate **20.8** with NBS to give **21.2** (Scheme 21). The structure of **21.2** was confirmed through X-ray crystallography. Both the advanced intermediates **20.8** and **21.2** were tested for their potency and both showed very little antimicrobial activity and cytotoxicity.



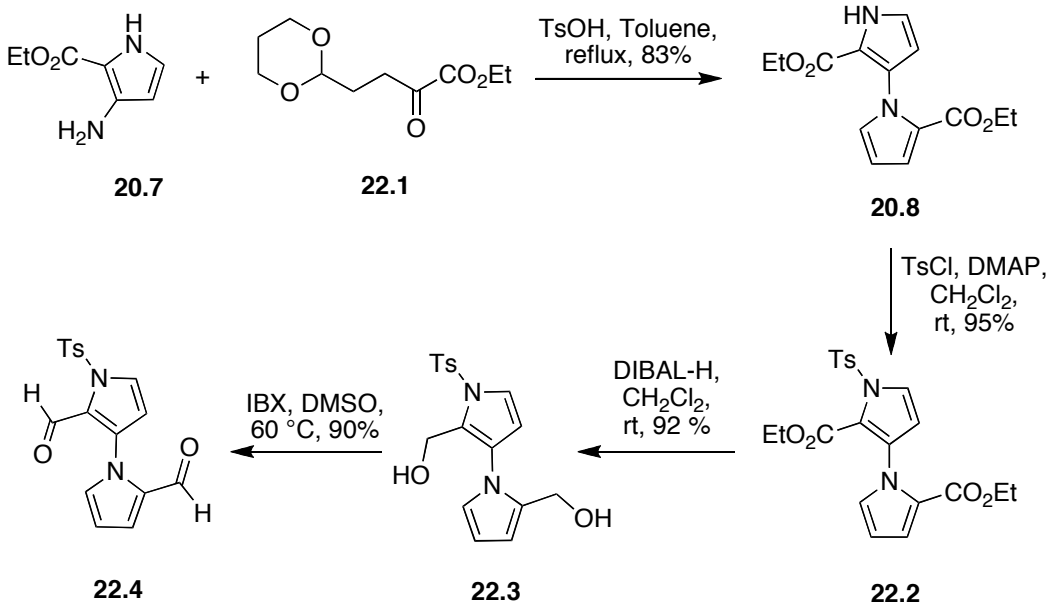

**Scheme 21**

## 1.6 First total synthesis of (±)-Marinopyrrole A.

In early 2010 Li and coworkers reported[1] the first total synthesis of racemic marinopyrrole A. The synthesis was accomplished in nine steps with an overall yield of 30%. Once the synthesis of marinopyrrole A was completed, the Li group also synthesized a library of marinopyrrole derivatives in order to investigate the potential antibiotic and anticancer activities of the marinopyrrole analogs. However, they were unable to synthesize marinopyrrole B, which obviously requires a high degree of regiochemical control in placement of the halogens.

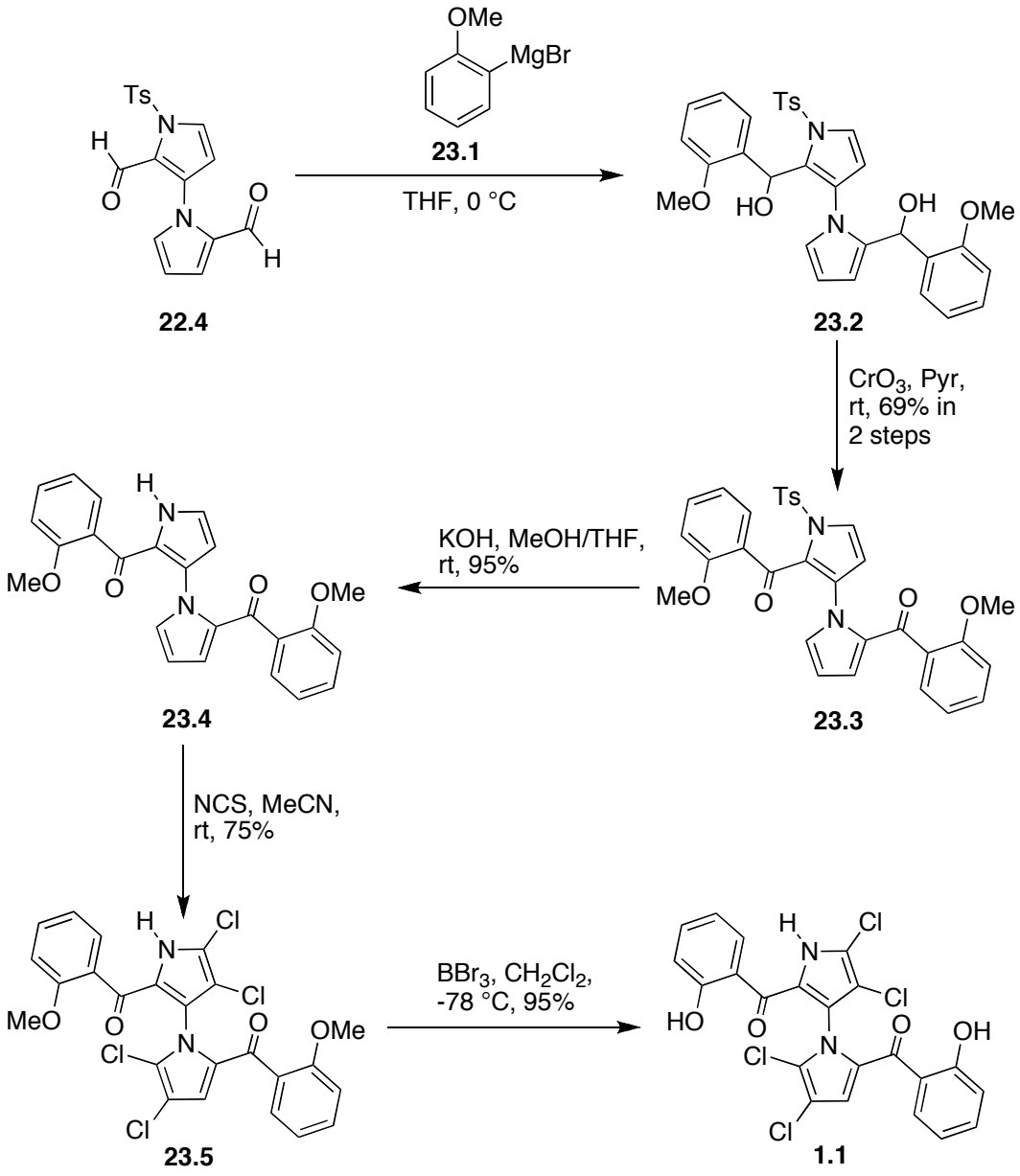
The synthesis of marinopyrrole A began with the known aminopyrrole ethyl ester **20.7**. The α-ketoester **22.1** was condensed onto the amine **20.7** in refluxing PhMe through a TsOH catalyzed Paal-Knorr reaction to give the

bispyrrole core **20.8** of the marinopyrroles. After protecting the nitrogen on the pyrrole ring (**22.2**) the two ester groups were reduced to their corresponding alcohols (**22.3**) using DIBAL-H at room temperature. The resulting hydroxyl groups were then oxidized with IBX in DMSO to give the dialdehyde **22.4**.




**Scheme 22**

With the dialdehyde **22.4** in hand, the Grignard reagent **23.1** was added in THF at 0 °C to get the diol **23.2**. The newly formed hydroxyls were oxidized to the corresponding ketones using $CrO_3$ under basic conditions to afford **23.3**. Removal of the tosyl group with KOH in MeOH/THF gave **23.4** which was the precursor for the halogenation of the bispyrrole core. Treatment of **23.4** with 4 equivalents of NCS in MeCN gave the regioselectively tetrachlorinated bispyrrole (**23.5)**.




**Scheme 23**

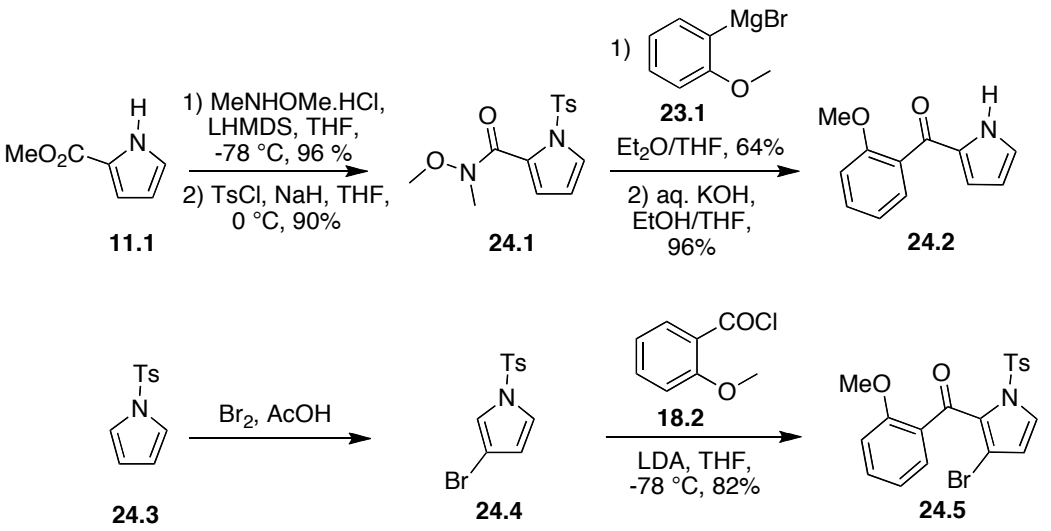
Once the most challenging step of regioselective tetrachlorination of the bispyrrole core had been accomplished, demethylation of **23.5** with $BBr_3$ liberated racemic marinopyrrole A (**1.1**). Attempts were made to brominate marinopyrrole A using NBS to get marinopyrrole B (**1.2**). However under various conditions

bromination was not successful, most probably due to the electron deficient character of the lower pyrrole ring, since it contains three electron withdrawing groups; the vacant position is also sterically shielded.

## 1.7 Second total synthesis of (±)-Marinopyrrole A.

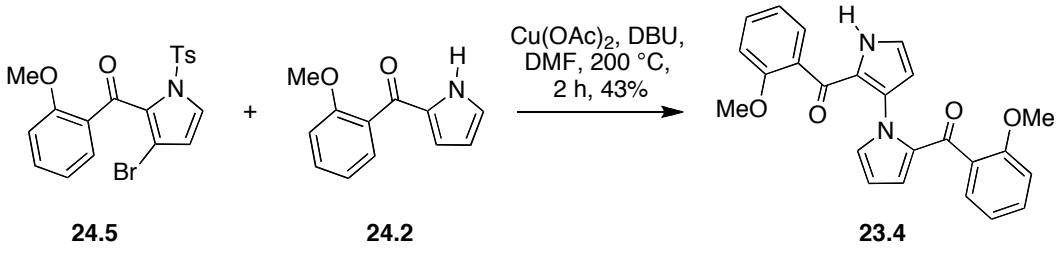
In late 2010 Sarli and Kanakis reported[24] the second total synthesis of (±)-marinopyrrole A. The total synthesis was done in six steps with an overall yield of 22%. It is well known[7] that a transition metal mediated coupling of the two fully functionalized pyrrole units to make the bispyrrole core is difficult due to steric hindrance caused by the ortho substituents around the biaryl bond. The authors have bypassed this difficulty by preparing the unfunctionalized bispyrrole core through the coupling of two nonhalogenated pyrrole units via a Cu mediated *N*-arylation and then halogenating the bispyrrole core with NCS in MeCN as was done by Li and coworkers.[1]

The synthesis began with the preparation of the two precursors **24.2** and **24.5** needed for the transition metal mediated coupling. Compound **24.2** was prepared starting from methyl pyrrole-2-carboxylate (**11.1**). The pyrrole nitrogen was tosylated and the methyl ester was converted into the corresponding Weinreb amide to get **24.1**. Addition of a Grignard reagent and deprotection of the nitrogen under basic conditions gave **24.2**. Compound **24.5** was prepared starting from *N*-tosylated pyrrole **24.3**. This was treated with $Br_2$ in AcOH to get the β-brominated **24.4**.[25] Deprotonation with LDA and treatment with the acid chloride **18.2** converted **24.4** into **24.5** (Scheme 24).



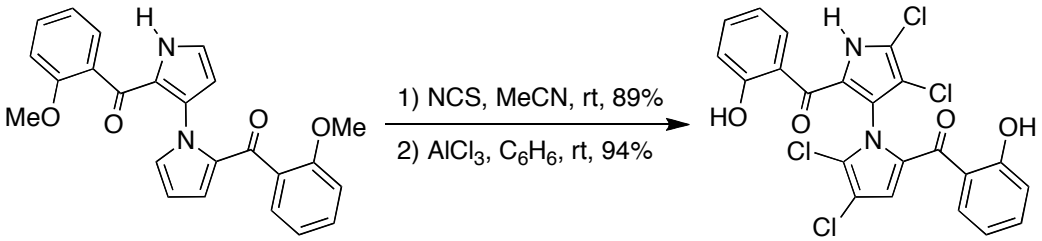

**Scheme 24**

With compounds **24.2** and **24.5** in hand, the two were coupled using $Cu(OAc)_2$ and DBU in DMF at 200 °C under microwave irradiation to give the bispyrrole **23.4** in 43% yield (Scheme 25). Several attempts at Cu mediated couplings were attempted using $CuI/Cs_2CO_3$, and $CuI/K_2PO_4$. However none of these methods gave satisfactory yields. In all experiments unreacted starting materials were recovered and prolonged reaction times did not improve the yields.




**Scheme 25**

The bispyrrole intermediate **23.4** was regioselectively tetrachlorinated using NCS in MeCN to get **23.5** in excellent yield (89%). Finally, demethylation of the phenolic methyl ethers with $AlCl_3$ in $C_6H_6$ gave (±)-marinopyrrole A in 94% yield (Scheme 26).




**23.4** **1.1**

**Scheme 26**

# 2. RESULTS AND DISCUSSION

## 2.1 Research objectives

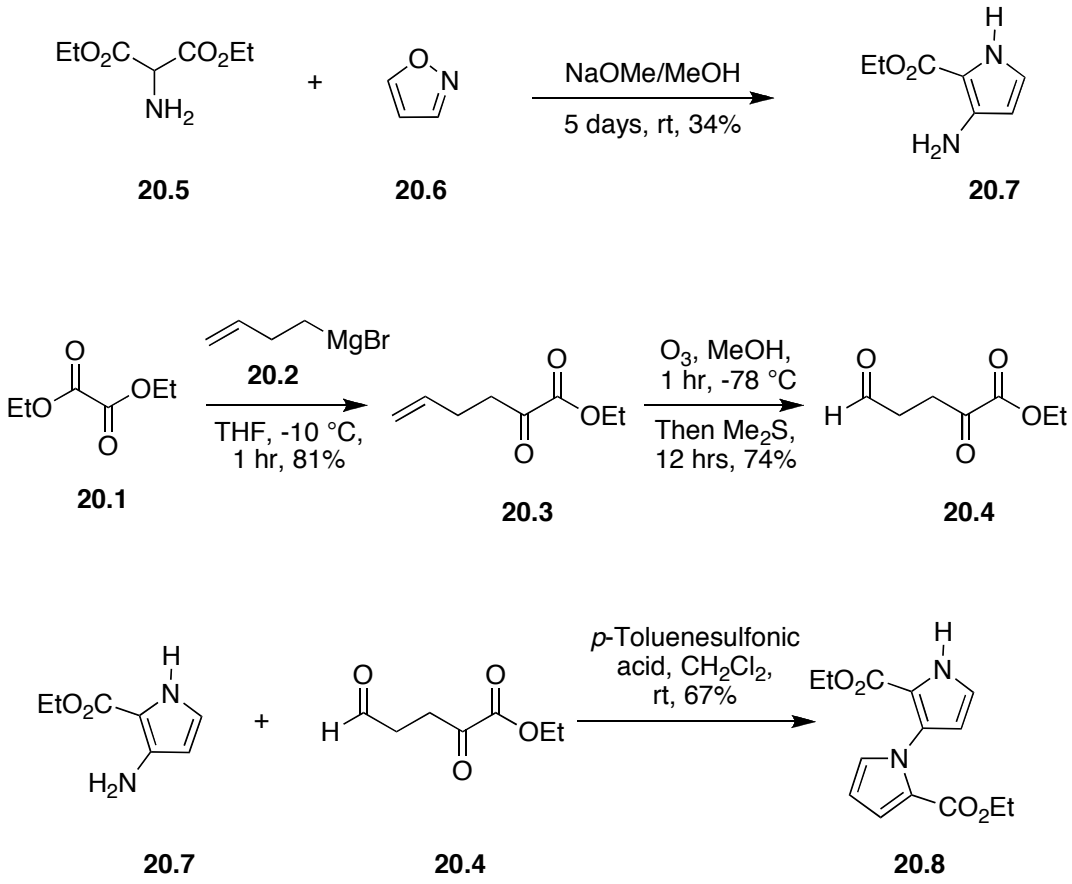
Marinopyrroles A and B are two marine antibiotic natural products that contain a densely halogenated bispyrrole core with an unprecedented *N,C*2 linkage. The marinopyrroles appear to have potential for the treatment of drug-resistant bacterial pathogens. Given the significance of the marinopyrroles as potential drug candidates, an investigation towards the total synthesis of the two marinopyrroles was undertaken.

## 2.2 Preparation and attempted regioselective halogenation of the bispyrrole core

The investigation began with the intention of making the bispyrrole core (**20.8**) first, followed by regioselective halogenation. To this end, the known aminopyrrole ethyl ester (**20.7**) was prepared starting with isoxazole (**20.6**) and diethyl aminomalonate (**20.5**). The preparation of **20.7** was troublesome, since the reaction took five days for completion and the maximum yield of cleanly isolated product was always less than 34%. Once **20.7** was in hand, the bispyrrole was to be prepared via a Paal-Knorr condensation of the α-ketoester aldehyde **20.4** onto the primary amino group of **20.7** to generate the bottom ring of the bispyrrole.

The preparation of α-ketoester aldehyde **20.4** started with the addition of the Grignard reagent **20.2** to $(CO_2Et)_2$ (**20.1**). Low temperature (-10 °C) addition

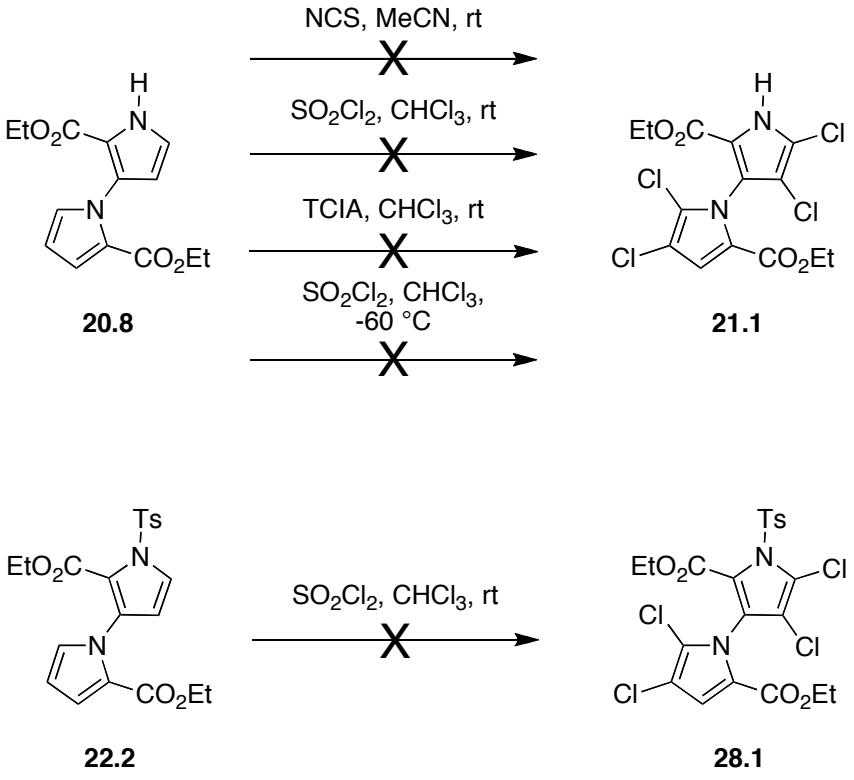
to the $(CO_2Et)_2$ gave the monoaddition product **20.3** cleanly in very good yield (81%). Ozonolysis of the double bond of **20.6** and reductive workup with $Me_2S$ gave the α-ketoester aldehyde **20.4** in good yield (74%). Condensation of the aminopyrrole ethyl ester **20.7** with **20.4** was done in $CH_2Cl_2$ under acid catalysis with TsOH to give the bispyrrole **20.8** very cleanly in 67% yield.




**Scheme 27**

The next step in the proposed synthetic route was the regioselective tetrachlorination of the bispyrrole **20.8** to get **21.1**. All attempts to chlorinate **20.8** regioselectively with NCS in MeCN,[19] $SO_2Cl_2$ in $CHCl_3$,[18] and

trichloroisocyanuric acid (TCIA) in $CHCl_3$[26] failed under several different reaction conditions. The reactions always gave an inseparable mixture of multiply chlorinated products, including the desired tetrachlorinated compound **21.1**. After careful separation of the desired product from the mixture so that only a minimum amount of impurities were present, the yield of the desired product was found to be less than 20%. The production of multichlorinated products was seen on TLC as early as 10 min after the addition of the chlorinating agents, suggesting that the unsubstituted carbons on the bispyrrole were highly reactive. Therefore the reaction was repeated using $SO_2Cl_2$ in $CHCl_3$ at -60 °C which is



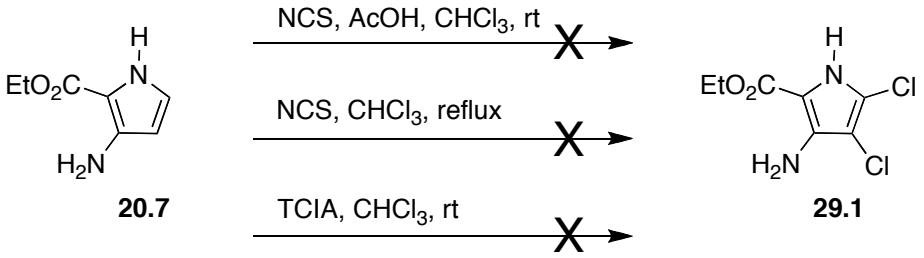

**Scheme 28**

just above the freezing point of $CHCl_3$. Even at -60 °C the same mixture of multichlorinated products was seen on TLC.

These observations suggests that even at very low temperatures the unsubstituted carbons of the bispyrrole are highly reactive and, unlike the situation in the mono substituted pyrroles, the vacant positions of the bispyrrole do not have distinct reactivities which would allow regioselective substitution. Tetrachlorination was also attempted on the bispyrrole with the pyrrole nitrogen protected as a tosylate (**22.2**). Even with the nitrogen protected, the reaction still gave a mixture of multichlorinated products indicating that the unprotected nitrogen had no substantive influence on the reactivity of the bispyrrole.

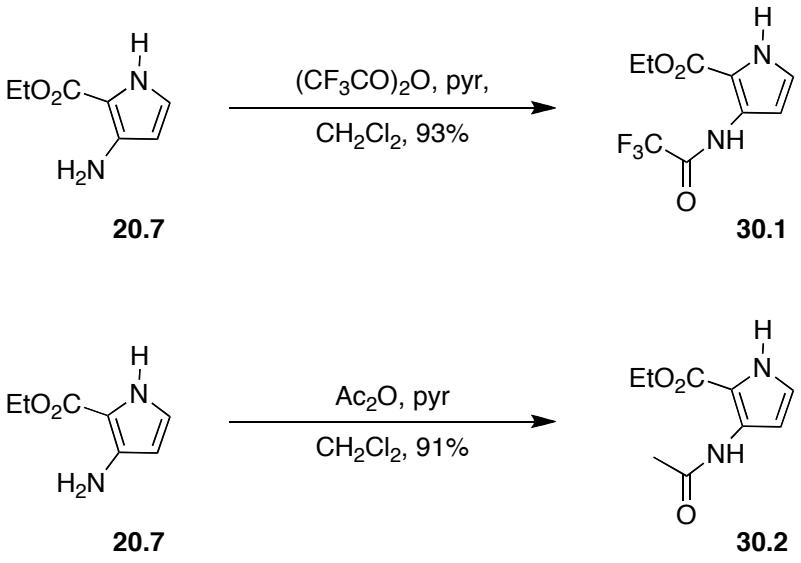
## 2.3 Attempts to fully functionalize the top pyrrole ring

Since chlorination of the bispyrrole was found to be unsatisfactory, a different approach towards chlorination of the pyrroles was needed. To this end, attempts were made to chlorinate the aminopyrrole ethyl ester (**20.7**) which constitutes the top ring of the bispyrrole prior to making the bottom pyrrole via a Paal-Knorr condensation. Chlorination of the aminopyrrole ethyl ester was attempted with NCS in AcOH/$CHCl_3$ at room temperature,[27] NCS in refluxing $CHCl_3$,[28] and TCIA in $CHCl_3$ at room temperature.[26] None of these chlorinating conditions gave the desired product **29.1** and in all experiments the starting aminopyrrole ethyl ester was destroyed.



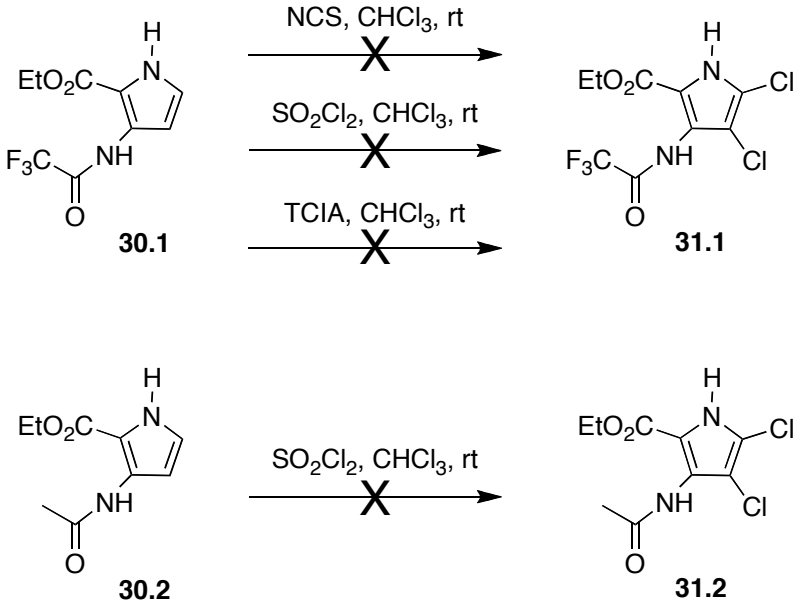

**Scheme 29**

Destruction of the starting material might be due to the fact that the unprotected primary amine of **20.7** was reacting with the chlorinating agents and so protection of the nitrogen seemed necessary. Consequently, the primary amine was converted into the trifluoroacetyl amide **30.1** and the acetyl amide **30.2** (Scheme 30). These acetyl protecting groups were used since their removal can be done smoothly at a later stage.




**Scheme 30**

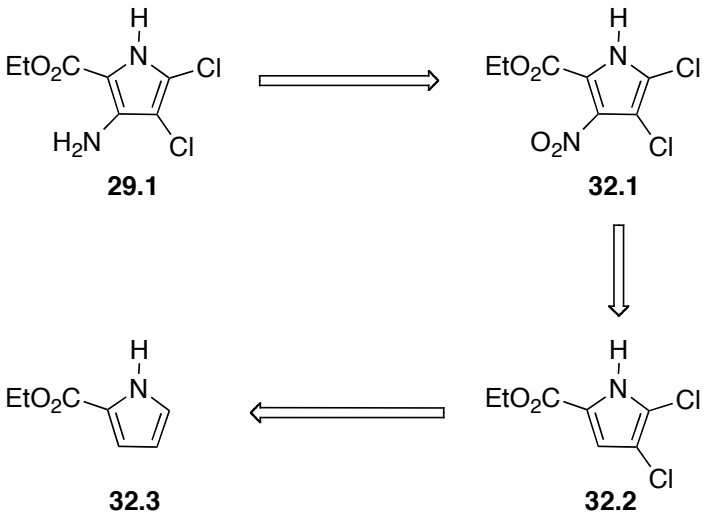
The chlorination experiments were repeated using the newly-prepared *N*-protected aminopyrrole ethyl esters **30.1** and **30.2**. Chlorination was attempted using $SO_2Cl_2$ in $CHCl_3$ with the acetyl protected aminopyrrole ethyl ester, and NCS in MeCN, $SO_2Cl_2$ in $CHCl_3$, and TCIA in $CHCl_3$ with the trifluoroacetyl protected aminopyrrole ethyl ester. All these reactions failed to give any desired chlorinated products **31.1** or **31.2** (Scheme 31). In the case of NCS, unreacted starting material was present in the reaction mixture after the reaction was quenched, and in the case of $SO_2Cl_2$ and TCIA the starting material was destroyed.




**Scheme 31**

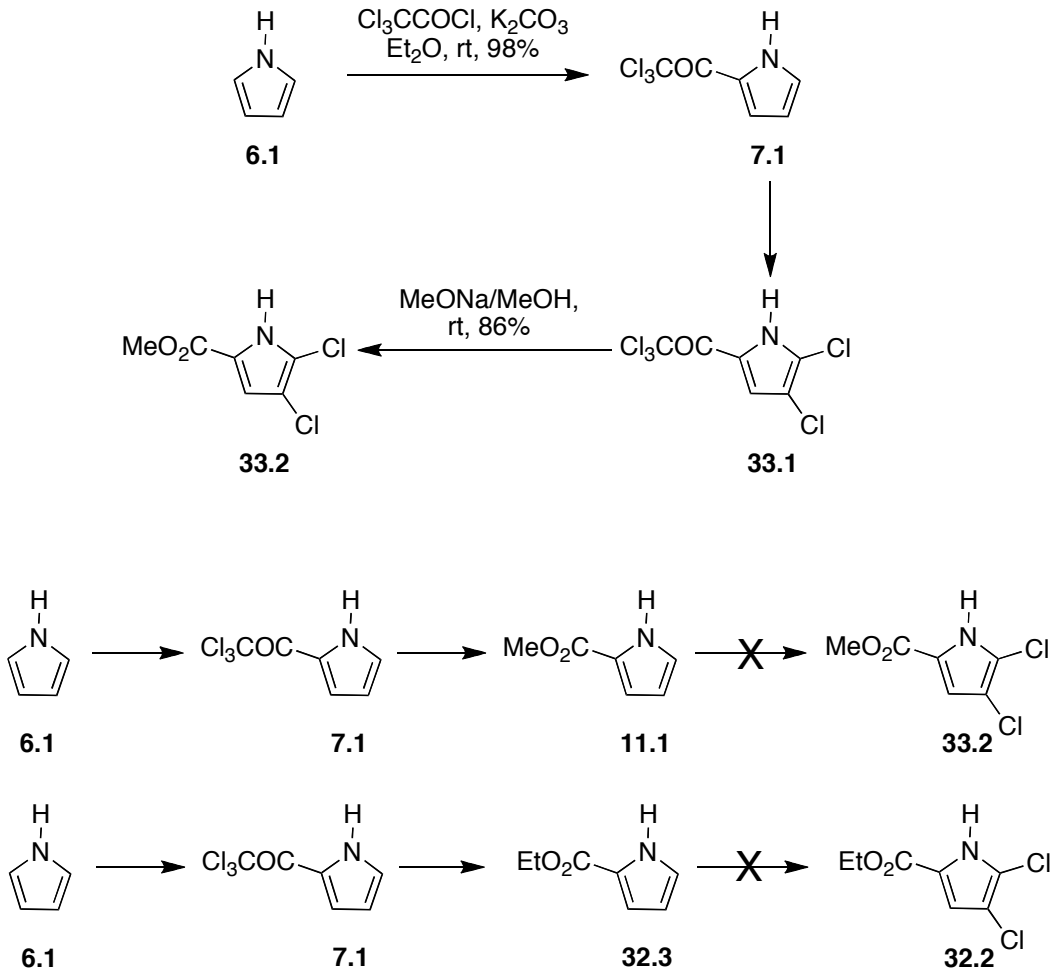
Possibly, the presence of nitrogen at the 3-position could be affecting the electronics of the pyrrole ring, preventing smooth chlorination. Therefore, it seemed reasonable to first chlorinate a 2-substituted pyrrole (**32.3→32.2**) and then

introduce the nitrogen via the nitration of the chlorinated pyrrole (**32.2→32.1)**. The amino group would then be obtained by reduction (**29.1**) (Scheme 32).



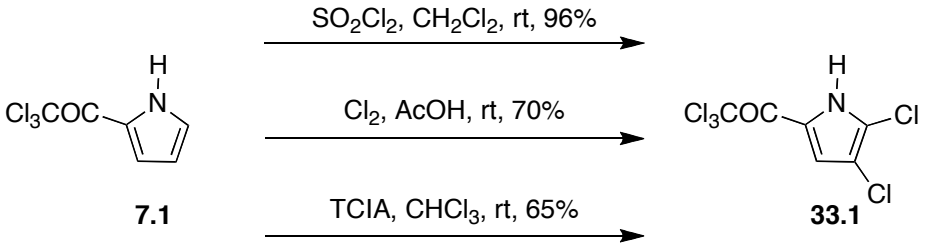

**Scheme 32**

The 2 substituted pyrrole was prepared following a literature procedure[29] starting with pyrrole (**6.1**) which was converted into the 2-pyrrolyl trichloromethyl ketone **7.1**. The 2-pyrrolyl trichloromethyl ketone was then regioselectively dichlorinated using $SO_2Cl_2$, $Cl_2$,[30] and TCIA under three different reaction conditions to give **33.1** (Scheme 34), and the trichloromethyl keto group was converted into the corresponding methyl ester by treatment with MeONa/MeOH to give **33.2** (Scheme 33).



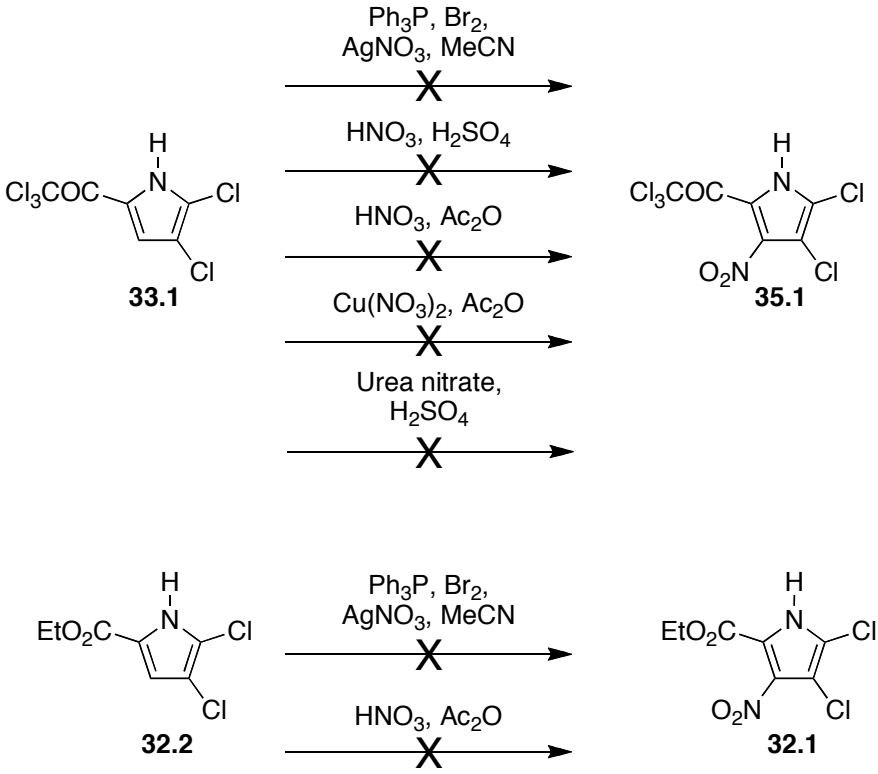

**Scheme 33**

Attempts to chlorinate the methyl pyrrole-2-carboxylate (**11.1**) and ethyl pyrrole-2-carboxylate (**32.3**) always gave a small amount of monochloro and trichloro products along with the desired dichloro product, the desired products could not be isolated cleanly in good yield.




**Scheme 34**

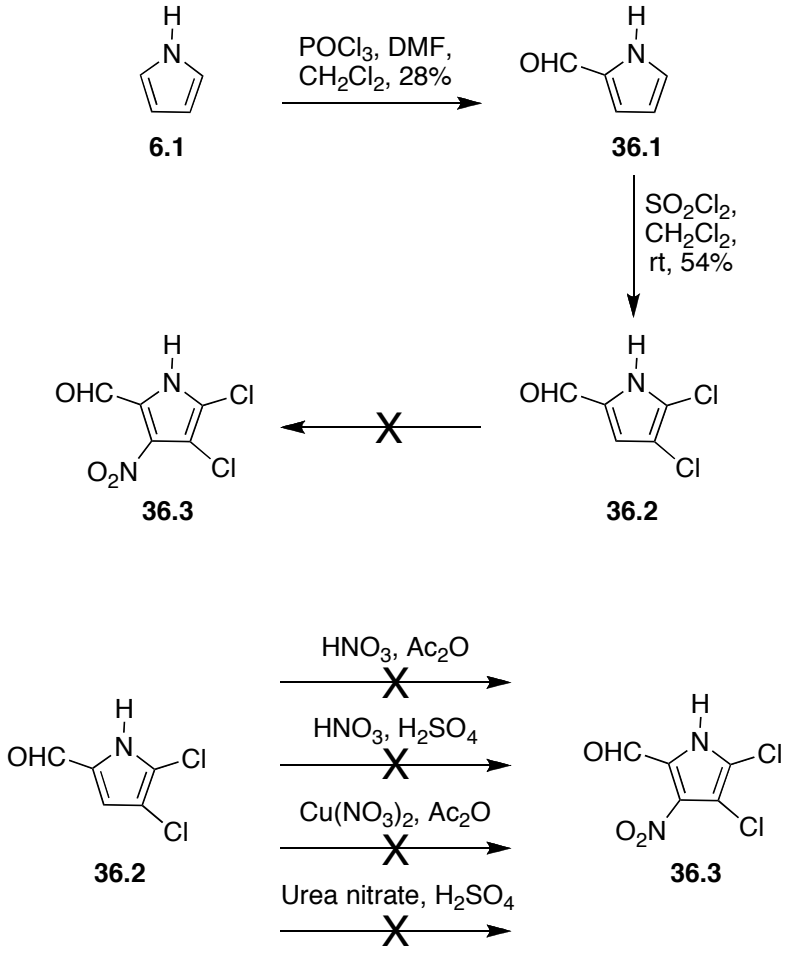
With the methyl 4,5-dichloropyrrole-2-carboxylate (**33.2**) and the 2-pyrrolyl trichloromethyl ketone (**33.1**) both in hand, they were subjected to nitration under different conditions using $HNO_3/Ac_2O$,[31] $HNO_3/H_2SO_4$,[32] $Ph_3P/Br_2/AgNO_3$,[33] $CuNO_3/Ac_2O$, urea nitrate/$H_2SO_4$.[34] None of the attempted




**Scheme 35**

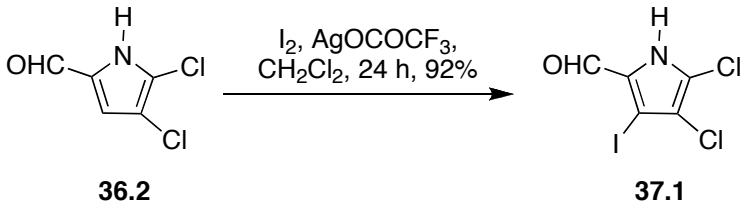
nitrations were successful and no product (**35.1** or **32.1**) was isolated (Scheme 35).

To investigate further the possibility of nitration of a dichloropyrrole, nitration was also attempted on 4,5-dichloropyrrole-2-carboxaldehyde (**36.2**). The carboxaldehyde was prepared according to a literature procedure[35] starting with pyrrole via a Vilsmeier-Haack reaction, using $POCl_3$ and DMF. The pyrrole-2-carboxaldehyde (**36.1**) was regioselectively dichlorinated smoothly using $SOCl_2$ in $CH_2Cl_2$, and the 4,5-dichloropyrrole-2-carboxaldehyde obtained was treated with $HNO_3/Ac_2O$ in an attempt to nitrate the vacant 3-position (**36.2→36.3**). However, no nitrated product nor any of the starting material was recovered from the reaction mixture (Scheme 36).




**Scheme 36**

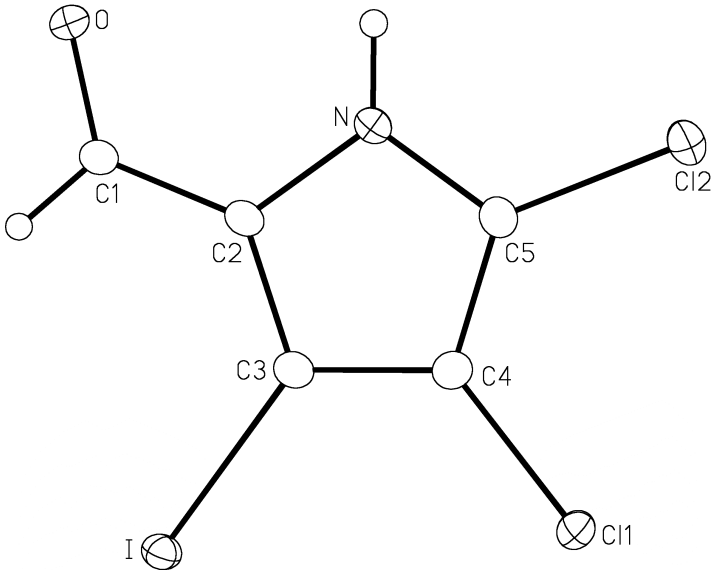
Once the nitration of 4,5-dichloropyrrole-2-carboxaldehyde **36.2** had failed it was of interest to investigate if the pyrrole ring of 4,5-dichloropyrrole-2-carboxaldehyde had lost its nucleophilicity due to the presence of the electron withdrawing substituents. To this end, the 4,5-dichloropyrrole-2-carboxaldehyde was treated with $I_2/AgOCOCF_3$ to iodinate the vacant 3-position. The carboxaldehyde did undergo iodination smoothly to give 4,5-dichloro-3-iodopyrrole-2-carboxaldehyde (**37.1**) in excellent yield (92%).




**36.2** **37.1**

**Scheme 37**

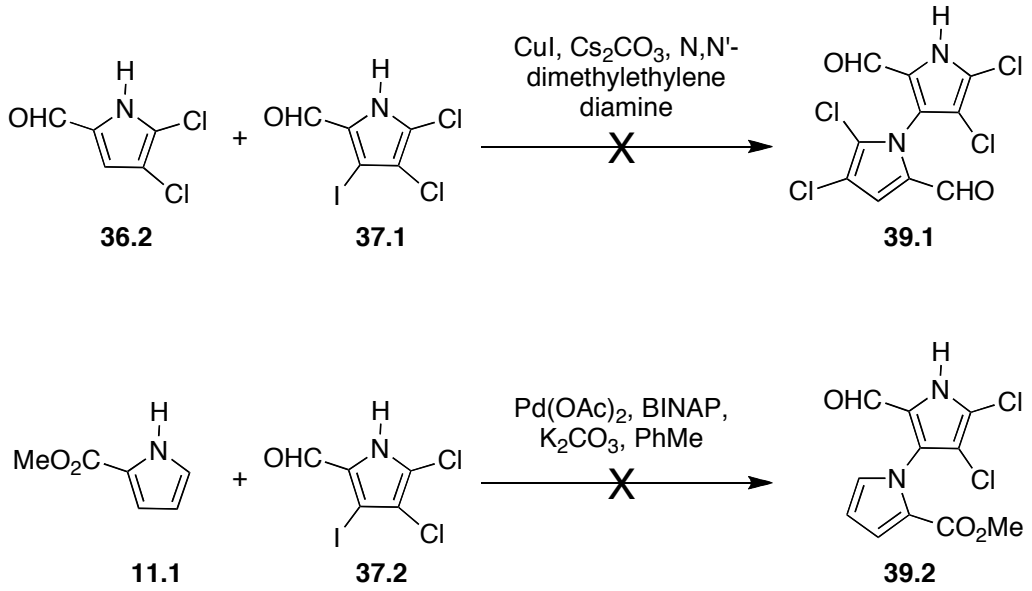
An X-ray crystal structure was obtained for the 4,5-dichloro-3-iodopyrrole-2-carboxaldehyde to verify the structure and to assure that the halogens were present in the expected positions (Scheme 38).




**Scheme 38**

Once we established that it was possible to iodinate 4,5-dichloropyrrole-2-carboxaldehyde we tried to prepare the bispyrrole through a Cu mediated coupling of 4,5-dichloropyrrole-2-carboxaldehyde (**36.2**) and 4,5-dichloro-3-iodopyrrole-2-carboxaldehyde (**37.1**) (Scheme 39). In order for the coupling of

the two pyrrole units to be a success, a biaryl bond between *C*3 of the 4,5-dichloro-3-iodopyrrole-2-carboxaldehyde and the nitrogen of the 4,5-dichloropyrrole-2-carboxaldehyde has to be formed. However, since each of the two atoms involved in the biaryl bond are doubly *ortho* substituted, the biaryl bond formation was unsuccessful, presumably due to steric hindrance. We also tried to prepare the bispyrrole through a Pd-mediated coupling of 4,5-dichloro-3-iodopyrrole-2-carboxaldehyde (**37.1**) and methyl pyrrolyl-2-carboxylate (**11.1**); with these compounds the steric hindrance from the ortho substituents would be less. However, once again the reaction failed, possibly due the presence of substituents ortho to the iodine on the 4,5-dichloro-3-iodopyrrole-2-carboxaldehyde.

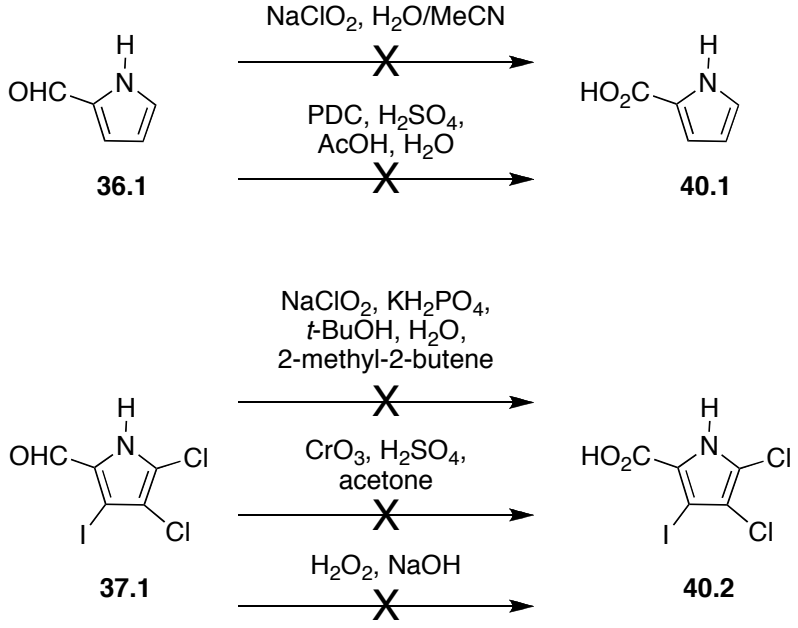



**36.2** **37.1** **39.1**

**11.1** **37.2** **39.2**

**Scheme 39**

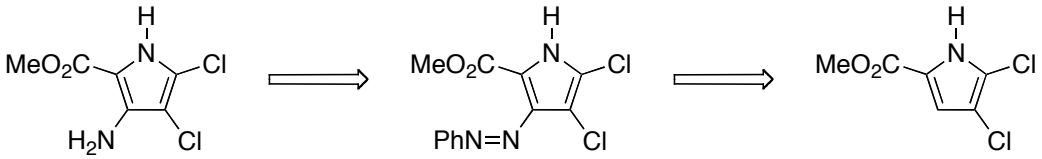
We also made several attempts to change the electron withdrawing aldehyde at the 2-position of pyrrole-2-carboxaldehyde and 4,5-dichloro-3-iodopyrrole-2-carboxaldehyde to the corresponding carboxylic acid, in order to investigate the chemistry of the pyrrole ring. For this purpose, pyrrole-2-carboxaldehyde was treated with $NaClO_2$,[36] or PDC in $H_2SO_4$,[37] while the 4,5-dichloro-3-iodopyrrole-2-carboxaldehyde was treated with Jones' reagent[38] ($CrO_3$ in $H_2SO_4$), $NaClO_2$,[39] or $H_2O_2$/NaOH[40] to get the corresponding carboxylic acids **40.1** and **40.2**. None of these attempted oxidations of the aldehyde to the carboxylic acid was successful, and in all cases the starting aldehyde was recovered unchanged (Scheme 40).




**Scheme 40**

We later found two references in the chemical literature[41,42] which mention that the aldehyde of pyrrole-2-carboxaldehyde is unreactive when the nitrogen of the pyrrole is unprotected. In order to manipulate the aldehyde, the nitrogen of the pyrrole has to be protected with, for example, Me, Ph, Bn, or Ts groups. However, since pyrrole-2-carboxylic acid could be prepared via base hydrolysis of ethyl pyrrole-2-carboxylate or 2-pyrrolyl trichloromethyl ketone which we had prepared previously, conversion of pyrrole-2-carboxaldehyde to the corresponding carboxylic acid was not pursued.

We next considered that it might be possible to introduce nitrogen at the 3-position through diazotization[43] and then cleavage of the resulting nitrogen-nitrogen double bond by use of Zn in AcOH (**33.2→41.2→41.1**) (Scheme 41).

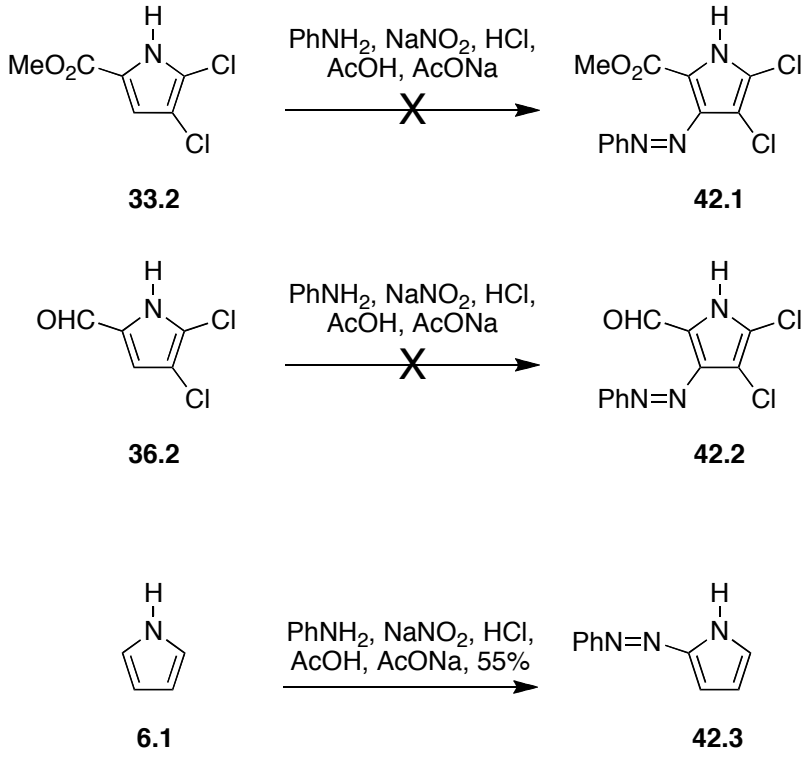



**41.1** **41.2** **33.2**

**Scheme 41**

Diazotization of methyl 4,5-dichloropyrrole-2-carboxylate and 4,5-dichloropyrrole-2-carboxaldehyde with phenyldiazonium chloride (aniline, $NaNO_2$, HCl) did not give any of the desired products and the unreacted starting materials were seen in the $^1$H-NMR spectra of the total product. In order to investigate if diazotization was possible on pyrroles, the diazotization was tried on pyrrole with no substitutions as a model study. This experiment was a success

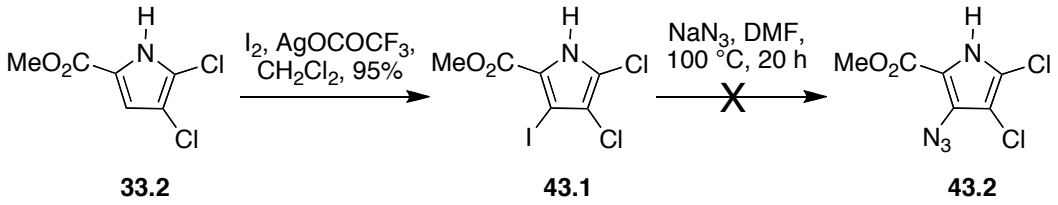
and gave the desired diazotized product **42.3** in a modest yield of 55% (Scheme 42). These experiments show that by attaching the two chlorine atoms, the pyrrole ring undergoes substantial alteration in its electronic and or steric properties and renders methyl 4,5-dichloropyrrole-2-carboxylate and 4,5-dichloropyrrole-2-carboxaldehyde insufficiently nucleophilic towards diazotization.




**Scheme 42**

It was also of interest to find out if nitrogen can be introduced at the 3-position via an addition elimination reaction when a good leaving group is placed at the 3-position. To investigate this possibility, methyl 4,5-dichloropyrrole-2-carboxylate (**33.2**) was treated with $I_2$ and $AgOCOCF_3$ to get methyl 4,5-dichloro-

3-iodopyrrole-2-carboxylate (**43.1**), where the iodide will serve as the leaving group for the addition elimination. The resulting methyl 4,5-dichloro-3-iodopyrrole-2-carboxylate was then treated with the nucleophilic nitrogen reagent $NaN_3$ in DMF at 100 °C for 20 h.[44] Even after such a prolonged reaction time at an elevated temperature the iodine was not replaced by azide and only the starting material was seen in the $^1$H-NMR spectrum of the crude reaction mixture (after removal of solvent). This experiment (Scheme 43) shows that either the 3 carbon which carried the iodine was not electrophilic enough to be attacked by azide, or the 3-position was too hindered due to the flanking ester and halogen.

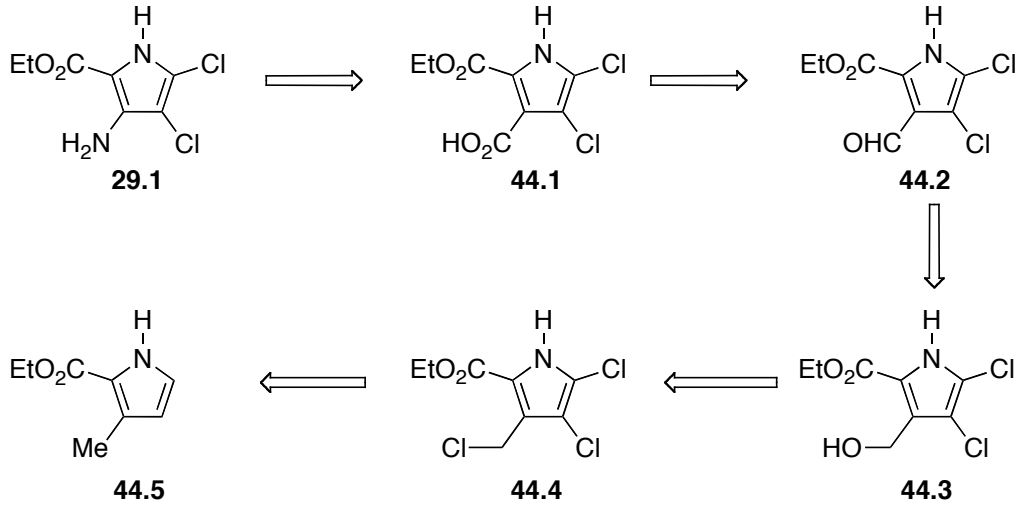



**33.2** **43.1** **43.2**

**Scheme 43**

Since it was quite clear from the above experiments that chlorination of a pyrrole ring at the 4,5-positions in the presence of a nitrogen at the 3-position, and the introduction of a nitrogen at the 3-position in the presence of two chlorines in the 4,5-positions was impossible, we attempted to place a carbon atom at the 3-position with the hope of replacing it with a nitrogen at a later stage (Scheme 44). Substitution of the 3-position of ethyl pyrrole-2-carboxylate with a methyl group (**44.5**) will allow a global chlorination at the 4,5-positions of the pyrrole ring and also on the methyl group (**44.4**). Displacement of the chlorine on the methyl

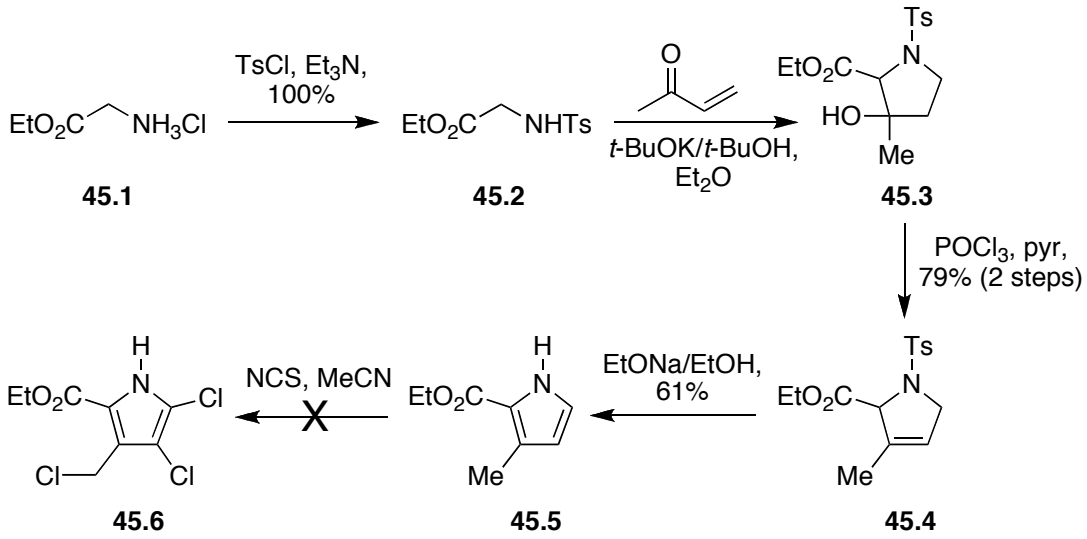
group with a nucleophilic oxygen and subsequent oxidation to the corresponding aldehyde and then to the carboxylic acid would give a precursor suitable for the introduction of the nitrogen at the 3-position (**44.4→44.3→44.2→44.1**). Once the carboxylic acid is placed at the 3-position, a Curtius rearrangement would give a nitrogen atom at the 3(β)-position (**29.1**).




**Scheme 44**

Preparation of ethyl 3-methylpyrrole-2-carboxylate was done following a literature procedure.[45] The route started with tosylation of ethyl glycine hydrochloride (**45.1→45.2**). The tosylate was condensed with methyl vinyl ketone to get the tertiary alcohol **45.3**. Upon dehydration of **45.3** with $POCl_3$ the pyrroline **45.4** was obtained. Treatment of **45.4** with EtONa/EtOH removed the sulfonyl group and aromatized the pyrroline to the corresponding pyrrole to give ethyl 3-methylpyrrole-2-carboxylate **45.5**. The next step in the synthesis was the trichlorination of **45.5**. However, **45.5** did not undergo trichlorination to give

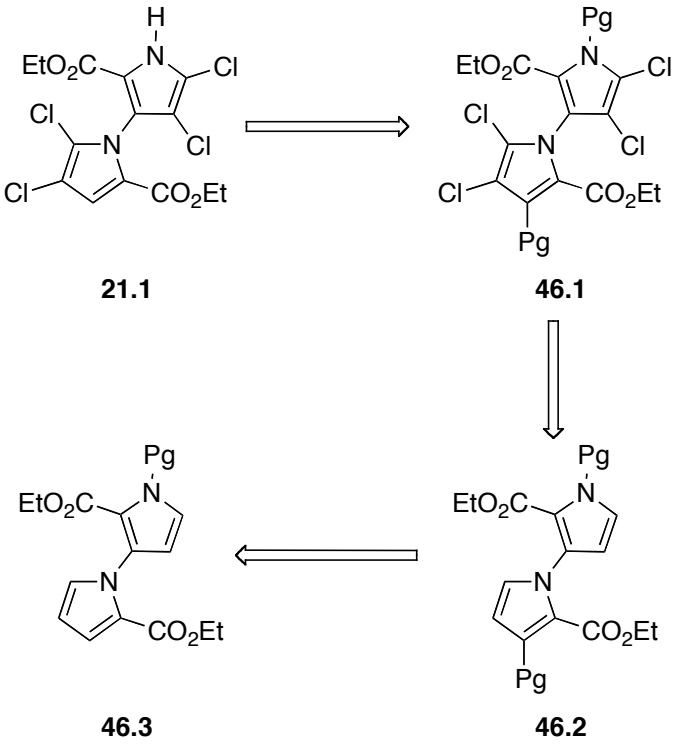
**45.6** with NCS or $SO_2Cl_2$. Attempted chlorinations caused the starting material to decompose and therefore an alternate approach was necessary.




**Scheme 45**

## 2.4 Attempts to place a removable blocking group at the 3'-position of a bispyrrole

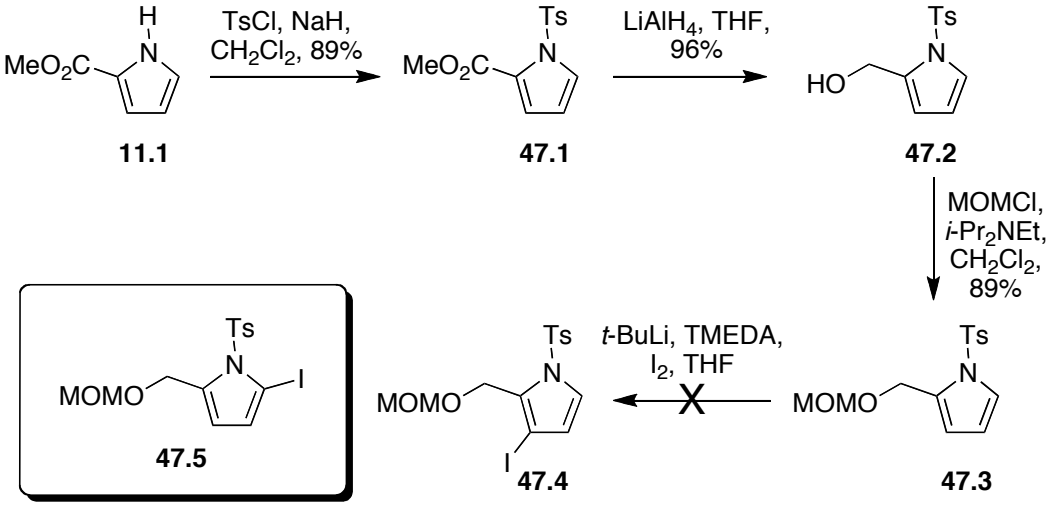
After the chlorinations and nitrations of the top ring had failed we pursued a new route to block the 3'-position on the bottom ring of the bispyrrole by a removable group so that we could tetrachlorinate the four vacant positions without having to deal with issues of regioselectivity (Scheme 46).




**Scheme 46**

It was decided that an iodide would be a suitable removable protecting group for the 3'-position. In principle, the iodine can be placed selectively at the 3'-position through an orthometallation reaction, if the 2'-position is substituted with a suitable directing group. Following previous work reported in the literature,[46] a MOM ether was chosen as a convenient directing group that can be placed at the 2'-position without difficulty. Also, since *t*-BuLi will be used for the orthometallation, the pyrrole nitrogen has to be protected with a removable group. Prior to the orthometallation of the bispyrrole, a model study was done on a monopyrrole with the pyrrole nitrogen protected as an *N*-tosylate. The precursor for the orthometallation (**47.3**) was prepared starting with methyl pyrrole-2-carboxylate (**11.1**). The nitrogen was protected by tosylation (**47.1**) and the

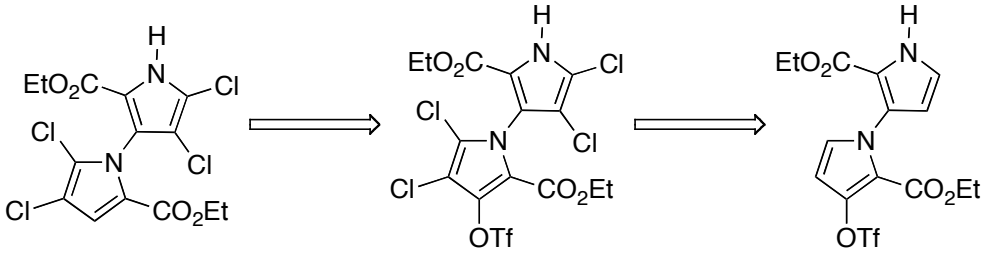
methyl ester was reduced to the corresponding alcohol (**47.2**). The alcohol was then protected as a MOM ether (**47.3**) which we planned to use as the directing group for the orthometallation. Compound **47.3** was treated with *t*-BuLi in the presence of TMEDA for the orthometallation and then with $I_2$. Unfortunately, this reaction did not place an iodine at the 3-position as desired; instead, the reaction gave **47.5**, which contains an iodine at the 5-position, an outcome which suggests that the tosyl group had acted as a directing group for the orthometallation reaction and is a better directing group than the MOM ether. To avoid interference by the tosyl group in the orthometallation, the pyrrole nitrogen was protected with a *i*-$Pr_3Si$ group. However, the *i*-$Pr_3Si$ group did not withstand the $LiAlH_4$ reduction and was cleaved.




**Scheme 47**

Since the orthometallation approach was found to be unsuccessful we turned our attention towards using an oxygen based removable protecting group

to block the 3'-position so that the tetrachlorination of the bispyrrole could be done smoothly (**48.2→48.1**). It was envisioned that if the 3'-position could be blocked by an OTf group then this oxygenated functional group could be removed later through a Pd mediated reduction (**48.1→21.1**) (Scheme 48).

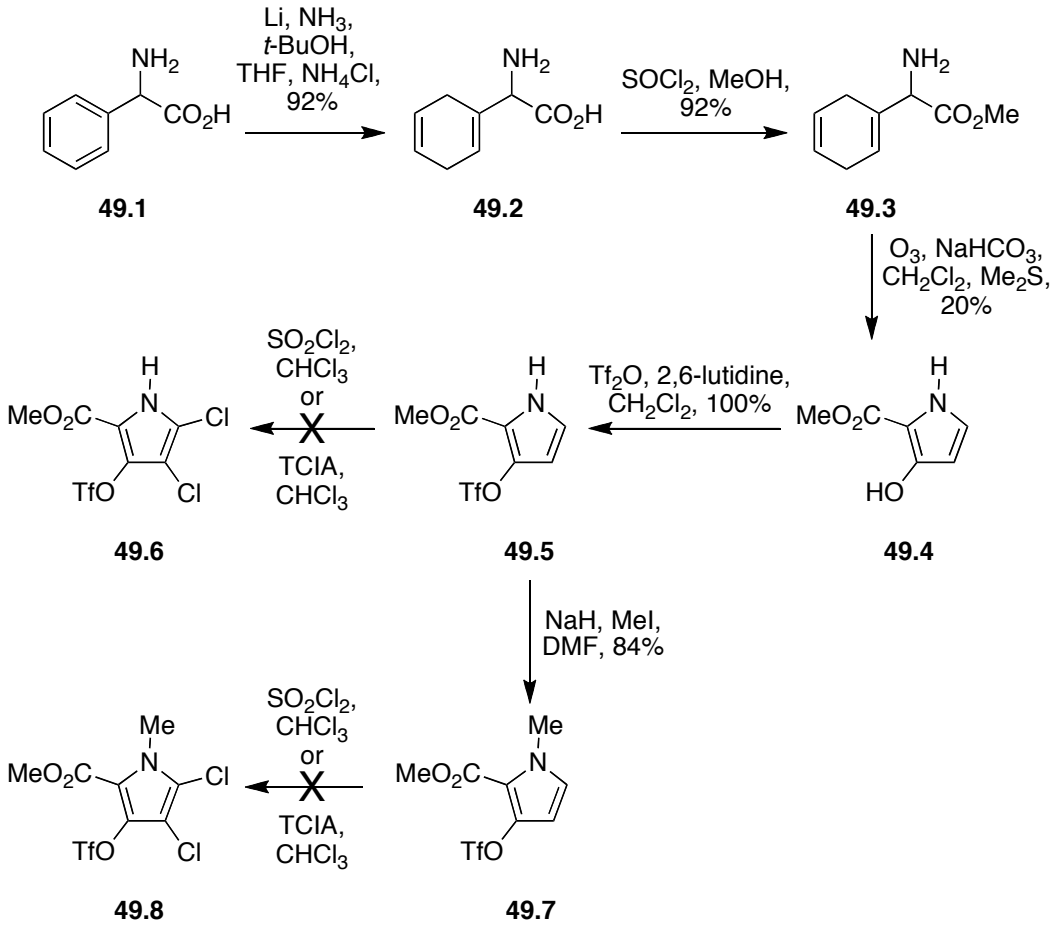



**Scheme 48**

Prior to investigating the possibility of using an oxygen based protecting group, it was also necessary to investigate if it was possible to remove the blocking group through Pd mediated reduction in the presence of the chlorines. A model study was done on a monopyrrole to test the possibility of chlorination in the presence of the blocking group at the 3-position. To this end, following a literature procedure,[47] compound **49.5** was prepared, starting from the non-natural amino acid phenyl glycine (**49.1**) (Scheme 49).

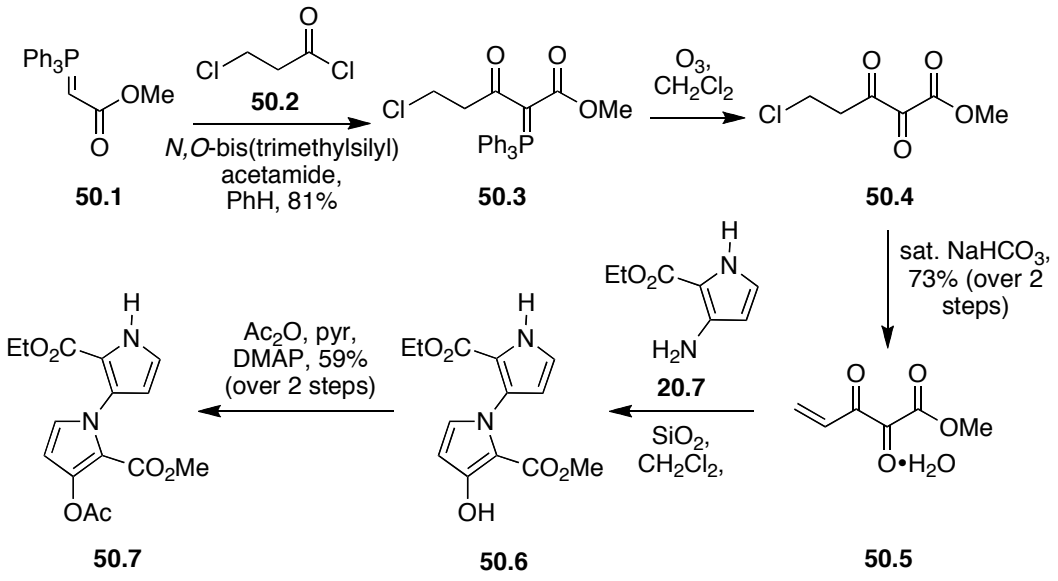
Birch reduction of phenyl glycine gave **49.2** in excellent yield. The carboxylic acid of **49.2** was converted into the corresponding methyl ester by treatment with $SOCl_2$ in MeOH to get **49.3**. Ozonolysis of **49.3** under basic conditions and in situ cyclization of the intermediate aldehyde gave methyl 3-hydroxypyrrole-2-carboxylate **49.4**. The hydroxyl group at the 3-position of the

newly formed pyrrole **49.4** was protected with $Tf_2O$ to give **49.5**. This protected hydroxy pyrrole (**49.5**) was the precursor for the chlorination model study and was treated with $SO_2Cl_2$ and TCIA in $CHCl_3$. Both attempted chlorinations were unfruitful since in both cases the starting material were destroyed and the reaction gave a complex mixture of inseparable substances that could not be characterized. The nitrogen of **49.5** was also protected by *N*-methylation to get **49.7** and this compound was then treated with $SO_2Cl_2$ and TCIA in $CHCl_3$. However, as in the case of the unprotected pyrrole **49.5**, the protected pyrrole **49.7** was also destroyed during the reaction with $SO_2Cl_2$ or TCIA and failed to give any chlorinated product.



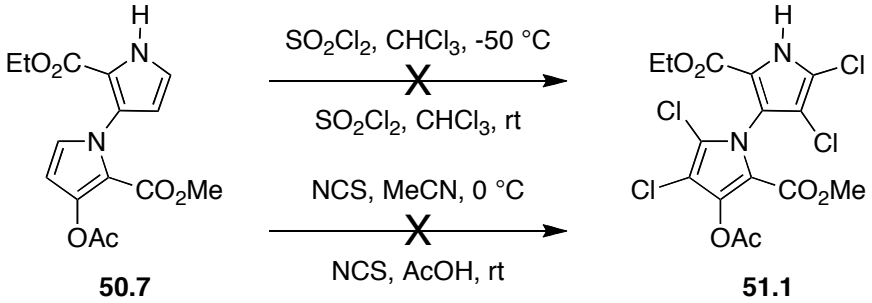

**Scheme 49**

Failure of the monopyrrole **49.5** to undergo chlorination once again suggests that with a heteroatom at the 3-position the pyrrole ring has lost its nucleophilicity probably due to alterations in its electronic structure. However, we hypothesized that since the two pyrrole rings of the bispyrrole are highly reactive, even with a protected hydroxyl group at the 3' the bispyrrole would still be sufficiently nucleophilic to undergo chlorination.




**Scheme 50**

Following a literature procedure,[48] the bispyrrole with an acetyl protected hydroxyl group at the 3'-position (**50.7**) was prepared (Scheme 50). The preparation of **50.7** began with the coupling between methyl (triphenylphosphoranylidine)acetate (**50.1**) and 3-chloropropionyl chloride (**50.2**) in $C_6H_6$ to give **50.3**. Ozonolysis of the carbon-phosphorous double bond followed by treatment with saturated aqueous $NaHCO_3$ converted **50.3** to the

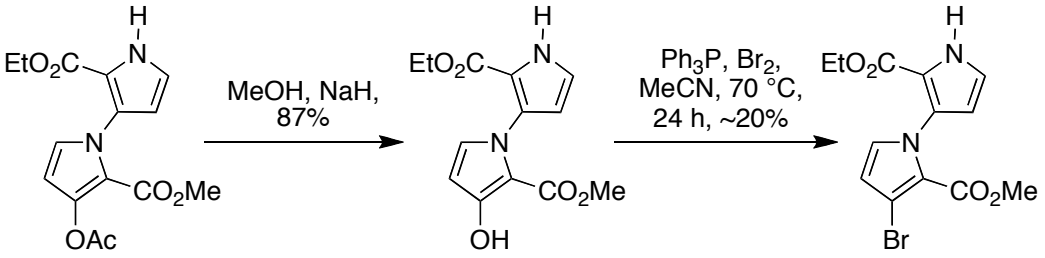



**Scheme 51**

tricarbonyl olefin **50.5**. Condensation of **50.5** onto the amine of the aminopyrrole ethyl ester **20.7** took place under catalysis by silica gel to give the 3'-hydroxy bispyrrole, which was directly acylated with acetic anhydride to give **50.7**.

Several attempts to chlorinate **50.7** with both $SO_2Cl_2$ and with NCS were unsuccessful (Scheme 51). When the chlorination reactions were done at lower temperatures with either reagent, the unreacted starting material was recovered. When the chlorination was done at room temperature the starting material was always destroyed.

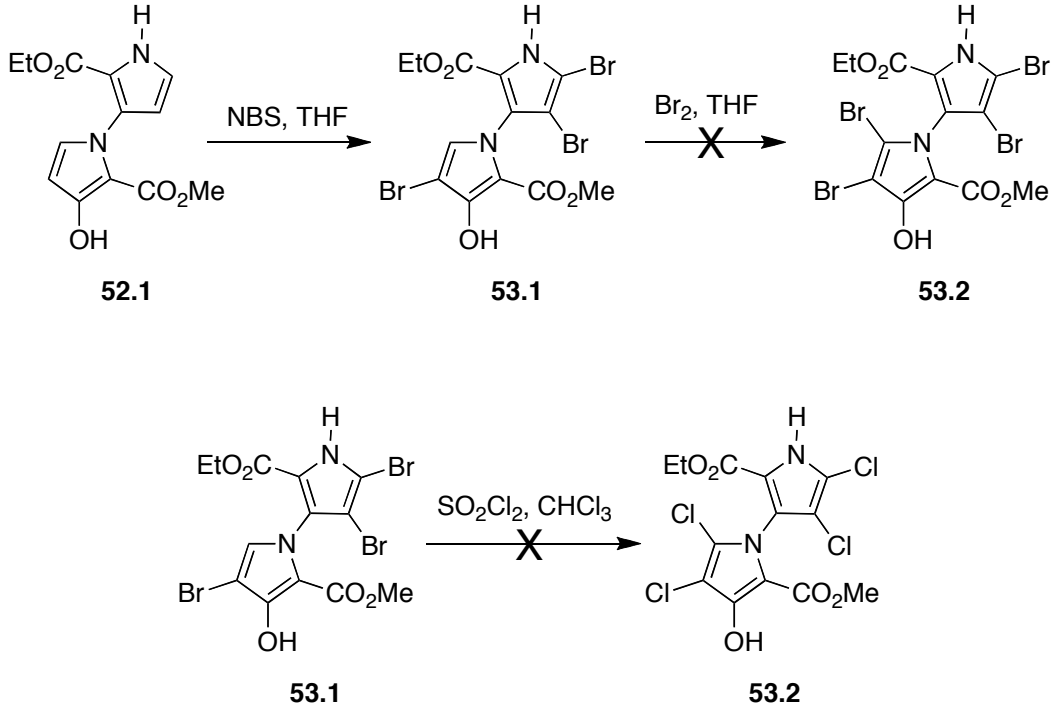
Since we were able to prepare the bispyrrole with a hydroxyl group at the 3'-position we attempted to replace the hydroxyl group of the bispyrrole by bromine and then tetrachlorinate the four vacant positions, which would be a convenient route to preparing the core of marinopyrrole B (Scheme 52). Consequently, we deprotected the acylated hydroxy bispyrrole (**50.7**) to expose the hydroxyl group (**52.1**) and then treated the product with $Ph_3P$ and $Br_2$ in MeCN. After 24 h of heating at 70 °C spectroscopic data ($^1$H-NMR and HRMS) showed that the hydroxyl group was converted into the corresponding bromide (**52.2**) in a quite low yield (~20%). However, the product could not be cleanly isolated free of impurities and the preparation of a 3' bromo bispyrrole was not pursued any further.




**50.7** **52.1** **52.2**

**Scheme 52**

Since tetrachlorination of the 3'-hydroxy bispyrrole had failed previously we attempted to tetrabrominate the four vacant positions first and then replace the bromines with chlorines through a debrominative chlorination[20] by treatment with $SO_2Cl_2$ (Scheme 53). When the 3'-hydroxy bispyrrole (**52.1**) was treated with NBS in THF, the $^1$H-NMR and HRMS showed the presence of only the 4,5,4'-tribrominated bispyrrole (**53.1**). The crude reaction mixture of the tribrominated product was treated with an excess of $Br_2$ in THF to brominate the vacant position (**53.2**), but no change took place and the tetrabrominated product was not formed. Therefore we treated the tribrominated product with $SO_2Cl_2$ in $CHCl_3$ to investigate the possibility of debrominative chlorination (**53.1→53.2**) and found that the tribrominated hydroxy bispyrrole could not withstand the chlorination conditions and was destroyed giving no identifiable product (Scheme 53).

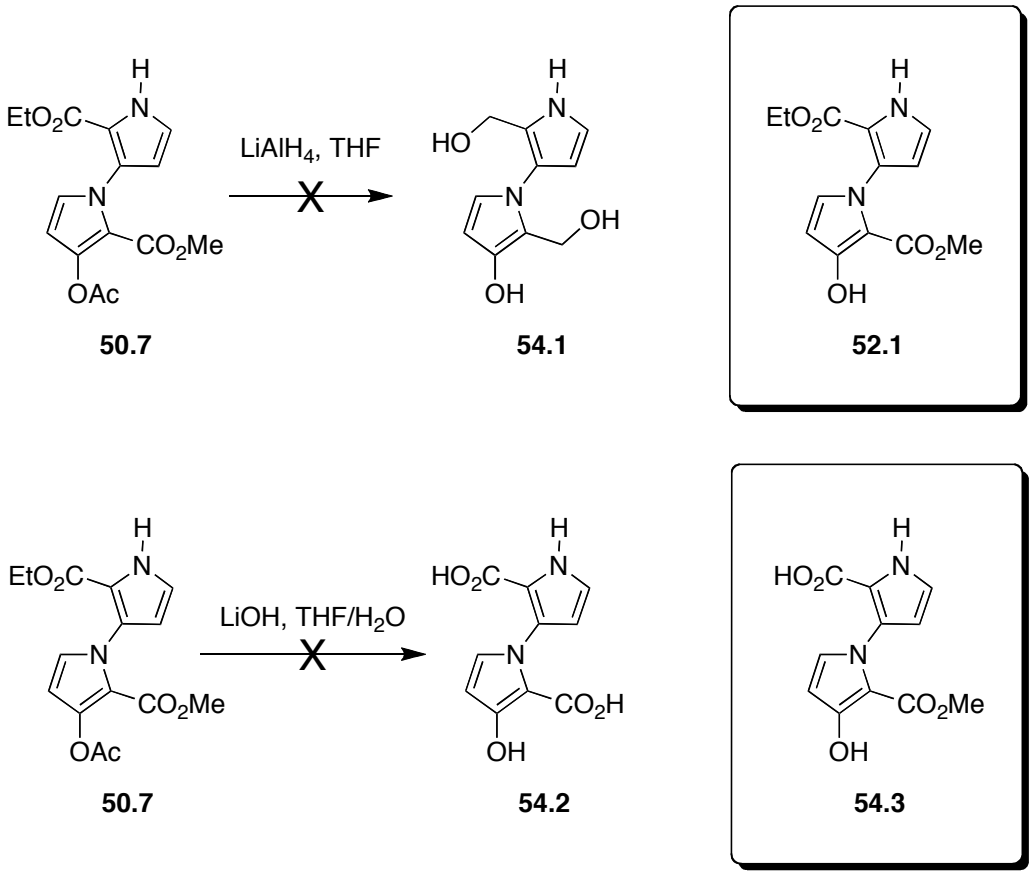



**Scheme 53**

After the above extensive studies on substituted pyrroles and bispyrroles we considered that it was possible that the electron withdrawing group at the 2-position for the pyrroles and at 2 and 2'-positions for the bispyrroles could be lowering the nucleophilicity of the pyrrole ring, and we thought it worth investigating the halogenation of a bispyrrole without an electron withdrawing substituent. Therefore it was decided that the esters on the bispyrrole should be reduced to the corresponding alcohols and the resulting bispyrrole then treated with chlorinating agents. To this end, the acylated hydroxy bispyrrole (**50.7**) was treated with $LiAlH_4$ in THF. It was found that at 0 °C and at room temperature only the acetyl group was reduced and the ethyl and the methyl esters at the 2 and 2'-positions remained unaffected (**52.1**). When the same experiment was repeated

in refluxing THF the starting material was destroyed and no product was obtained.

To test the stability of the bispyrrole esters, the acetyl protected hydroxy bispyrrole **50.7** was treated with aqueous LiOH in THF and after 20 h at room temperature and 2 h at 50 °C only the acetyl protecting the hydroxyl and the ethyl ester at the 2-position were hydrolyzed while the methyl ester at the 2'-position remained unaffected (**54.3**). This confirms that the two esters on the bispyrrole are somewhat unreactive and harsher conditions are required to perform any manipulations of the esters.



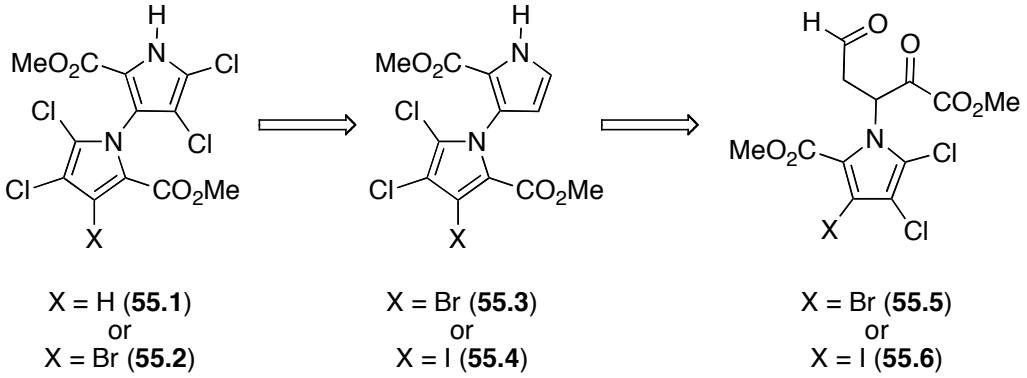

**50.7** **54.1** **52.1**

**50.7** **54.2** **54.3**

**Scheme 54**

## 2.5 Attempts to prepare the fully functionalized bottom ring first

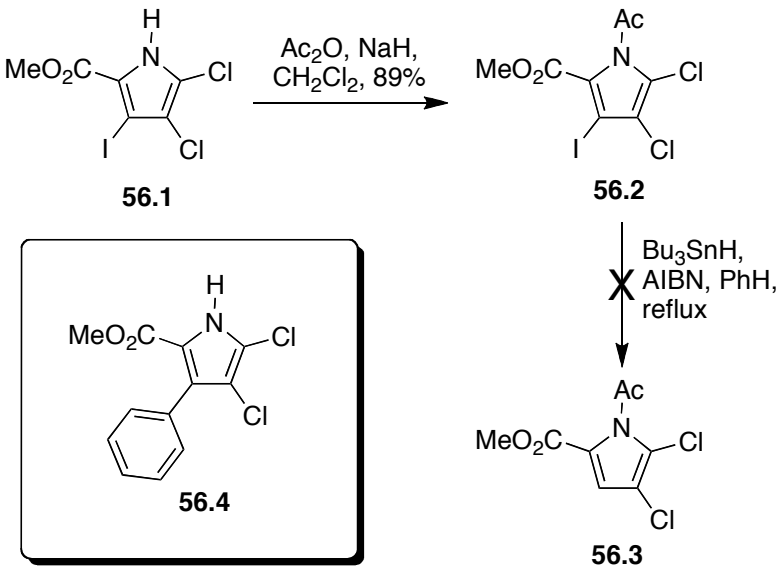
At this point in our studies we decided to change our approach. Since we were thwarted by a regioselectivity issue in the halogenation of the bispyrrole core and since the problem arose in the halogenation of the bottom ring we felt that it was wise to prepare the fully functionalized bottom ring first and then build and functionalize the top ring of the bispyrrole core (Scheme 55). The top ring can be built via a Paal-Knorr condensation of the dicarbonyl compounds **55.5** and **55.6** with $NH_3$.




**Scheme 55**

The new strategy can be applied towards the preparation of marinopyrrole B if the bottom ring is functionalized such that "X" is a bromine and it can be applied towards the preparation of marinopyrrole A if "X" is initially an iodine which is later reduced and replaced by hydrogen after the tetrachlorination (Scheme 55). The iodine will act as a blocking group during the chlorination in the preparation of marinopyrrole A and will be reduced later using a tin radical. To test the feasibility of using an iodine as a blocking group followed by

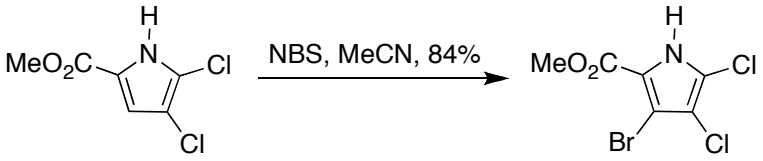
subsequent removal through stannane reduction, a model study was conducted starting with methyl 4,5-dichloro-3-iodopyrrole-2-carboxylate (**56.1**). The pyrrole nitrogen had to be acylated (**56.2**) first as the hydrogen on the pyrrole nitrogen could interfere with the tributylstannane reduction. The *N*-acetyl iodide **56.2** was treated with $Bu_3SnH$ and AIBN in $C_6H_6$ and the mixture was heated at reflux. Even though reduction of the iodide by the tin radicals did take place as expected, the reaction did not give the desired product **56.3**. Instead, it gave the product **56.4** in excellent yield (90%), where the reduced pyrrole had undergone arylation by the solvent and had also lost the acetyl protecting group. While reaction of radicals with $C_6H_6$ is well-known,[49] the loss of the *N*-acetyl group is puzzling.




**Scheme 56**

Since reduction of the iodide requires further investigation, we focused our attention on the preparation of marinopyrrole B, where we could use a

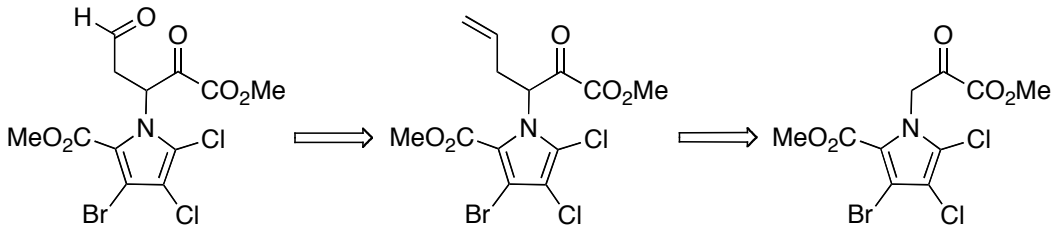
bromine as a blocking group that does not have to be removed, since marinopyrrole B does have a bromide at the 3'-position. We tested the preparation of the fully functionalized bottom ring of marinopyrrole B by brominating methyl 4,5-dichloropyrrole-2-carboxylate. The bromination occurred smoothly giving **57.1** in good yield (84%).




**33.2** **57.1**

**Scheme 57**

Once we had discovered that the bottom ring of marinopyrrole B could be made with ease we attempted to mount the dicarbonyl fragment on top of the bottom ring (**55.5**) to set the stage for the Paal-Knorr condensation. Of the two carbonyls, we envisioned that the aldehyde would come from oxidative cleavage

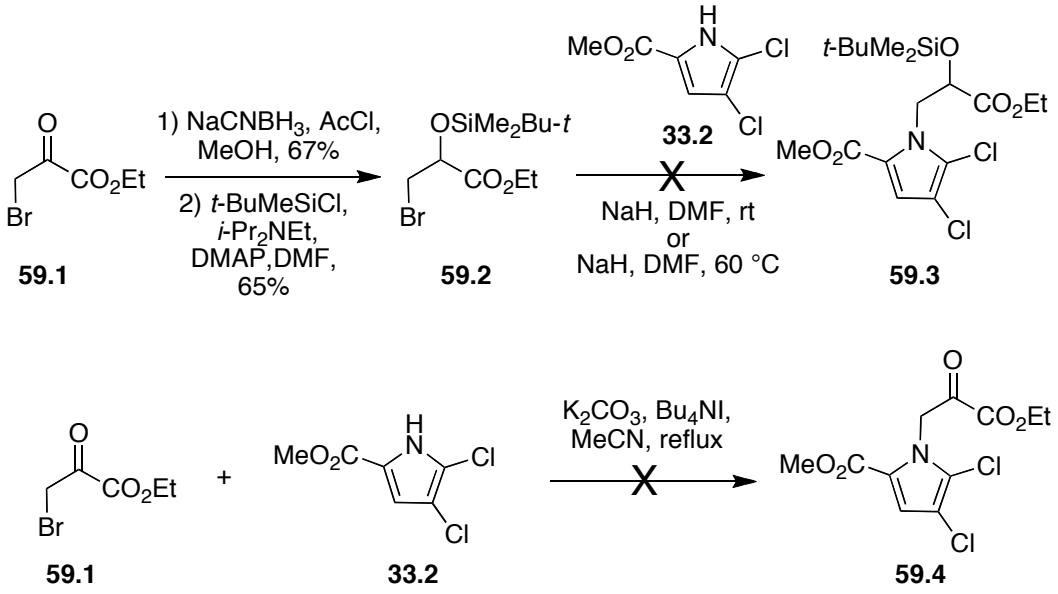



**55.5** **58.1** **58.2**

**Scheme 58**

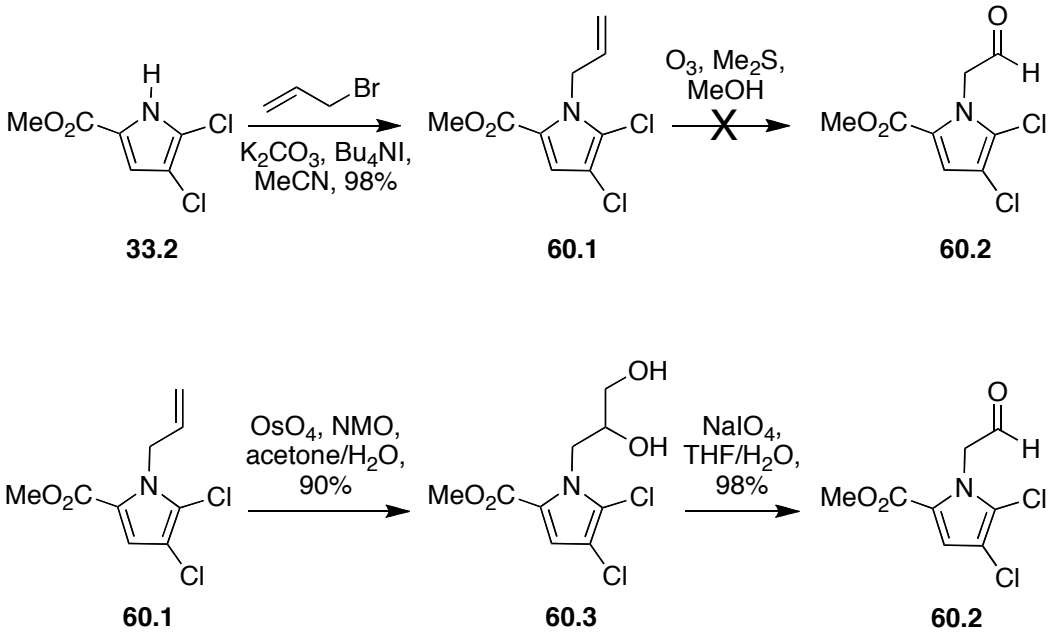
of the terminal olefin of **58.1**, and the ketone would come from pyruvate, as in **58.2**.

The synthetic route began with reduction of the ketone of ethyl bromopyruvate (**59.1**) to the corresponding secondary alcohol and silyl protection of the alcohol (**59.2**). Several attempts were made to couple **59.2** with methyl 4,5-dichloropyrrole-2-carboxylate. However, in all cases when the reaction was done at room temperature the two starting materials were recovered and no product was formed. When the reaction was done at elevated temperatures only the starting pyrrole was recovered and the pyruvate derivative (**59.2**) was destroyed. We also attempted to couple the pyruvate **59.1** directly to the pyrrole under basic conditions ($K_2CO_3$, MeCN, reflux) at elevated temperatures. The $^1$H-NMR spectrum of the reaction mixture showed no product and the pyruvate had polymerized under the reaction conditions. These experiments showed that the pyruvate derivative could not survive harsh conditions and therefore the use of pyruvate as a precursor to attach the top fragment had to be abandoned.




**Scheme 59**

In the hope of introducing the ester functionality of the top ring at a later stage we first tried to put the two carbonyls in place. To this end, we allylated[50] the bottom pyrrole (**60.1**) and attempted to convert the olefin into an aldehyde (**60.2**) through ozonolysis. However $O_3$ was soon found to be detrimental to the substrate when a TLC analysis of the reaction mixture of the ozonolysis showed that the starting material was destroyed as early as 2 min after starting to bubble $O_3$ though the solution even at -78 °C. We then switched to the $OsO_4/NaIO_4$ method[51,52] for double bond cleavage. We were able to dihydroxylate the olefin smoothly using $OsO_4$ (**60.3**) and the diol was cleaved with $NaIO_4$ to give the required aldehyde (**60.2**) in excellent yield (Scheme 60).

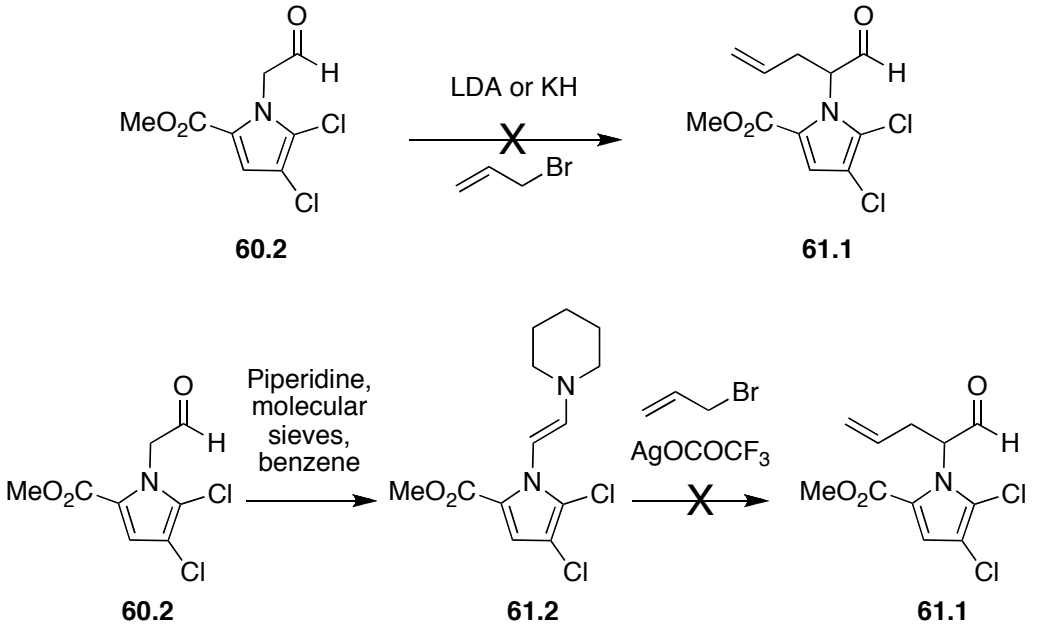



**33.2** **60.1** **60.2**

**60.1** **60.3** **60.2**

**Scheme 60**

Once aldehyde **60.2** was available, we investigated the possibility of installing the second carbonyl. We expected to obtain the second aldehyde through the oxidative cleavage of a terminal olefin, as before. Attempts were therefore made to α allylate the aldehyde of **60.2** by treatment with a strong base and allyl bromide.



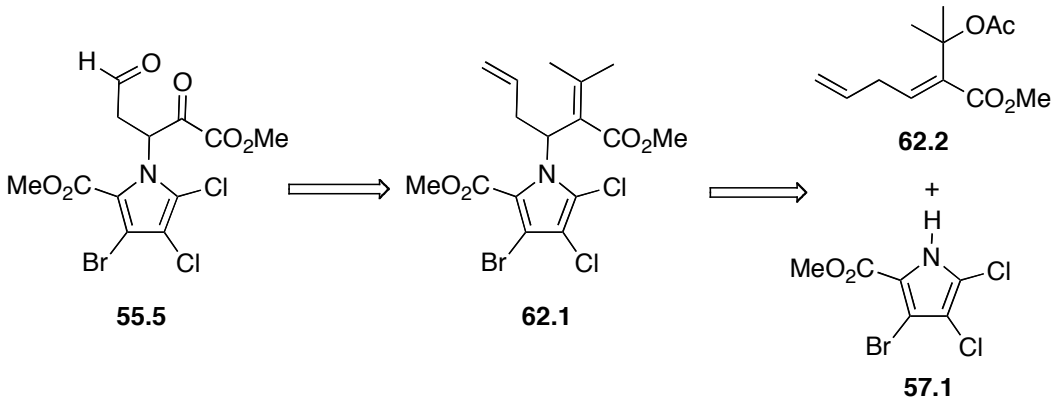

**60.2** **61.1** **60.2** **61.2** **61.1**

**Scheme 61**

In two different reactions the aldehyde was deprotonated with LDA and with KH and then treated with ally bromide. Both reactions not only failed to give the desired product, but also destroyed the starting material. Since it was evident that the substrate was vulnerable to strongly basic conditions allylation had to be done by first converting the aldehyde to an enamine and followed by treatment with allyl bromide. Stirring the aldehyde with piperidine in the presence of molecular sieves in $C_6H_6$ gave the required enamine **61.2** as shown by the $^1$H-NMR spectrum. However, no condensation took place when allyl bromide was added to the reaction mixture even in the presence of $AgOCOCF_3$. A $^1$H-NMR spectrum of the reaction mixture taken without quenching showed that the unreacted enamine **61.2** was still present along with allyl bromide. These

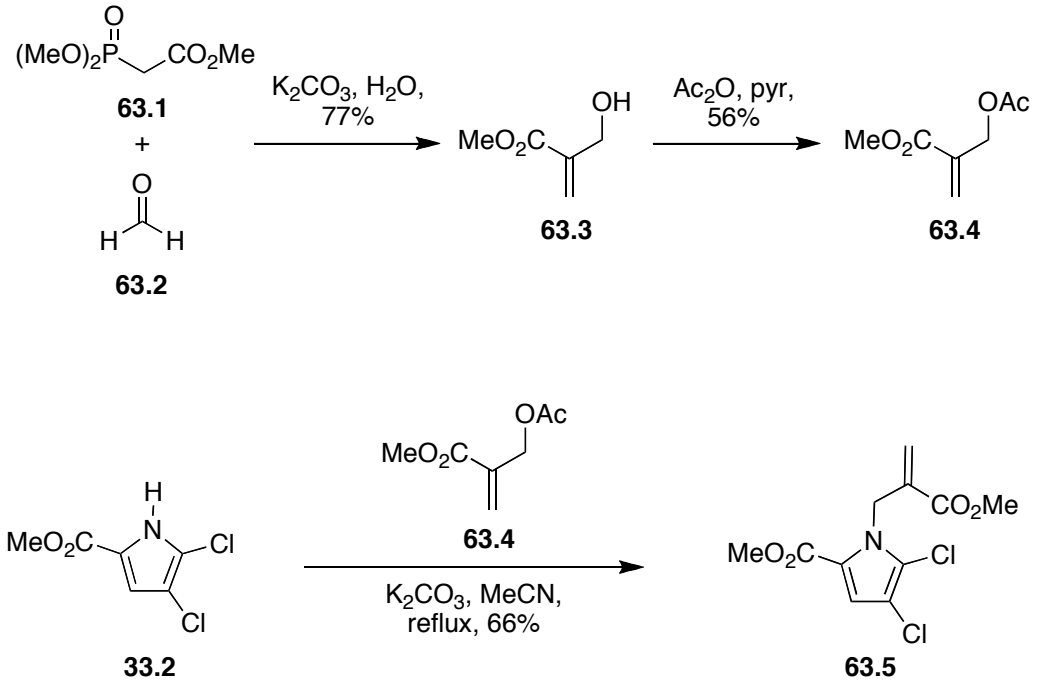
experimental results shows that the enamine of the aldehyde **60.2** has a very low nucleophilicity.

We anticipated that the dicarbonyl fragment that will eventually make the top ring of the bispyrrole core can be placed onto the bottom pyrrole through a intermolecular conjugate displacement (ICD) reaction (Scheme 62).



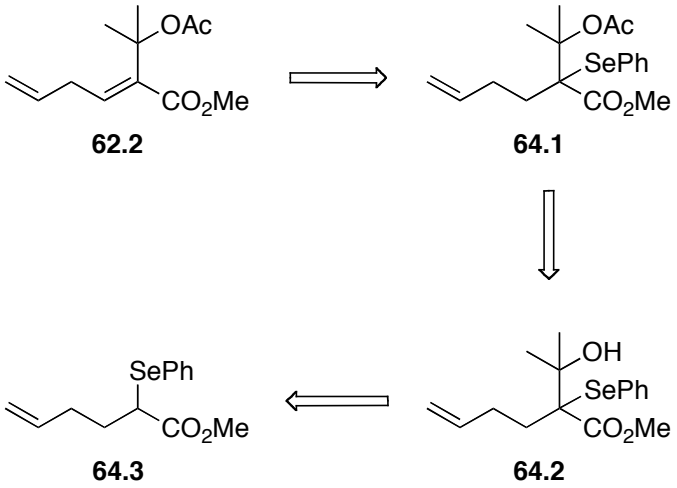

**Scheme 62**

In order to do a successful ICD reaction we need the fragment **62.2**. Since we were interested in finding out the feasibility of an ICD reaction with the halogenated pyrrole, prior to preparing the fragment **62.2**, we prepared[53] fragment **63.4** as a model compound as shown in Scheme 63.




**Scheme 63**

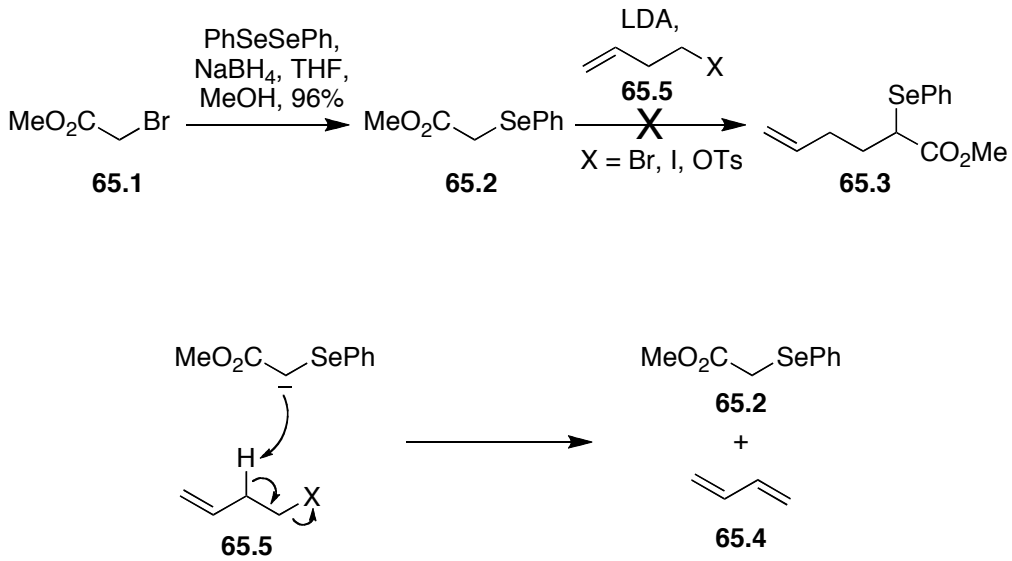
With **63.4** in hand we coupled it successfully with methyl 4,5-dichloropyrrole-2-carboxylate using $K_2CO_3$ in MeCN[50] to give compound **63.5** in moderate yield (66%). We appreciate that formation of **63.5** may involve a direct $S_N2$ displacement rather than an ICD process, it is for this reason that **62.2** has a gem dimethyl group to suppress an $S_N2$ reaction. Once we had successfully carried out the desired ICD reaction, we turned our attention to the preparation of compound **62.2** which is the precursor for the ICD reaction, and which would make the top pyrrole ring. Compound **62.2** should be available by oxidation and selenoxide fragmentation of **64.1**. Acyl protection of the tertiary alcohol of **64.2** would give **64.1**. Deprotonation and capturing of the selenium stabilized carbanion of **64.3** with acetone would give **64.2**.




**Scheme 64**

Preparation of **64.3** was the initial step towards the ICD reaction. Firstly, methyl bromoacetate was treated with PhSeNa, which was prepared by $NaBH_4$ reduction of PhSeSePh, to get methyl (phenylseleno)acetate (**65.2**).[54] Next, compound **65.2** was deprotonated with LDA and treated with 4-bromo-1-butene. We noticed that deprotonated **65.2** did not condense with 4-bromo-1-butene (Scheme 65). We also tried the corresponding iodide[55] and the *O*-tosylate, but no product was formed. To test if the deprotonation step was problematic we treated **65.2** with LDA and quenched the anion with $D_2O$. The $^1$H-NMR spectrum of the product obtained after $D_2O$ quenching showed deuterium incorporation. This proved that the deprotonation step did occur smoothly and that it is the condensation step that is problematic. When the reaction was quenched with $D_2O$ after being treated with the butene we noticed that there was no deuterium incorporation in **65.2** ($^1$H-NMR). These observations led us to the conclusion that even though alkylations with 4-bromo-1-butene are known,[56] in this case instead

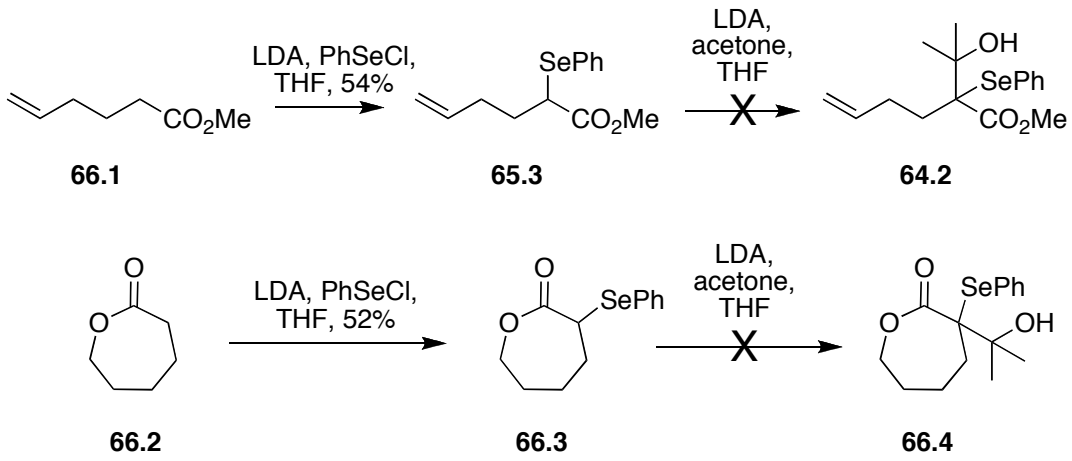
of the expected displacement reaction the butene undergoes an elimination to give the conjugated butadiene (**65.4**) (Scheme 65).




**Scheme 65**

Since the condensation with a butene was problematic we switched to a different approach, where we could start with methyl 5-hexenoate (**66.1**). Deprotonation of **66.1** α to the ester with LDA and treatment with PhSeCl[57] gave **65.3**. The next step towards the preparation of **62.2** was to deprotonate **65.3** and capture the resulting anion with acetone. However we were not able to deprotonate **65.3** with LDA or with KH. The reactions were quenched with $D_2O$ to test for any signs of deprotonation and we always found the starting **65.3** without any deuterium incorporation (Scheme 66). Once the route had failed with methyl 5-hexenoate, we repeated the experiments starting with caprolactone (**66.2**), hoping to open the lactone at a later stage. We were able to prepare the α-

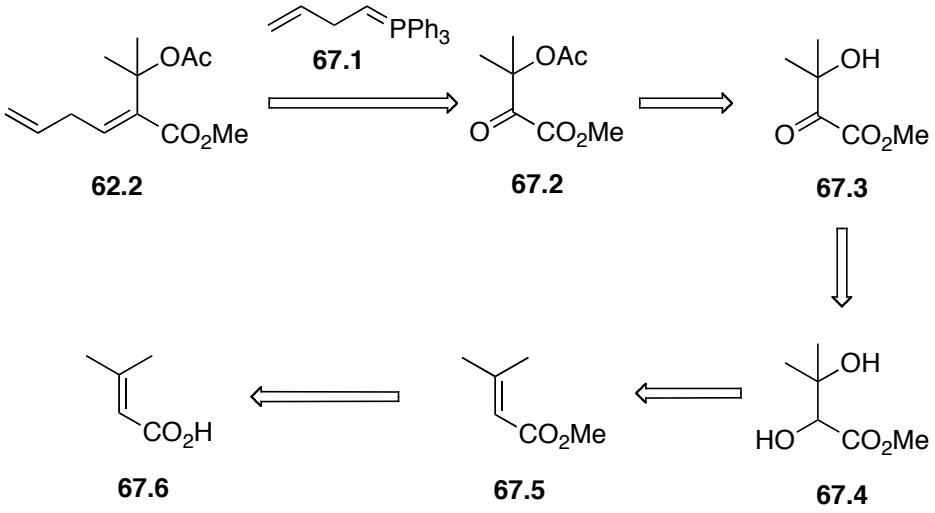
(phenylseleno)caprolactone (**66.3**) without difficulty, as in the case with methyl 5-hexenoate. However, the next step of deprotonation and condensation with acetone failed, giving only the starting α-(phenylseleno)caprolactone.




**Scheme 66**

## 2.6 Work in progress

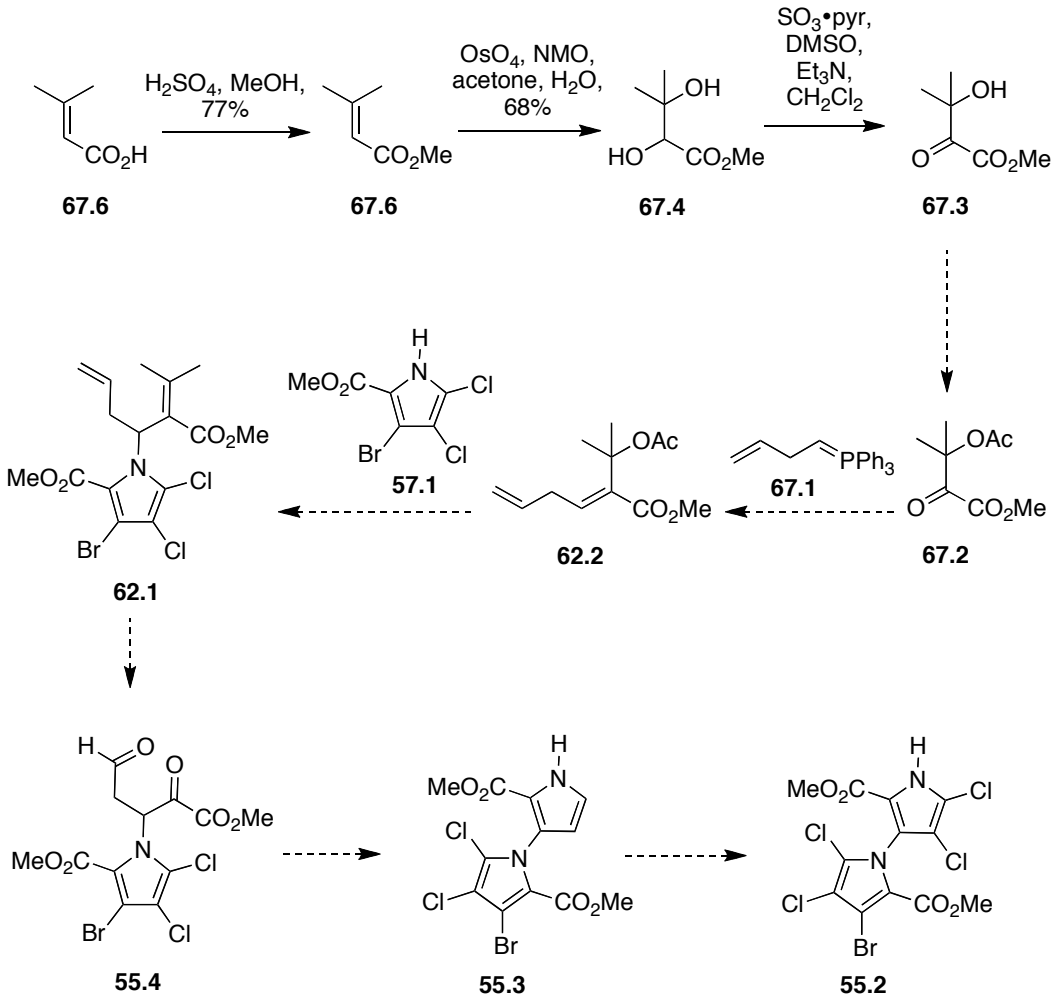
Since the preparation of **62.2** through the condensation of a (phenylseleno)ester with a ketone seems to be difficult, we adopted a new strategy which would give us **62.2** via a Wittig reaction (Scheme 67).




**Scheme 67**

The Wittig reaction approach started with the unsaturated acid **67.6** (Scheme 68). The acid was esterified using MeOH and a catalytic amount of $H_2SO_4$ to give the methyl ester **67.5**. The olefin of the methyl ester was then dihydroxylated using $OsO_4$ and NMO to give the diol **67.4**. The attempted oxidations of the secondary alcohol of **67.4** to the corresponding ketone failed with PCC in $CH_2Cl_2$, NBS and pyridine in $CCl_4$,[58] TPAP and NMO in MeCN.[59] The oxidized product **67.3** was seen on TLC and by $^1$H-NMR of the crude reaction mixture when the oxidation was done under Parikh-Doering conditions using $SO_3$•Pyr, DMSO and $Et_3N$ in $CH_2Cl_2$. Now that we have successfully oxidized the diol to the corresponding ketone future work involves protection of the tertiary alcohol either as an acetate (**67.2**) or a pivaloate and we will then do a Wittig reaction to afford **62.2**, which is the precursor for the ICD reaction with the halogenated bottom pyrrole. If the ICD process works, the two olefins can be oxidatively cleaved to get the corresponding aldehyde and the α keto ester, setting

the stage for condensation with $NH_3$ in a Paal-Knorr reaction to prepare the top pyrrole ring. Since the bottom pyrrole ring has been fully functionalized we might be able to dichlorinate the two vacant-positions of the top pyrrole ring without incident to give the bispyrrole core of marinopyrrole B (Scheme 68). During this route we will be able to successfully bypass the regioselectivity issue of the halogenation which is considered the most challenging step in the synthesis of the marinopyrroles.




**Scheme 68**

# 3. CONCLUSION

Natural products have been a major component of drugs used by humans since historic times. Recently, marine natural products have captured the interest of many researchers as drug candidates. As the emergence of drug resistant bacteria is a continuing problem, marinopyrroles A and B appear to be suitable drug candidates that show biological activity against drug resistant bacteria and are of synthetic interest.

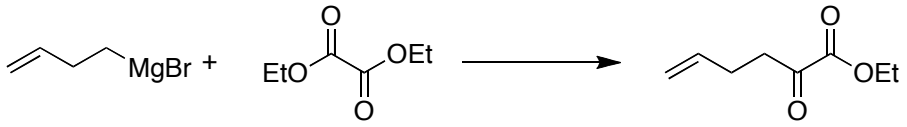
Synthetic studies on the marinopyrroles began with the preparation of the bispyrrole core via an acid catalyzed Paal-Knorr reaction. However, the preparation of the densely halogenated core of the marinopyrroles by regioselective halogenation could not be achieved. Preparation of the fully functionalized top ring prior to the Paal-Knorr reaction was also unsuccessful due to significant alterations to the electronic structure of the pyrrole ring by the electron withdrawing substituents.

Placement of removable blocking groups at the 3'-position was not fruitful due to poor selectivity in the orthometallation reaction. Also, the low nucleophilicity of the bispyrroles in the presence of an oxygen at the 3'-position prevented the desired halogenation. The synthetic approach was switched from preparation of the top ring first to the preparation of the fully functionalized bottom ring first. An ICD experiment done on a model compound showed that it is possible to couple the fully functionalized bottom ring to the precursor that would eventually make the top ring. Work is in progress to prepare the precursor to the top ring via a Wittig reaction.

# 4. EXPERIMENTAL

The same general techniques were used as reported in Chapter 1.

**Ethyl 2-oxohex-5-enoate (20.3).**[7]

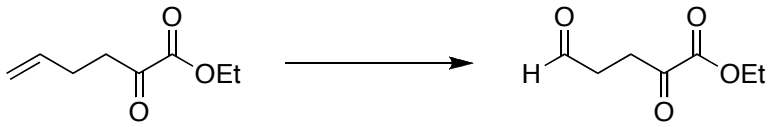



**20.2** **20.1** **20.3**

4-Bromobutene (0.5 mL, 5 mmol) was added to a flask charged with Mg (250 mg, 10 mmol) and dry THF (5 mL). The mixture was heated gently until an exothermic reaction occurred and then the mixture was refluxed for 20 min. After being cooled to room temperature the Grignard mixture (**20.2**) was added slowly to a mixture of diethyl oxalate (**20.1**) (0.8 mL, 6 mmol) in THF (5 mL) at -10 °C. The resulting mixture was stirred for 1 h at -10 °C and allowed to reach room temperature. After being quenched with aqueous $NH_4Cl$ the solvent was evaporated. Water was added and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 0-20% EtOAc in hexane, gave **20.3** (628 mg, 81%) as a colorless oil: FTIR (microscope) 3482, 3080, 2979, 2928, 2851 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.37 (t, $J$ = 7.1 Hz, 3 H), 2.35-2.45 (m, 2 H), 2.95 (t, $J$ = 7.4 Hz, 2 H), 4.33 (q, $J$ = 7.2 Hz, 2 H), 4.99-5.12 (m, 2 H), 5.75-5.90 (m, 1 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 14.1 (q), 27.0

(t), 38.5 (t), 62.5 (t), 115.9 (t), 136.2 (d), 161.1 (s), 193.9 (s); exact mass *m*/*z* calcd for $C_8H_{12}O_3$ 156.07864, found 156.07870.

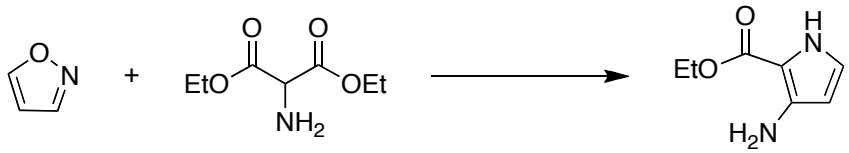
**Ethyl 2,5-dioxopentanoate (20.4).**[7]




**20.3** **20.4**

Ozonized oxygen was bubbled through a solution of **20.3** (480 mg, 3.1 mmol) in MeOH (12 mL) for 1 h at -78 °C. $Me_2S$ (1.1 mL, 15.5 mmol) was added at a fast dropwise rate at -78 °C and the mixture was stirred overnight without recharging the cold acetone bath. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 25 cm), using 0-20% EtOAc in hexane, gave **20.4** (364 mg, 74%) as a pale yellow oil: $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.39 (t, *J* = 7.1 Hz, 3 H), 2.87 (t, *J* = 6.7 Hz, 2 H), 3.16 (t, *J* = 6.7 Hz, 2 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 9.82 (s, 1 H).

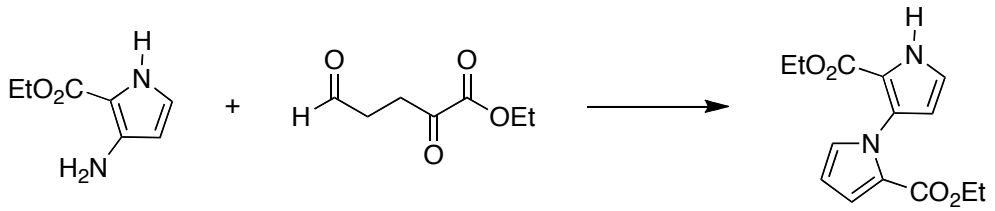
**Ethyl 3-amino-1*H*-pyrrole-2-carboxylate (20.7).**[7]




**20.6** **20.5** **20.7**

Isoxazole (**20.6**) (2.0 g, 1.85 mL, 29 mmol) was added to a stirred and cooled (0 °C) solution of EtONa in EtOH [2 M, prepared by adding NaH (2.4 g) to EtOH (50 ml) at -78 °C and allowing the mixture to warm to 0 °C]. The mixture was stirred for 1 h at 0 °C and AcOH (0.55 mL, 10 mmol), NaOAc (1.6 g, 20 mmol), and diethyl aminomalonate (**20.5**) (4.1 g, 19 mmol) were added. This mixture was stirred for 2 days at room temperature and most of the EtOH was then evaporated. The residue was partitioned between water and $CHCl_3$ and the aqueous phase was extracted with $CHCl_3$. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. The crude residue was dissolved in cold (0 °C) ethanolic EtONa [0.5 M EtONa in EtOH (prepared by adding NaH (0.6 g) to EtOH (50 ml) at -78 °C and allowing the mixture to warm up to 0 °C )] and the mixture was stirred for 3 days at room temperature. AcOH (1.2 mL) was added and the EtOH was evaporated. The residue was partitioned between water and $CHCl_3$ and the aqueous phase was extracted with $CHCl_3$. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using first 100% hexane and then 40% EtOAc in hexane, gave **20.7** (665 mg, 23%) as a pale yellow oil: FTIR ($CH_2Cl_2$ cast film) 3339, 2981, 2933, 2200, 1666 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.35 (t, $J$ = 7.1 Hz, 3 H), 4.20-4.40 (m, 4 H), 5.73 (t, $J$ = 2.9 Hz, 1 H), 6.68 (t, $J$ = 2.6 Hz, 1 H), 6.25 (br s, 1 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) (mixture of two rotamers) δ 14.7 (q), 14.7 (q), 59.4 (t), 60.1 (t), 99.3 (d), 99.4 (d), 105.4 (s), 106.6 (s), 122.5 (d), 124.0 (s), 139.4 (s), 142.2 (s), 161.2 (s), 162.3 (s); exact mass $m/z$ calcd for $C_7H_{10}N_2O_2$ 154.07423, found 154.07429.

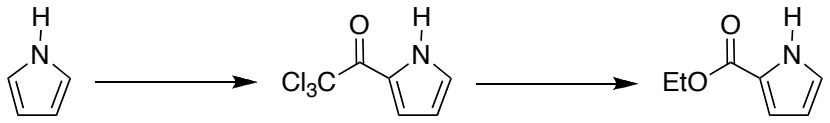
**Ethyl 3-[2-(ethoxycarbonyl)-1*H*-pyrrol-1-yl]-1*H*-pyrrole-2-carboxylate (20.8).**[7]




**20.7** **20.4** **20.8**

A solution of **20.7** (55 mg, 0.35 mmol), **20.4** (33 mg, 0.20 mmol) and a catalytic amount of $TsOH•H_2O$ (12 mg, 0.05 mmol) in $CH_2Cl_2$ (5.0 mL) was stirred at room temperature overnight. The mixture was quenched with $NaHCO_3$ and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 25 cm), using 0-20% EtOAc in hexane, gave **20.8** (37 mg, 67%) as a pale yellow oil: FTIR (microscope) 3308, 3133, 2982, 2938, 2905, 1698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.11 (t, $J$ = 7.1 Hz, 3 H), 1.23 (t, $J$ = 7.1 Hz, 3 H), 4.13 (q, $J$ = 7.1 Hz, 2 H), 4.16 (q, $J$ = 7.1 Hz, 2 H), 6.25 (dd, $J$ = 3.9, 2.7 Hz, 1 H), 6.31 (t, $J$ = 2.9 Hz, 1 H), 6.87-6.92 (m, 2H), 7.06 (dd, $J$ = 3.9, 1.8 Hz, 1 H), 9.21 (br s, 1 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 14.2 (q), 59.6 (t), 60.3 (t), 108.5 (d), 109.9 (d), 117.6 (s), 117.8 (d), 120.3 (d), 124.6 (s), 129.7 (s), 130.0 (d), 160.0 (s), 160.5 (s); exact mass $m/z$ calcd for $C_{14}H_{16}N_2O_4$ 276.11099, found 276.11117.

**Ethyl 1*H*-pyrrole-2-carboxylate (7.1→32.3).**[29]



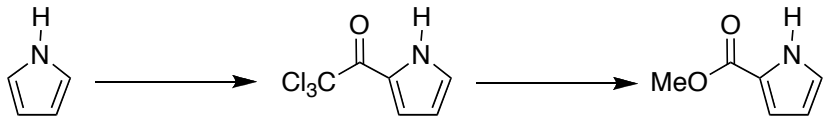

**6.1** **7.1** **32.3**

Pyrrole (**6.1**) (500 mg, 7.5 mmol) in $Et_2O$ (7 mL) was added over 6 h at room temperature to a stirred solution of $Cl_3CCOCl$ (0.9 mL, 8 mmol) in $Et_2O$ (2 mL) in a flask equipped with a reflux condenser. Stirring at room temperature was continued overnight and the mixture was quenched with an aqueous solution of $K_2CO_3$ [625 mg in water (2 mL)] which was added at a slow dropwise rate to avoid excessive bubbling. The organic phase was separated and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. The residue was recrystallized from hexane to give **7.1** with some impurities: FTIR (microscope) 3878, 3322, 3144, 3067, 2992, 2952, 1657 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 6.39 (dt, $J$ = 4.1, 2.5 Hz, 1 H), 7.15-7.19 (m, 1 H), 7.37-7.41 (m, 1 H), 9.46 (br s, 1 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 94.9 (s), 111.8 (d), 121.1 (d), 123.0 (s), 127.0 (d), 173.2 (s); exact mass *m*/*z* calcd for $C_6H_4Cl_3NNaO$ 233.92507, found 233.92536.

Solid **7.1** was added portionwise over a ~10 min to a stirred and cooled (0 °C) solution of EtONa in EtOH [prepared by adding Na (100 mg) to EtOH (20 mL)]. The mixture was stirred at room temperature overnight and most of the EtOH was evaporated. The residue was partitioned between $Et_2O$ and 3 M hydrochloric acid. The organic phase was separated and the aqueous phase was

extracted with $Et_2O$. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 0-30% EtOAc in hexane, gave **32.3** (1.02 g, 98% over two steps from the pyrrole) as a light brown oil: FTIR (microscope) 3315, 3135, 2982, 2930, 1687 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.36 (t, *J* = 7.1 Hz, 3 H), 4.32 (q, *J* = 7.1 Hz, 1 H), 6.27 (dt, *J* = 3.7, 2.6 Hz, 1 H), 6.90-6.96 (m, 2 H), 9.05 (br s, 1 H); exact mass *m*/*z* calcd for $C_7H_9NNaO_2$ 162.05255, found 162.05243.

**Methyl 1*H*-pyrrole-2-carboxylate (11.1).**[29]

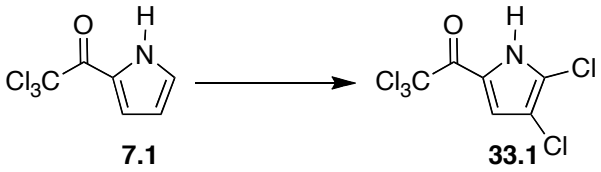



**6.1** **7.1** **11.1**

Solid **7.1** (445 mg, 2.10), prepared as described above, was added portionwise over a ~10 min to a stirred and cooled (0 °C) solution of MeONa in MeOH [prepared by adding Na (50 mg) to MeOH (5 mL)] . The mixture was stirred at room temperature overnight and most of the MeOH was evaporated. The residue was partitioned between $Et_2O$ and 3 M hydrochloric acid. The organic phase was separated and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 0-30% EtOAc in hexane, gave **11.1** (247 mg, 94% over two steps from the pyrrole) as a yellow semisolid: mp 67-69 °C; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 3.86 (s, 3 H), 6.26 (dt, *J*

= 3.7, 2.9 Hz, 1 H), 6.91-6.94 (m, 1 H), 6.95-6.97 (m, 1 H), 9.19 (br s, 1 H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 51.4 (q), 110.5 (d), 115.2 (d), 122.6 (s), 122.8 (d), 161.6 (s).

**2,2,2-Trichloro-1-(4,5-dichloro-1*H*-pyrrol-2-yl)ethan-1-one (33.1).**




**7.1** **33.1**

*Chlorination by $SO_2Cl_2$:*[18]

$SO_2Cl_2$ (0.43 mL, 5.4 mmol) was added to a stirred solution of **7.1** (384 mg, 1.8 mmol) in $CH_2Cl_2$ (5 mL) at room temperature. The mixture was stirred for 4 h at room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 25 cm), using 0-10% EtOAc in hexane, gave **33.1** (488 mg, 96%) as a pale yellow oil: FTIR (microscope) 3378, 3271, 3163, 3140, 2994, 1656 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.32 (d, $J$ = 3.1 Hz, 1 H), 9.83 (br s, 1 H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 93.9 (s), 113.2 (s), 120.3 (s), 120.4 (d), 123.5 (s), 172.2 (s); exact mass $m/z$ calcd for $C_6HCl_5NO$ 277.85063, found 277.85062.

*Chlorination by $Cl_2$ gas:*[30]

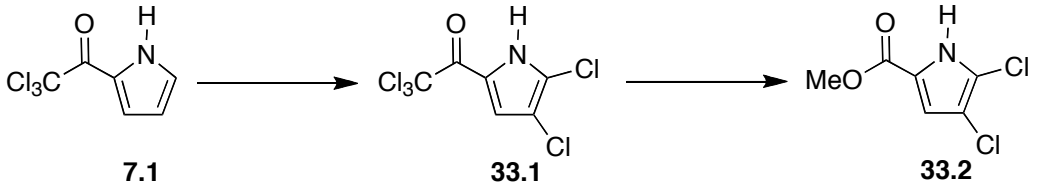
A three necked flask was charged with solid $KMnO_4$ and concentrated hydrochloric acid was added dropwise from a dropping funnel (6.2 mL

hydrochloric acid/1.0 g $KMnO_4$). The $Cl_2$ gas produced was first passed through a Dreschel bottle containing water and a second Dreschel bottle containing concentrated $H_2SO_4$. The mixture was heated gently when the rate of gas production decreased (1.0 g of $KMnO_4$ produces a maximum of 1.125 g of $Cl_2$ gas). The $Cl_2$ was bubbled through AcOH (10 mL) to prepare a solution of $Cl_2$ in AcOH. A solution of $Cl_2$ (1.1 g, 15 mmol) in AcOH was added to **7.1** (1.26 g, 5.9 mmol) in AcOH (10 mL) and the mixture was stirred until **7.1** disappeared (ca 24 h, TLC control). The solvent was evaporated and recrystallization of the residue from PhH gave **33.1** (1.15 g, 70 %) as a pale yellow oil.

*Chlorination by TCIA*:[26]

TCIA (500 mg, 2.15 mmol) was added as a solid to a stirred solution of **7.1** (455 mg, 2.15 mmol) in $CHCl_3$ (10 mL). The completion of the reaction was monitored by TLC (reaction time was generally under 30 min). The mixture was quenched with water and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 25 cm), using 0-20% EtOAc in hexane, gave **33.1** (393 mg, 65%) as a pale yellow oil.

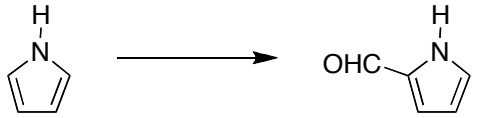
**Methyl 4,5-dichloro-1*H*-pyrrole-2-carboxylate (33.2).**[18,29]




**7.1** **33.1** **33.2**

The trichloromethyl ketone **33.1** was prepared as described above, using **7.1** (616 mg, 2.9 mmol). A solution of the resulting crude **33.1** in MeOH (5 mL) was added to a stirred and cooled (0 °C) solution of MeONa/MeOH (100 mg of Na in 20 mL MeOH). The mixture was stirred overnight at room temperature and most of the MeOH was evaporated. The residue was partitioned between $Et_2O$ and 3 M hydrochloric acid. The organic phase was separated and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 0-30% EtOAc in hexane, gave **33.2** (480 mg, 86% over two steps from **7.1**) as a yellow oil: FTIR (cast film microscope) 3252, 3127, 3013, 2960, 2899, 1702 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 3.87 (s, 1 H), 6.82 (d, $J$ = 3.0 Hz, 1 H), 9.15 (s, 1 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 52.0 (q), 111.5 (s), 115.1 (d), 118.0 (s), 120.2 (s), 160.3 (s); exact mass $m/z$ calcd for $C_6H_5{}^{35}Cl_2NO_2$ 192.96973, found 192.97013.

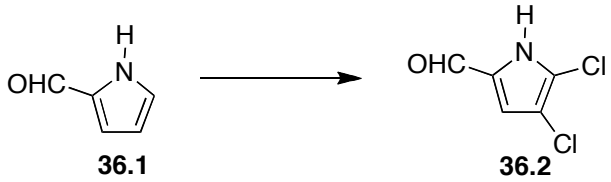
**1*H*-Pyrrole-2-carbaldehyde (36.1).**[34]




**6.1** **36.1**

$POCl_3$ (7.5 mL, 80 mmol) was added dropwise over a 5 min to a stirred and cooled (0 °C) portion of DMF (6.2 mL, 80 mmol) and the mixture was stirred for 15 min. The ice bath was removed and the mixture was diluted with $CH_2Cl_2$ (20 mL). The solution was allowed to reach ~5 °C and pyrrole (**6.1**) (5.0 g, 75 mmol) in $CH_2Cl_2$ (20 mL) was added at a slow dropwise rate. The stirred mixture was refluxed for 15 min and cooled to room temperature. A solution of NaOAc in water (75%$^{w}/_{v}$, 100 mL) was added dropwise and the mixture was refluxed for 15 min. The organic phase was separated and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried ($Na_2SO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using 0-20% EtOAc in hexane, gave **36.1** (2.02 g, 28%) as a colorless oil: FTIR (microscope) 3146, 3084, 2981, 3870, 2759 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 6.36 (dt, $J$ = 3.8, 2.4 Hz, 1 H), 6.97-7.00 (m, 1 H), 7.11-7.14 (m, 1 H), 9.37 (br s, 1 H), 9.54 (s, 1 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 111.4 (d), 121.5 (d), 126.5 (d), 132.9 (s), 179.3 (d); exact mass $m/z$ calcd for $C_5H_5NO$ 95.03712, found 95.03698.

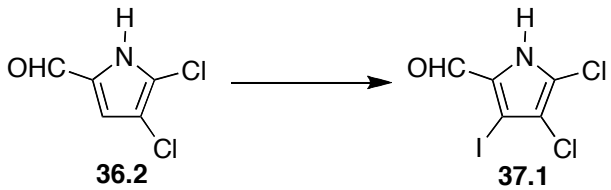
**4,5-Dichloro-1*H*-pyrrole-2-carbaldehyde (36.2).**[18]




**36.1** **36.2**

$SO_2Cl_2$ (0.2 mL, 2.52 mmol) was added to a stirred solution of **36.1** (120 mg, 1.26 mmol) in $CH_2Cl_2$ (5 mL) at room temperature and the reaction mixture was stirred for 4 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 25 cm), using 0-10% EtOAc in hexane, gave **36.2** (130 mg, 64%) as a white solid: mp 137-139 °C; FTIR (microscope) 3199, 3125, 3090, 2995, 2847 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 6.20 (s, 1 H), 9.56 (s, 1 H), 9.95 (br s, 1 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 112.8 (s), 120.3 (d), 123.5 (s), 129.5 (s), 178.1 (d); exact mass *m*/*z* calcd for $C_5H_3{}^{35}Cl_2NO$ 162.95917, found 162.95921.

**4,5-Dichloro-3-iodo-1*H*-pyrrole-2-carbaldehyde (37.1).**[18]

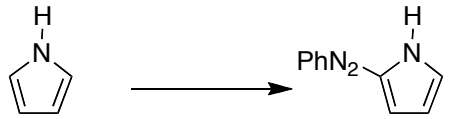



**36.2** **37.1**

$I_2$ (350 mg, 1.4 mmol) and $AgOCOCF_3$ (315 mg, 1.4 mmol) were added to a stirred solution of **36.2** (215 mg, 1.3 mmol) in $CH_2Cl_2$ (20 mL). Stirring under

inert atmosphere was continued for 24 h at room temperature with exclusion of light. The solvent was evaporated and flash chromatography of the residue over silica gel (1 x 15 cm), using 0-10% EtOAc in hexane, gave **37.1** (346 mg, 92%) as a white solid: mp 196-197 °C; FTIR (microscope) 3160, 3045, 2960, 2885, 2851 $cm^{-1}$; $^{1}H$ NMR ($CDCl_3$, 300 MHz) δ 9.31 (s, 1 H), 9.85 (br s, 1 H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 78.6 (s), 118.3 (s), 122.1 (s), 129.5 (s), 179.0 (d); exact mass *m*/*z* calcd for $C_5H_2{}^{35}Cl_2INO$ 288.85583, found 288.85590.

**2-[2-Phenyldiazen-1-yl]-1*H*-pyrrole (42.1).**[42]

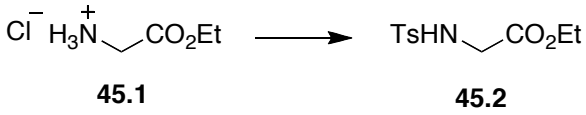



**6.1** **42.1**

A solution of $NaNO_2$ (69 mg, 1.0 mmol) in water (2 mL) was added at a slow dropwise rate (over 1 min) to a stirred and cooled (0 °C) solution of aniline (93 mg, 1.0 mmol) in 6 M hydrochloric acid (2 mL). A solution of **6.1** (67 mg, 1.0 mmol) in AcOH (5 mL)/AcONa (250 mg) buffer was added dropwise at 0 °C. The mixture was stirred for 1 h at 0 °C and poured onto crushed ice. The solid was collected and washed with 9:1 water-EtOH. Recrystallization of the residue from EtOH gave **42.1** (94 mg, 55%): $^{1}H$ NMR ($CDCl_3$, 400 MHz) δ 6.40 (dd, *J* = 3.8, 2.9 Hz, 1 H), 6.94 (t, *J* = 6.4 Hz, 1 H), 7.02 (dd, *J* = 3.8, 1.4 Hz, 1 H), 7.36-7.41 (m, 1 H), 7.44-7.50 (m, 2 H), 7.77-7.81 (m, 2 H), 9.24 (br s, 1 H); $^{13}C$ NMR

($CDCl_3$, 100 MHz) δ 111.6 (d), 115.3 (d), 121.5 (d), 122.0 (d), 129.0 (d), 129.6 (d), 145.9 (s), 152.6 (s).

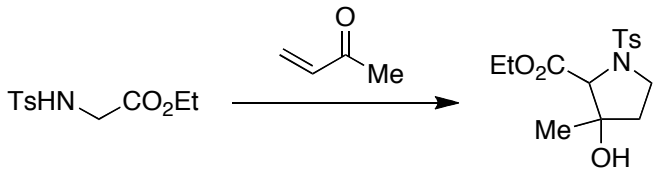
**Ethyl 2-[(4-methylbenzene)sulfonamido]acetate (45.2).**[44]




**45.1** **45.2**

TsCl (4.3 g, 22.5 mmol) was added to a stirred and cooled (0 °C) solution of **45.1** (3 g, 21.3 mmol) and $Et_3N$ (4.5 mL, 30 mmol) in $CH_2Cl_2$ (50 mL). The mixture was stirred for 10 min at 0 °C, the ice bath was removed, and the mixture was stirred for 24 h. Water was added and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 0-30% EtOAc in hexane, gave **45.2** (5.5 g, 100%) as a colorless oil: FTIR (microscope) 3471, 3262, 2995, 2981, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.19 (t, $J$ = 7.1 Hz, 3 H), 2.43 (s, 3 H), 3.77 (d, $J$ = 5.5 Hz, 2 H), 4.09 (q, $J$ = 7.1 Hz, 1 H), 5.03 (t, $J$ = 4.0 Hz, 1 H), 7.31 (d, $J$ = 8.1 Hz, 2 H), 7.75 (d, $J$ = 8.3 Hz, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 14.0 (q), 21.5 (q), 44.2 (t), 61.9 (t), 127.3 (d), 129.7 (d), 136.2 (s), 143.8 (s), 168.7 (s); exact mass $m/z$ calcd for $C_{11}H_{15}NNaO_4S$ 280.06140, found 280.06112.

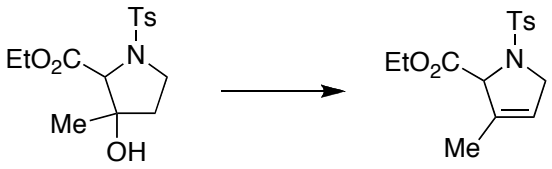
**Ethyl 3-hydroxy-3-methyl-1-[(4-methylbenzene)sulfonyl]pyrrolidine-2-carboxylate (45.3).**[44]




**45.2** **45.3**

Methyl vinyl ketone (0.28 mL, 3.5 mmol) was added to a stirred mixture of **45.2** (650 mg, 2.5 mmol), *t*-BuOK (7 mg), and *t*-BuOH (0.6 mL) in $Et_2O$ (9 mL). The mixture was stirred at room temperature for 3 days and the solvent was evaporated. Water was added to the oily residue and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were washed with dilute hydrochloric acid (0.1 M) and dried ($Na_2SO_4$). Evaporation of the solvent gave a pale yellow crude **45.3** which was used directly in the next step without further purification.

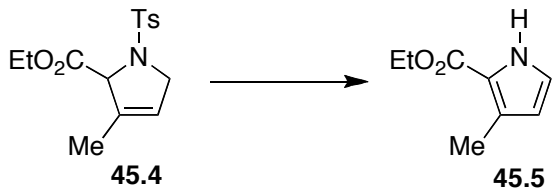
**Ethyl 3-methyl-1-[(4-methylbenzene)sulfonyl]-2,5-dihydro-1*H*-pyrrole-2-carboxylate (45.4).**[44]




**45.3** **45.4**

$POCl_3$ (1.2 ml, 13 mmol) was added at a slow dropwise rate (over 1 min) to a solution of the crude **45.3** in pyridine (10 mL). The mixture was stirred at room temperature for 18 h. The mixture was then poured into a beaker containing crushed ice and the solid formed was collected by filtration. Recrystallization from aqueous EtOH (95%) gave **45.4** (610 mg, 79% over two steps) as a white solid: mp 118-120 °C. The $^1$H NMR ($CDCl_3$, 300 MHz) spectrum indicated the presence of a mixture of compounds, but the crude material proved suitable for conversion to pyrrole **45.5**.

**Ethyl 3-methyl-1*H*-pyrrole-2-carboxylate (45.5).**[44]




A solution of **45.4** (610 mg, 1.97 mmol) in EtOH was added to 1.0 M solution of EtONa in EtOH [made by adding Na (230 mg) to EtOH (10 mL)] and the mixture was stirred for 3 h at room temperature. The precipitate was removed by filtration and the filtrate was evaporated. Water was added and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were dried ($Na_2SO_4$) and evaporated and the residue was recrystallized from petroleum ether to afford **45.5** (183 mg, 61%): mp 62-64 °C; $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.36 (t, $J$ = 7.1 Hz, 3 H), 2.37 (s, 3 H), 4.32 (q, $J$ = 7.1 Hz, 2 H), 6.09 (t, $J$ = 2.7 Hz, 1

H), 6.82 (t, *J* = 2.8 Hz, 1 H), 8.91 (br s, 1 H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 12.7 (q), 14.5 (q), 59.9 (t), 112.6 (d), 119.4 (s), 121.4 (d), 127.9 (s), 161.7 (s).

**Methyl 1-[(4-methylbenzene)sulfonyl]-1*H*-pyrrole-2-carboxylate (47.1).**


**11.1** **47.1**

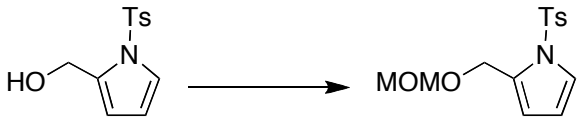
NaH (55 mg, 2.25 mmol) was added to a stirred and cooled (0 °C) solution of **11.1** (280 mg, 2.25 mmol) in $CH_2Cl_2$ (10 mL). The mixture was stirred for 10 min at 0 °C and TsCl (430 mg, 2.25 mmol) was added. The mixture was stirred for 10 min, the ice bath was removed and stirring was continued until all of **11.1** had disappeared (TLC control). The mixture was quenched with water and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 0-20% EtOAc in hexane, gave **47.1** (555 mg, 89%) as a yellow oil: FTIR ($CH_2Cl_2$ cast film) 3152, 2953, 1730, 1597 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) δ 2.42 (s, 3 H), 3.73 (s, 3H), 6.30 (t, *J* = 3.3 Hz, 1 H), 7.05 (dd, *J* = 3.7, 1.9 Hz, 1 H), 7.32 (d, *J* = 8.7 Hz, 2 H), 7.72 (dd, *J* = 3.2, 1.9 Hz, 1 H), 7.87 (d, *J* = 8.6 Hz, 2 H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 21.7 (q), 51.7 (q), 110.3 (d), 123.3 (d), 124.8 (s), 128.2 (d), 129.1 (d), 129.4 (d), 135.8 (s), 144.9 (s), 159.1 (s); exact mass *m*/*z* calcd for $C_{13}H_{13}NNaO_4S$ 302.04575, found 302.04544.

**[1-[(4-Methylbenzene)sulfonyl]-1*H*-pyrrol-2-yl]methanol (47.2).**


**47.1** **47.2**

$LiAlH_4$ (100 mg, 2.6 mmol) was added to a stirred and cooled (0 °C) solution of **47.1** (540 mg, 1.9 mmol) in THF (15 mL). The mixture was stirred for 15 min at 0 °C and, once TLC analysis showed the disappearance of starting material, MeOH was added to destroy excess $LiAlH_4$. Water was added and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 0-40% EtOAc in hexane, gave **47.2** (460 mg, 96%) as a yellow oil: FTIR ($CHCl_3$ cast film) 3561, 3402, 3148, 3066, 2926, 2879 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 2.42 (s, 3 H), 2.67 (br s, 1 H), 4.60 (s, 2 H), 6.22-6.27 (m, 2 H), 7.25-7.34 (m, 3 H), 7.68-7.74 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 21.6 (q), 56.8 (s), 111.8 (d), 115.2 (d), 123.6 (d), 126.6 (d), 130.1 (d), 134.5 (s), 136.1 (s), 145.2 (s); exact mass *m*/*z* calcd for $C_{12}H_{13}NNaO_3S$ 274.05084, found 274.05064.

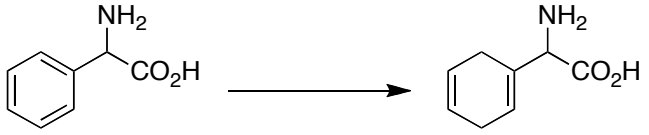
**2-[(Methoxymethoxy)methyl]-1-[(4-methylbenzene)sulfonyl]-1*H*-pyrrole (47.3).**




**47.2** **47.3**

*i*-$Pr_2NEt$ (0.52 mL, 3 mmol) was added to a stirred and cooled (0 °C) solution of **47.2** (455 mg, 1.8 mmol) in $CH_2Cl_2$ (15 mL). The mixture was stirred for 5 min and MOMCl (160 mg, 2 mmol) was added dropwise. The ice bath was left in place but not recharged and stirring was continued overnight. The mixture was quenched with saturated aqueous $NH_4Cl$ and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 0-20% EtOAc in hexane, gave **47.3** (475 mg, 89%) as a yellow oil: FTIR (microscope) 3146, 3066, 2933, 2885, 2824, 2781 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 2.40 (s, 3 H), 3.34 (s, 3 H), 4.50 (s, 2 H), 4.69 (s, 2 H), 6.23 (t, *J* = 3.4 Hz, 1 H), 6.27-6.30 (m, 1 H), 7.24-7.30 (m, 2 H), 7.31 (dd, *J* = 3.4, 1.8 Hz, 1 H), 7.71-7.77 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 21.6 (q), 55.4 (q), 60.6 (t), 95.0 (t), 111.3 (d), 116.3 (d), 123.9 (d), 127.0 (d), 129.7 (d), 130.9 (s), 136.5 (s), 144.7 (s);); exact mass *m/z* calcd for $C_{14}H_{17}NNaO_4S$ 318.07705, found 318.07706.

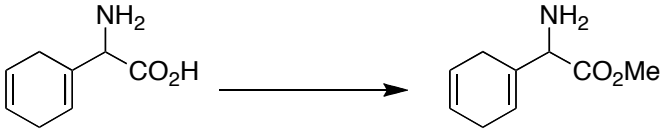
**2-Amino-2-(cyclohexa-1,4-dien-1-yl)acetic acid (49.2).**[46]




**49.1** **49.2**

*t*-BuOH (2.6 mL, 27 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **49.1** (1.0 g, 6.6 mmol) in $NH_3$ (~100 mL). The ice bath was removed and replaced from time to time to prevent the mixture from solidifying. Small portions of Li (170 mg, 24 mmol) were added over 1 h until a persistent blue color appeared. The mixture was stirred for another 1 h and solid $NH_4Cl$ was added. The mixture was allowed to reach room temperature during which the $NH_3$ evaporated. The residue was taken up in a 1:1 mixture of MeOH and water (4 mL) and added to 1:1 $CHCl_3$-acetone (10 mL). The precipitated impure solid (933 mg, 92%) was filtered off and used directly in the next step: FTIR (neat) 3027, 2946, 2883, 2822, 2613, 2126, 1590, 1512 $cm^{-1}$; $^1H$ NMR ($D_2O$, 300 MHz) δ 2.40-2.80 (m, 4 H), 3.79 (s, 1 H), 5.75-5.84 (m, 3 H); $^{13}C$ NMR ($D_2O$, 125 MHz) δ 25.0 (t), 26.4 (t), 62.4 (d), 122.0 (d), 124.7 (d), 124.7 (d), 134.9 (s), 181.2 (s); exact mass *m*/*z* calcd for $C_8H_{10}NO_2$ 152.0717, found 152.0717.

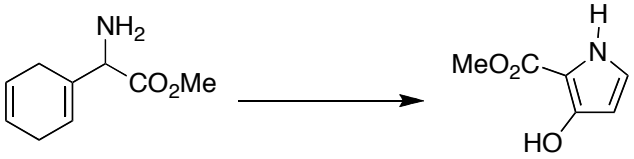
**Methyl 2-amino-2-(cyclohexa-1,4-dien-1-yl)acetate (49.3).**[46]




**49.2** **49.3**

$SOCl_2$ (1.6 mL, 13 mmol) was added to a stirred suspension of **49.2** (1.0 g, 6.54 mmol) in MeOH (40 mL) at room temperature. The mixture was refluxed for 4 h, cooled to room temperature, and the MeOH was evaporated. Saturated aqueous $NaHCO_3$ was added to the residue and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried ($Na_2SO_4$) and evaporated to give **49.3** (1.0 g, 92%) as a colorless oil: FTIR (neat) 3301, 3030, 2954, 2926, 2858, 2823, 1741, 1675 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.68 (br s, 2 H), 2.43-2.86 (m, 4 H), 3.72 (s, 3 H), 3.98 (s, 1 H), 5.60-5.78 (m, 3 H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 25.5 (t), 26.7 (t), 52.2 (q), 60.3 (d), 122.5 (d), 123.7 (d), 123.7 (d), 133.8 (s), 174.2 (s); exact mass *m*/*z* calcd for $C_9H_{14}Cl_2NO_2$ 168.1019, found 168.1016.

**Methyl 3-hydroxy-1*H*-pyrrole-2-carboxylate (49.4).**[46]




**49.3** **49.4**

Ozonized oxygen was bubbled for 2 h through a stirred and cooled (-78 °C) solution of **49.3** in $CH_2Cl_2$ containing solid $NaHCO_3$ (100 mg) The flask was flushed with $O_2$ for 30 min and $Me_2S$ (1 mL) was added. The reaction mixture was kept at -78 °C for 2 h and stirred overnight at room temperature. The solid $NaHCO_3$ was filtered off and the $CH_2Cl_2$ was evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using first 100% hexane and then 20% EtOAc in hexane, gave **49.4** (80 mg, 20%) as a colorless oil: $^1$H NMR ($CDCl_3$, 400 MHz) δ 3.88 (s, 1 H), 3.97 (s, 1 H), 5.88 (t, *J* = 2.9 Hz, 1 H), 6.72 (s, 1 H), 8.09 (br s, 1H).

**Methyl 3-[[(trifluoromethane)sulfonyl]oxy]-1*H*-pyrrole-2-carboxylate (49.5).**


**49.4** **49.5**

$Tf_2O$ (0.06 mL, 0.35 mmol) was added to a stirred and cooled (-78 °C) solution of **49.4** (33 mg, 0.23 mmol) and 2,6-lutidine (0.04 mL, 0.35 mmol) in $CH_2Cl_2$ (4 mL). The mixture was stirred at -78 °C for 1 h, warmed to room temperature, and quenched with dilute hydrochloric acid (0.1 M). The aqueous phase was extracted with EtOAc and the combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel

(0.5 x 20 cm), using first 100% hexane and then 20% EtOAc in hexane, gave **49.5** (52 mg, 83%) as a pale yellow oil: $^{1}$H NMR ($CDCl_3$, 400 MHz) δ 3.92 (s, 3 H), 6.23 (t, *J* = 3.0 Hz, 1 H), 6.87 (t, *J* = 3.1 Hz, 1 H), 8.99 (br s, 1 H); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 52.4, 104.4, 120.9, 138.1. 160.0.

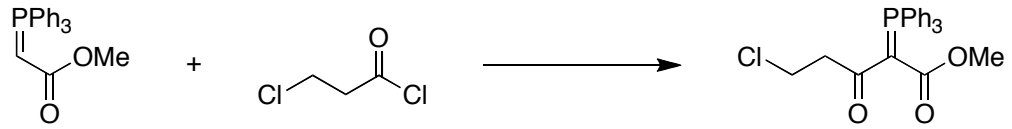
**Methyl 1-methyl-3-[[(trifluoromethane)sulfonyl]oxy]-1*H*-pyrrole-2-carbox-ylate (49.7).**


**49.5** **49.7**

NaH (24 mg, 1.0 mmol) was added in one portion to a stirred and cooled (0 °C) solution of **49.5** (200 mg, 0.7 mmol) in DMF (5 mL). Stirring was continued for 5 min and MeI was added. The cold bath was left in place but not recharged and stirring was continued overnight. The mixture was quenched with water and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 20 cm), using first 100% hexane and then 10% EtOAc in hexane, gave **49.7** (168 mg, 84%) as a pale yellow oil: FTIR (neat) 3144, 3004, 2958, 2850, 1716 cm$^{-1}$; $^{1}$H NMR ($CDCl_3$, 400 MHz) δ 3.88 (s, 3 H), 3.92 (s, 3 H), 6.02 (d, *J* = 3.1 Hz, 1 H), 6.69 (d, *J* = 3.1 Hz, 1 H); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 38.0 (q), 51.4 (q), 101.7 (d), 114.0 (s), 118.8 (q, *J* = 320,

$CF_3$), 126.2 (d), 139.0 (s), 159.9 (s); exact mass *m*/*z* calcd for $C_8H_8F_3NNaO_5S$ 309.9967, found 309.9967.

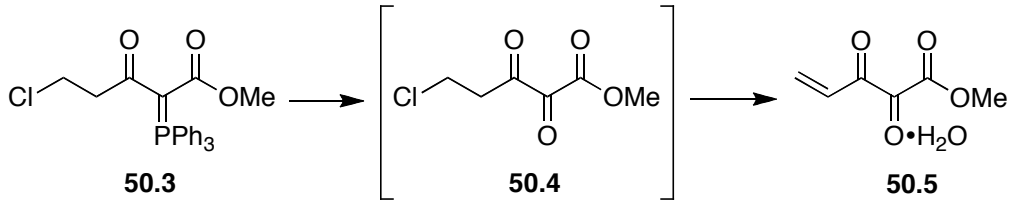
**Methyl 5-chloro-3-oxo-2-(triphenylphosphoranylidene)pentanoate (50.3).**[47]




**50.1** **50.2** **50.3**

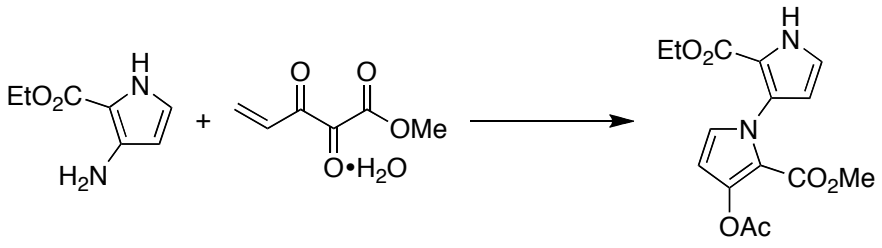
Bis(trimethylsilyl)acetamide (0.75 mL, 3 mmol) and **50.2** (3-chloropropionyl chloride) (0.2 mL, 2 mmol) were added to a stirred and cooled (0 °C) solution of **50.1** (methyl triphenylphosphoranylidene acetate) (670 mg, 2 mmol) in PhH (10 mL). The mixture was stirred at 0 °C for 10 min and at room temperature for 30 min. The mixture was quenched with water and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using first 100% hexane and then 40% EtOAc in hexane, gave **50.3** (687 mg, 81%) as a pale yellow oil: $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.17 (s, 3 H), 3.40 (t, *J* = 6.7 Hz, 2 H), 3.82 (t, *J* = 6.9 Hz, 2 H), 7.41-7.57 (m, 9 H), 7.61-7.72 (m, 6 H); exact mass *m*/*z* calcd for $C_{24}H_{23}ClO_3P$ 425.1068, found 425.1068.

**Methyl 2,3-dioxopent-4-enoate monohydrate (50.5).**[47]




Ozonized oxygen was bubbled through a cooled (-78 °C) solution of **50.3** (860 mg, 2 mmol) in $CH_2Cl_2$ (10 mL) until a permanent blue color persisted (this took 15-20 min). The solvent was evaporated and the residue was dissolved in THF (10 mL) and saturated aqueous $NaHCO_3$ [prepared from solid $NaHCO_3$ and deionized water (10 mL)] was added at 0 °C. After 15 min the ice bath was removed and the mixture was stirred for 4 h. The mixture was diluted with water and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using first 100% hexane and then 40% EtOAc in hexane, gave **50.5** (234 mg, 73%) as a pale yellow oil which was unstable at room temperature and was used immediately in the next step: $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.85 (s, 3 H), 4.97 (s, 2 H), 6.03 (dd, $J$ = 7.5, 4.3 Hz, 1 H), 6.59-6.62 (m, 2 H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 54.0 (q), 128.9 (d), 133.9 (t), 169.7 (s), 182.5 (s), 191.1 (s).

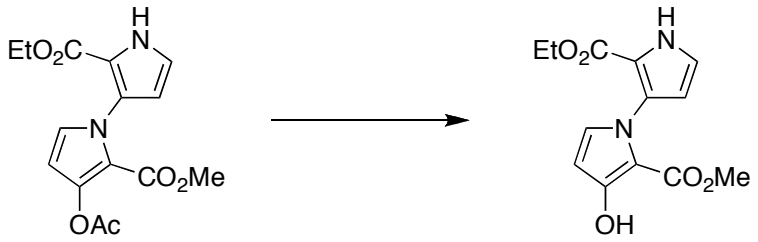
**Methyl 3-(acetyloxy)-1-[2-(ethoxycarbonyl)-1*H*-pyrrol-3-yl]-1*H*-pyrrole-2-carboxylate (50.7).**[48]




**20.7** **50.5** **50.7**

**50.5** (64 mg, 0.4 mmol) in $CH_2Cl_2$ (1 mL) was added at room temperature to a stirred solution of **20.7** (53 mg, 0.34 mmol) in $CH_2Cl_2$ (5 mL). The mixture was stirred at room temperature for 15 min and silica gel (100 mg) was added. The mixture was stirred for 3 h, filtered through a pad of Celite (3 x 5 cm) and evaporated. The residue was dissolved in $CH_2Cl_2$ (5 mL) and DMAP (20 mg, 0.16 mmol), pyridine (0.3 mL, 4 mmol), and $Ac_2O$ (0.1 mL, 1.0 mmol) were added. This mixture was stirred overnight (12 h) and quenched with 0.5 M hydrochloric acid. The aqueous phase was extracted with $CH_2Cl_2$ and the combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using first 100% hexane and then 40% EtOAc in hexane, gave **50.7** (64 mg, 59% over two steps) as a pale yellow oil: $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.15 (t, $J$ = 7.1 Hz, 3 H), 2.31 (s, 3 H), 3.67 (s, 3 H), 4.15 (q, $J$ = 7.1 Hz, 2 H), 6.14 (d, $J$ = 3.1 Hz, 1 H), 6.33 (t, $J$ = 2.8 Hz, 1 H), 6.79 (d, $J$ = 3.1 Hz, 1 H), 6.92 (t, $J$ = 3.0 Hz, 1 H), 9.09 (br s, 1 H); exact mass $m/z$ calcd for $C_{15}H_{16}N_2NaO_6$ 343.0901, found 343.0903.

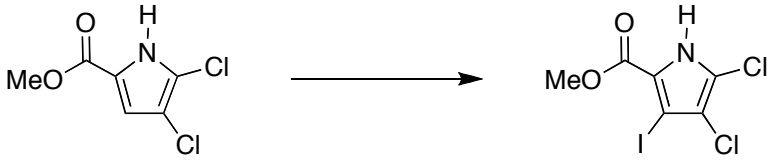
**Methyl 1-[2-(ethoxycarbonyl)-1*H*-pyrrol-3-yl]-3-hydroxy-1*H*-pyrrole-2-carboxylate (50.6).**




**50.7** **50.6**

NaH (24 mg, 1.0 mmol) was added to a stirred and cooled (0 °C) solution of **50.7** (45 mg, 0.14 mmol) in MeOH (5 mL). The mixture was stirred at 0 °C for 5 min and for 2 h at 50 °C. The mixture was cooled to room temperature and most of the MeOH was evaporated. Water was added to the residue and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using first 100% hexane and then 40% EtOAc in hexane, gave **50.6** (34 mg, 87%) as a pale yellow oil: FTIR ($CHCl_3$ cast film) 3309, 3138, 2955, 2925, 2854, 1699, 1649 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.16 (t, $J$ = 7.1 Hz, 3 H), 3.67 (s, 3 H), 4.17 (q, $J$ = 7.1 Hz, 2 H), 5.94 (d, $J$ = 3.0 Hz, 1 H), 6.27 (t, $J$ = 2.9 Hz, 1 H), 6.68 (d, $J$ = 3.1 Hz, 1 H), 6.90 (t, $J$ = 3.1 Hz, 1 H), 8.30 (br s, 1 H ), 9.03 (br s, 1 H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 14.5 (q), 50.8 (q), 60.5 (t), 97.8 (d), 107.5 (s), 110.3 (d), 117.6 (s), 120.2 (d), 129.4 (d), 129.6 (s), 160.1 (s); exact mass $m/z$ calcd for $C_{13}H_{14}N_2NaO_5$ 301.07950, found 301.07920.

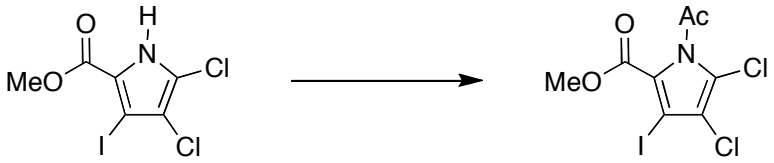
**Methyl 4,5-dichloro-3-iodo-1*H*-pyrrole-2-carboxylate (56.1).**[18]




**33.2** **56.1**

$I_2$ (38 mg, 0.15 mmol) and $AgOCOCF_3$ (34 mg, 0.15 mmol) were added to a stirred solution of **33.2** (20 mg, 0.10 mmol) in $CH_2Cl_2$ (20 mL). The mixture was stirred under an inert atmosphere for 20 h with the exclusion of light. Water was added and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 20 cm), using first 100% hexane and then 10% EtOAc in hexane, gave **56.1** (30.4 mg, 95%) as a white solid: mp 186-190 °C; $^1$H NMR ($CDCl_3$, 400 MHz) δ 3.92 (s, 3 H), 9.31 (br s, 1H); exact mass *m*/*z* calcd for $C_6H_3Cl_2INO_2$ 317.8591, found 317.8591.

**Methyl 1-acetyl-4,5-dichloro-3-iodo-1*H*-pyrrole-2-carboxylate (56.2).**

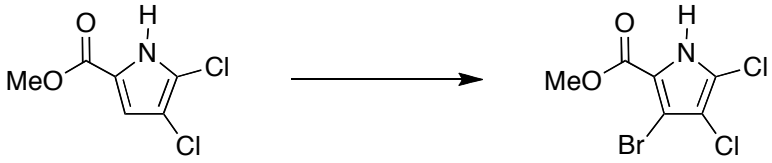



**56.1** **56.2**

NaH (2 mg, 0.07 mmol) was added in one portion to a stirred and cooled (0 °C) solution of **56.1** (11 mg, 0.035 mmol) in $CH_2Cl_2$ (5 mL). Stirring was

continued for 10 min and $Ac_2O$ (7 μL, 0.07 mmol) was added. The ice bath was removed and stirring was continued for 3 h. The mixture was quenched with saturated aqueous $NaHCO_3$ and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 x 6 cm), using first 100% hexane and then 10% EtOAc in hexane, gave **56.2** (11.2 mg, 89%) as a as a white solid: mp 112-115 °C; FTIR (neat) 3381, 3027, 3001, 2953, 2842, 1762, 1698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 2.63 (s, 3 H), 3.91 (s, 3 H); $^{13}C$ NMR ($CDCl_3$, 175 MHz) δ 27.9 (q), 52.4 (q), 76.3 (s), 117.0 (s), 119.6 (s), 124.0 (s), 159.3 (s), 169.6 (s); exact mass *m*/*z* calcd for $C_8H_6Cl_2INO_3$ 360.87695, found 360.87694.

**Methyl 3-bromo-4,5-dichloro-1*H*-pyrrole-2-carboxylate (57.1).**[19]

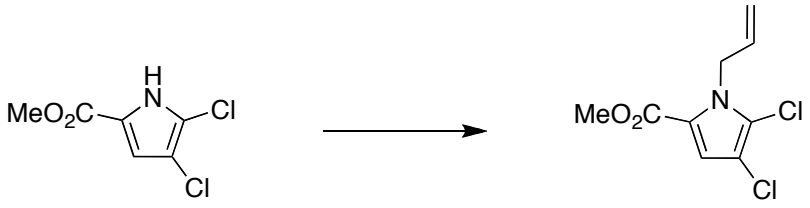



**33.2** **57.1**

NBS (20 mg, 0.11 mmol) was added to a stirred solution of **33.2** (22 mg, 0.11 mmol) in MeCN (3 mL) at room temperature. The mixture was stirred for 24 h, and the solvent was then evaporated. The residue was partitioned between water and $Et_2O$ and the organic extracts was separated. The aqueous phase was extracted with $Et_2O$ and the combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 20 cm),

using first 100% hexane and then 20% EtOAc in hexane, gave **57.1** (25 mg, 84%) as a white solid: mp 196-200 °C; FTIR (neat) 3306, 3232, 3077, 3032, 3009, 2985, 2955, 1682 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) δ 3.92 (s, 3 H), 9.51 (br s, 1 H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 52.3 (q), 104.0 (s), 114.1 (s), 117.8 (s), 118.9 (s), 159.5 (s); exact mass *m*/*z* calcd for $C_6H_3BrCl_2NO_2$ 269.873, found 269.8731.

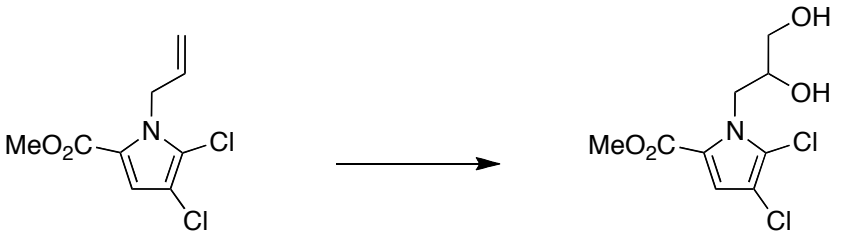
**Methyl 4,5-dichloro-1-(prop-2-en-1-yl)-1*H*-pyrrole-2-carboxylate (60.1).**[50]




Allyl bromide (0.1 mL, 1.2 mmol) was added to a stirred solution of **33.2** (224 mg, 1.16 mmol), $K_2CO_3$ (635 mg, 4.65 mmol), and $Bu_4NI$ (50 mg, 0.14 mmol) in MeCN (6 mL). The mixture was stirred and refluxed for 24 h and quenched with water. The aqueous phase was extracted with $CH_2Cl_2$ and the combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using first 100% hexane and then 20% EtOAc in hexane, gave **60.1** (265 mg, 98%) as a colorless oil: FTIR ($CHCl_3$ cast film) 3136, 3088, 2988, 2952, 2853, 1715 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 3.81 (s, 3 H), 4.91-5.20 (m, 5 H), 5.85-5.97 (m, 1 H), 6.95 (s, 1 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 48.3 (t), 51.5 (q), 110.2 (s), 116.7 (d),

117.0 (s), 120.4 (s), 121.7 (t), 132.7 (d), 160.1 (s); exact mass *m*/*z* calcd for $C_9H_9{}^{35}Cl^{37}ClNO_2$ 234.99808, found 234.99854.

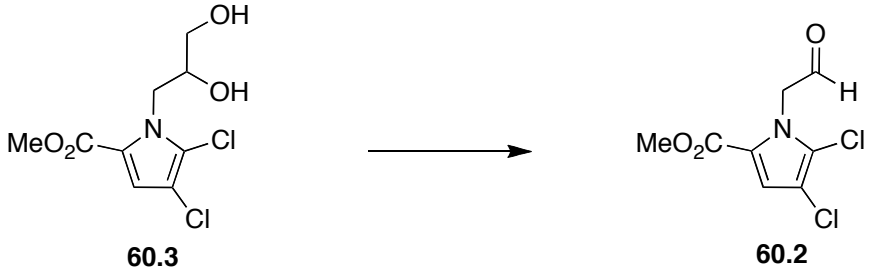
**Methyl 4,5-dichloro-1-(2,3-dihydroxypropyl)-1*H*-pyrrole-2-carboxylate (60.3).**[51]




**60.1** **60.3**

$OsO_4$ (0.63 mL, 0.1 mmol) was added to a vigorously stirred solution of **60.1** (111 mg, 0.48 mmol) and NMO•$H_2O$ (135 mg, 1.0 mmol) in 4:1 acetone-water (10 mL) at room temperature. The mixture was stirred for 6 h and quenched with 1.0 M hydrochloric acid. The aqueous phase was extracted with EtOAc and the combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 25 cm), using first 100% hexane and then 50% EtOAc in hexane, gave **60.3** (128 mg, 100%) as a pale yellow oil: FTIR (neat) 3435, 3247, 3011, 2971, 2957, 2937, 1703 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 2.55 (br s, 1 H), 3.11 (br s, 1 H), 3.54-3.62 (m, 1 H), 3.68-3.75 (m, 1 H), 3.94-4.04 (m, 1 H), 4.40-4.57 (m, 2 H), 6.96 (s, 1 H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 48.4 (t), 52.2 (q), 63.5 (t), 71.3 (d), 110.8 (s), 117.4 (d), 120.7 (s), 122.7 (s), 161.6 (s); exact mass *m*/*z* calcd for $C_9H_{11}Cl_2NNaO_4$ 289.99570, found 289.99570.

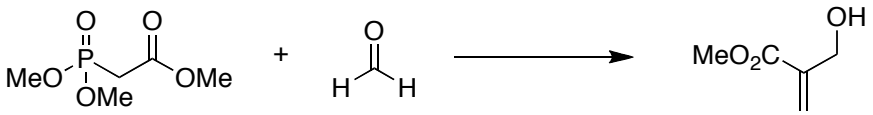
**Methyl 4,5-dichloro-1-(2-oxoethyl)-1*H*-pyrrole-2-carboxylate (60.2).**[52]




**60.3** **60.2**

$NaIO_4$ (214 mg, 1.0 mmol) was added to a stirred solution of **60.3** (114 mg, 0.43 mmol) in 2:1 THF-water (9.0 mL) at room temperature. The mixture was stirred for 6 h and quenched with water. The aqueous phase was extracted with EtOAc and the combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 20 cm), using first 100% hexane and then 30% EtOAc in hexane, gave **60.2** (99 mg, 98%) as a pale yellow oil: FTIR (neat) 3457, 3136, 2954, 2847, 2722, 1710 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) δ 3.80 (s, 3 H), 5.25 (s, 2 H), 6.99 (s, 1 H), 9.64 (s, 1 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 51.8 (q), 55.2 (t), 111.1 (s), 117.0 (d), 120.9 (s), 122.0 (s), 160.4 (s), 193.8 (d); exact mass *m/z* calcd for $C_8H_8Cl_2NO_3$ 235.98760, found 235.98770.

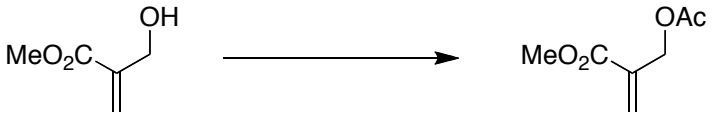
**Methyl 2-(hydroxymethyl)prop-2-enoate (63.3).**[50]




**63.1** **63.2** **63.3**

A three necked round bottom flask fitted with an addition funnel, a reflux condenser, and a thermometer was charged with paraformaldehyde (**63.2**) (1.84 g, 61.3 mmol), $H_3PO_4$ (1 N, 0.15 mL) and water (4.2 mL). The mixture was stirred at 90 °C for 1.5 h, cooled to room temperature, and trimethyl phosphonoacetate (**63.1**) (2.8 g, 15.3 mmol) was added. A solution of $K_2CO_3$ (2.33 g, 16.9 mmol) in water (2.3 mL) was added slowly while maintaining the temperature at 35-40 °C. The reaction mixture was stirred at 40 °C for another 5 min and cooled rapidly to room temperature, using an ice bath while adding $Et_2O$ (7.7 mL) and brine (5.7 mL). The organic layer was separated and the aqueous layer was extracted with $Et_2O$. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel, using first 100% hexane and then 40% EtOAc in hexane, gave **63.3** (1.36 g, 77%) as a colorless oil: $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 3 H), 4.30 (dd, $J$ = 1.5, 0.9 Hz, 2 H), 4.81 (s, 1 H), 5.83 (q, $J$ = 1.4 Hz, 1 H), 6.23 (q, $J$ = 0.9 Hz, 1 H).

**Methyl 2-[(acetyloxy)methyl]prop-2-enoate (63.4).**[50]

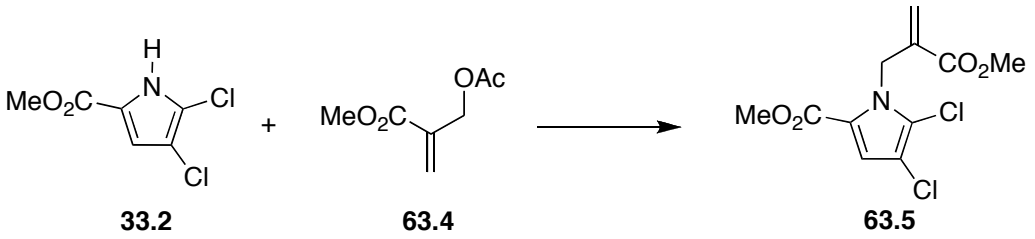



**63.3** **63.4**

$Ac_2O$ (0.24 mL, 2.5 mmol) was added to a stirred solution of **63.3**(147 mg, 1.3 mmol) and pyridine (0.2 mL, 2.5 mmol) in $CH_2Cl_2$ (4 mL) at room temperature. The reaction mixture was stirred overnight and quenched with

water. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic extracts were dried ($Na_2SO_4$) and evaporated to give **63.4** (113 mg, 56%) as a pale yellow oil: $^1$H NMR ($CDCl_3$, 300 MHz) δ 2.07 (s, 3 H), 3.76 (s, 3 H), 4.78 (dd, *J* = 1.5, 0.9 Hz, 2 H), 5.83 (q, *J* = 1.5 Hz, 1 H), 6.33 (q, *J* = 0.9 Hz, 1 H).

**Methyl 4,5-dichloro-1-(3-methoxy-2-methylidene-3-oxopropyl)-1*H*-pyrrole-2-carboxylate (63.5).**[50]

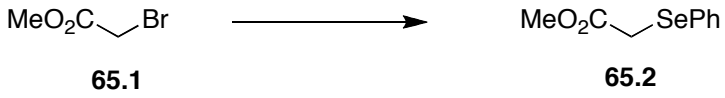



**33.2** **63.4** **63.5**

A solution of **63.4** (10 mg, 0.06 mmol) in MeCN (1 mL) was added to a stirred mixture of **33.2** (10 mg, 0.05 mmol) and $K_2CO_3$ (28 mg, 0.2 mmol) in MeCN (4 mL). The mixture was refluxed for 24 h, cooled to room temperature, and diluted with water. The aqueous phase was extracted with EtOAc and the combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 20 cm), using first 100% hexane and then 20% EtOAc in hexane, gave **63.5** (10 mg, 66%) as a colorless oil: FTIR (neat film) 3113, 2954, 2926, 2855, 1713 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) δ 3.80 (s, 3 H), 3.83 (s, 3 H), 4.85 (t, *J* = 2.0 Hz, 1 H), 5.30 (t, *J* = 2.0 Hz, 1 H), 6.23 (t, *J* = 2.0 Hz, 1 H), 6.98 (s, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 46.5 (t),

51.6 (q), 52.2 (q), 110.6 (s), 117.0 (d), 120.7 (s), 121.9 (s), 124.3 (s), 136.1 (t), 159.8 (s), 165.5 (s); exact mass *m*/*z* calcd for $C_{11}H_{11}Cl_2NNaO_4$ 313.99570, found 313.99580.

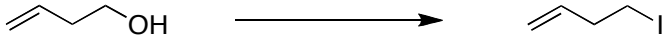
**Methyl 2-(phenylselanyl)acetate (65.2).**[54]




**65.1** **65.2**

$NaBH_4$ (150 mg, 4.0 mmol) was added portionwise to a stirred and cooled (0 °C) solution of PhSeSePh (1.0 g, 3.2 mmol) in 4:1 THF:MeOH (20 mL). Once the solution had turned colorless, **65.1** (0.6 mL, 0.64 mmol) was added and the mixture was stirred at 0 °C for 30 min and at room temperature overnight. The mixture was diluted with EtOAc and saturate $NaHCO_3$ was added. The organic phase was separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.0 x 20 cm), using first 100% hexane and then 20% EtOAc in hexane, gave **65.2** (1.4 g, 96%) as a pale yellow oil: $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.53 (s, 1 H), 3.69 (s, 3 H), 7.28-7.32 (m, 3 H), 7.56-7.62 (m, 2 H); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 27.4 (q), 52.4 (t), 128.0 (d), 129.2 (s), 129.3 (d), 133.5 (d), 171.4 (s).

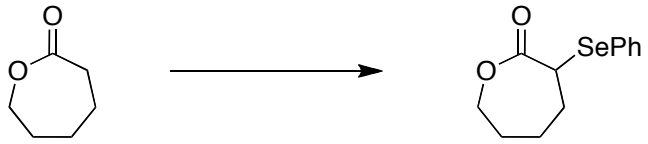
**4-Iodobut-1-ene (65.5).**[54]




**65.5**

$I_2$ (5.33 g, 21 mmol) was added in several portions to a stirred and cooled (0 °C) solution of $Ph_3P$ (5.51 g, 21 mmol) and imidazole (1.43 g, 21 mmol) in $CH_2Cl_2$ (50 mL). The mixture was stirred at 0 °C for 15 min and 3-buten-1-ol (1.44g, 20 mmol) was added neat at a slow dropwise rate (ca. 1 min). The ice bath was removed and the mixture was stirred at room temperature for 12 h. Most of the solvent was evaporated and pentane was added. The mixture was filtered through a pad of Celite (3 cm) and the solvent was evaporated. The residue was purified by distillation to give **65.5** (1.7 g, 47%) as a colorless oil: $^1$H NMR ($CDCl_3$, 400 MHz) δ 2.63 (qt, *J* = 7.1, 1.3 Hz, 2 H), 3.19 (t, *J* = 7.2 Hz, 2 H), 5.09-5.16 (m, 2 H), 5.71-5.82 (m, 1 H).

**3-(Phenylselanyl)oxepan-2-one (66.3).**[56]

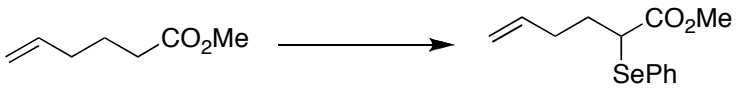



**66.2** **66.3**

BuLi (0.8 mL, 2.0 mmol) was added to a stirred and cooled (-78 °C) solution of *i*-$Pr_2NH$ (0.3 mL, 2.2 mmol) in THF (5 mL). The mixture was stirred

at -78 °C for 30 min and **66.2** (0.44 mL, 4.0 mmol) in THF (1 mL) was added. The mixture was stirred at -78 °C for 30 min and PhSeBr (236 mg, 1.0 mmol) in THF (1 mL) was added rapidly. After 1 min, saturated aqueous $NH_4Cl$ was added and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 20 cm), using first 100% hexane and then 20% EtOAc in hexane, gave **66.3** (141 mg, 52%) as a pale yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) δ 1.64-1.76 (m, 1 H), 1.80-1.95 (m, 3 H), 2.01-2.18 (m, 2 H), 4.23 (dd, *J* = 8.6, 2.7, 1 H), 4.29 (dd, *J* = 7.3, 1.3, 1 H), 4.55-4.62 (m, 1 H), 7.28-7.36 (m, 3 H), 7.58-7.63 (m, 2 H); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 27.5 (t), 29.2 (t), 30.5 (t), 46.5 (d), 69.4 (t), 128.4 (d), 128.7 (q), 129.4 (d), 134.7 (d), 173.6 (s).

**Methyl 2-(phenylselanyl)hex-5-enoate (65.3).**[56]

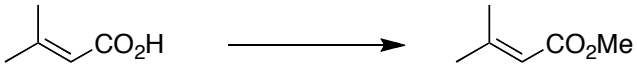



**66.1** **65.3**

BuLi (0.8 mL, 2.0 mmol) was added to a stirred and cooled (-78 °C) solution *i*-$Pr_2NH$ (0.3 mL, 2.2 mmol) in THF (5 mL). The mixture was stirred at -78 °C for 30 min and **66.1** (0.44 mL, 3.0 mmol) in THF (1 mL) was added. The mixture was stirred at -78 °C for 30 min and PhSeCl (192 mg, 1.0 mmol) in THF (1 mL) was added rapidly. Saturated aqueous $NH_4Cl$ was added and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried

($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 20 cm), using first 100% hexane and then 20% EtOAc in hexane, gave **65.3** (153 mg, 54%) as a pale yellow oil: FTIR (neat) 3074, 3060, 2976, 2949, 2928, 2853, 1731 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 0.89 (sextet, *J* = 7.1 Hz 1 H), 1.00-1.11 (m, 1 H), 1.20 (q, *J* = 6.8 Hz, 2 H), 2.66 (dd, *J* = 8.5, 6.9 Hz, 1 H), 2.67 (s, 3 H), 3.99-4.07 (m, 2 H), 4.71-483 (m, 1 H), 6.30-6.40 (m, 3 H), 6.60-6.65 (m, 2 H); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 30.9 (t), 32.0 (t), 42.7 (q), 52.0 (d), 115.9 (d), 127.7 (s), 128.5 (d), 129.0 (d), 135.7 (d), 136.8 (t), 173.3 (s); exact mass *m*/*z* calcd for $C_{13}H_{16}O_2{}^{80}Se$ 284.03156, found 284.03207.

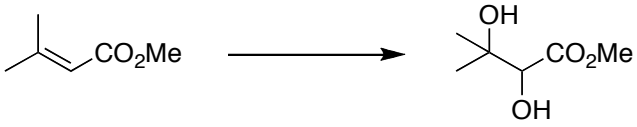
**Methyl 3-methylbut-2-enoate (67.5).**[44]




**67.6** **67.5**

$H_2SO_4$ (0.1 mL) was added to **67.6** (3.0 g, 30 mmol) in MeOH (10 mL) and the mixture was refluxed for 20 h. Water was added and the aqueous phase was extracted with $Et_2O$. The combined organic extracts were dried ($Na_2SO_4$) and evaporated to give **67.5** (2.65 g, 77%) as a pale yellow oil which did not require further purification: $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.90 (d, *J* = 1.4 Hz, 3 H), 2.17 (d, *J* = 1.4 Hz, 3 H), 3.68 (s, 3 H), 5.68 (septet, *J* = 1.4 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 20.2 (q), 27.3 (q), 50.7 (q), 115.7 (d), 156.7 (s), 167.1 (s).

**Methyl 2,3-dihydroxy-3-methylbutanoate (67.4).**[51]




**67.5** **67.4**

$OsO_4$ in $H_2O$ (5.0 mL, 4% w/v, 0.8 mmol) and $NMO.H_2O$ (4.05 g, 30 mmol) was added to a stirred solution of **67.5** (2.65 g, 23 mmol) in 4:1 acetone-water (50 mL) at room temperature. The mixture was stirred for 6 h and quenched with 1.0 N hydrochloric acid. The aqueous phase was extracted with EtOAc and the aqueous phase was checked by TLC for completion of extraction. The combined organic extracts were dried ($Na_2SO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.0 x 20 cm), using 50% EtOAc in hexane, gave **67.4** (2.31 g, 68%) as a light brown oil: $^1$H NMR ($CDCl_3$, 500 MHz) δ 1.22 (s, 3 H), 1.29 (s, 3 H), 2.56 (s, 1 H), 3.15 (d, $J$ = 6.7 Hz, 1 H), 3.84 (s, 3 H), 3.98 (d, $J$ = 6.7 Hz, 1 H); $^{13}$C NMR ($CDCl_3$, 125 MHz) δ 25.0 (q), 25.6 (q), 52.6 (q), 72.0 (s), 77.2 (d), 173.6 (s).

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