University of Alberta

Formal radical cyclization onto aromatic rings, cascade intramolecular conjugate displacement and synthetic studies on marinopyrroles

by

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DEDICATED TO

MY WIFE RUILING AND MY FAMILY

ABSTRACT

The first chapter of this thesis describes the development of a general method for indirectly effecting radical carbocyclization of an alkyl chain onto an aromatic ring. This process involves a Birch reductive alkylation of aromatic *tert*-butyl esters, chromium(VI)-mediated oxidation and radical cyclization. The cyclized products are easily oxidized to the corresponding cross-conjugated ketones via Saegusa oxidation. Addition of organolithium or Grignard reagents and treatment with bismuth trichloride affords aromatized benzo-fused carbocycles.

The second chapter describes a method for converting Morita-Baylis-Hillman acetates into unusual seven-membered heterocycles containing both nitrogen and sulfur. *N*-Deprotection of the MBH acetates and trapping with CS_2 affords the desired 2-thioxo-1,3-thiazepines. In a modification of this process, when the original nitrogen is substituted with a carbon chain, an azepine derivative is generated. The ring closures occur by intramolecular conjugate displacement.

The last chapter of this thesis describes synthetic studies towards the marine antibiotic alkaloid, marinopyrrole B. Due to the difficulty of bromination of the pyrrole system, it is known that marinopyrrole B cannot be directly made from marinopyrrole A. Our plan was based on brominating the bottom pyrrole at an early stage and constructing the top pyrrole ring later. Previous studies

towards the core structure of marinopyrrole A suggested that the Paal-Knorr reaction is an ideal method for construction of the top ring. Preparation of the precursor for the Paal-Knorr reaction was planned via an intermolecular conjugate displacement between a densely halogenated pyrrole and a Morita-Baylis-Hillman carbonate. However, this approach was unsuccessful and further studies are in hand.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetone
AIBN	2,2'-azobisisobutyronitrile
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
n-Bu	butyl
t-Bu	*tert*-butyl
Cbz	benzyloxycarbonyl
MCPBA	*meta*-chloroperoxybenzoic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
$(DHQD)_2PHAL$	hydroquinidine 1,4-phthalazinediyl diether
DIBAL-H	diisobutylaluminum hydride
DIAD	diisopropyl azodicarboxylate
DMAP	4-(dimethylamino)pyridine
DMSO	dimethyl sulfoxide
DMF	*N*,*N*-dimethylformamide
dppp	1,3-bis(diphenylphosphino)propane
Et	ethyl
h	hour
Hünig's base	diisopropylethylamine

ICD	intramolecular conjugate displacement
ImH	imidazole
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
Lys	lysine
Me	methyl
min	minute(s)
Ms	methanesulfonyl
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NCE	new chemical entity
NIS	*N*-iodosuccinimide
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
Pg	protecting group
Ph	phenyl
Pyr	pyridine
i-Pr	isopropyl
rt	room temperature
TLC	thin layer chromatography
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
TsOH	*p*-toluenesulfonic acid

Chapter 1

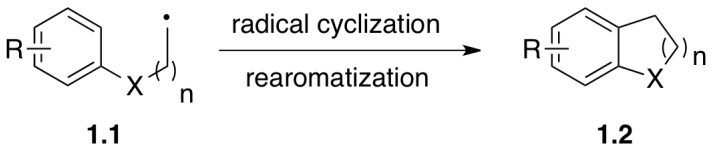
Formal radical cyclization onto aromatic rings:

a general route to carbocycles

1. INTRODUCTION

1.1 *General*

Cyclization of sp^2 or sp^3 carbon radicals onto double and triple bonds has been known for a long time.[1] However, similar processes onto aromatic rings are fairly difficult: a large mount of initiator is required and the mechanism is not fully understood.[2] Several examples of this type of cyclization have been reported for sp^2 hybridized radicals closing onto aromatic rings[3,4,5] but reports for cyclization of sp^3 radicals are rare, as mentioned later.



1.1 **1.2**

Scheme 1

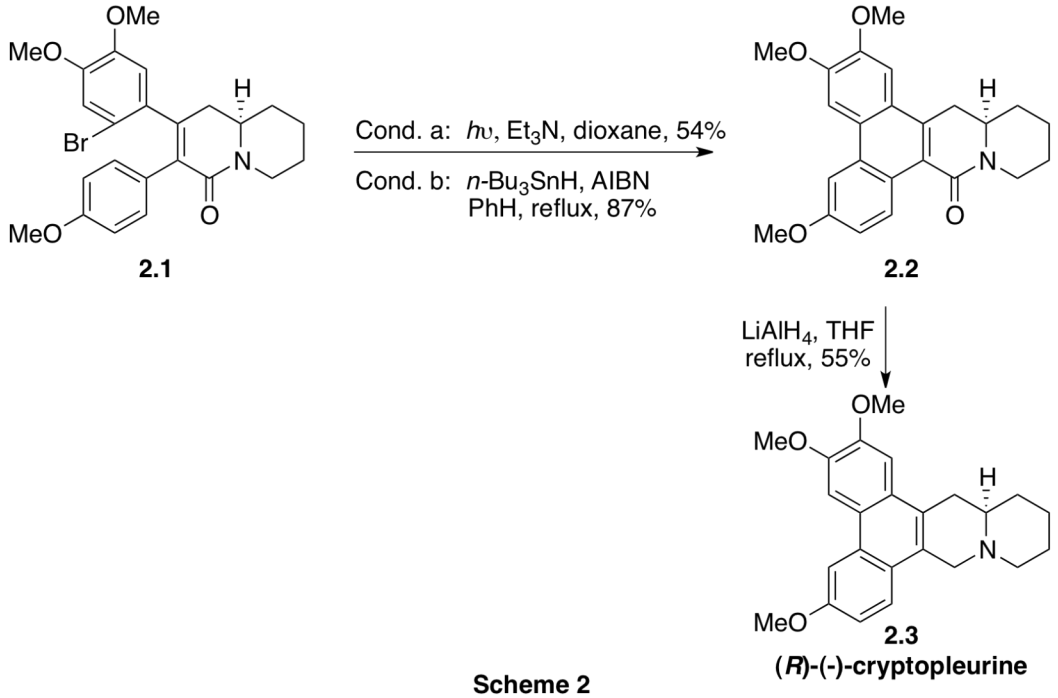
1.2 *Radical cyclization onto arenes and heteroarenes*

Direct cyclizations of radicals onto arenes and heteroarenes have drawn a lot of attention since they provide a convenient access to polycyclic arenes and heteroarenes. Many of these compounds are mimics of pharmaceutical compounds and natural products.[6] Unlike the traditional tributyltin hydride method, various reaction conditions were developed for these types of processes.[7]

1.2.1 *Aryl radical cyclization*

Aryl radical cyclizations onto arenes have been studied extensively and used for the synthesis of phenanthrenes.[8] For example, photocyclization of **2.1**

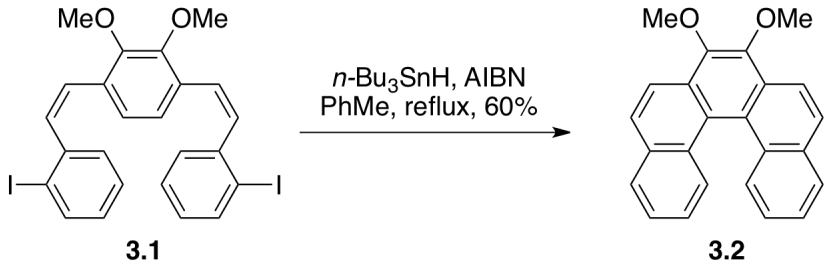
(*h*ν, Et_3N, dioxane, probably via 6-π electrocyclic closure) generated 9-oxocrytopleurine **2.2** in 54% yield. In contrast, standard radical cyclization conditions (Bu_3SnH, AIBN, PhH, reflux) provided the cyclized product **2.2** in a dramatically improved yield (87%). $LiAlH_4$ reduction of lactam **2.2** afforded the desired enantiopure alkaloid (*R*)-(-)-cryptopleurine.[9]



Scheme 2

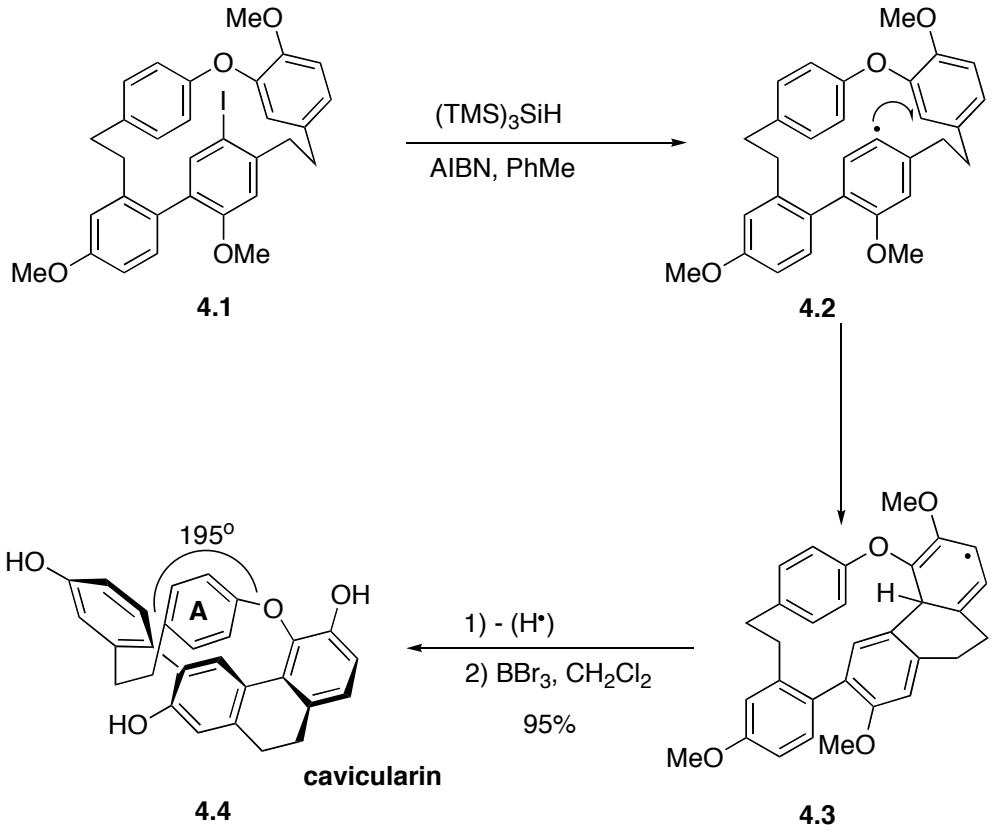
Harrowven and coworkers reported[10] the utility of aryl radical cyclization for the synthesis of substituted [5]- and [7]-helicenes. A general example is shown in Scheme 3. Complete double cyclization required a large excess of *n*-Bu_3SnH (4-5 equiv) and the desired product **3.2** was obtained in 60% yield. Due to the extension of the aromatic system, rearomatization strongly favored the formation of helicenes and the resonance energy was sufficient to overcome the

rotational barrier of the carbon-carbon single bond between the double bond and the aryl group.



3.1 **3.2**

Scheme 3



4.1 **4.2** **4.3**

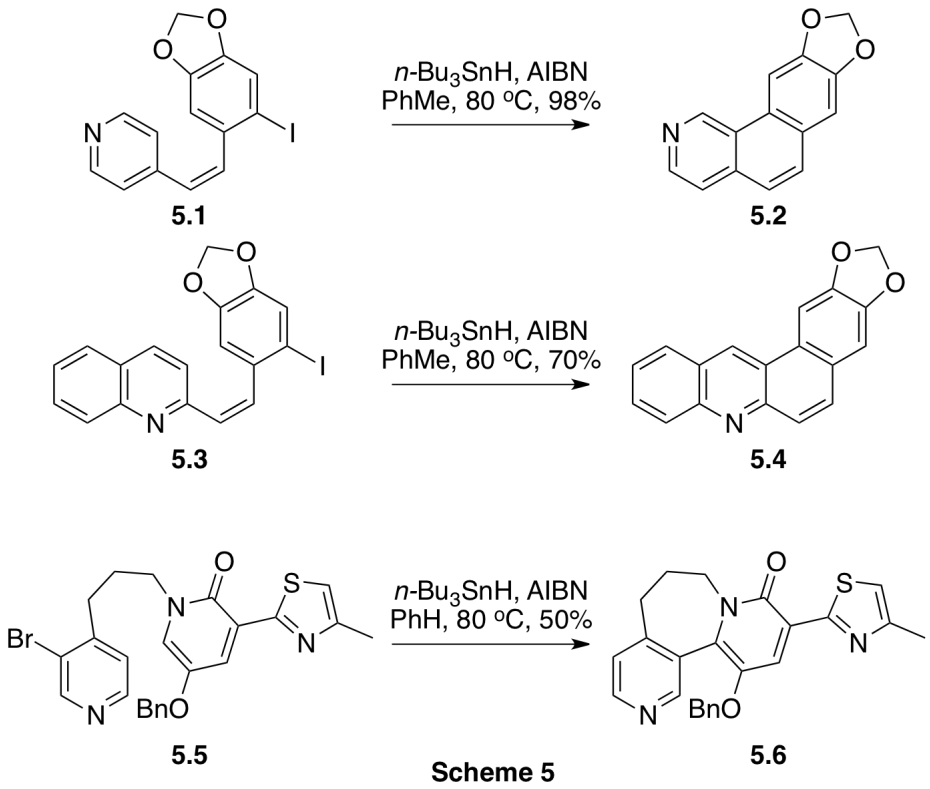
cavicularin

4.4

Scheme 4

The same group also reported[11] the synthesis of cavicularin (**4.4**), using an aryl radical cyclization. The macrocyclic core of cavicularin involves

considerable strain and renders the compound a structurally unique natural product. A key step applied here was the transannular radical cyclization (**4.1** → **4.3**). Unfortunately, a mixture of reduced product and cyclized product was obtained in a 2:1 ratio, in favor of the reduced product. Only partial cyclization occurred and the majority of the starting material suffered simple reduction. Removal of the methyl groups with BBr_3 yielded cavicularin.

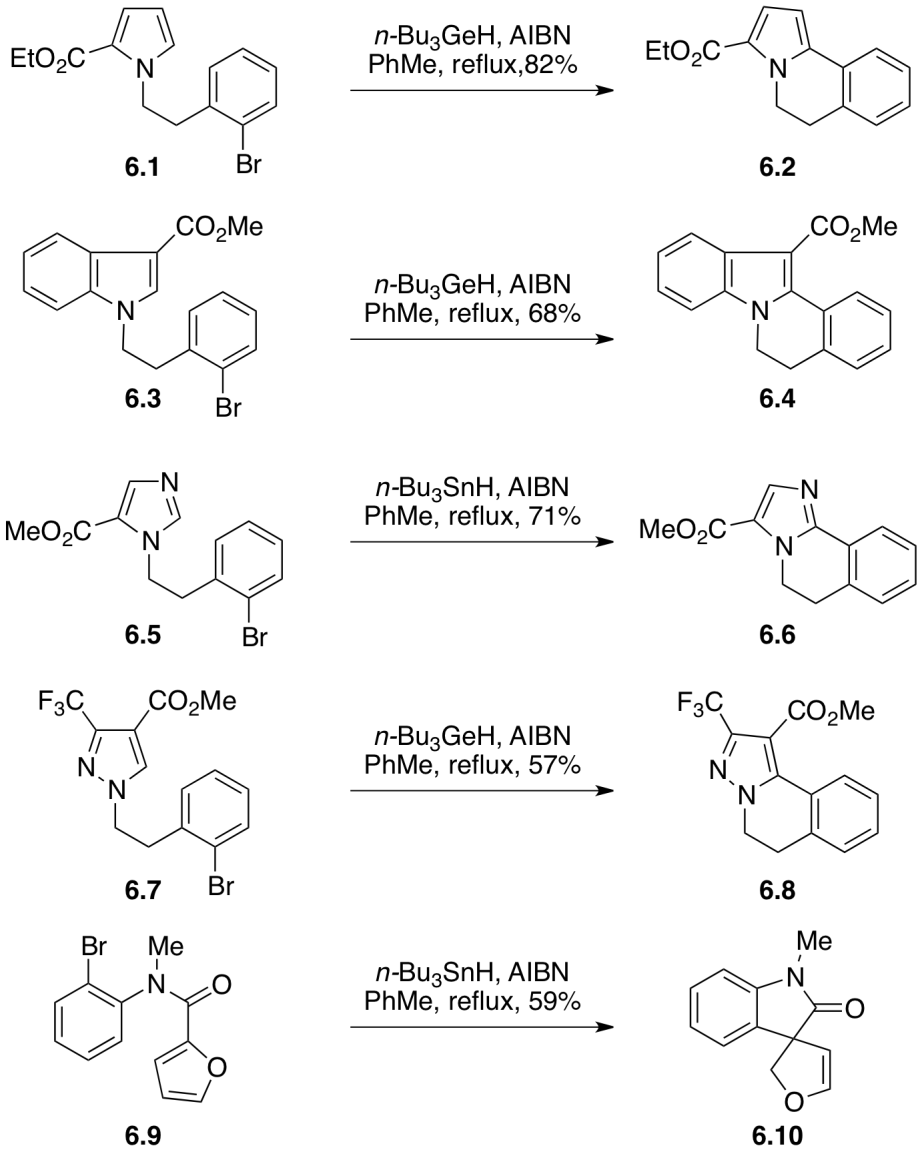


Scheme 5

Aryl radical cyclizations were also applied to heteroarenes such as pyridines,[12] quinolines[13] and pyridinones.[14] Several examples are presented in Scheme 5. Intramolecular radical cyclization onto the β-carbon of pyridine **5.1**, mediated by *n*-Bu_3SnH and AIBN, afforded cyclized product **5.2** in 98% yield. Similar reaction conditions were applied to quinoline **5.3** and the desired

polycyclic quinoline **5.4** was obtained. Such a process opens up new routes towards the synthesis of condensed heterocycles. A major drawback of such a process is that formation a five-membered ring was unsuccessful. Generally, aryl iodides were more efficient than aryl bromides.[13] With pyridone **5.5**, the rarely observed 7-*exo* trigonal pathway was followed when an excess of *n*-Bu_3SnH and a stoichiometric amount of AIBN were used. A small amount of reduced product was also obtained.[14]

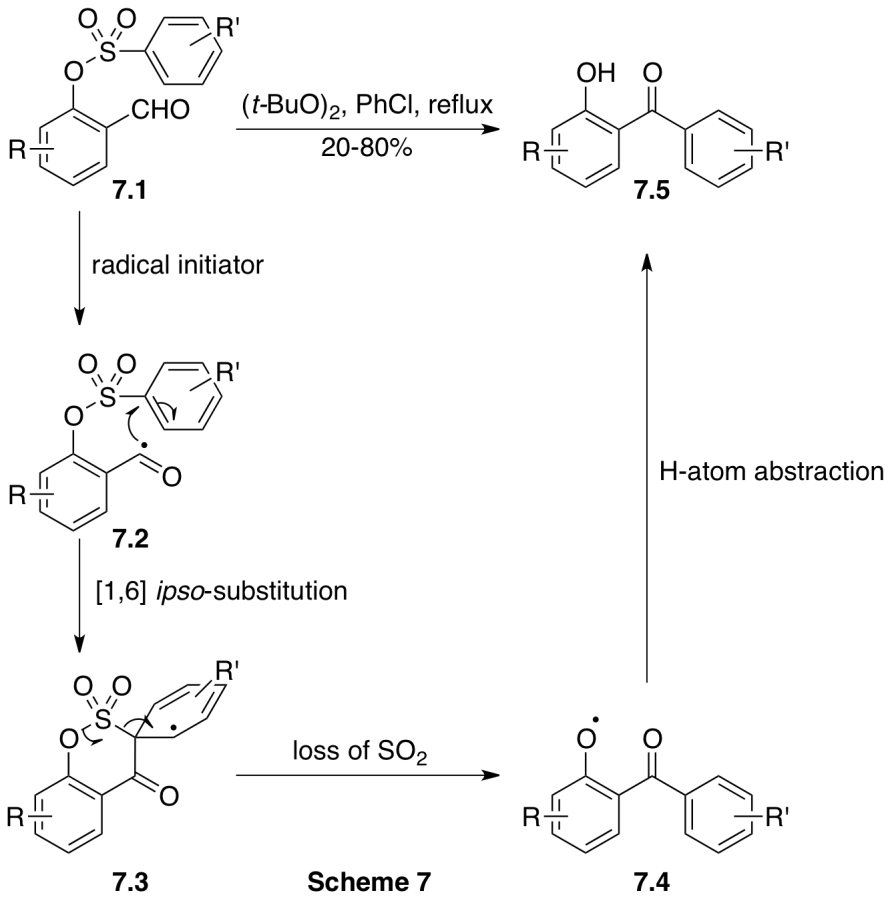
Aryl radical cyclizations onto five-membered azoles is also reported in the literature. Some examples of such processes are presented in Scheme 6. The common azoles that have been studied include pyrrole,[15] indoles,[15] imidazoles,[15] pyrazoles[15] and furans.[16] In general, reactions such as those described above proceeded better when *n*-Bu_3GeH was used instead of *n*-Bu_3SnH. Only the imidazole **6.5** gave a better result with *n*-Bu_3SnH. Notably, when furan **6.9** was subjected to the reaction conditions, the spirocycle **6.10** was the major isolated product.



Scheme 6

1.2.2 Acyl radical cyclization

Acyl radicals[17] were discovered almost a century ago but only recently has their synthetic utility been studied. Motherwell and coworkers reported an interesting approach for the formation of hydroxy diaryl ketones via an intramolecular acyl radical cyclization.[18]

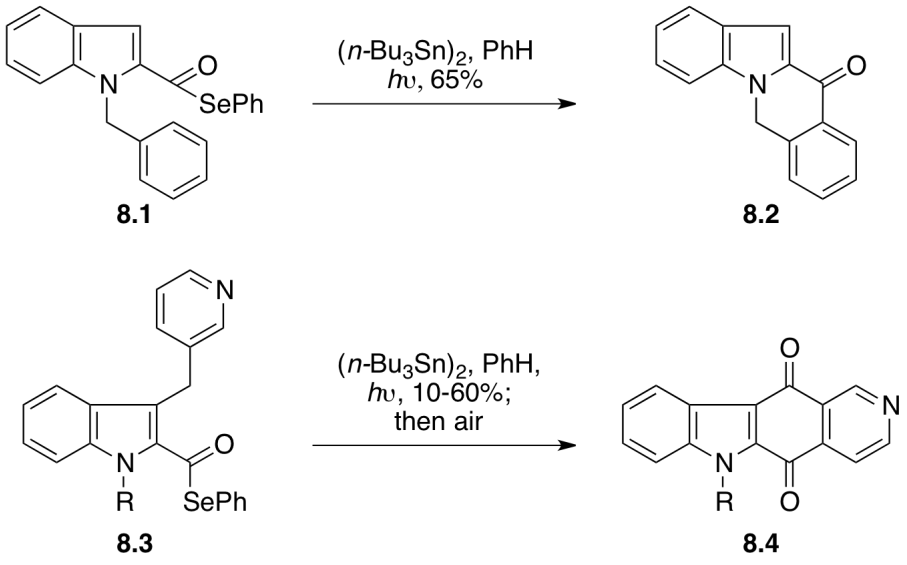


Scheme 7

Sulfonates **7.1** were subjected to the radical cyclization conditions [(*t*-BuO)$_2$, PhCl, reflux] and gave the desired diaryl ketones **7.5** (28-80%). Both electron-withdrawing and electron-donating groups are compatible with the reaction conditions. Notably, decarbonylation products and [1,7]-addition products were not isolated. The general mechanism given in Scheme 7 was proposed.

In 2004, Bennasar and coworkers reported a general approach towards polycyclic aryl indolyl ketones, using the cyclization of the 2-indolylacyl radical onto arenes. These structures show similarities with many natural products and medicinal compounds.[19] Treatment of selenoester **8.1** under non-reductive

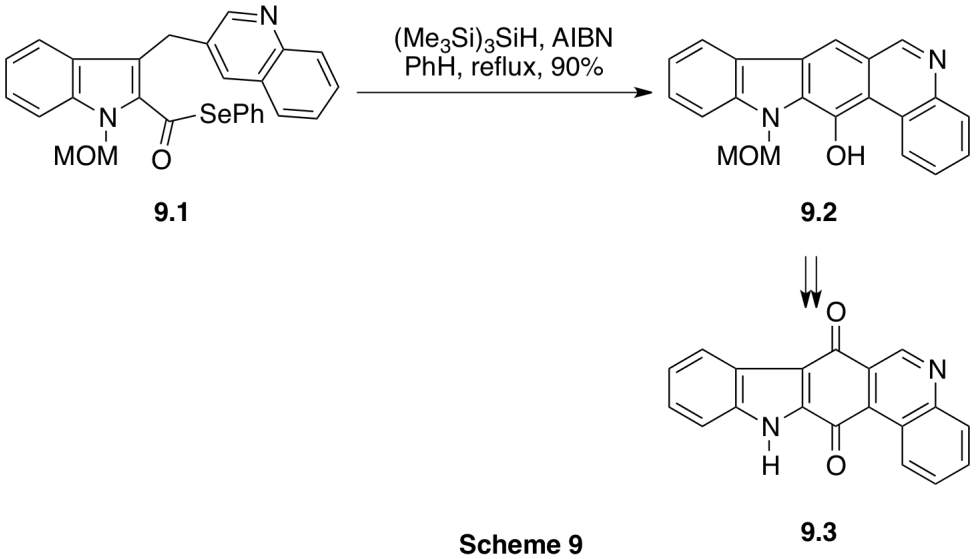
cyclization conditions [(n-$Bu_3Sn)_2$, $h\nu$] provided the tetracycle **8.2** in 65% yield. No reduced product was isolated.[20] The same idea has also been applied to heteroarenes. For example, a pyridine ring was tested in the case of **8.3** and the desired ellipticine quinone **8.4** was obtained as a synthetic mimic of the anticancer alkaloid ellipticine.[21] None of the reduced product was isolated and, interestingly, a subsequent *in situ* oxidation readily occurred to furnish the quinone. The authors believe that the $Bu_3SnOO\cdot$ radical might be the major oxidizing agent. In the case of a free indole nitrogen (**8.3**, R = H) the desired pathway was disfavored due to competing cyclization onto the 2-position of the pyridine ring. All attempts to improve the yield (R = H) failed and starting material was recovered.



Scheme 8

Another example is the case of indol-2-yl acyl radicals, which can be successfully cyclized onto quinolines. The selenoester **9.1** was subjected to standard cyclization conditions for the use of silanes [$(Me_3Si)_3SiH$, AIBN, PhH,

reflux] and the pentacyclic phenol **9.2** was produced, which was easily elaborated to calothrixin B (**9.3**). Calothrixin B has antimalarial and anticancer properties.[22]



9.1 **9.2** **9.3**

Scheme 9

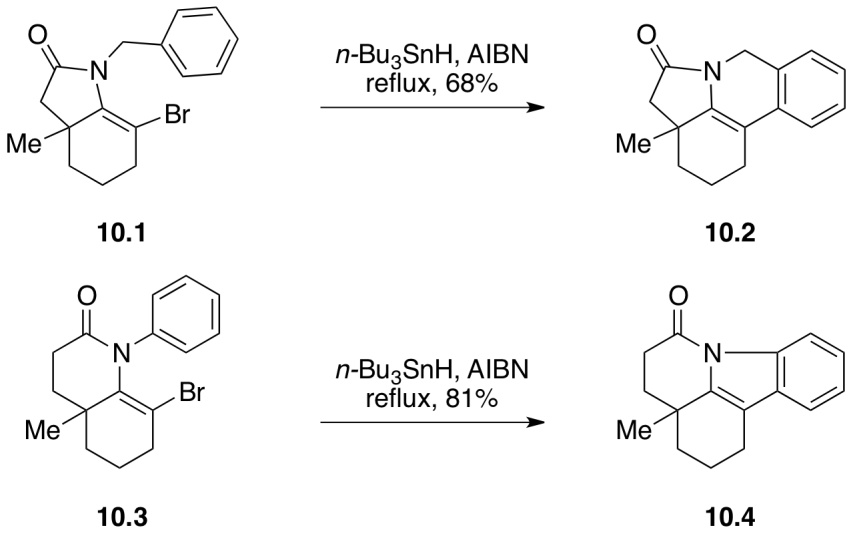
1.2.3 *Alkenyl and imidoyl radical cyclization*

Recently, Padwa and coworkers found that alkenyl radical cyclization onto arenes could be used to construct various systems closely related to the core of the aspidosperma alkaloids.[23]

Bromoenamide **10.1** was exposed to standard *n*-Bu_3SnH mediated radical cyclization conditions and the cyclized product **10.2** was obtained in 68% yield along with 27% of the reduced product (Br in **10.1** replaced by H). However, when **10.3** was used under the same conditions, only the cyclized product **10.4** was obtained (81% yield).

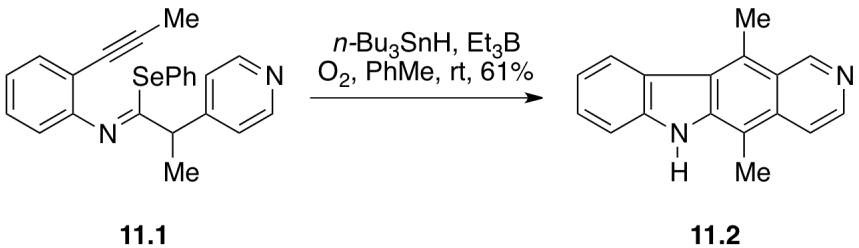
Imidoyl radicals can be formed easily by either addition of radicals to isonitriles or by abstraction of a hydrogen atom from the corresponding imines. These radical species have been widely studied for cyclizations, annulations and

cascade reactions, most often for the construction of nitrogen-containing substances.[24]

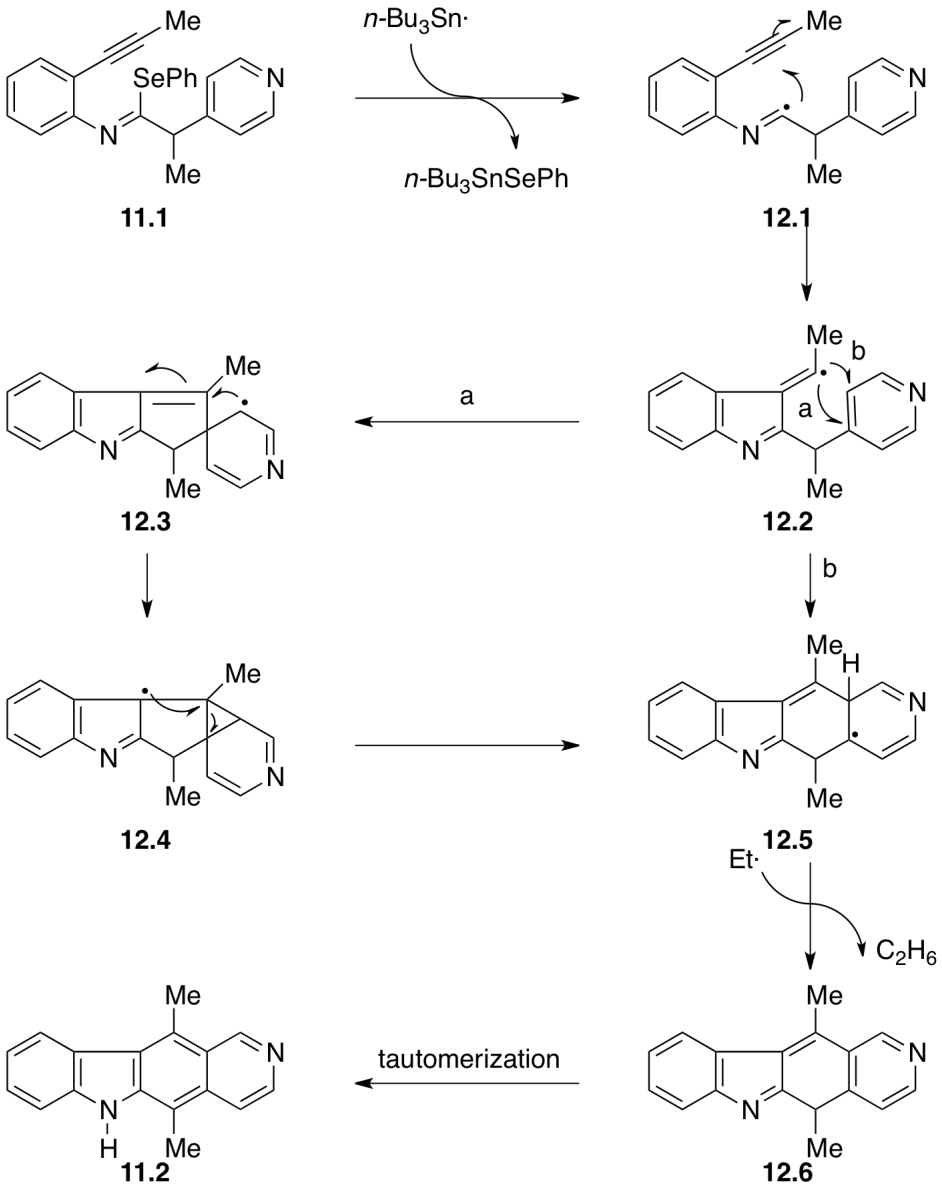


Scheme 10

Bowman and coworkers demonstrated a cascade process involving both imidoyl radical cyclization and alkenyl radical cyclization.[25] The product, ellipticine (**11.2**), is an anticancer alkaloid. Standard stannane mediated conditions gave a poor yield of the desired product. However, when Et_3B was used, the cyclized product was obtained in 61% yield.



Scheme 11

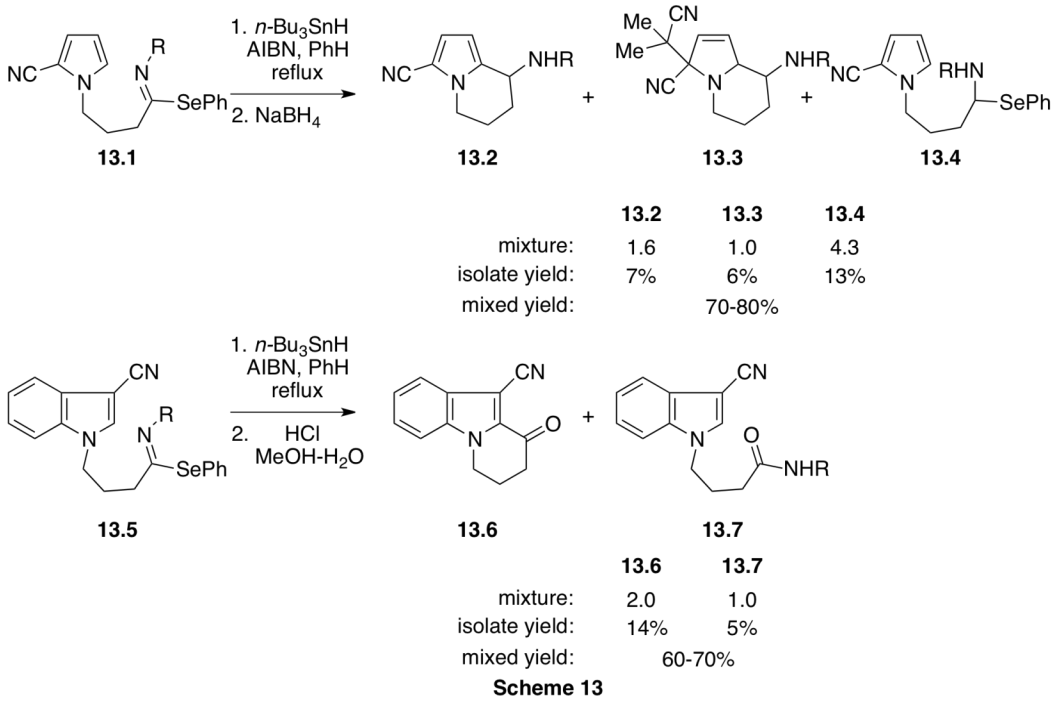


Scheme 12

A general mechanism has been proposed for such a radical cascade, which is initiated by tributyltin radical. The imidoyl radical **12.1** undergoes a 5-*exo-digonal* cyclization onto the triple bond. The resulting alkenyl radical **12.2** then adds onto the pyridine ring, possibly, via a 5-*ipso trig* cyclization, followed by a neophyl rearrangement (**12.3** → **12.5**). However, direct cyclization to a six-membered ring cannot be ruled out (**12.2** → **12.5**). It was suggested that

hydrogen abstraction is effected by ethyl radicals. Rapid tautomerization of **12.6** provided **11.2**.

Similar synthetic strategies have been applied to heteroarenes such as pyrroles and indoles.[26] In both cases, an electron-withdrawing group was required to facilitate nucleophilic attack by the imidoyl radicals. After radical cyclization, the mixture was reduced with $NaBH_4$. The isolated yield of the desired product was quite poor and some side products were also isolated. Nevertheless, imidoyl radicals can also be used for construction of polycyclic azoles via radical cyclization.



Scheme 13

1.2.4 Alkyl radical cyclization

Alkyl radical cyclization onto arenes is not well known, compared to similar process onto heteroarenes.[27] Generally, the addition of aryl radicals onto

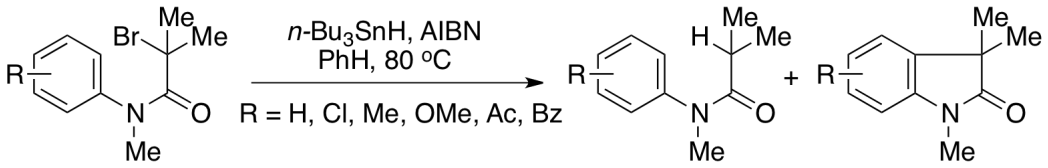
arenes gives better yields than the similar process with alky radicals. Due to the lower reactivity, such additions are often too slow and ineffective to be considered as useful synthetic methods and so one cannot generally take advantage of the regioselectivity of intramolecular alkyl radical cyclizations where the acceptor is an arene.

Beckwith and Storey reported alkyl radical cyclizations onto arenes as a general access to indolones.[28] For example, when bromide **14.1** was subjected to standard stannane mediated conditions, only the reduced product **14.2** was isolated (98%). With $(t\text{-BuO})_2$ as initiator, use of an elevated reaction temperature gave the cyclization product in 66% yield. Lowering of the concentration also favored cyclization. However, the high reaction temperature limited the utility of such cyclizations.

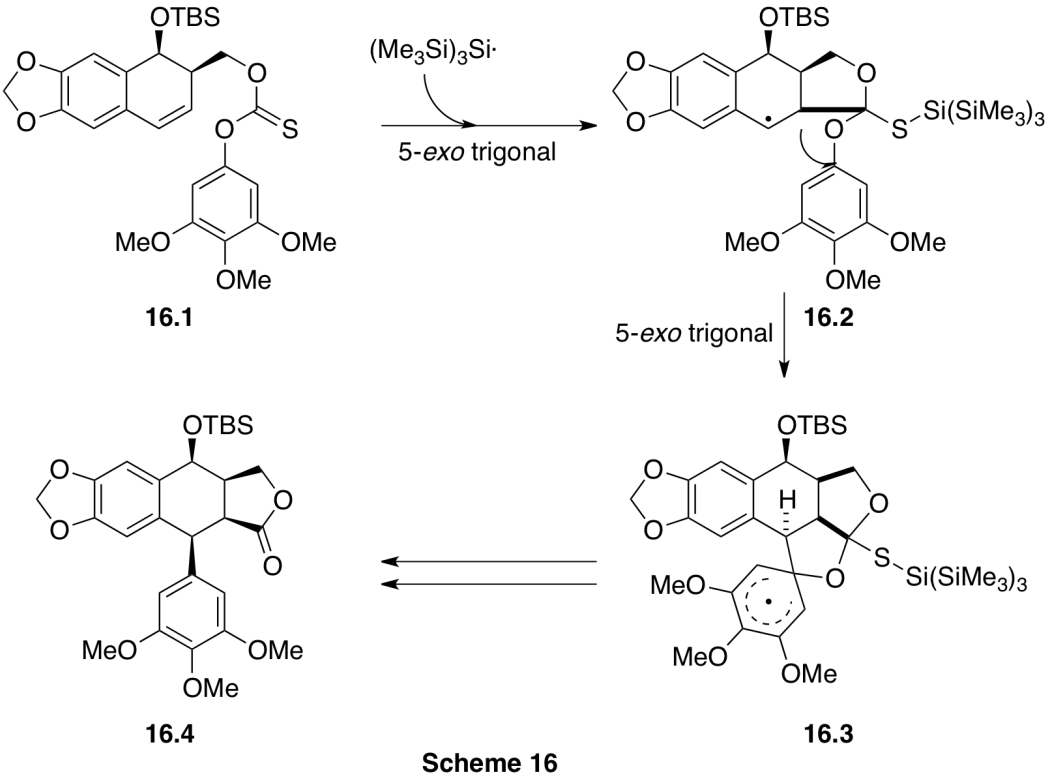
14.1 **14.2** **14.3**

Scheme 14

Nishio studied slightly modified systems related to Beckwith and Storey's substrate **15.1**.[29] The new substrates had *para* or *ortho* substituents (both electron-withdrawing and electron-donating). Both the reduced products and cyclized products were obtained with the cyclized products being favored. The same reaction could be performed with Ni powder in *i*-PrOH with comparable yields.



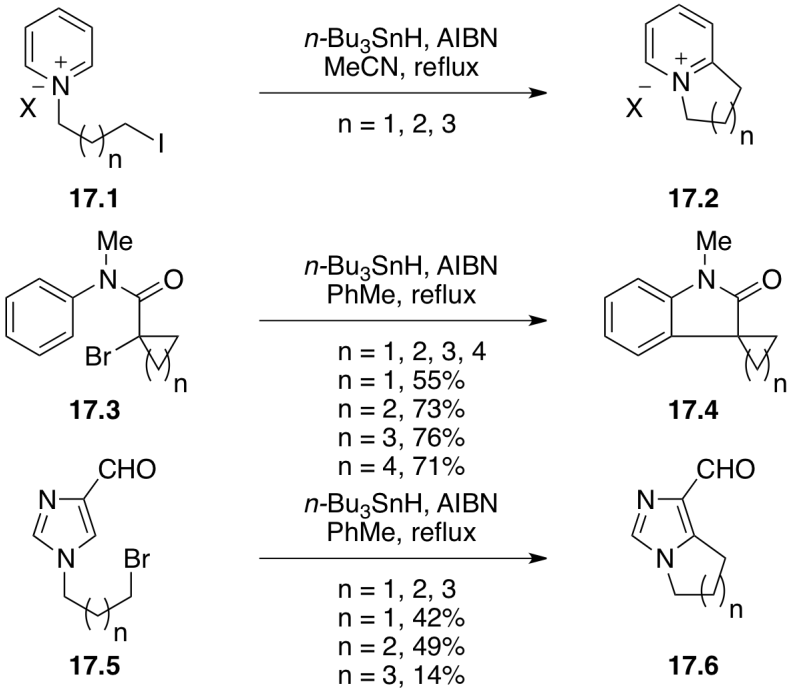
Scheme 15



Scheme 16

During synthetic studies on podophyllotoxin, Reynolds and coworkers examined an alkyl radical cyclization onto the proximal arene as a key step.[30] Thiocarbonate **16.1** was subjected to $(Me_3Si)_3SiH$ and AIBN in refluxing PhH, to form the benzylic radical **16.2** after the initial cyclization. An *ipso* addition then occurred and loss of the sulfur unit afforded lactone **16.4** in 40% yield.

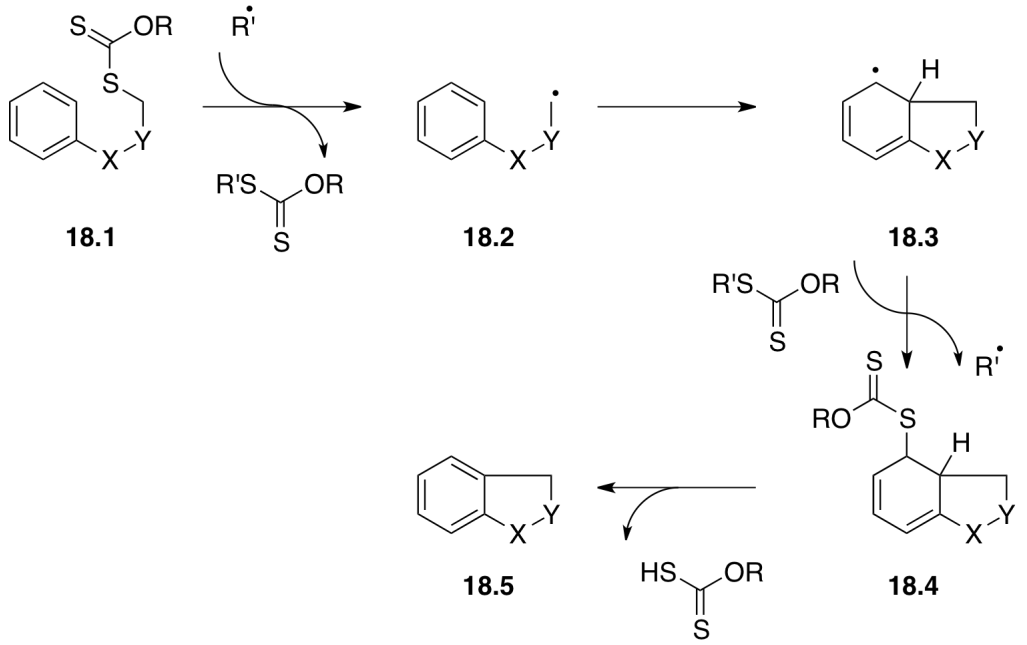
Due to pharmaceutical interest in heteroaromatic compounds, alkyl radical cyclizations onto heteroarenes have been well studied in the past. Several examples of alkyl radical additions onto pyridinium salts,[31] pyridines[32] and imidazoles[33] are shown below. Competing formation of reduced compounds was again the major side reactions. Formation of a 6-membered ring is the most favored pathway while no 8-membered cyclization products were isolated.



Scheme 17

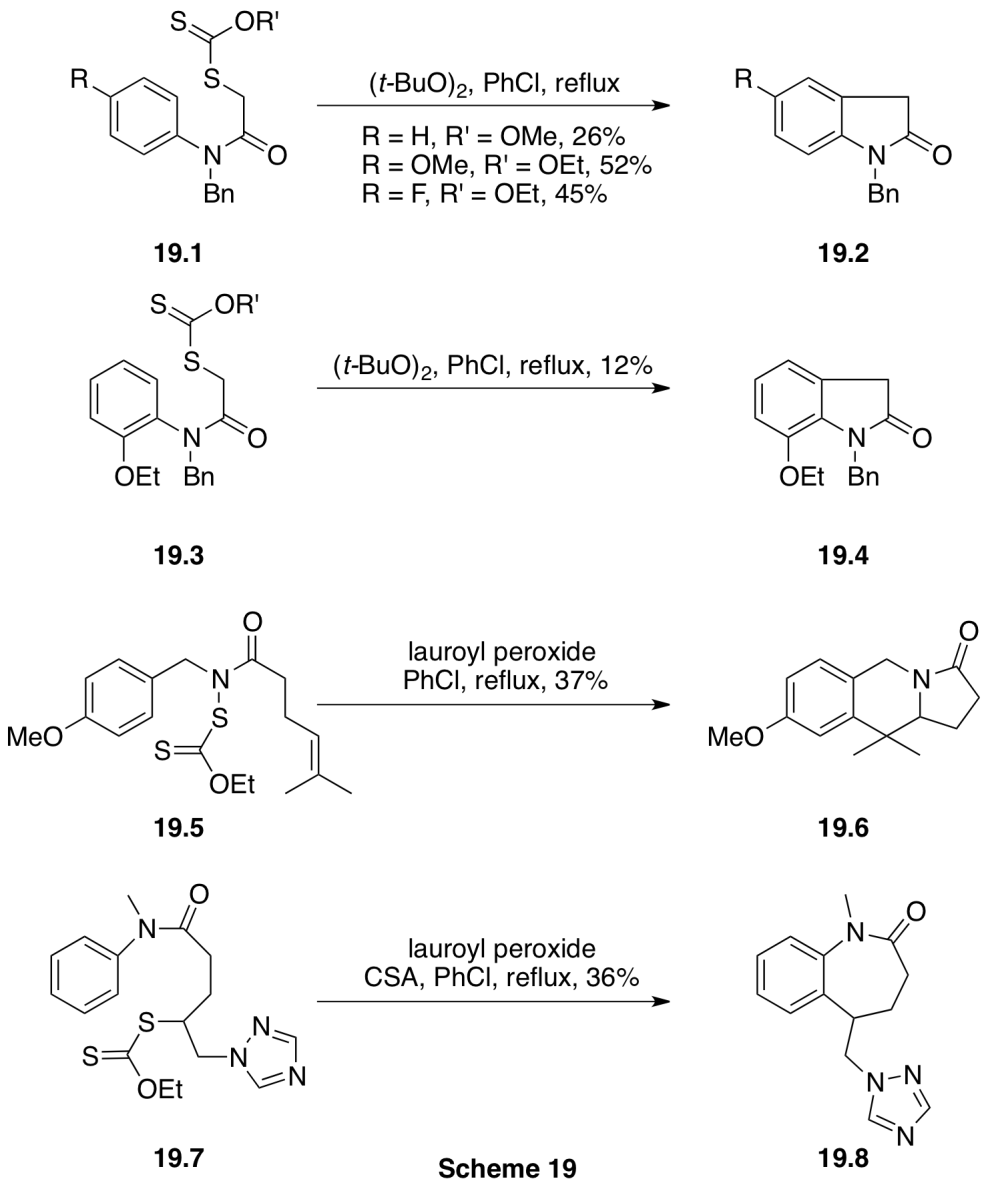
1.3 *Zard's protocol with xanthates and peroxides*

Zard and coworkers systematically studied direct radical cyclization onto arenes and heteroarenes and reported their work in a series of publications.[34] The general procedure required xanthates as starting materials and peroxides (commonly dilauroyl peroxide) as initiators. *n*-Bu_3SnH and *n*-Bu_3GeH were not used for generating alkyl radicals. Zard's conditions strongly favor oxidative rearomatization of the initial cyclization products.



Scheme 18

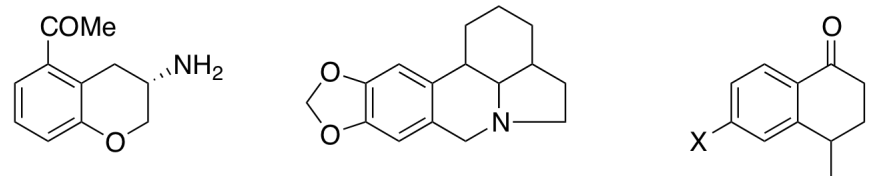
A major advantage of Zard's protocol is that the xanthate and the derived radical exist in equilibrium, a fact which strongly prolongs the effective lifetime of the radical species. This equilibrium allows the radicals to be temporarily stored without undergoing any side reactions. Some typical examples are presented in Scheme 19.[34,35]



Scheme 19

Like general radical closures, 5-, 6- and 7-membered rings could be made via this process. A cascade reaction was achieved when compound **19.5** was subjected to the reaction conditions. Initial 5-*exo* trigonal cyclization generates a relatively sterically hindered tertiary radical which then underwent another radical cyclization and rearomatization to form the tricycle **19.6**. Notably, camphorsulfonic acid was required to accelerate the final radical cyclization.[36]

This approach was used for the synthesis of benzo-fused natural products, as well as some common intermediates for the synthesis of biologically active compounds (Scheme 20).[34,37]



20.1
(*S*)-aminochroman

20.2
(±)-lycorane

20.3
tetralones

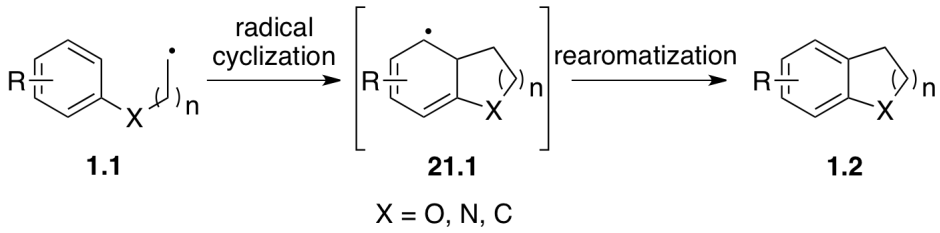
Scheme 20

Several advantages[38] of Zard's protocol can be listed as follows: (1) No toxic heavy metals are required. (2) The starting materials are readily accessible and inexpensive. (3) There is no requirement for low concentrations. The major drawbacks are the large amount of initiator and the high reaction temperature.

2. RESULTS AND DISCUSSION

2.1 *Research objectives*

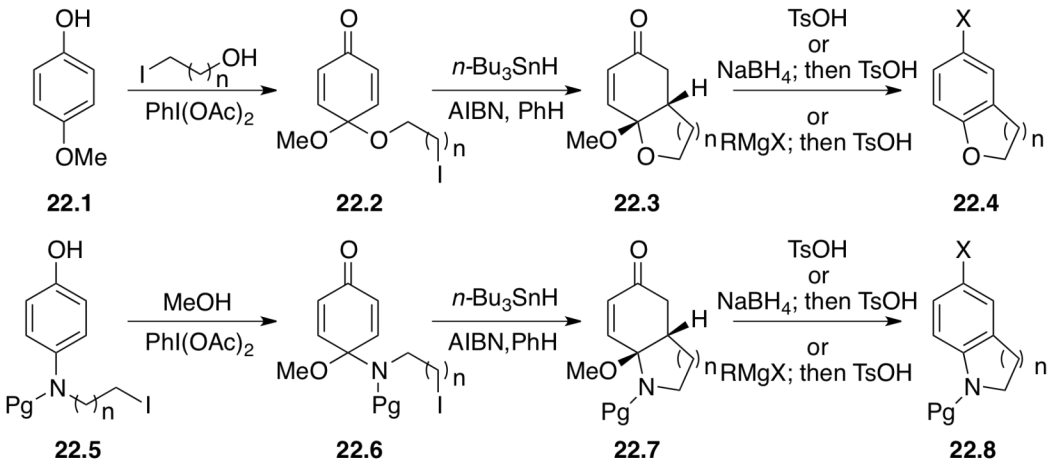
As mentioned in the introduction to this chapter, alkyl radical cyclization onto an aromatic ring represents a largely undeveloped, but potentially important, area. Direct oxidative radical cyclization of an alkyl radical onto a benzene ring, as depicted in Scheme 21 would offer a useful route to benzo-fused compounds such as oxygen heterocycles (X = O) or nitrogen heterocycles (X = N) and benzo-fused carbocycles (X = C).



Scheme 21

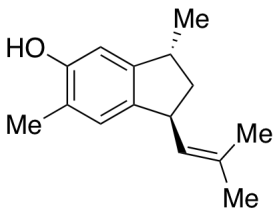
As mentioned in the introduction, the methods of direct radical cyclization are not general and have major limitations. Only Zard's protocol can be considered as a general approach. However, high reaction temperatures, stoichiometric amounts of initiator might limit the synthetic utility of these reactions, although the process is clearly a very important contribution to synthetic chemistry. In contrast, recent publications[39] from this laboratory presented an indirect approach towards the synthesis of benzo-fused heterocycles. Due to the difficulty of dearomatizing the aryl ring, direct radical cyclization onto aromatic rings is not an easy process since the energy barriers which need to be

overcome are high. However, our approach starts by converting the aromatic rings into the corresponding cross-conjugated ketones (**22.2** and **22.6**). Addition of oxygen or nitrogen nucleophiles to *p*-methoxyphenol under oxidative conditions gave cross-conjugated ketones carrying a chain with a halogen at its terminus. Direct radical cyclization of the derived alkyl radicals onto the double bond of the cross-conjugated ketones afforded conjugated ketones (**22.3** and **22.7**). A series of phenols could be obtained via direct rearomatization (**22.4** and **22.8,** X = OH). Reduction with $NaBH_4$ and rearomatization under acid conditions provided a large number of compounds as benzo-fused heterocycles (**22.4** and **22.8,** X = H). A substituent could also be introduced if the cross-conjugated ketones are treated with a Grignard reagent. Again, rearomatization readily occurred and the corresponding benzo-fused heterocycles (**22.4** and **22.8**, X = alkyl, alkenyl, alkynyl, aryl, heteroaryl) were formed.

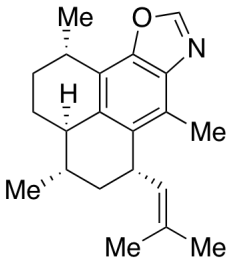


Scheme 22

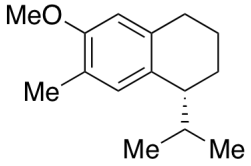
An extension of the above processes was to modify it for the synthesis of benzo-fused carbocycles. Many natural products have this type of structural subunit and a general synthetic method would be useful for making derivatives for biological testing. Several examples of natural products with benzo-fused carbocyclic subunits are as follows:[40]



(+)-mutisianthol 23.1



pseudopteraxazole 23.2



dimethyl calamenen 23.3

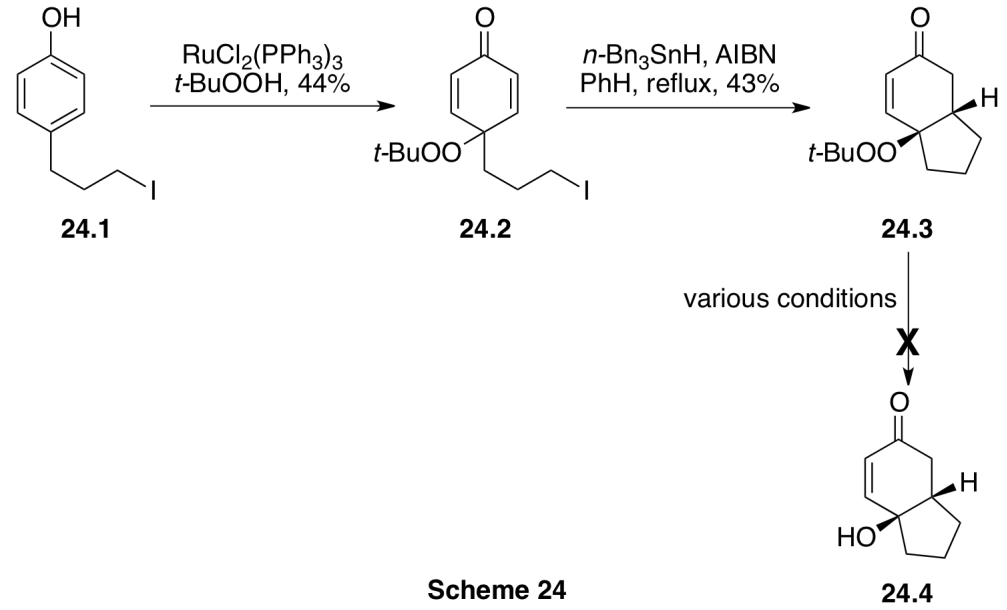
Scheme 23

2.2 *General approach to formal radical closure onto aromatic rings*

A requirement of such a general process was that it should be mild and highly tolerant of various functional groups, and it was found by Dr. R. Sunasee that standard radical cyclization conditions do fulfill these requirements.

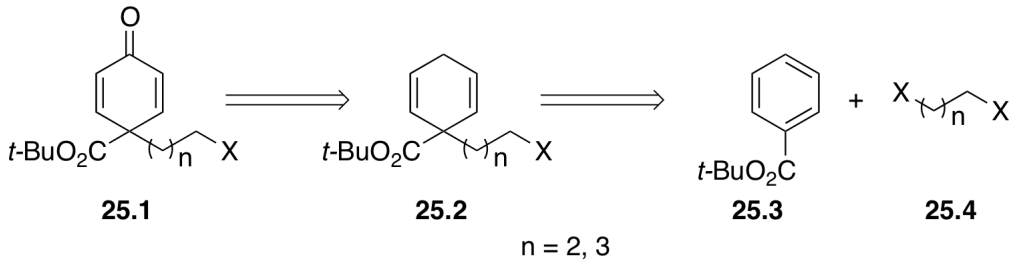
He found that addition of peroxides to *p*-alkyl phenols (e.g. **24.1**) did yield the desired cross-conjugated ketone. However, the yields were low and no significant improvement could be achieved upon attempted optimization of the reaction conditions.[41,42,43] In the best case [$RuCl_2(PPh_3)_3$, *t*-BuOOH], only 44% of the desired product **24.2** was isolated. Like the previous cases, radical cyclization of **24.2** did occur, but the yield was much lower that the normal

cyclizations. Reduction of the peroxide **24.3** to the corresponding alcohol failed and no better solution could be found for this particular peroxide.



Scheme 24

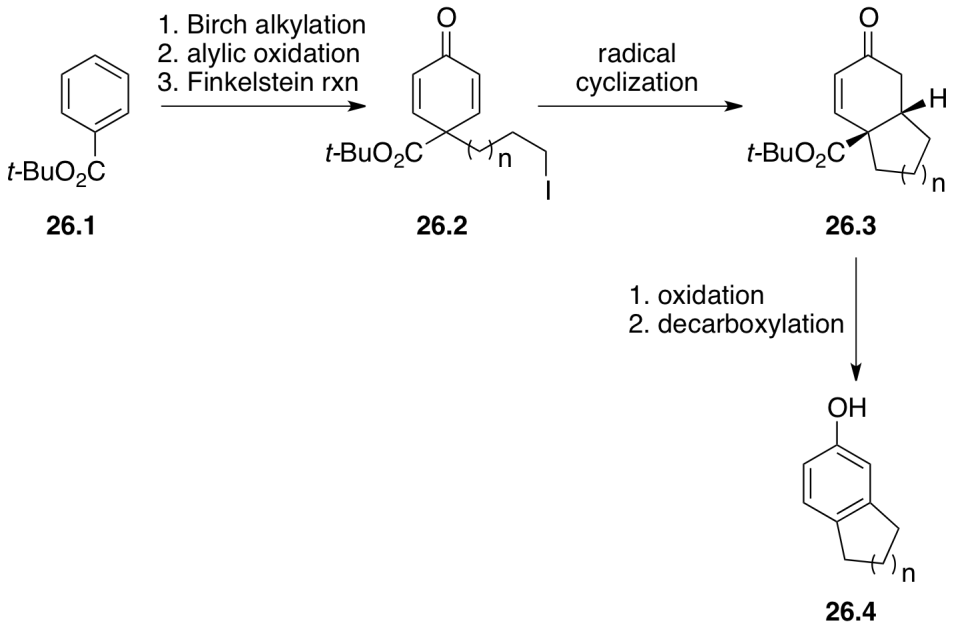
Failure of such reactions indicated that an alternative removable functional group needed to be installed at the *para*-position of the phenol that could be easily removed for the final dearomatization.



Scheme 25

The *t*-butyl ester group was chosen as a suitable candidate for such an investigation. Cross-conjugated ketones **25.1** could be generated from diene **25.2**

via allylic oxidation. Dienes **25.2** were accessible by Birch reductive alkylation of *tert*-butyl benzoate **25.3** with suitable dihalides **25.4**.[44] The corresponding methyl ester did not provide a satisfactory yield in the Birch reductive alkylation. The general sequence of this approach is summarized in Scheme 26. Dr. Sunasee illustrated the general method with a number of examples and I then took over the project and extended the range of examples.

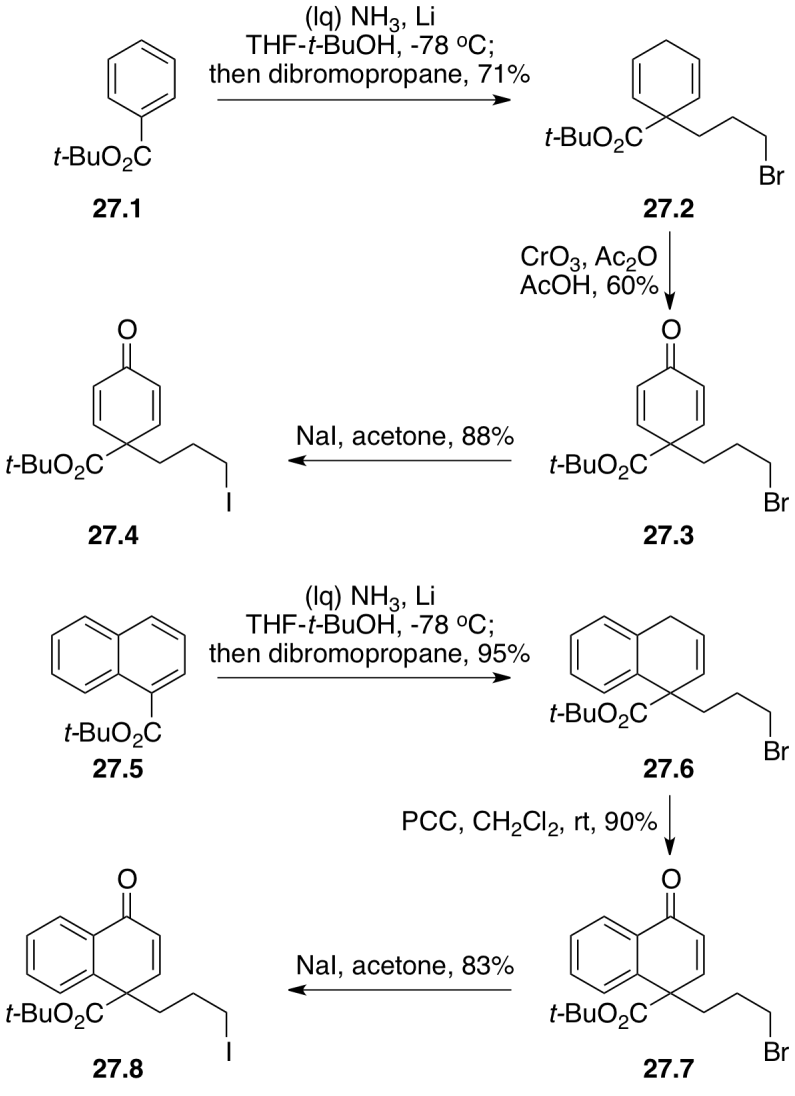


Scheme 26

2.2.1 Preparation of radical cyclization precursors

Birch reductive alkylations were examined with the following two *tert*-butyl esters: **27.1** and **27.5**. The reaction was carried out at -78 °C and 1,3-dibromopropane was added in one portion. Slow addition of 1,3-dibromopropane generated some dialkylated product. The reaction goes smoothly and the yields were 71% and 95%. With **27.2** and **27.6** in hand, the allylic oxidations were

examined. Initially, the cross-conjugated ketones were obtained by using CrO_3 in AcOH-Ac_2O[45] (around 60% yield). The latter case (**27.6**) showed that direct use of PCC in CH_2Cl_2 at room temperature for 3 days gave the desired product **27.6** in 90% yield.

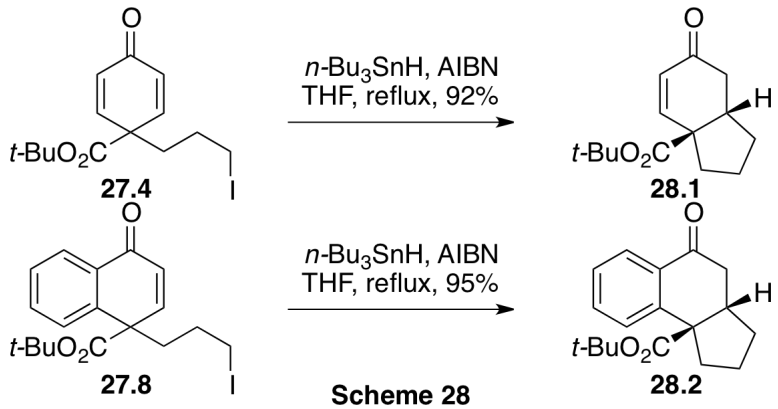


Scheme 27

Transformation of the bromides into the corresponding iodides was achieved under standard Finkelstein conditions (NaI in refluxing acetone) in yields around 85%.

2.2.2 Radical cyclization and oxidation of the bicycles

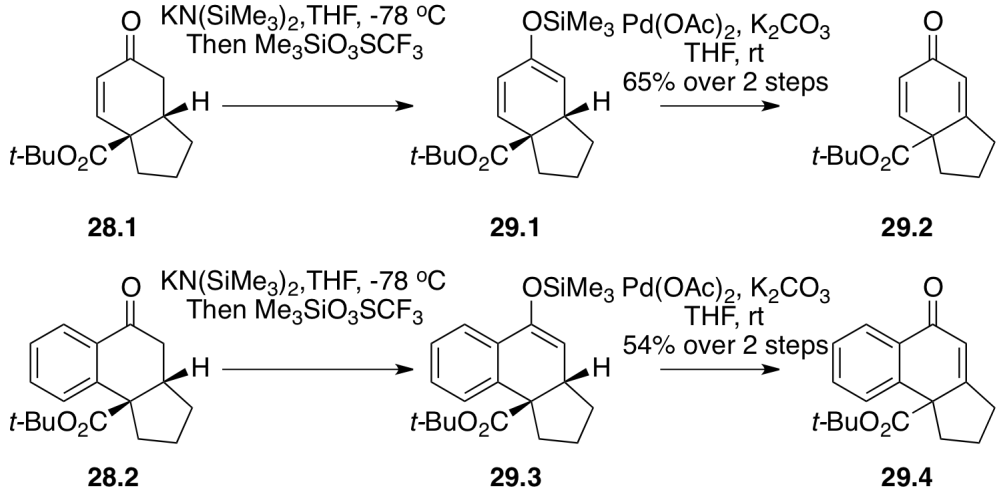
In both cases, radical cyclization occurred smoothly via slow addition (over ca 5 h) of a solution of *n*-Bu_3SnH and AIBN in PhH to a refluxing solution of the starting materials in PhH. The reaction mixtures were refluxed overnight and the desired products were obtained in about 80% yield. Interestingly, when THF was used as the solvent, which normally gives poorer yields than PhH, the yields of the radical cyclization were improved to about 95%. The stannane residue was removed by KF-silica gel chromatography. Dr. Sunasee also attempted to use bromides as the radical precursors. However, such bromides did not lead to good yields for this key step. It appears necessary to use iodides since attempts to use bromide **27.3** as a radical precursor gave a poor yield, presumably because bromides react with tributylstannyl radicals about 100 times more slowly than iodides[46] leading to an unfavorable competition between dienone reduction and C-Br homolysis.



Scheme 28

The cyclized products, ketones **28.1** and **28.2**, were then oxidized to form the corresponding cross-conjugated ketones **29.1** and **29.2**. Selenoxide

fragmentation,[47] Saegusa oxidation[48] and Nicolaou's IBX protocol[49] were examined. Only the Saegusa oxidation provided satisfactory results and stoichiometric amounts of $Pd(OAc)_2$ were required. The selenium method suffered from the fact that only one of two diastereomers had the correct stereochemistry to undergo the syn selenoxide fragmentation. Nicolaou's IBX protocol failed to give any desired product. A catalytic Saegusa oxidation was also tested.[48b] Unfortunately, none of the desired product could be isolated.

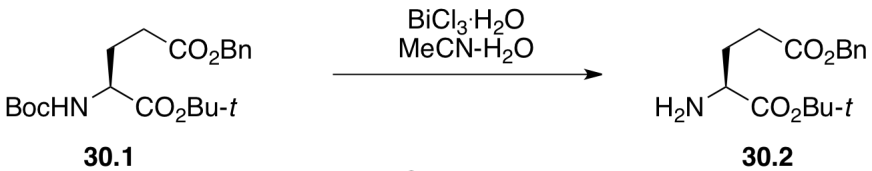


Scheme 29

2.2.3 Addition of Grignard reagents and rearomatization

Dr Sunasee found that removal of the *tert*-butyl ester and rearomatization could be achieved via $BiCl_3 \cdot H_2O$ mediated reactions.[50] Such a process had been reported for chemoselective removal of *N*-Boc groups from protected amino acids or peptides (Scheme 30), and it had been found that prolonged reaction times started to cause the loss of *tert*-butyl groups from *tert*-butyl esters. This clue

suggested the perfect solution for decarboxylation of our esters since a mild deprotection of *tert*-butyl ester was required.



30.1 **30.2**

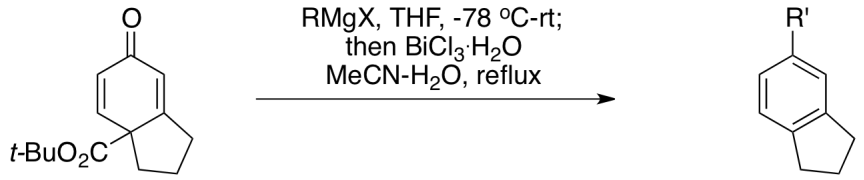
Scheme 30

The second unsolved problem was whether substituents could be introduced onto the aromatic ring so that further functionality manipulations are possible. The general idea applied here was addition of a Grignard reagent or organolithium reagent to the carbonyl. The corresponding alcohols (diastereomers) were then converted to the corresponding benzo-fused carbocycles.

Various Grignard reagents and organolithium reagents were added to the cross-conjugated ketones and the corresponding alcohols were rearomatized to form the benzo-fused carbocycles. Various functionalities could be introduced onto the newly formed benzene ring at the *para*-position to the carbon tether.

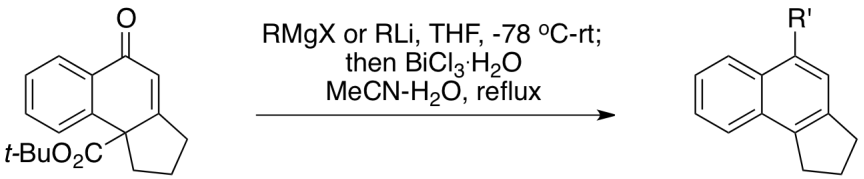
The addition of Grignard reagents was successful and the alcohols were used directly for the next step without further purification. A stoichiometric amount of $BiCl_3 \cdot H_2O$ was required for the reaction to be complete within 5 h. An alternative procedure was to add 20 mol% of $BiCl_3 \cdot H_2O$ in the beginning and another 20 mol% mol after refluxing for 2 h. Both methods gave similar results. Aryl, alkyl, alkynyl, allyl, propargyl and heteroaromatic rings could be introduced.

The mechanism of the formation of **31.9** is not clear. The second aromatic ring must play an important role in this particular process.



29.2 **31.1**

Entry	RMgX	R'	yield (%)
31.2	AllylMgBr	Allyl	75
31.3	PhMgCl	Ph	85
31.4	Ph—≡—MgBr	Ph—≡—	62
31.5	Me_3Si—≡—MgBr	H—≡—	57
31.6	MgBr, $HgCl_2$	≡—	73

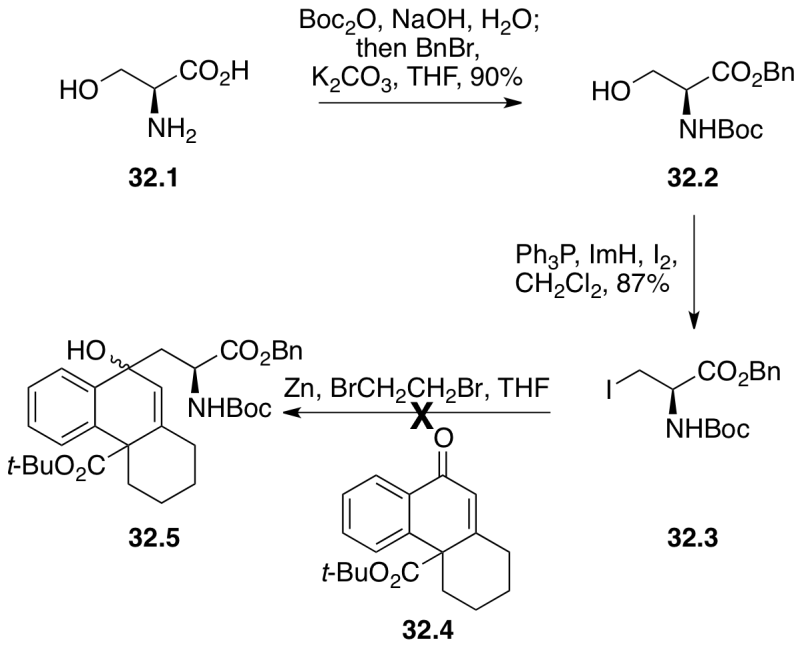


29.4 **31.7**

Entry	RMgX	R'	yield (%)
31.8	AllylMgCl	Allyl	60
31.9	Me_3Si—≡—MgBr	Cl	40
31.10	O—Li	O—	69

Scheme 31

We also attempted to introduce an amino acid functionality as a substituent on the aromatic ring. Our plan included as a key step an addition between a 6-membered cross-conjugated ketone and an organozinc reagent formed from a protected amino acid. (*R*)-Serine (**32.1**) was protected by *N*-Boc and *O*-benzyl groups. Displacement of the hydroxyl group by iodide provided the corresponding iodide **32.3**.[51] The addition between organozinc reagent of **32.3** and **32.4** failed to furnish alcohol **32.5**. The low reactivity of organozincs prevented such an addition. It is also known that the addition of organozincs normally occurs with aldehydes but not generally with ketones.



Scheme 32

3. CONCLUSION

Based on previous studies in our group, the formal alkyl radical cyclization onto aromatic rings, which had been heavily studied for the construction of benzo-fused heterocycles, was extended by additional examples described in this chapter; the method is useful for making benzo-fused carbocycles. Unlike the previous studies, a new way of preparing radical cyclization precursors was introduced; it involved a reductive alkylation-allylic oxidation-iodination sequence. Common benzo-fused 5- and 6-membered rings were synthesized via standard alkyl radical cyclizations followed by rearomatization which was catalyzed by $BiCl_3$. With some functionality manipulations, various functional groups (aryl, alkyl, alkenyl, alkynyl, and heteroaryl) could be installed as substituents on the aromatic rings. A general method for removal of *tert*-butyl ester groups was used as the key step for rearomatization of the radical cyclization products.

4. EXPERIMENTAL

1-(3-Bromopropyl)cyclohexa-2,5-dienecarboxylic acid *tert*-butyl ester (27.2).

27.1 **27.2**

The apparatus consisted of a three-necked round-bottomed flask containing a magnetic stirring bar and fitted with a cold finger condenser fused onto one of the necks. The exit of the condenser was fitted with a drying tube filled with $CaSO_4$. An external mark on the flask indicated the level corresponding to the desired volume of liquid ammonia. The central neck was closed by a septum carrying a nitrogen inlet. The flask was stoppered and cooled in a dry ice-acetone bath. The cold finger was charged with dry ice-acetone. Another round-bottomed flask was half-filled with liquid ammonia (around 50 mL) and several small pieces of Na were added, so as to form a permanently blue solution. This flask was connected via bent adaptors and dry Tygon tubing to the third neck of the other flask. A solution of **27.1** (2.14g, 12.0 mmol) in dry THF (15 mL) and *t*-BuOH (1.29 mL, 13.2 mmol) was injected into the three-necked flask, and liquid ammonia was allowed to condense into the flask. Lithium wire (252 mg, 36.0 mmol), cut into small pieces, was added rapidly to the vigorously

stirred solution. Stirring at -78 °C was continued for 15 min, until a dark blue color persisted. Dibromopropane (2.88 mL, 30.0 mmol) in THF (5 mL) was then added dropwise from a syringe over ca 2 min, and the resulting yellow solution was stirred for 1 h at -78 °C. The cooling bath was removed and the NH_3 was allowed to evaporate under a stream of N_2 (3 h). Water was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using first hexane and then 9:1 hexane-EtOAc, gave **27.2** (1.04 g, 81%) as an oil: FTIR (CH_2Cl_2 cast) 2927, 2854, 1716, 1456, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9 H), 1.77-1.79 (m, 4 H), 2.63-2.64 (m, 2 H), 3.36-3.38 (m, 2 H), 5.71 (apparent dt, J = 10.6, 2.1 Hz, 2 H), 5.86-5.90 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.1 (t), 27.9 (q), 28.0 (t), 33.7 (t), 37.9 (t), 47.9 (s), 80.8 (s), 125.0 (d), 125.7 (d), 127.1 (d), 127.6 (d), 173.5 (s); exact mass m/z calcd for $C_{14}H_{21}{}^{79}BrNaO_2$ [M+Na] 323.0617, found 323.0618.

1-(3-Bromopropyl)-4-oxocyclohexa-2,5-dienecarboxylic acid *tert*-butyl ester (27.3).

27.2 **27.3**

A stirred solution of CrO_3 (1.67 g, 11.0 mmol) and Ac_2O (2.08 mL, 22.0 mmol) in AcOH (3.77 mL, 66 mmol) was cooled to 7 °C and diluted with dry PhH (15 mL). A solution of **27.2** (661 mg, 2.19 mmol) in PhH (5 mL) was added dropwise and stirring at 7 °C was continued for 3 h. The reaction mixture was diluted with EtOAc (20 mL) and carefully quenched with saturated aqueous $NaHCO_3$ (3 x 30 mL), washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x15 cm), using first hexane and then 7:3 hexane-EtOAc, gave the cross-conjugated ketone **27.3** (413 mg, 60%), as an oil: FTIR (CH_2Cl_2 cast) 2982, 2918, 1728, 1668, 1457, 1266 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.41 (s, 9 H), 1.70-1.73 (m, 2 H), 1.74-2.05 (m, 2 H), 3.32 (t, J = 6.4 Hz, 2H), 6.30 (d, J = 9.8 Hz, 2 H), 6.95 (d, J = 9.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.3 (t), 27.7 (q), 32.6 (t), 36.4 (t), 52.5 (s), 83.3 (s), 130.1 (d), 148.0 (d), 168.6 (s), 184.9 (s); exact mass m/z calcd for $C_{14}H_{19}{}^{79}BrNaO_3$ [M+Na] 337.0410, found 337.0411.

1-(3-Iodopropyl)-4-oxocyclohexa-2,5-dienecarboxylic acid *tert*-butyl ester (27.4).

27.3 **27.4**

Acetone (distilled from $KMnO_4$ and dried over 4Å molecular sieves) was added to a stirred mixture of **27.3** (1.16g, 3.67 mmol) and anhydrous NaI (2.75 g, 18.4 mmol). The mixture was stirred and refluxed overnight, cooled and partitioned between Et_2O (25 mL) and water (25 mL). The mixture was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using first hexane and then 1:9 EtOAc-hexane, gave **27.4** (1.17g, 88%) as an oil: FTIR (CH_2Cl_2 cast) 2927, 2854, 1716, 1456, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9 H), 1.77-1.79 (m, 4 H), 2.63-2.64 (m, 2 H), 3.36-3.38 (m, 2 H), 5.71 (apparent dt, J = 10.6, 2.1 Hz, 2 H), 5.86-5.90 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.1 (t), 27.9 (q), 28.0 (t), 33.7 (t), 37.9 (t), 47.9 (s), 80.8 (s), 125.0 (d), 125.7 (d), 127.1 (d), 127.6 (d), 173.5 (s); exact mass *m*/*z* calcd for $C_{14}H_{21}{}^{79}BrNaO_2$ [M+Na] 323.0617, found 323.0618.

6-Oxo-1,2,3,6,7,7a-hexahydroindene-3a-carboxylic acid *tert*-butyl ester (28.1).

27.4 **28.1**

A solution of Bu_3SnH (0.58 mL, 2.15 mmol) and AIBN (15 mg, 0.07 mmol) in dry THF (10 mL) was added over 5 h (syringe pump) to a stirred and heated (85 °C) solution of **27.4** (652 mg, 1.79 mmol) in THF (25 mL). Heating was continued overnight after the addition. Evaporation of the solvent and flash chromatography of the residue over KF-flash chromatography silica gel (10%w/w KF, 2.5 x 15 cm), using 9:1 to 7:3 hexane-EtOAc, gave **28.1** (123 mg, 96%) as an oil: FTIR (CH_2Cl_2 cast) 2966, 2875, 1722, 1680, 1266 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.36-1.40 (m, 1 H), 1.51 (s, 9 H), 1.53- 1.69 (m, 2 H), 1.84-1.98 (m, 2 H), 2.15-2.22 (m, 1 H), 2.38 (dd, *J* = 16.9, 3.2 Hz, 1 H), 2.69 (dd, *J* = 16.8, 5.6 Hz, 1 H), 2.82-2.84 (m, 2 H), 5.95 (d, *J* = 10.2 Hz, 1 H), 6.60 (dd, *J* = 10.2, 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.1 (t), 27.8 (q), 30.5 (t), 38.1 (t), 38.7 (t), 41.1 (d), 54.3 (s), 81.5 (s), 128.5 (d), 149.8 (d), 172.4 (s), 198.4 (s); exact mass *m*/*z* calcd for $C_{14}H_{20}O_3$ 236.1413, found 236.1414.

6-Oxo-1,2,3,6-tetrahydroindene-3a-carboxylic acid *tert*-butyl ester (29.2).

28.1 **29.2**

A solution of **28.1** (492 mg, 2.08 mmol) was added dropwise into a stirred and cooled (-78 °C) solution of $KN(SiMe_3)_2$ (0.5 M in PhMe, 5 mL, 2.5 mmol) in THF (10 mL). Stirring at -78 °C was continued for 15 min and Me_3SiCl (0.48 mL, 3.75 mmol) was then added dropwise. The cooling bath was removed and the mixture was stirred for 1 h. The mixture was then quenched by addition of saturated aqueous $NaHCO_3$. The mixture was diluted with CH_2Cl_2 (20 mL) and the organic layer was dried ($MgSO_4$) and evaporated. The residual **29.1** was used without further purification. MeCN (8 mL) was added, followed by $Pd(OAc)_2$ (467 mg, 2.08 mmol) and K_2CO_3 (574 mg, 4.16 mmol). Stirring was continued overnight. The mixture was filtered through a pad of Celite, using CH_2Cl_2. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.5 x 15 cm), using 9:1 hexane-EtOAc, gave **29.2** (315 mg, 65%) as an oil: FTIR ($CDCl_3$ cast) 3012, 2979, 1727, 1666, 1641, 1243, 1146 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37 (s, 9 H), 1.54-1.59 (m, 1 H), 1.91-1.97 (m, 2 H), 2.44-2.60 (m, 2 H), 2.71-2.83 (m, 1 H), 6.14 (s, 1 H), 6.25 (dd, J = 9.8, 1.4 Hz, 1 H), 6.95 (d, J =

9.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9 (t), 27.5 (q), 29.5 (t), 34.3 (t), 59.1 (s), 82.7 (s), 123.7 (d), 130.4 (d), 145.1 (d), 166.9 (s), 168.6 (s) 186.5 (s); exact mass *m*/*z* calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1261.

5-Allylindan (31.2)

29.2 **31.2**

Allylmagnesium bromide (1 M in Et_2O, 0.33 mL, 0.33 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **29.2** (51 mg, 0.22 mmol) in Et_2O (5 mL). The cold bath was removed and stirring was continued for 1 h. The mixture was cooled to 0 °C, quenched by dropwise addition of water, and extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated. The crude product was used directly in the next step. $BiCl_3 \cdot H_2O$ (74 mg, 0.22 mmol) was added to a solution of the crude product in a mixture of MeCN (5 mL) and water (0.1 mL), and the mixture was stirred at 70 °C for 3 h. Solid $NaHCO_3$ was added and mixture was stirred at room temperature for 10 min, and then filtered through a pad of Celite, using CH_2Cl_2 (2 x 10 mL) as a rinse. The filtrate was washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using hexane, gave **31.2** (20 mg, 75%) as an oil: FTIR ($CDCl_3$ cast) 3076, 3007, 2951, 2844, 1639, 1489, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.07 (apparent quintet, J = 7.4 Hz, 2 H), 2.88 (t, J = 7.4 Hz, 2 H), 2.89 (t, J = 7.4 Hz, 2 H), 3.36 (d, J = 6.8 Hz, 2 H), 5.05 (ddd, J = 10.0, 2.0, 1.2

Hz, 1 H), 5.10 (ddd J = 16.8, 1.6, 1.6 Hz, 1 H), 5.98 (ddd, J = 16.8, 10.0, 6.8 Hz, 1 H), 6.97 (d, J = 6.8 Hz, 1 H), 7.08 (s, 1 H), 7.16 (d, J = 7.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.4 (t), 32.4 (t), 32.7 (t), 40.0 (t), 115.2 (t), 124.1 (d), 124.4 (d), 126.2 (d), 137.7 (s), 137.8 (d), 141.8 (s), 144.4 (s); exact mass m/z calcd for $C_{12}H_{14}$ 158.1096, found 158.1099.

5-Phenylindan (31.3).

29.2 **31.3**

PhMgCl (2 M in THF, 0.22 mL, 0.44 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **29.2** (51 mg, 0.22 mmol) in Et_2O (5 mL). The cold bath was removed and stirring was continued for 1 h. The mixture was cooled to 0 °C, quenched by dropwise addition of saturated aqueous NH_4Cl (10 mL), and extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated. The crude product was used directly in the next step. $BiCl_3 \cdot H_2O$ (73 mg, 0.22 mmol) was added to a solution of the crude product in a mixture of MeCN (5 mL) and water (0.1 mL), and the mixture was stirred at 70 °C for 3 h. Solid $NaHCO_3$ was added and mixture was stirred at room temperature for 10 min, and then filtered through a pad of Celite, using CH_2Cl_2 (2 x 10 mL) as a rinse. The filtrate was washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using hexane, gave **31.3** (36 mg, 85%) as an oil: FTIR ($CDCl_3$ cast) 3058, 3030, 2950, 2842, 1599, 1480 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.16 (apparent quintet, J = 7.4 Hz, 2 H), 2.89 (two overlapping apparent q, J = 7.6 Hz, 4 H), 7.34-7.63 (m, 8 H); ^{13}C NMR ($CDCl_3$,

100 MHz) δ 25.6 (t), 32.6 (t), 32.9 (t), 123.2 (d), 124.6 (d), 125.2 (d), 126.8 (d), 127.2 (d), 128.7 (d), 139.5 (s), 141.8 (d), 143.4 (s), 144.9 (s); exact mass *m*/*z* calcd for $C_{15}H_{14}$ 194.1096, found 194.1091.

5-Phenylethynylindan (31.4).

29.2 **31.4**

i-PrMgBr (2.0 M in Et_2O, 0.16 mL, 0.33 mmol) was added at a slow dropwise rate to a stirred and cooled (-78 °C) solution of phenylacetylene (36 μL, 0.33 mmol) in dry THF (3 mL). The cooling bath was removed and stirring was continued for 1 h. The resulting acetylenic Grignard reagent was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **29.2** (50 mg, 0.22 mmol) in Et_2O (5 mL). The cold bath was removed and stirring was continued overnight. The mixture was cooled to 0 °C, quenched by dropwise addition of saturated aqueous NH_4Cl (10 mL), and extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated. The crude product was used directly in the next step. $BiCl_3 \cdot H_2O$ (73 mg, 0.22 mmol) was added to a solution of the crude product in a mixture of MeCN (5 mL) and water (0.1 mL), and the mixture was stirred at 70 °C for 3 h. Solid $NaHCO_3$ was added and mixture was stirred at room temperature for 10 min, and then filtered through a pad of Celite, using CH_2Cl_2 (2 x 10 mL) as a rinse. The filtrate was washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash

chromatography of the residue over silica gel, using hexane, gave **31.4** (29 mg, 62%) as an oil: FTIR ($CDCl_3$ cast) 3061, 3032, 2953, 2843, 2207, 1597, 1494 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.16 (apparent quintet, J = 7.5 Hz, 2 H), 2.93 (two overlapping apparent t, J = 7.5 Hz, 4 H), 7.19-7.56 (m, 8 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.3 (t), 32.7 (t), 32.9 (t), 88.2 (s), 90.1 (s), 120.7 (s), 123.6 (s), 124.3 (d), 127.5 (d), 127.9 (d), 128.3 (d), 129.6 (d), 131.5 (d), 144.4 (s), 144.8 (s); exact mass m/z calcd for $C_{17}H_{14}$ 218.1096, found 218.1094.

5-Ethynylindan (31.5).

29.2 **31.5**

Trimethylsilylacetylene (0.16 mL, 1.1 mmol) was added at a slow dropwise rate to a stirred and cooled (-78 °C) solution of *i*-PrMgBr (2.0 M in Et_2O, 0.55 mL, 1.1 mmol). The cooling bath was removed and stirring was continued for 2 h. The resulting Grignard reagent was taken up into a syringe and added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **29.2** (52 mg, 0.22 mmol) in Et_2O (5 mL). The cold bath was removed and stirring was continued overnight. The mixture was cooled to 0 °C, quenched by dropwise addition of saturated aqueous NH_4Cl (10 mL), and extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product was used directly in the next step. $BiCl_3 \cdot H_2O$ (73 mg, 0.22 mmol) was added to a solution of the crude product in a mixture of MeCN (5 mL) and water (0.1 mL), and the mixture was stirred at 70 °C for 3 h. Solid $NaHCO_3$ was added and mixture was stirred at room temperature for 10 min, and then filtered through a pad of Celite, using CH_2Cl_2 (2 x 10 mL) as a rinse. The filtrate was washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using hexane, gave **31.5** (18 mg,

57%) as an oil: FTIR ($CDCl_3$ cast) 3292, 2952, 2868, 2843, 2104, 1485 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.08 (apparent quintet J = 7.6 Hz, 2 H), 2.90 (two overlapping apparent q, J = 7.2 Hz, 4 H), 3.01 (s, 1 H), 7.16-7.36 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.3 (t), 32.6 (t), 32.9 (t), 75.9 (d), 84.4 (s), 119.5 (s), 124.3 (d), 128.0 (d), 130.2 (d), 144.3 (s), 145.4 (s); exact mass m/z calcd for $C_{11}H_{10}$ 142.0782, found 142.0782.

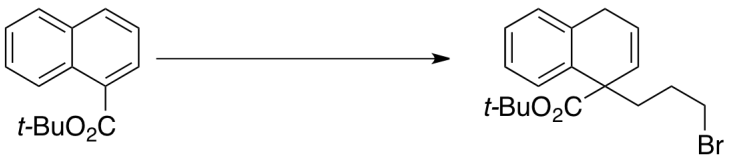
5-(Prop-2-ynyl)indane (31.6).

29.2 **31.6**

A mixture of propargyl bromide (80%$^{w}/_{w}$ in PhMe, 0.12 mL, 1.1 mmol), Mg (25 mg, 1.1 mmol) and $HgCl_2$ (1 mg, 0.004 mmol) was heated to reflux. The Mg dissolved, at which point the heat source was removed, and stirring was continued for 45 min. The resulting propargylmagnesium bromide was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **29.2** (84 mg, 0.358 mmol) in Et_2O (5 mL). The cold bath was removed and stirring was continued overnight. The mixture was cooled to 0 °C, quenched by dropwise addition of saturated aqueous NH_4Cl (10 mL), and extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product was used directly in the next step. $BiCl_3 \cdot H_2O$ (120 mg, 0.36 mmol) was added to a solution of the crude product in a mixture of MeCN (5 mL) and water (0.1 mL), and the mixture was stirred at 70 °C for 3 h. Solid $NaHCO_3$ was added and mixture was stirred at room temperature for 10 min, and then filtered through a pad of Celite, using CH_2Cl_2 (2 x 10 mL) as a rinse. The filtrate was washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using hexane,

gave **31.6** (41 mg, 73%) as an oil: FTIR ($CDCl_3$ cast) 3298, 3011, 2950, 2867, 2843, 2120, 1490 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.10 (apparent quintet, J = 7.6 Hz, 2 H), 2.19 (t, J = 2.8 Hz, 1 H), 2.92 (apparent q, J = 7.2 Hz, 4 H), 3.60 (d, J = 2.8 Hz, 2 H), 7.12-7.27 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.5 (t), 25.5 (t), 32.4 (t), 32.7 (t), 70.0 (d), 82.5 (s), 123.8 (d), 124.3 (d), 125.6 (d), 133.8 (s), 142.6 (s), 144.7 (s); exact mass m/z calcd for $C_{12}H_{12}$ 156.0939, found 156.0940.

1-(3-Bromopropyl)-1,4-dihydronaphthalene-1-carboxylic acid *tert*-butyl ester (27.6).

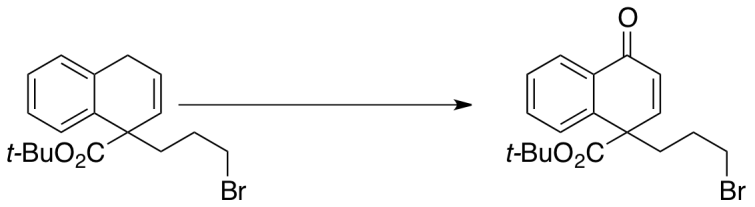


27.5 **27.6**

The apparatus consists of a three-necked round-bottomed flask containing a magnetic stirring bar and fitted with a cold finger condenser fused onto one of the necks. The exit of the condenser was fitted with a drying tube filled with $CaSO_4$. An external mark on the flask indicated the level corresponding to the desired volume of liquid ammonia. The central neck was closed by a septum carrying a nitrogen inlet. The flask was stoppered and cooled in a dry ice-acetone bath. The cold finger was charged with dry ice-acetone. Another round-bottomed flask was half-filled with liquid ammonia (around 50 mL) and several small pieces of Na were added, so as to form a permanently blue solution. This flask was connected via bent adaptors and dry Tygon tubing to the third neck of the other flask. A solution of **27.5** (2.28g, 12.0 mmol) in dry THF (15 mL) and *t*-BuOH (1.08 mL, 11.0 mmol) was injected into the three-necked flask, and liquid ammonia was allowed to condense into the flask. Lithium wire (154 mg, 22 mmol), cut into small pieces, was added rapidly to the vigorously stirred solution. Stirring at -78 °C was continued for 15 min, until a dark blue color persisted. Dibromopropane (2.88 mL, 30 mmol) in THF (5 mL) was then added dropwise

from a syringe over ca 2 min, and the resulting yellow solution was stirred for 1 h at -78 °C. The cooling bath was removed and the NH_3 was allowed to evaporate under a stream of N_2 (3 h). Water was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using first hexane and then 9:1 hexane-EtOAc, gave **27.6** (3.32 g, 95%) as an oil: FTIR (CH_2Cl_2 cast) 2977, 2932, 1726, 1664, 1599, 1456, 1251 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 9 H), 1.37-1.42 (m, 1 H), 1.58-1.81 (m, 1 H), 1.99-2.09 (m, 1 H), 2.21-2.31 (m, 1 H), 3.30 (t, *J* = 6.8 Hz, 2 H), 3.40-3.43 (m, 2 H), 5.66-5.70 (m, 1 H), 6.12-7.13 (m, 1 H), 7.15-7.18 (m, 3 H), 7.21-7.29 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.8 (q), 28.1 (t), 29.8 (t), 33.9 (t), 37.7 (t), 51.4 (s), 80.9 (s), 126.1 (d), 126.3 (d), 126.4 (d), 126.7 (d), 128.1 (d), 128.5 (d), 134.1 (s), 135.2 (s), 173.5 (s); exact mass *m*/*z* calcd for $C_{18}H_{23}{}^{79}BrNaO_2$ (M+Na) 373.0774, found 373.0770.

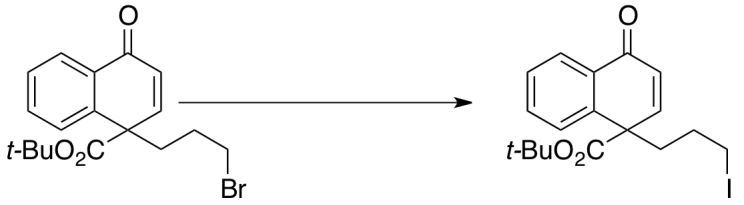
1-(3-Bromopropyl)-4-oxo-1,4-dihydronaphthalene-1-carboxylic acid *tert*-butyl ester (27.7).



27.6 **27.7**

PCC (1.08 g, 5.0 mmol) was added to a stirred solution of **27.6** (365 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) and stirring was continued for 3 days. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and then filtered through a pad of Celite, using CH_2Cl_2 (2 x 20 mL) as a rinse. Flash chromatography of the residue over silica gel (2.5 x15 cm), using first hexane and then 7:3 hexane-EtOAc, gave the cross-conjugated ketone **27.7** (342 mg, 60%), as an oil: FTIR (CH_2Cl_2 cast) 2978, 2932, 1730, 1667, 1456, 1247 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.22-1.26 (m, 1 H), 1.29 (s, 9 H), 1.53-1.61 (m, 1 H), 2.27 (ddd, *J* = 13.7, 11.9, 4.7 Hz, 1 H), 2.39 (ddd, *J* = 13.7, 12.1, 4.7 Hz, 1 H), 2.49-3.24 (m, 2 H), 6.55 (d, *J* = 10.2 Hz, 1 H), 6.90 (d, *J* = 10.2 Hz, 1 H), 7.42 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1 H), 7.51-7.57 (m, 2 H), 8.16 (dd, *J* = 7.8, 1.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.2 (t), 27.6 (q), 33.0 (t), 37.0 (t), 53.1 (s), 82.7 (s), 126.4 (d), 126.8 (d), 127.9 (d), 129.9 (d), 131.8 (s), 132.8 (d), 141.5 (s), 148.0 (d), 170.0 (s), 184.3 (s); exact mass *m*/*z* calcd for $C_{18}H_{21}{}^{79}BrNaO_3$ [M+Na] 387.0566, found 387.0564.

1-(3-Iodopropyl)-4-oxo-1,4-dihydronaphthalene-1-carboxylic acid *tert*-butyl ester (27.8).

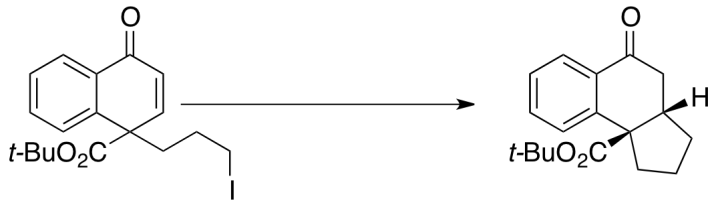


27.7 **27.8**

Acetone (distilled from $KMnO_4$ and dried over 4Å molecular sieves) was added to a stirred mixture of **27.7** (2.64 g, 7.24 mmol) and anhydrous NaI (5.43 g, 36.2 mmol). The mixture was stirred and refluxed overnight, cooled and partitioned between Et_2O (25 mL) and water (25 mL). The mixture was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using first hexane and then 1:9 EtOAc-hexane, gave **27.8** (2.49g, 84%) as an oil: FTIR (CH_2Cl_2 cast) 2978, 2931, 1729, 1666, 1600, 1244 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22-1.27 (m, 1 H), 1.32 (s, 9 H), 1.38-1.39 (m, 1 H), 2.26 (ddd, *J* = 13.8, 11.9, 4.4 Hz, 1 H), 2.46 (ddd, *J* = 16.7, 12.0, 4.7 Hz, 1 H), 3.03 (t, *J* = 6.8 Hz, 2 H), 6.60 (d, *J* = 10.2 Hz, 1 H), 6.91 (d, *J* = 10.3 Hz, 1 H), 7.46-7.49 (m, 1 H), 7.56-7.60 (m, 2 H), 8.21 (ddd, *J* = 7.9, 1.5, 0.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.6 (t), 27.4 (q), 27.6 (t), 39.1 (t), 52.9 (s), 82.6 (s), 126.3 (d), 126.8 (d), 127.8 (d), 129.8 (d), 131.7 (s), 132.7 (d), 141.4 (s), 147.9 (d), 169.9 (s), 184.2 (s); exact mass *m*/*z* calcd for $C_{18}H_{21}INaO_3$ [M+Na] 435.0428,

found 435.0425.

5-Oxo-1,2,3,3a,4,5-hexahydrocyclopenta[*a*]naphthalene-9b-carboxylic acid *tert*-butyl ester (28.2).



27.8 **28.2**

A solution of Bu_3SnH (0.36 mL, 1.35 mmol) and AIBN (8 mg, 0.05 mmol) in dry THF (10 mL) was added over 5 h (syringe pump) to a stirred and heated (85 °C) solution of **27.8** (480 mg, 1.13 mmol) in THF (20 mL). Heating was continued overnight after the addition. Evaporation of the solvent and flash chromatography of the residue over KF-flash chromatography silica gel (10%w/w KF, 2 x 15 cm), using 9:1 to 7:3 hexane-EtOAc, gave **28.2** (293 mg, 91%) as an oil: FTIR (CH_2Cl_2 cast) 2974, 2874, 1721, 1690, 1288 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 9 H), 1.43-1.45 (m, 2 H), 1.68-1.73 (m, 1 H), 1.95-2.01 (m, 1 H), 2.17-2.24 (m, 1 H), 2.52-2.66 (m, 2 H), 2.86-2.91 (m, 1 H), 3.04 (dd, *J* = 16.5, 5.5 Hz, 1 H), 7.32 (ddd, *J* = 7.8, 7.2, 1.3 Hz, 1 H), 7.40-7.42 (m, 1 H), 7.53 (ddd, *J* = 7.9, 7.2, 1.5 Hz, 1 H), 7.99 (ddd, *J* = 7.8, 1.5, 0.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4 (t), 27.8 (q), 30.5 (t), 38.3 (t), 39.7 (t), 42.3 (d), 56.5 (s), 81.2 (s), 126.5 (d), 127.0 (d), 128.0 (d), 132.0 (s), 133.9 (d), 143.6 (s), 173.7 (s), 197.8 (s); exact mass *m*/*z* calcd for $C_{18}H_{22}NaO_3$ [M+Na] 309.1461, found 309.1464.

5-Oxo-1,2,3,5-tetrahydrocyclopenta[*a*]naphthalene-9b-carboxylic acid *tert*-butyl ester (29.4).

28.2 **29.4**

A solution of **28.2** (282 mg, 0.99 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of $KN(SiMe_3)_2$ (0.5 M in PhMe, 2.96 mL, 1.48 mmol) in THF (6 mL). Stirring at -78 °C was continued for 15 min and Me_3SiCl (0.25 mL, 1.98 mmol) was then added dropwise. The cooling bath was removed and the mixture was stirred for 1 h. The mixture was then quenched by addition of saturated aqueous $NaHCO_3$. The mixture was diluted with CH_2Cl_2 (20 mL) and the organic layer was dried ($MgSO_4$) and evaporated. The residual **29.3** was used without further purification. MeCN (6 mL) was added, followed by $Pd(OAc)_2$ (222 mg, 0.99 mmol) and K_2CO_3 (69 mg, 0.50 mmol). Stirring was continued overnight. The mixture was filtered through a pad of Celite, using CH_2Cl_2. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.0 x 15 cm), using 9:1 hexane-EtOAc, gave **29.4** (152 mg, 54%) as a white solid: mp 63-64 °C; FTIR (CH_2Cl_2 cast) 2923, 2850, 1725, 1663, 1599, 1246 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.22 (s, 9 H), 1.73-2.00 (m, 1 H), 2.01-2.05 (m, 2 H), 2.59-2.68 (m, 1 H), 2.77-2.86 (m, 1 H), 3.11 (ddd, J = 8.8, 4.3, 4.3

Hz, 1 H), 6.39 (s, 1 H), 7.41-7.53 (m, 3 H), 8.14 (ddd, *J* = 7.7, 1.4, 0.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.8 (t), 27.4 (q), 29.4 (t), 34.4 (t), 59.3 (s), 82.3 (s), 123.7 (d), 126.4 (d), 126.5 (d), 127.6 (d), 131.4 (s), 131.8 (d), 142.0 (s), 166.5 (s), 169.6 (s), 185.8 (s); exact mass *m*/*z* calcd for $C_{18}H_{20}NaO_3$ (M + Na) 307.1305, found 307.1307.

5-Allyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalene (31.8).

29.4 **31.8**

Allylmagnesium bromide (1.0 M in Et_2O, 0.24 mL, 0.24 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **29.4** (46 mg, 0.16 mmol) in Et_2O (5 mL). The cold bath was removed and stirring was continued overnight. The mixture was cooled to 0 °C, quenched by dropwise addition of saturated aqueous NH_4Cl (10 mL), and extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$) and evaporated. The crude product was used directly in the next step. $BiCl_3 \cdot H_2O$ (53 mg, 0.16 mmol) was added to a solution of the crude product in a mixture of MeCN (5 mL) and water (0.1 mL), and the mixture was stirred at 70 °C for 3 h. Solid $NaHCO_3$ was added and mixture was stirred at room temperature for 10 min, and then filtered through a pad of Celite, using CH_2Cl_2 (2 x 10 mL) as a rinse. The filtrate was washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using hexane, gave **31.8** (20 mg, 60%) as an oil: FTIR (CH_2Cl_2 cast) 3074, 2950, 2844, 1638, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.25 (apparent quintet, J = 7.4 Hz, 2 H), 3.11 (t, J = 7.6 Hz, 2 H), 3.27 (t, J = 7.6 Hz, 2 H), 3.84 (d, J = 6.4 Hz, 2

H), 5.10 (t, J = 1.6 Hz, 1 H), 5.12-5.15 (m, 1 H), 6.09-6.19 (m, 1 H), 7.30 (s, 1 H), 7.44-8.05 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.5 (t), 31.2 (t), 33.9 (t), 37.5 (t), 115.9 (t), 123.8 (d), 124.6 (d), 124.7 (d), 125.0 (d), 125.5 (d), 130.8 (s), 130.9 (s), 134.7 (s), 137.4 (d), 138.1 (s), 140.7 (s); exact mass m/z calcd for $C_{16}H_{16}$ 208.1252, found 208.1251.

5-(1-Chlorovinyl)-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalene (31.9).

29.4 **31.9**

Trimethylsilylacetylene (0.12 mL, 0.8 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of *i*-PrMgBr (2.0 M in Et_2O, 0.4 mL, 0.8 mmol). The cooling bath was removed and the stirring was continued for 2 h. The resulting Grignard reagent was taken up into a syringe and added at fast dropwise rate to a stirred and cooled (-78 °C) solution of **29.4** (152 mg, 0.535 mmol) in Et_2O (5 mL). The cold bath was removed and the stirring was continued overnight. The mixture was cooled to 0 °C, quenched by dropwise addition of saturated aqueous NH_4Cl (10 mL), and extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and evaporated. The crude product was used directly in the next step. $BiCl_3 \cdot H_2O$ (178 mg, 0.54 mmol) was added to a solution of the crude product in a mixture of MeCN (5 mL) and water (0.1 mL), and the mixture was stirred at 70 °C for 3 h. Solid $NaHCO_3$ was added and the mixture was stirred at room temperature for 10 min, and then filtered through a pad of Celite, using CH_2Cl_2 (2 x 10 mL) as a rinse. The filtrate was washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using

hexane, gave **31.9** (49 mg, 40%) as an oil: FTIR (CH_2Cl_2 cast) 3063, 2952, 2844, 1628, 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.29 (apparent quintet, J = 7.6 Hz, 2 H), 3.14 (t, J = 7.6 Hz, 2 H), 3.30 (t, J = 7.6 Hz, 2 H), 5.57 (d, J = 1.2 Hz, 1 H), 5.85 (d, J = 1.2 Hz, 1 H), 7.49-8.23 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.4 (t), 31.3 (t), 33.6 (t), 117.3 (t), 124.1 (d), 124.6 (d), 125.2 (d), 125.9 (d), 126.1 (d), 129.3 (s), 130.4 (s), 135.4 (s), 139.1 (s), 140.1 (s), 141.2 (s); exact mass m/z calcd for $C_{15}H_{13}{}^{35}Cl$ 228.0706, found 228.0706.

2-(2,3-Dihydro-1*H*-cyclopenta[*a*]naphthalen-5-yl)furan (31.10).

29.4 **31.10**

n-BuLi (1.6 M in hexane, 3.13 mL, 5 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of furan (0.36 mL, 5 mmol) and TMEDA (0.75 mL, 5 mmol) in Et_2O (1.8 mL). The cooling bath was replaced by an ice bath and stirring was continued for 45 min. The resulting furanyllithium (0.46 mL) was taken up into a syringe and added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **29.4** (65 mg, 0.23 mmol) in Et_2O (5 mL). The cold bath was replaced by an ice bath and stirring was continued overnight. The mixture was cooled to 0 °C, quenched by dropwise addition of saturated aqueous NH_4Cl, and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product was used directly in the next step. $BiCl_3 \cdot H_2O$ (77 mg, 0.23 mmol) was added to a solution of the crude product in a mixture of MeCN (5 mL) and water (0.1 mL), and the mixture was stirred at 70 °C for 3 h. Solid $NaHCO_3$ was added and mixture was stirred at room temperature for 10 min, and then filtered through a pad of Celite, using CH_2Cl_2 (2 x 10 mL) as a rinse. The filtrate was washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using

hexane, gave **31.10** (37 mg, 69%) as an oil: FTIR (CH_2Cl_2 cast) 3063, 2952, 2844, 1579, 1514, 1498, 1457 cm^{-1};^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.29 (apparent quintet, *J* = 7.5 Hz, 2 H), 3.15 (t, *J* = 7.8 Hz, 2 H), 3.30 (t, *J* = 7.8 Hz, 2 H), 6.57-6.59 (m, 1 H), 6.66-6.67 (m, 1 H), 7.47-8.38 (m, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.4 (t), 31.3 (t), 33.7 (t), 108.6 (d), 111.1 (d), 123.6 (d), 124.7 (d), 125.2 (d), 125.8 (d), 126.1 (d), 127.3 (s), 129.6 (s), 130.7 (s), 140.2(s), 140.4 (s), 142.0 (s), 153.4 (s); exact mass *m*/*z* calcd for $C_{17}H_{14}O$ 234.1045, found 234.1044.

5. References

1 (a) For addition to carbon-carbon double bonds: Togo, H.; Kikuchi, O. *Tetrahedron Lett*. **1988**, *29*, 4133-4134. Dittami, J. P.; Ramanthan, H. *Tetrahedron Lett*. **1988**, *29*, 45-48. Clark, A. J.; Jones, K. *Tetrahedron Lett*. **1989**, *30*, 5485-5488. Jones, K.; Brunton, S. A. Gosain, R. *Tetrahedron Lett*. **1999**, *40*, 8935-8938. (b) For addition to carbon-carbon triple bonds: Brunton, S. A.; Jones, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 763-768.

2 (a) Crich, D.; Hwang, J.-T. *J. Org. Chem*. **1998**, *63*, 2765-2770. (b) Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Story, J. M. D. *Angew. Chem. Int. Ed.* **2004**, *43*, 95-98.

3 For leading references to cyclization of aryl radicals onto aromatic rings: Clyne, M. A.; Aldaggagh, F. *Org. Biomol. Chem.* **2006**, *4*, 268-277.

4 Example of cyclization of vinyl radicals onto aromatic rings: Du, W.; Curran, D. P. *Org. Lett*. **2003**, *5*, 1765-1768.

5 Gowrisankar, S.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett*. **2007**,*48*, 3105-3108.

6 Bowman, W. R.; Storey, J. M. D. *Chem. Soc. Rev*. **2007**, *36*, 1803-1822.

7 (a) Studer, A.; Amrein, A. *Synthesis* **2002**, 835-839. (b) Parsons, A. *Chem. Brit*. **2002**, 42-45.

8 (a) Narasimhan, N. S.; Aidhen, I. S. *Tetrahedron Lett*. **1988**, *29*, 2987-2988. (b) Estévez, J. C.; Villaverde, M. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **1995**, *51*, 4075-4082.

9 Suzuki, H.; Aoyagi. S.; Kibayashi, C. *Tetrahedron Lett*. **1995**, *36*, 935-936.

10 (a) Harrowven, D. C.; Guy, I. L.; Nanson, L. *Angew. Chem. Int. Ed*. **2006**, *45*, 2242-2245. (b) Harrowven, D. C.; Nunn, M. I. T.; Fenwick, D. R. *Tetrahedron Lett*. **2002**, *43*, 7345-7347. (c) Harrowven, D. C.; Nunn, M. I. T.; Fenwick, D. R. *Tetrahedron Lett*. **2002**, *43*, 3189-3191.

11 Woodcock, T.; Howes, P. D. *Angew. Chem. Int. Ed*. **2005**, *44*, 3899-3901.

12 Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron Lett*. **2001**, *42*, 9061-9064.

13 (a) Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron Lett*. **2001**, *42*, 2907-2910. (b) Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron* **2002**, *58*, 3387-3400.

14 Nadin, A.; Harrisson, T. *Tetrahedron Lett*. **1999**, *40*, 4073-4076.

15 Allin, S. M.; Bowman, W, R.; Elsegood, M. R. J.; McKee, V.; Karim, R.; Rahman, S. S. *Tetrahedron* **2005**, *61*, 2689-2696.

16 Ganguly, A. K.; Wang, C. H.; Chan, T. M.; Ing, Y. M.; Buevich, A. V. *Tetrahedron Lett*. **2004**, *45*, 883-886.

17 For reviews on acyl radical chemistry: (a) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177-194. (b) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991-2069.

18 Motherwell, W. B.; Vázquez, S. *Tetrahedron Lett*. **2000**, *41*, 9667-9671.

19 Sundberg, R. J. *Indoles*; Academic Press: New York, **1996**; pp 105-134.

20 Bennasar, M. L.; Roca, T.; Ferrando, F. *Tetrahedron Lett*. **2004**, *45*, 5605-5609.

21 Bennasar, M. L.; Roca, T.; Ferrando, F. *J. Org. Chem*. **2005**, *70*, 9077-9080.

22 Bennasar, M. L.; Roca, T.; Ferrando, F. *Org. Lett*. **2006**, *8*, 561-564.

23 Padwa, A.; Rashatasakhon, P.; Ozdemir, A. D.; Willis, J. *J. Org. Chem*. **2005**, *70*, 519-528.

24 Benati, L.; Leardini, R.; Minozzi, M.; Nanni, D.; Spangnolo, P.; Zanardi, G. *J. Org. Chem*. **2000**, *65*, 8669-8674 and references therein.

25 Pedersen, J. M.; Bowman, W. R.; Elsegood, M. R. J.; Fletcher, A. J.; Lovell, P. J. *J. Org. Chem*. **2005**, *70*, 10615-10618.

26 Bowman, W. R.; Fletcher, A. J.; Pedersen, J. M.; Lovell, P. J.; Elsegood, M. R. J.; Lopez, E. H. *Tetrahedron* **2007**, *63*, 191-203.

27 Typical examples of alkyl radical cyclization onto heteroaromatic rings: (a) Murphy, J. A.; Sherburn, M. S. *Tetrahedron* **1991**, *47*, 4077-4088. (b) Moody, C. J.; Norton, C. L. *J. Chem. Soc., Perkin Trans 1* **1997**, 2639-2643. (c) Aldabbagh, F.; Bowman, W. R.; Mann, E.; Slawin, A. M. Z. *Tetrahedron* **1999**, *55*, 8111-8128. (d) Marco-Contelles, J.; Rodríguez-Fernández, M. *Tetrahedron Lett*. **2000**, *41*, 381-384. (e) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Romero, Y.; Muchowski, J. M. *Tetrahedron Lett*. **2000**, *41*, 10181-10184. (f) Bowman, W. R.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans 1* **2002**, 2747-2762. (g) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron*

Lett. **2002**, *43*, 4191-4193. (h) Gagosz, F.; Zard, S. Z. *Org. Lett*. **2002**, *4*, 4345-4348.

28 Beckwith, A. L.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun*. **1995**, 977-978.

29 Nishio, T.; Iseki, K.; Araki, N.; Miyazaki, T. *Helv. Chim. Acta* **2005**, *88*, 35-41.

30 Reynolds, A. J.; Scott, A. J.; Turner, C. I.; Sherburn, M. S. *J. Am. Chem. Soc*. **2003**, *125*, 12108-12109.

31 (a) Murphy, J. A.; Sherburn, M. S. *Tetrahedron* **1991**, *47*, 4077-4088. (b) Murphy, J. A.; Sherburn, M. S. *Tetrahedron Lett*. **1990**, *31*, 3495-3496.

32 Storey, J. D.; Ladwa, M. M. *Tetrahedron Lett*. **2006**, *47*, 381-383.

33 (a) Aldabbagh, F.; Bowman, W. R.; Mann, E. *Tetrahedron Lett*. **1997**, *38*, 7937-7940. (b) Aldabbagh, F.; Bowman, W. R.; Mann, E.; Slawin, A. M. Z. *Tetrahedron* **1999**, *55*, 8111-8128.

34 (a) Axon, J.; Boiteau, L.; Boivin, J.; Forbes, J. E.; Zard, S. Z. *Tetrahedron Lett*. **1994**, *35*, 1719-1722. (b) Liard, A.; Quiclet-Sire, B.; Saicic, R.; Zard, S. Z. *Tetrahedron Lett*. **1997**, *38*, 1759-1762. (c) Cholleton, N.; Zard, S. Z. *Tetrahedron Lett*. **1998**, *39*, 7295-7298. (d) Hoang-Cong, X.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett*. **1999**, *40*, 2125-2126. (e) Ly, T.-M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett*. **1999**, *40*, 2533-2536. (f) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem. Int. Ed*. **2000**, *39*, 731-733. (g) Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun*. **2002**, 1692-1693. (h)

Quiclet-Sire, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun*. **2002**, 2306-2307. (i) Zard, S. Z. *Aust. J. Chem*. **2006**, *59*, 663-668.

35 Gagosz, F.; Moutrille, C.; Zard, S. Z. *Org. Lett*. **2002**, *4*, 2707-2709.

36 Gagosz, F.; Zard, S. Z. *Org. Lett*. **2002**, *4*, 4345-4348.

37 Pave, G.; Usse-Versluys, S.; Viaud-Maussard, M. C.; Guillaumet, G. *Org. Lett*. **2003**, *5*, 4253-4256.

38 Zard, S. Z. *Angew. Chem. Int. Ed*. **1997**, *36*, 672-685.

39 (a) Clive, D. L. J.; Fletcher, S. P.; Liu, D. *J. Org. Chem*. **2004**, *69*, 3282-3293. (b) Fletcher, S. P.; Clive, D. L. J.; Peng, J.; Wingert, D. A. *Org. Lett*. **2005**, *7*, 23-26. (c) Clive, D. L. J.; Peng, J.; Fletcher, S. P.; Ziffle, V. E.; Wingert, D. A. *J. Org. Chem*. **2008**, *73*, 2330-2344.

40 (a) Bolmann, F.; Zdero, C.; Le Van, N. *Phytochemistry* **1979**, *18*, 99. (b) Johnson, T. W.; Corey, E. J. *J. Am. Chem. Soc*. **2001**, *123*, 4475-4479. (c) Nicolaou, K. C.; Reingruber, R.; Sarlah, D.; Brase, S. *J. Am. Chem. Soc*. **2009**, *131*, 2086-2087.

41 (a) Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677-680. (b) Pelter, A.; Ward. R. S.; Abd-El-Ghani, A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2249-2251. (c) McKillop, A.; McLaren, L.; Taylor. R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2047-2048. (d) Goldstein, D. M.; Wipf, P. *Tetrahedron Lett*. **1996**, *37*, 739-742. (e) McKillop, A. .; McLaren, L.; Taylor, R. J. K.; Watson. R. J.; Lewis, N. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1385-1393. (f) Karam, O.; Martin, A.; Jouannetaud, M.-P.; Jacquesy, J.-C. *Tetrahedron Lett*. **1999**, *40*, 4183-4186. (g) Camps, P.;

González, A.; Muñoz-Torrero, D.; Simon, M.; Zúñiga, A. ; Martins, M. A.; Font-Bardia, M.; Solan, X. *Tetrahedron* **2000**, *56*, 8141-8151. (h) Van De Water, R. W.; Hoarau, C.; Pettus, T. R. R. *Tetrahedron Lett.* **2003**, *44*, 5109-5113. (i) Liu, Q.; Rovis, T. *J. Am. Chem. Soc*. **2006**, *128*, 2552-2553. (j) Carreño, M. C.; González-López, M.; Urbano, A. *Angew. Chem. Int. Ed*. **2006**, *45*, 2737-2741. (k) Oxidation of trimethylsilyl ethers of *para-aryl* phenols gives yields in the range 66-82%: Felpin, F.-X. *Tetrahedron Lett*. **2007**, *48*, 409-412. We found that the triisopropylsilyl ether of *p*-propylphenol did not react with $PhI(OCOCF_3)_2$. (l) Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem. Soc*. **2008**, *130*, 404-405.

42 Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki. M.; Yakura, T. *J. Org. Chem*. **1991**, *56*, 435-438.

43 (a) Murahashi, S.-I.; Naota, T.; Miyaguchi, N.; Noda, S. *J. Am. Chem. Soc*. **1996**, *118*, 2509-2510. (b) Ochiai, M.; Nakanishi, A.; Yamada, A. *Tetrahedron Lett*. **1997**, *38*, 3927-2930.

44 (a) Bachi, M. D.; Epstein, J. W.; Herzberg-Minzly, Y.; Loewenthal, H. J. E. *J. Org. Chem.* **1969**, *34*, 126-135. (b) Van Bekkum, H.; Van den Bosch, C. B.; Van Minnen-Pathuis, G.; De Mos, J. C.; Van Wijk, A. M. *Rec. Trav. Chim*. **1971**, *90*, 137-149. (c) Taber, D. F. *J. Org. Chem*. **1976**, *41*, 2649-2650. (d) Birch, A. J.; Slobbe, J. *Aust. J. Chem*. **1977**, *30*, 1045-1049. (e) Hook, J. M.; Mander, L. N. *J. Org. Chem*. **1980**, *45*, 1722-1724.

(f) Schultz, A. G.; Dittami, J. P.; Lavieri, F. P.; Salowey, C.; Sundararaman, P.; Szymula, M. B. *J. Org. Chem*. **1984**, *49*, 4429-4440.

45 Schultz, A. G.; Lavieri, F. P.; Macielag, M.; Plummer, M. *J. Am. Chem. Soc*. **1987**, ***109***, 3991-4000.

46 (a) Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc*. **1986**, *108*, 5893-5901. (b) Ingold, K. U.; Lusztyk, J.; Scaiano, J. C. *J. Am. Chem. Soc*. **1984**, *106*, 343-384.

47 (a) Clive, D. L. J. *J. Chem. Soc.*, *Chem. Commun.* **1973**, 695-696. (b) Clive, D. L. J. *J. Chem. Soc. Chem.*, *Commun.* **1974**, 100. (c) Clive, D. L. J.; Chittattu, G. *J. Chem. Soc. Chem.*, *Commun.* **1977**, 484-485.

48 Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.*, **1978**, *43*, 1011-1013.

49 Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem. Int. Ed.* **2002**, *41*, 996-1000.

50 Navath, R. S.; Pabbisetty, K. B.; Hu, L. *Tetrahedron Lett*. **2006**, *47*, 389-393.

51 Koseki, Y.; Yamada, H.; Usuki, T. *Tetrahedron: Asymmetry*, **2011**, *22*, 580-586.

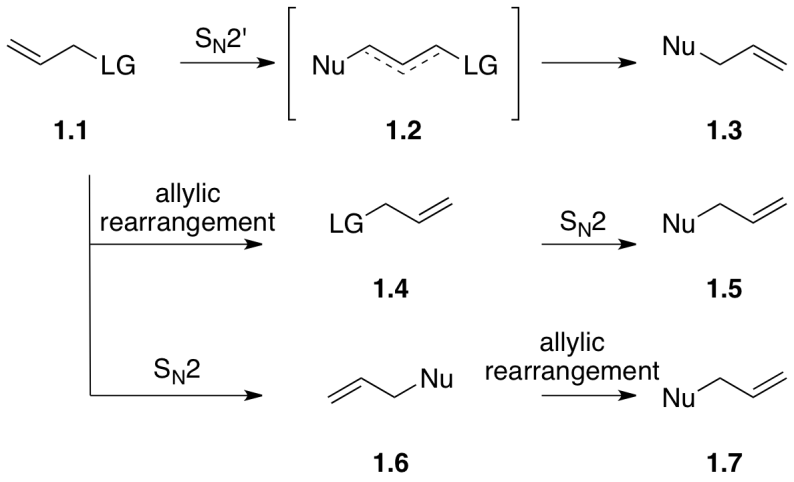
Chapter 2

Formation of unusual seven-membered heterocycles incorporating nitrogen and sulfur by intramolecular conjugate displacement

1. INTRODUCTION

1.1 *General*

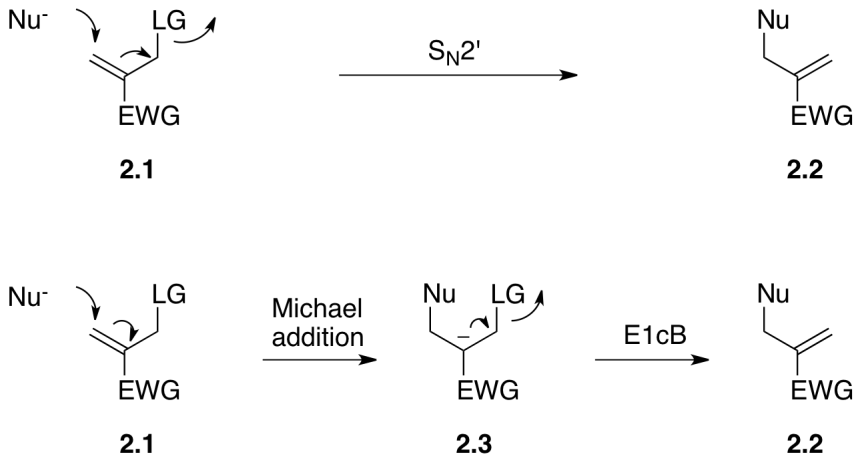
In general, in S_N2' reactions, a nucleophile attacks the double bond of an allylic system which leads to migration of the double bond and ejection of the leaving group. In most cases, such processes are considered to occur in a concerted manner.[1] However, in certain allylic systems the mechanism is not settled. The S_N2' reaction can also be imagined as an S_N2 reaction followed by an allylic rearrangement or an initial allylic rearrangement along with a direct S_N2 displacement (Scheme 1). Elimination of the later possibilities is required to identify a genuinely concerted S_N2' reaction.



Scheme 1

Enhancement of the S_N2' pathway can be achieved when an electron-withdrawing group is attached to the central carbon of the allylic system. In terms of reaction mechanism, such a reaction would be visualized as a hybrid of a

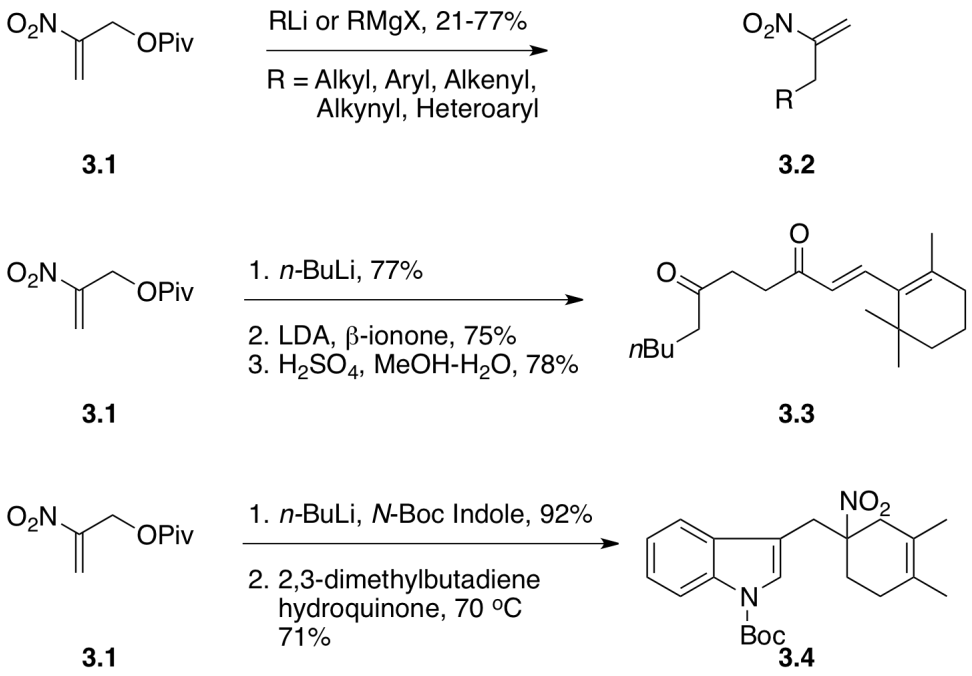
classical Michael addition and an E1cB reaction. The outcome of the reaction will be the same as an ideal S_N2' process. However, a direct, concerted S_N2' mechanism cannot be ruled out since the electron-withdrawing group lowers the LUMO of the allylic system which favors attack by a nucleophile.



Scheme 2

1.2 Intermolecular and intramolecular conjugate displacements with carbon nucleophiles

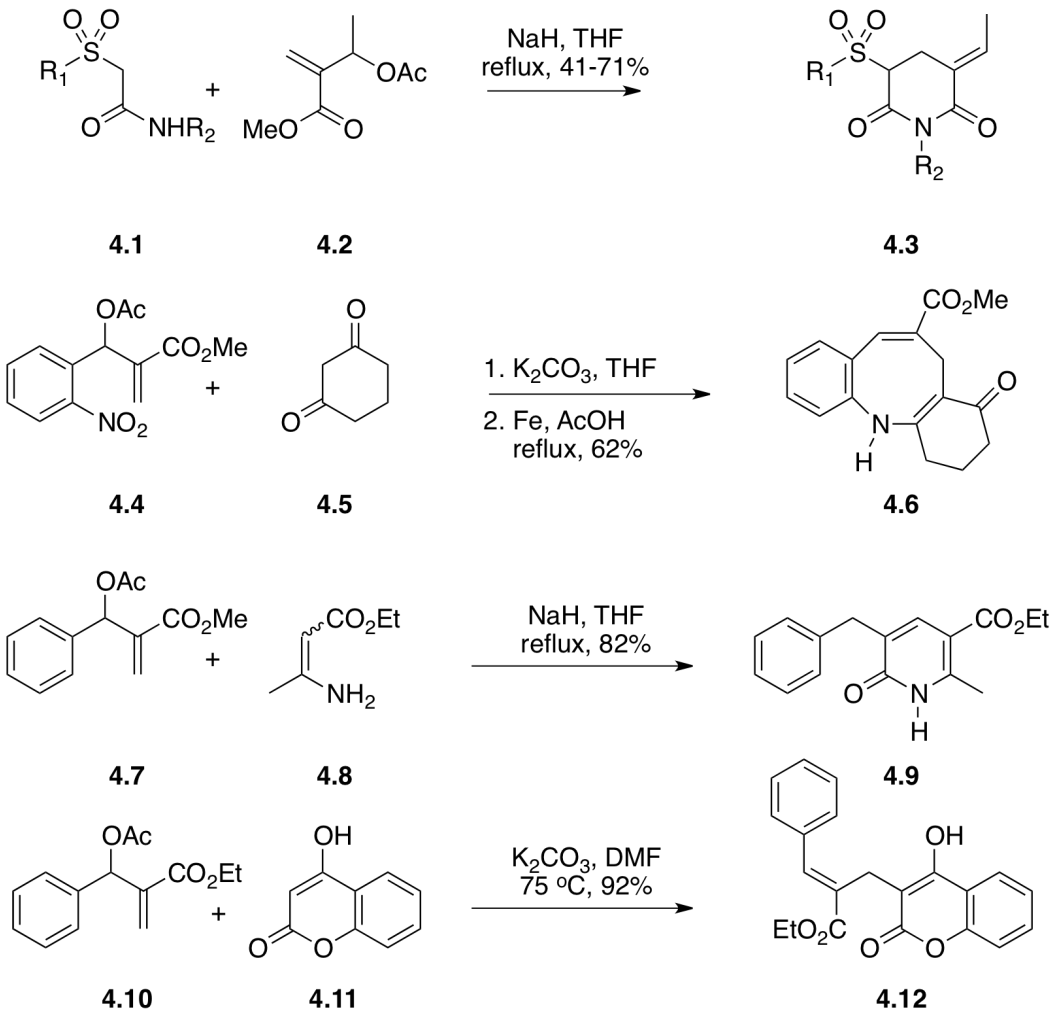
Early examples of these reactions in an intermolecular mode were reported by Seebach and coworkers.[2] Hard nucleophiles, such as Grignard reagents and organolithiums, were added to allyl pivaloate and its derivatives. The desired S_N2' reactions readily occurred and the double bond shifted products **3.2** were obtained in moderate to good yields. Subsequent Michael additions, followed by $E1_CB$ reactions, furnished α,α'-functionalized ketones **3.3**. Nitroethylenes were perfect substrates for a subsequent Diels-Alder reaction. Some general examples of both types of transformations are shown in Scheme 3.



Scheme 3

The previously discussed intermolecular processes have received considerable attention and have been studied in many research groups. Both carbanions and heteroatoms were successfully used as nucleophiles. The general starting materials were allyl acetates bearing an electron-withdrawing group on the central carbon. These compounds could be simply synthesized via Morita-Baylis-Hillman (MBH) reaction followed by acetylation of the resulting alcohol.[3] Allyl halides could also be used in a similar way.

In general, the carbanions used as nucleophiles usually carried two electron-withdrawing groups which strongly enhanced the reactivity. 1,3-Dicarbonyl compounds were very good nucleophiles.[4] Some examples of the intermolecular reactions are presented in Scheme 4.



4.1 **4.2** **4.3**

4.4 **4.5** **4.6**

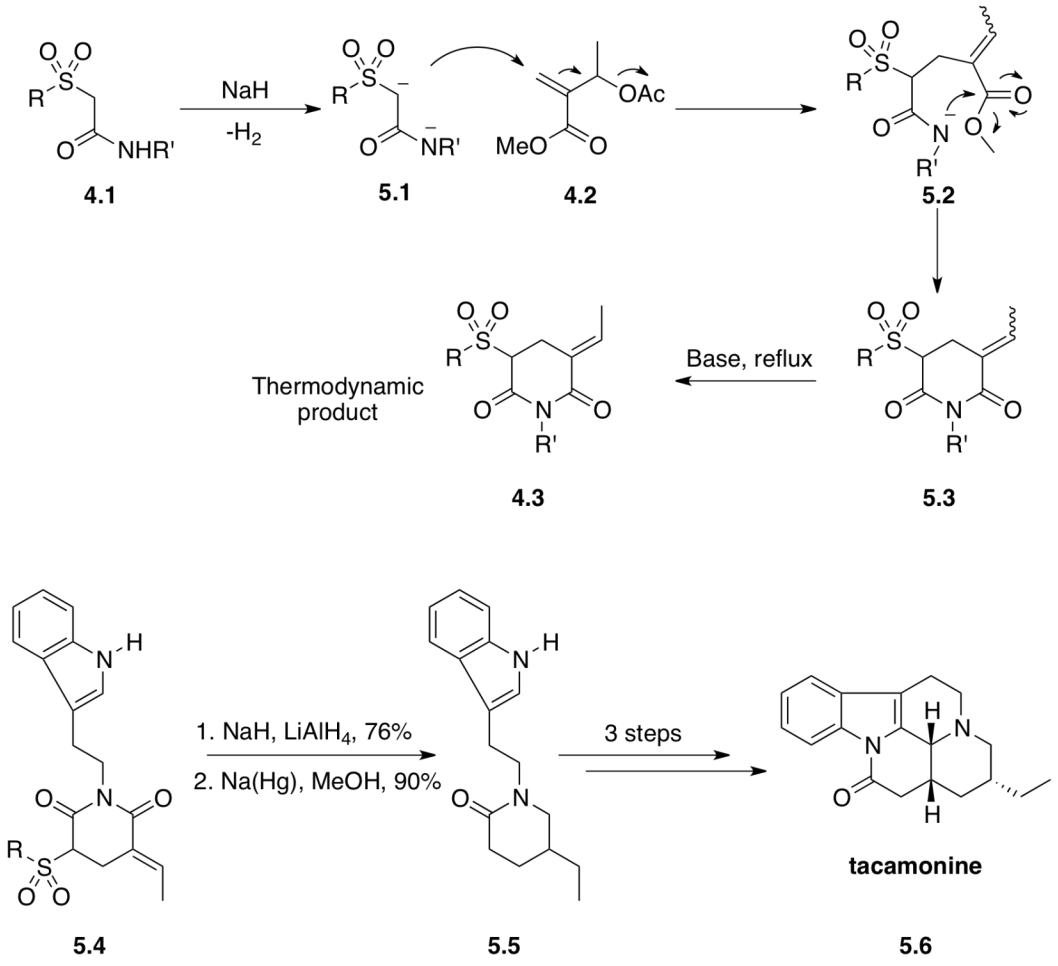
4.7 **4.8** **4.9**

4.10 **4.11** **4.12**

Scheme 4

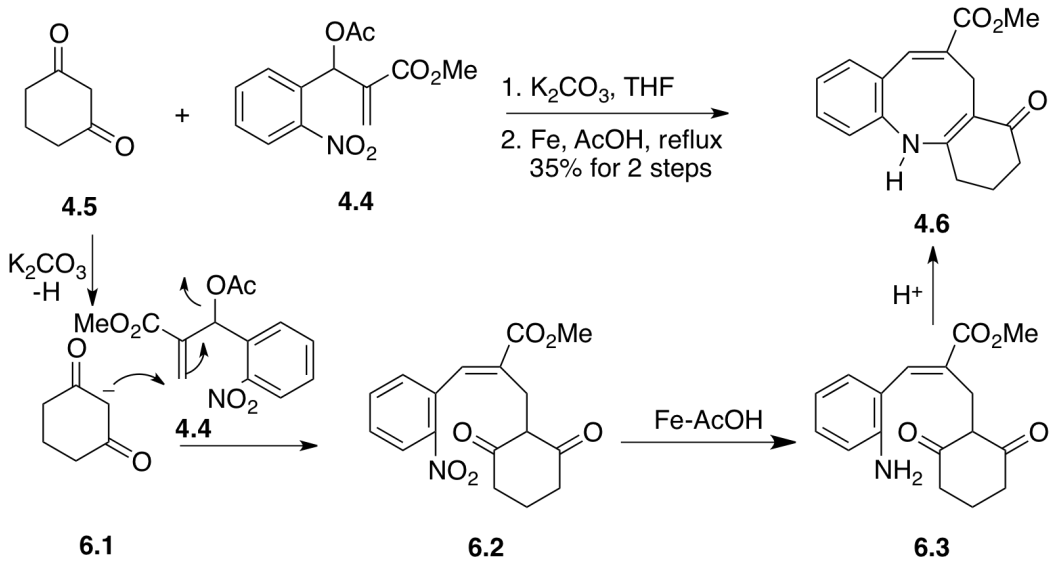
Chang and coworkers used this synthetic method for the synthesis of piperidine-2,6-diones (glutarimides).[4b] A formal synthesis of tacamonine was also achieved via this methodology as the key step. The detailed mechanism of such a reaction can be explained in the following way (Scheme 5): Treatment with sodium hydride removed both the amide proton and the α proton. The relatively soft carbanion attacked the MBH acetate by an S_N2' pathway which shifted the double bond and expelled the acetate leaving group. The nitrogen anion then attacked the ester group and formed the glutarimide **5.3**. Refluxing

under basic conditions provided the thermodynamically favored product **4.3** with the desired double bond geometry. Using the very the same method, **5.4** was synthesized. **It** was then treated with NaH and $LiAlH_4$, followed by sodium amalgam to obtain **5.5** (by reduction of imide, 1,4-reduction of the unsaturated amide and desulfonylation). Compound **5.5** could be converted to racemic tacanonine (**5.6**) in 3 additional steps.



Scheme 5

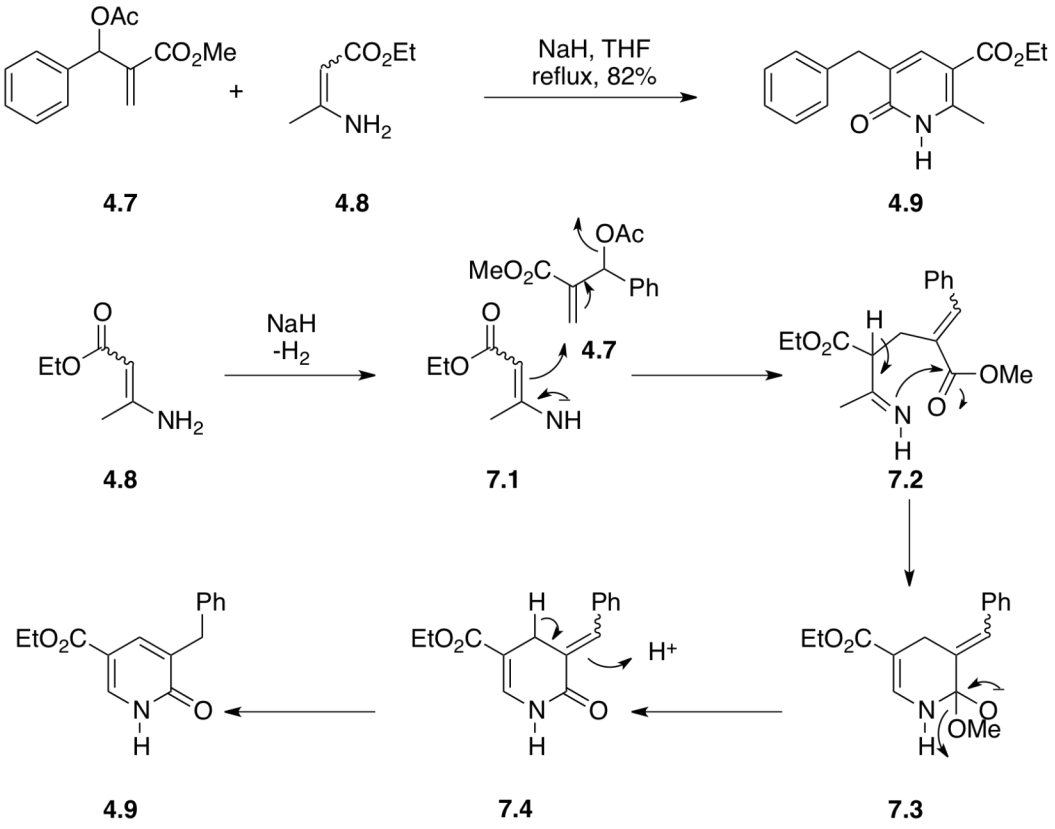
Basavaiah and coworkers reported the synthesis of functionalized tricyclic and tetracyclic frameworks containing the azocine moiety via intermolecular conjugate displacement.[4d] 1,3-Cyclohexanedione was used as the nucleophile and the intermolecular conjugate displacement readily occurred to furnish **6.2**. The reduction of the nitro group of **6.2** yielded **6.3**, which was then condensed under acid conditions to give the tricycle **4.6**.



Scheme 6

Rao and coworkers used enamines as nucleophiles to attack similar MBH acetates for the synthesis of pyridones, such as **4.9**.[4g] Initial deprotonation of the amine activated the enamine **4.8** as a carbanion to attack the MBH acetate via a S_N2' pathway. Loss of the α-proton of the intermediate imine **7.2** and tautomerization gave an enamine anion that rapidly attacked the ester group and generated lactam **7.4**. Migration of the double bond gave the pyridone as the thermodynamically favored product due to aromatic stabilization.

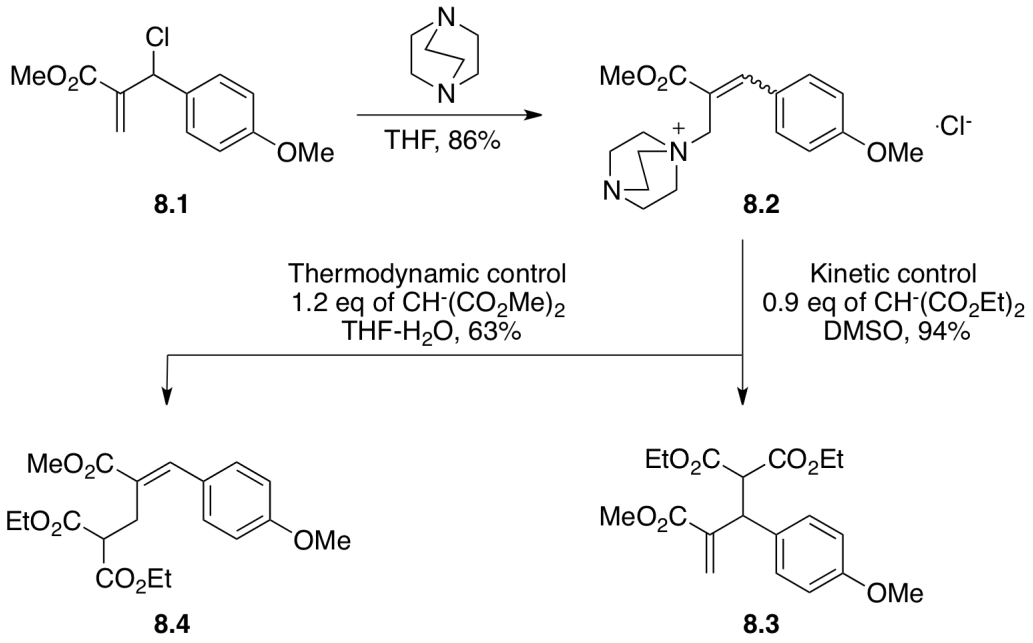
Retaining the regiochemistry of the double bond in intermolecular conjugate displacements would be interesting since a general S_N2 process may be difficult to achieve. Instead of an S_N2 reaction, an S_N2'-S_N2' sequence could be used since the intermolecular conjugate addition strongly favors the S_N2' pathway. In such a case, a promoter, commonly a phosphine or a tertiary amine, is required.



Scheme 7

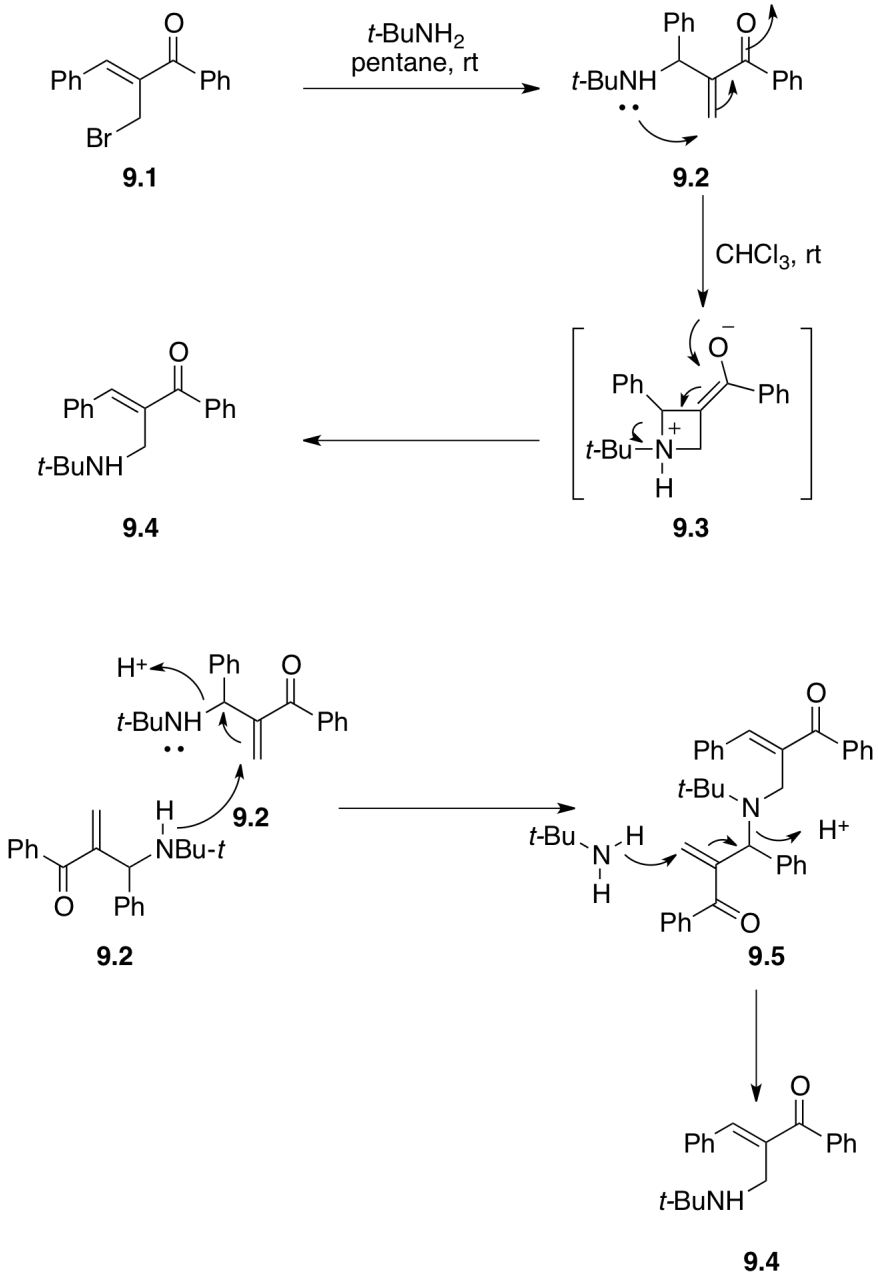
Mayr and coworkers reported the retention of regiochemistry of the double of MBH halides by using DABCO as a promoter, followed by an S_N2' reaction to furnished the (formal) S_N2 type product.[4i] The adduct of the first step, the ammonium salt, was isolated and treated with a solution of carbanion to yield the

S_N2 type product. A control experiment showed that when 0.9 equivalent of carbanion (in DMSO) was used, only the S_N2 type product **8.3** was obtained. However, under thermodynamic conditions (1.2 equivalent of carbanion, THF-H_2O), the S_N2' product was exclusively formed. These observations can be explained by attack of the carbanion on **8.3** via an S_N2' mechanism to afford the thermodynamically favored product **8.4**.



Scheme 8

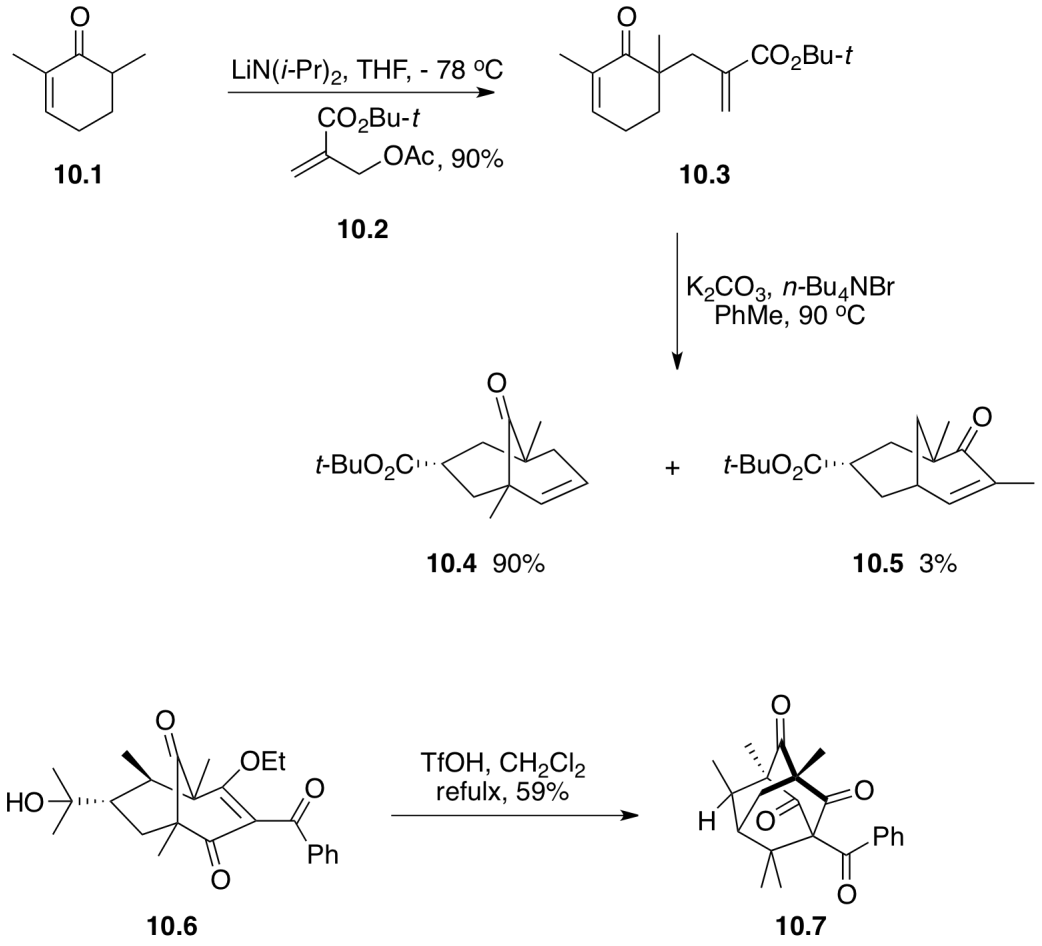
Similar processes occur when the nucleophile can also act as a leaving group.[5] An intramolecular example is the following: Cromwell and coworkers found that when MBH bromide **9.1** was treated with *tert*-butylamine, the kinetic product **9.2** was exclusively formed via a intermolecular conjugate displacement. The adduct **9.2** was then dissolved in chloroform and it slowly isomerized to form



Scheme 9

the thermodynamically stable product **9.4** via a 4-membered intermediate. However, such a 4-*endo trig* attack is strongly disfavored by Baldwin's rules.[6] An alternative mechanism was proposed and involved a bimolecular process.

Besides stabilized carbanions, enolates and their synthetic equivalents can also be used as nucleophiles for such a transformation.[7] By use of chiral organocatalysis, high enantiomeric excesses could be achieved.

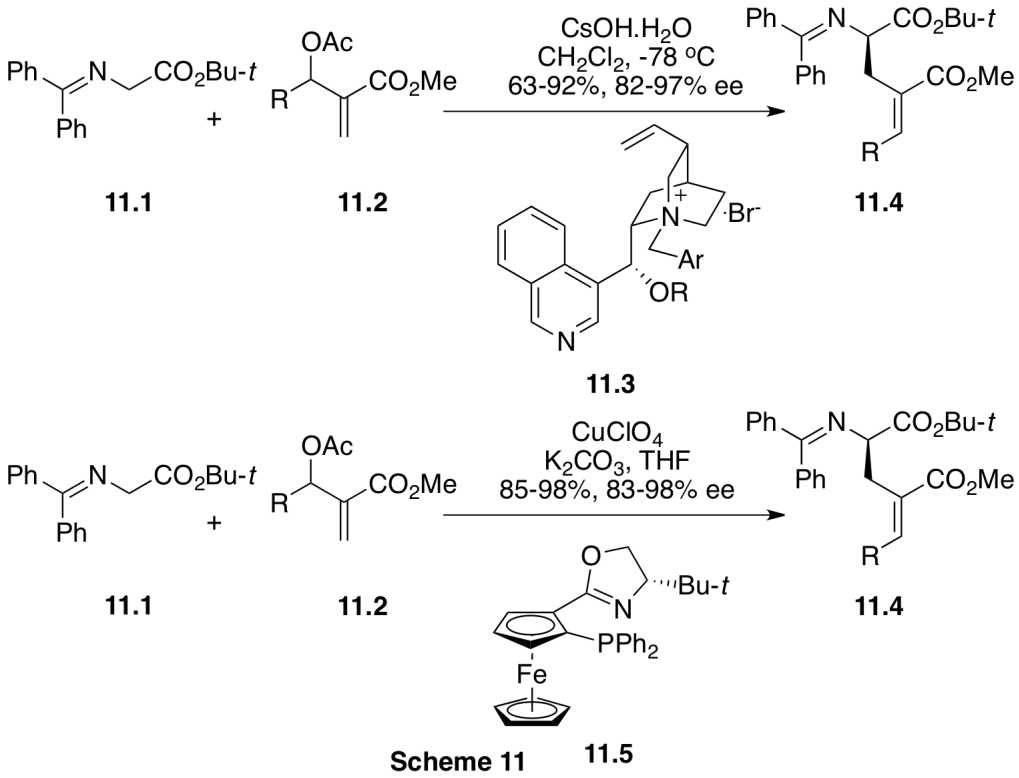


Scheme 10

Takagi and coworkers reported that the enolate of **10.1** could be used as the nucleophile for an S_N2' process with allyl acetate **10.2**.[7b] In basic conditions, both α-*endo* adduct **10.4** and γ-*endo* adduct **10.5** were obtained with **10.4** being the major product. This methodology was used for the synthesis of the core structure of plukenetione A.[7c] Advanced intermediate **10.6** was furnished via this

methodology. Upon acidic treatment, **10.7**, which resembles the core structure of plukenetione A, was obtained.

Some of the asymmetric methods of intermolecular conjugate displacement will now be discussed: Ramachandran and coworkers used a chiral alkaline counterion with an enolate to induce enantioselectivity.[8] The benzophenone imine of glycine *tert*-butyl ester **11.1** was used as nucleophile to attack MBH acetate **11.2**.

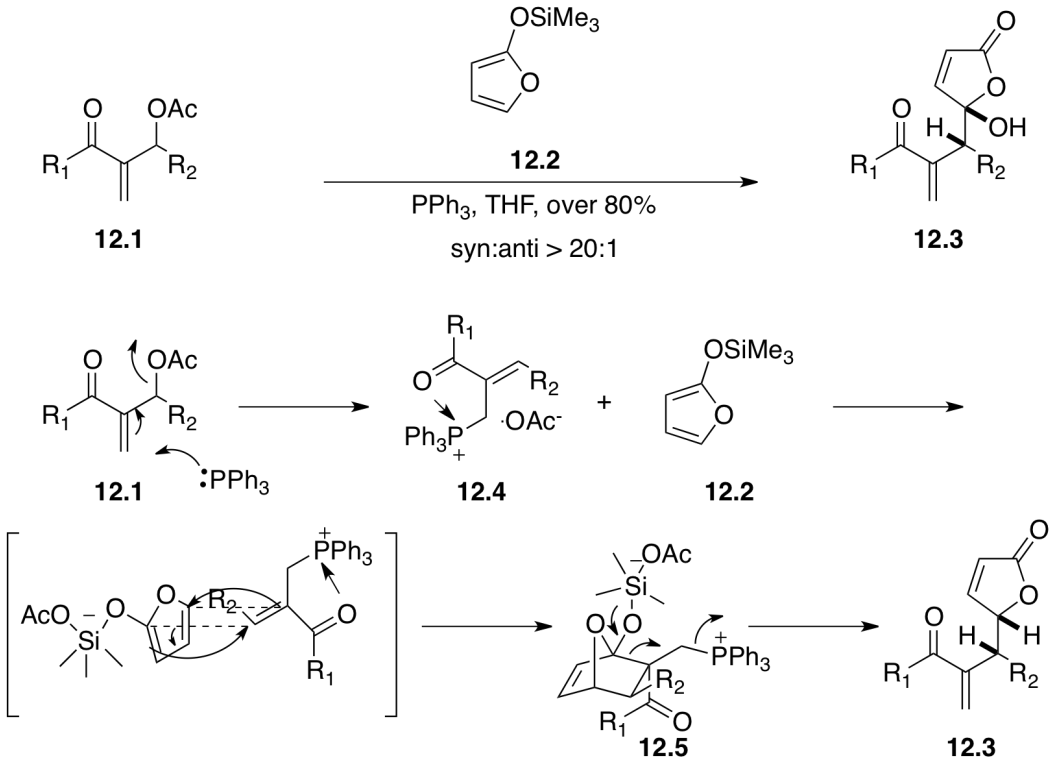


Scheme 11

Using the glycine ester **11.1**, Hou and coworkers also synthesized glutamic acid derivatives via a similar process.[9] This time a copper salt and a chiral ferrocenyl ligand were used as the chiral environment. However, such

reactions with other amino acid derivatives gave both lower yields and lower ee values, probably due to steric hindrance at α-position.

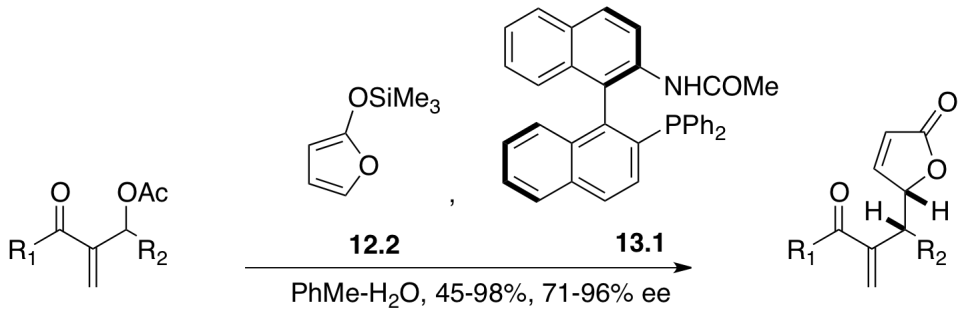
Krische and coworkers reported that 2-(trimethylsiloxy)furan could be used as a nucleophile to attack MBH acetates.[10] A phosphine was needed as the promoter for an initial S_N2' reaction. The resulting salt (see Scheme 12) then underwent Diels-Alder cycloaddition to give the bicycle **12.5**. Rearrangement of **12.5** furnished **12.3** with the indicated stereochemistry.



Scheme 12

Shi and coworkers also developed their own system for this type of addition.[11] A BINAP type chiral phosphine was used as the promoter. A similar

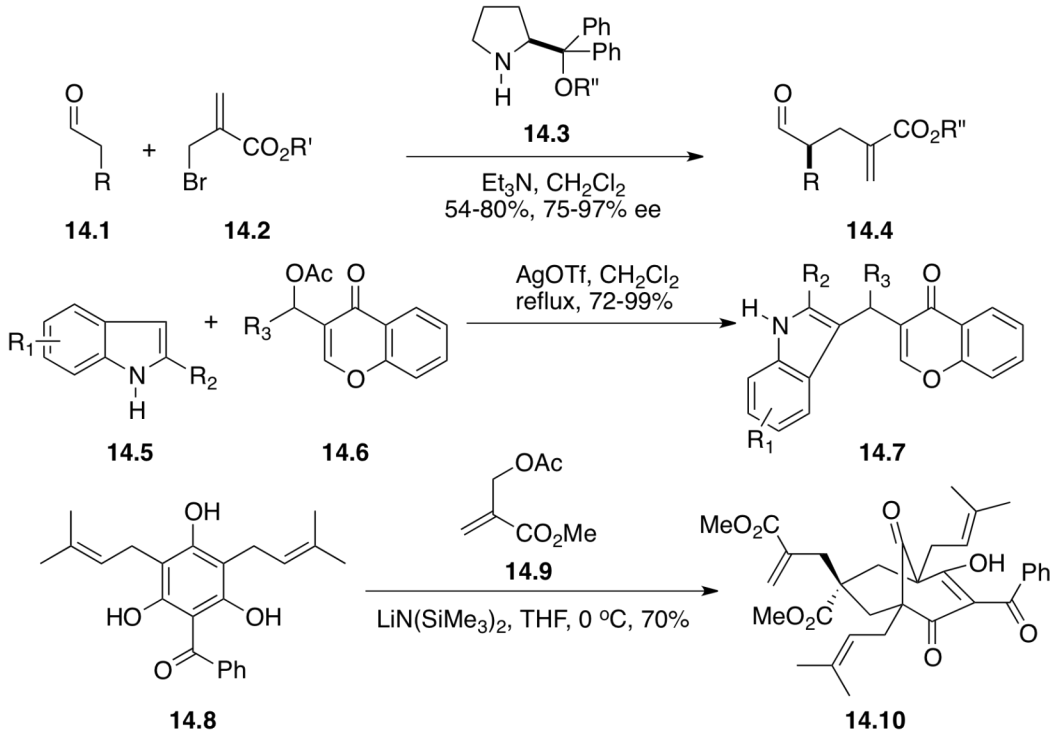
type of transition state was proposed and the desire products (**12.3**) were obtained with acceptable ee values.



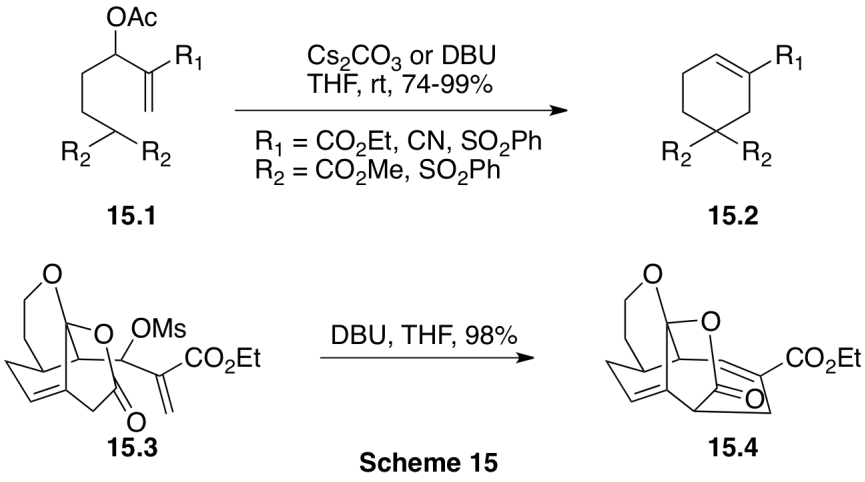
Scheme 13

Examples using enamines,[12] indoles[13] and phenols[14] as nucleophiles have also been studied. For the enamine case, moderate yields and ee values were obtained. The products (**14.4**) could be further used as Michael accepters. Unlike previously mentioned methods, which used tertiary amines or phosphines as catalysts, AgOTf was used as a promoter to activate the S_N2'-S_N2' sequence in the indole example. Finally, the phenoxide generated from phenol **14.8**, was used to construct the highly functionalized core structure (**14.10**) of clusianone. The racemic natural product was then obtained in 7 more steps in 24.6% yield overall from **14.10**.

Other members of this research group have used this method to construct carbocycles via an *intra*molecular conjugate displacement (Scheme 15).[15] Various soft nucleophiles were examined and the reactions were found to be to be general and efficient. The method was used to synthesize a major segment of the core structure of the complex natural product CP-225,917.



Scheme 14



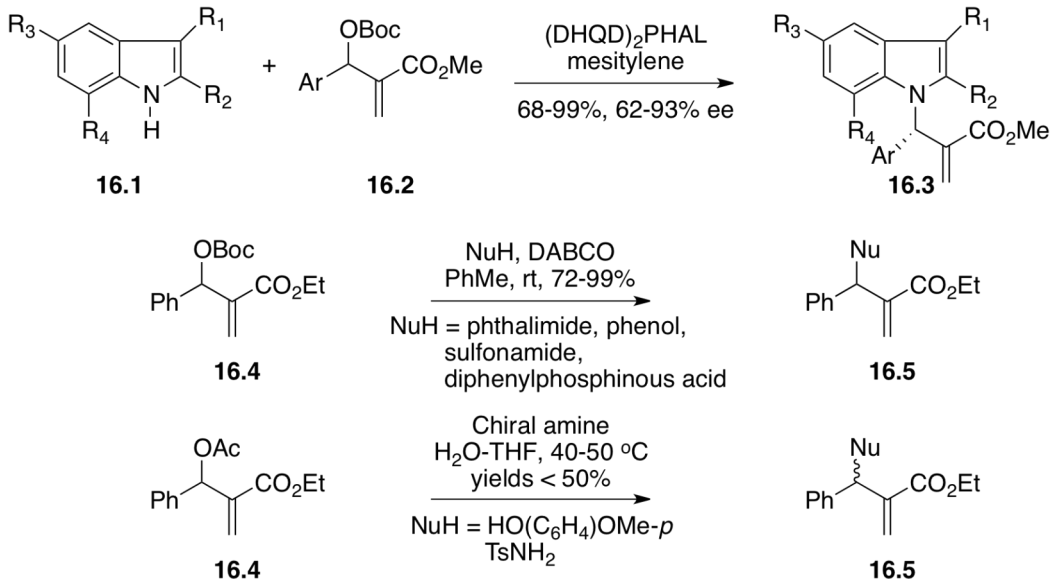
Scheme 15

1.3 Intermolecular and intramolecular conjugate displacements with heteroatom nucleophiles

Besides carbon nucleophiles, heteroatom nucleophiles can also be used for such S_N2' processes. Generally, various nitrogen based nucleophiles have been

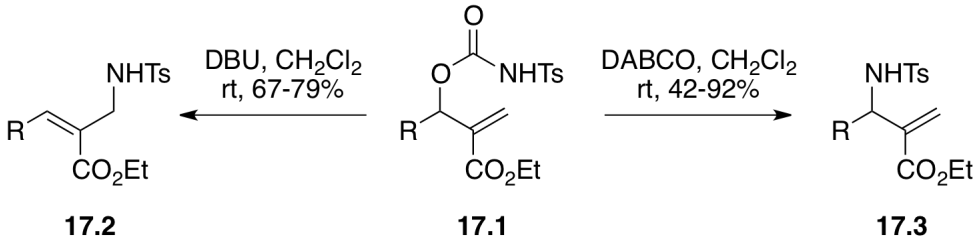
found to be good candidates for this type of addition, in both S_N2' and S_N2'-S_N2' sequences.[16] Some oxygen nucleophiles have been used as well.[17]

In the previous examples, a AgOTf catalyzed S_N2'-S_N2' sequence between indoles and an MBH acetate was established. In contrast, using a tertiary amine as the base led to the formation of an *N*-substituted intermolecular conjugate displacement product (**16.3**).[16f] It was found that a carbonate leaving group is crucial. The indole nitrogen is a weak nucleophile which requires the chiral amine-$(DHQD)_2PHAL$ to activate the MBH acetate. However, direct deprotonation of the indole did not facilitate the reaction since direct S_N2' displacement was a competing process. As an alternative solution, the carbonate was used as the leaving group. Upon treatment with $(DHQD)_2PHAL$, the OBoc group was displaced. Further decomposition of the expelled carbonate provided the strong *t*-butoxide anion which subsequently deprotonated the indole and led to the observed addition to give **16.3**. Similar reactions were reported by Lu and coworkers in their earlier publications.[18] Various nucleophiles, such as phthalimide, phenol, sulfonamide and diphenylphosphinous acid, were examined and most of them proved to be efficient for such additions. Kim and coworkers found that acetate could also be used as the leaving group, although reactions required a long time and yields were generally low.[16j]



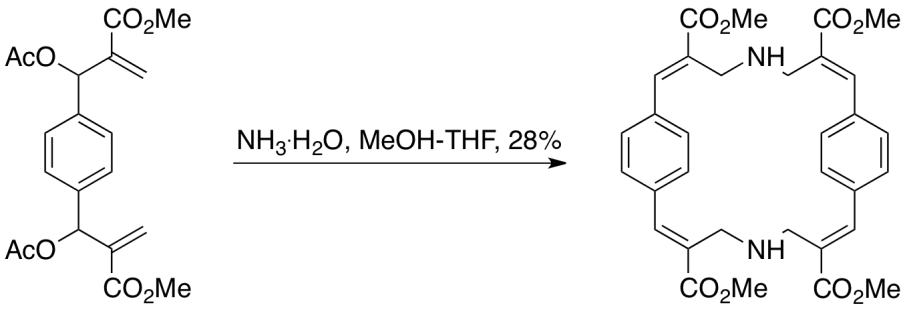
Scheme 16

Orena and coworkers reported an interesting observation on the regioselectivity of the conjugate displacement process.[16i] Upon treatment with two different bases, the MBH carbamate **17.1** reacted by two individual pathways. Use of DBU promoted intramolecular conjugate displacement, while treatment with DABCO gave the S_N2'-S_N2' product.



Scheme 17

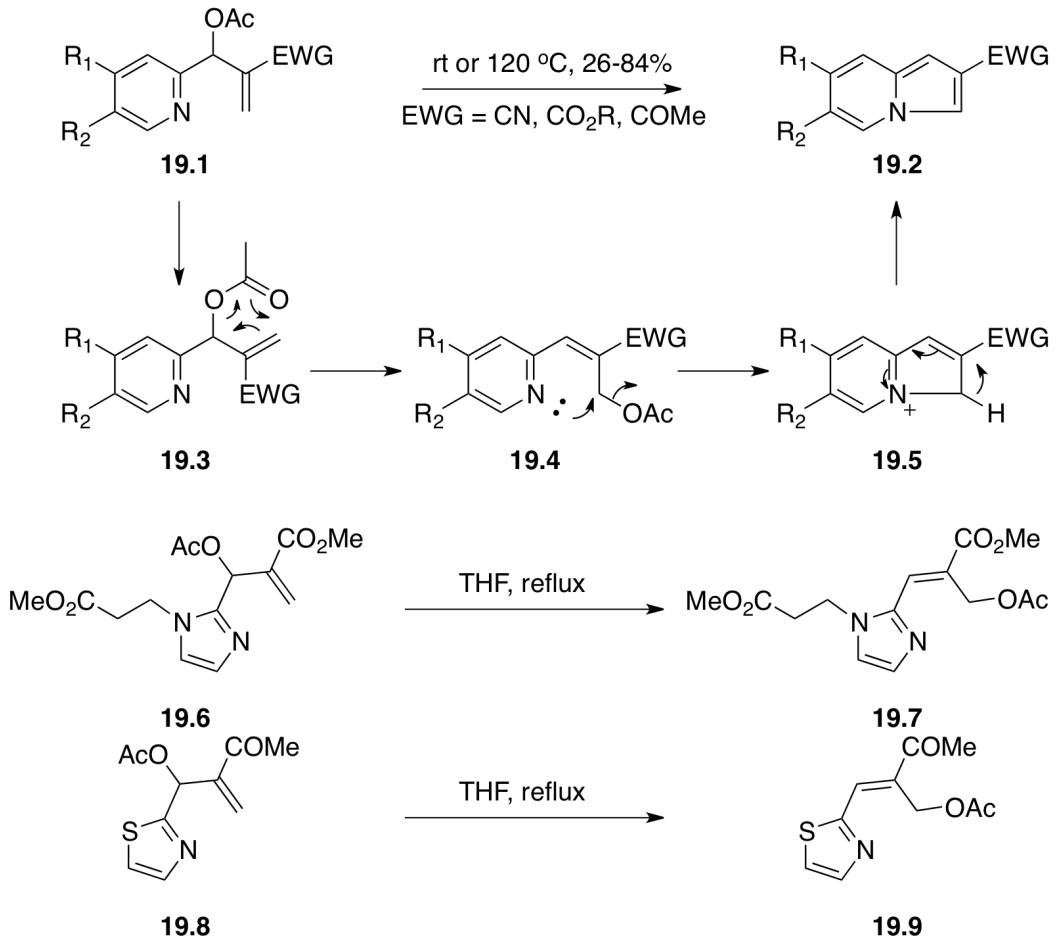
Foucaud and coworkers reported the synthesis of the paracyclophane **18.2** via both intermolecular and intramolecular conjugate displacement with nitrogen nucleophiles (Scheme 18).[19]



18.1 **18.2**

Scheme 18

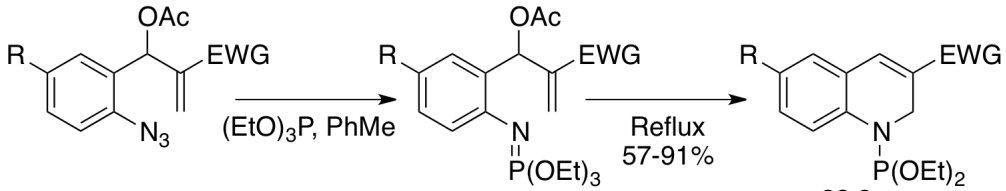
Kaye and coworkers found that indolizines could be synthesized via intramolecular conjugate displacement.[21] MBH acetate **19.1** underwent intramolecular conjugate displacement to afford the cyclized product **19.2**. Again, such a 5-*endo-trig* cyclization is disfavored by Baldwin's rules. It is most probably that the initial allyl acetate first underwent a 1,3-sigmatropic rearrangement (see **19.3**) and then a simple S_N2 reaction for cyclization (see **19.4**). Migration of the double bond afforded the final product. Some similar examples of the formation of rearranged allyl acetates are also presented in Scheme 19. An allyl cation mechanism cannot be ruled out since the stabilized allyl cation could be formed under the reaction conditions (refluxing solvent). In such cases, the reaction may undergo a Nazarov type 4π-electrocyclic closure to construct the desired products.



Scheme 19

Lee and coworkers investigated iminophosphoranes as nucleophiles for intramolecular conjugate displacement.[21] Azide **20.1** was treated with $(EtO)_3P$ in PhMe to give **20.2**. Further refluxing of the mixture afforded the desired dihydroquinoline derivatives **20.3**.

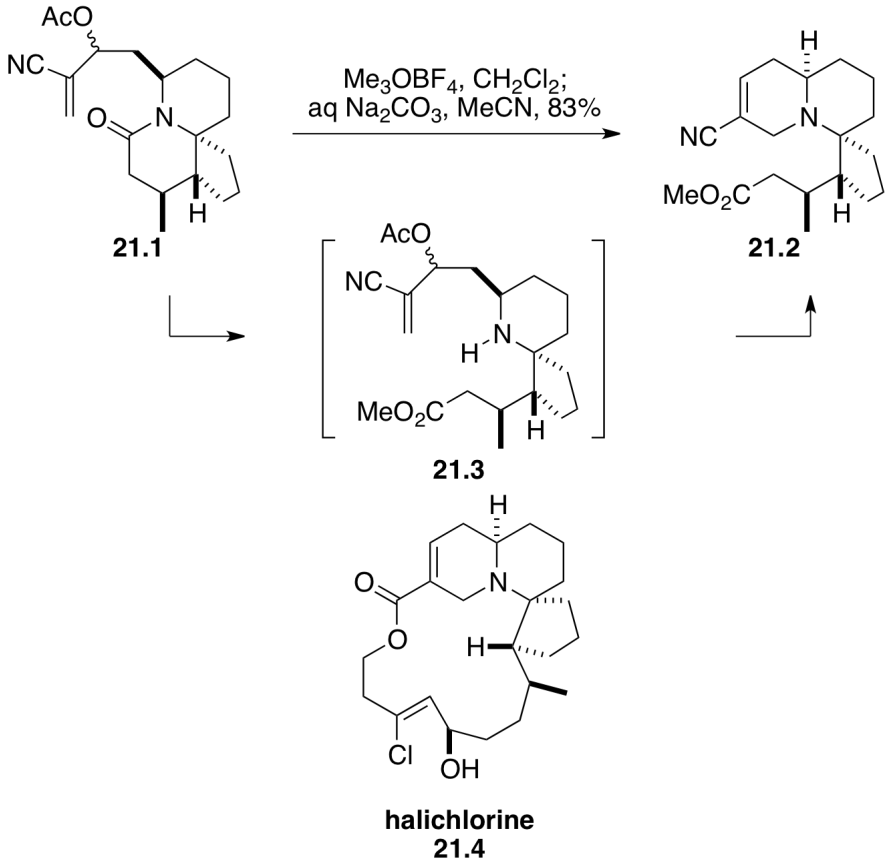
Many nitrogen-based ICD examples have been studied in this research group. The method was originally developed during the total synthesis of the marine alkaloid halichlorine.[22] The core structure of halichlorine was synthesized via an intramolecular conjugate displacement by a nitrogen atom. Methylation of the amide oxygen of **21.1**, followed by basic hydrolysis, gave the intermediate



20.1 **20.2** **20.3**

Scheme 20

21.3, which rapidly cyclized to afford tricycle **21.2**, which represents the core of halichlorine.



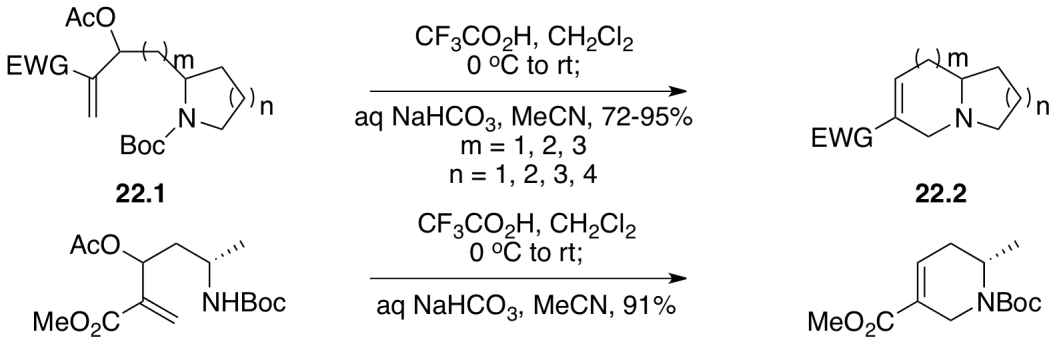
21.1 **21.2** **21.3**

halichlorine
21.4

Scheme 21

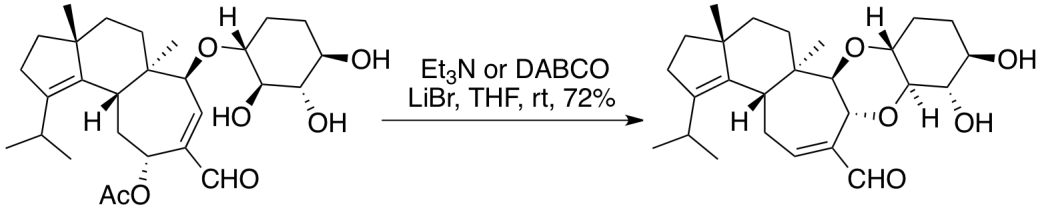
This nitrogen-based ICD reaction proved to be a general method for making nitrogen-containing heterocycles.[22e] Several monocyclic and bicyclic

compounds were prepared in good yields. β-Substitution of the α,β-unsaturated acceptor disfavored the reaction, probably due to steric hindrance.



Scheme 22

For oxygen nucleophiles, one example we have found in the literature is in the synthesis of (-)-erinacine B.[17b] Nakada and coworkers found that exposure to Et_3N-LiBr in THF at room temperature smoothly converted erinacine P (**23.1**) to erinacine B (**23.2**). It is believed that the biosynthesis of erinacine B follows the same pathway.



erinacine P
23.1

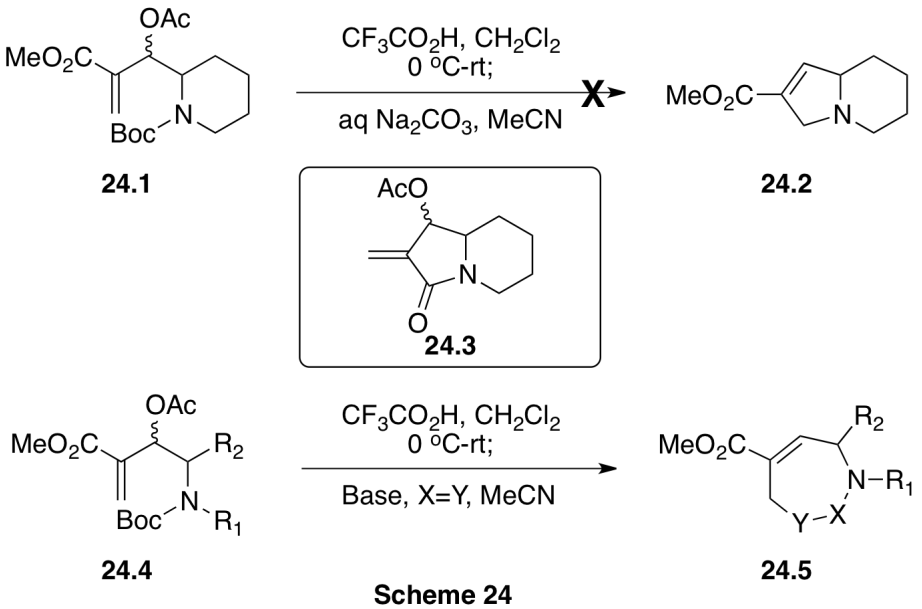
(-)-erinacine B
23.2

Scheme 23

2. RESULTS AND DISCUSSION

2.1 *Research objectives*

During the research on nitrogen-based intramolecular conjugate displacement, a former member of this research group, Dr Li, found an interesting result that I have followed up. MBH acetate **24.1** did not undergo intramolecular conjugate displacement. Instead, lactam **24.3** was produced. The desired addition to give **24.2**, defined as *5-endo-trig* addition, is disfavored according to Baldwin's rules.[6] Although none of the desired product was obtained, the formation of **24.3** suggested an extension to the normal ICD process. If we can trap the free amine (resulting from removal of the Boc group) with a 1,2-dipole (X=Y), which is attacked at the X terminus to build up a negative charge on the Y terminus, the newly formed anion could undergo intramolecular conjugate displacement to yield a 7-membered ring. Various heterocycles could then be synthesized via this



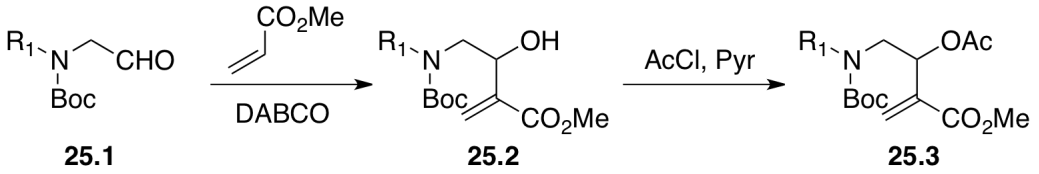
24.1 **24.2** **24.3** **24.4** **24.5**

Scheme 24

methodology. However, suitable 1,2-dipoles were required for both trapping the free amine and subsequent ICD addition. Several possible candidates are: Michael acceptors, carbon dioxide, isocyanates, carbon disulfide, and isothiocyanates.

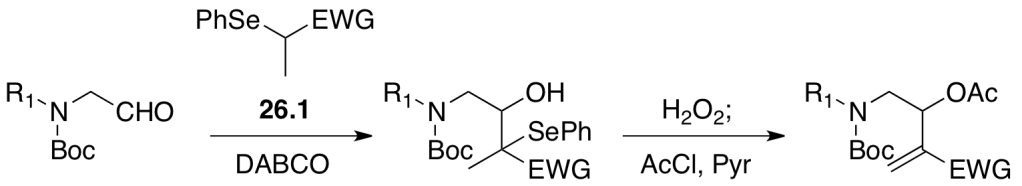
2.2 Preparation of MBH acetate precursors

We planned to synthesize the precursors for the intramolecular conjugate displacement, MBH acetates, via a simple 2-step sequence. A MBH reaction between aldehydes **25.1** and methyl acrylate would yield the MBH alcohols **25.2**. Subsequent acetylation should afford the desired MBH acetates **25.3**.[22e] Based on previous research results, some olefins are unsuitable for use in the MBH-condensation, depending on the nature of the electron-withdrawing group and the degree of substitution of the double bond; in certain cases the normal condensation is unacceptably slow or does not work at all.[23] For example, phenyl vinyl sulfone is reported to react very slowly,[24] as does methyl crotonate.[24c] In cases of certain electron withdrawing groups (SO_2R, NO_2, etc), an alternative route was described[22] in previous publications from this laboratory. Selenium compound **26.1** can be deprotonated and the resulting carbanion attacks the carbonyl of aldehyde **25.1**. Selenoxide elimination from **26.2** is always away from the hydroxyl-bearing carbon and acetylation gives **26.3**.[25]



25.1 **25.2** **25.3**

Scheme 25

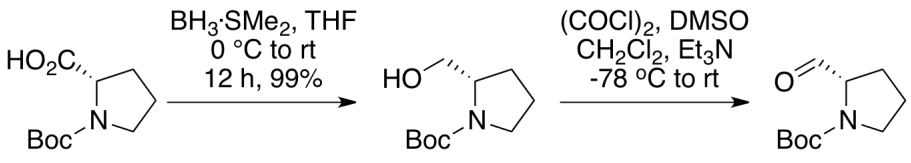


25.1 EWG = SO_2R, CN, NO_2 **26.2** **26.3**

Scheme 26

Our first task was to synthesize the starting materials **25.1** and both cyclic and acyclic *N*-protected amino aldehydes were produced.

For cyclic cases, 5-, 6-, and 7-membered amino aldehydes were obtained via their *N*-protected amino alcohols. For the 5-membered case, *N*-Boc-(L)-proline **27.1** was reduced by borane-dimethyl sulfide complex to yield *N*-Boc prolinol (**27.2**). Swern oxidation of **27.2** afforded amino aldehyde **27.3**.[22e]

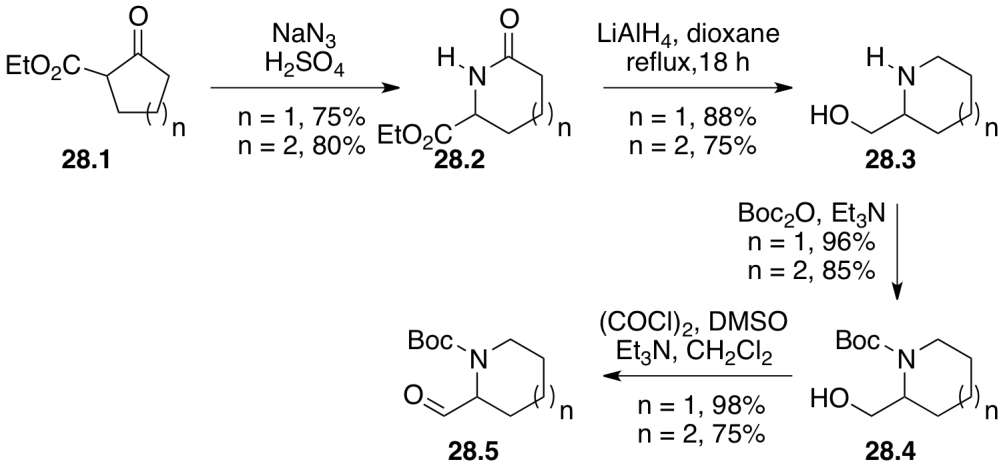


27.1 **27.2** **27.3**

Scheme 27

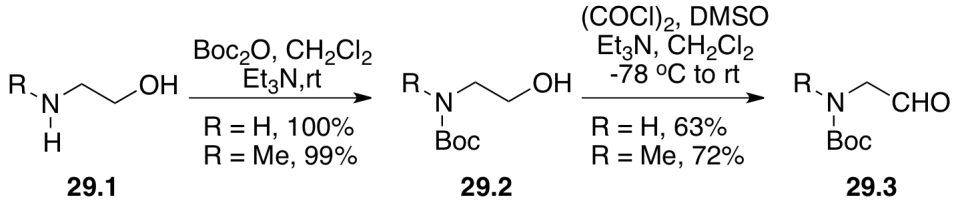
Synthesis of the 6- and 7-membered cases is more complicated due to the fact that the appropriate *N*-Boc protected amino acids are not commercially available. We used another route which starts from dicarbonyl compounds **28.1**.

Schmidt rearrangement of **28.1**, under acid conditions with sodium azide, afforded amides **28.2.** Treatment of **28.2** with $LiAlH_4$ reduced both ester and amide functionalities and amino alcohols **28.3** were produced. Protection of the free amine with a Boc group and oxidation of the resulting alcohols **28.4** provided cyclic amino aldehydes **28.5**.[26]



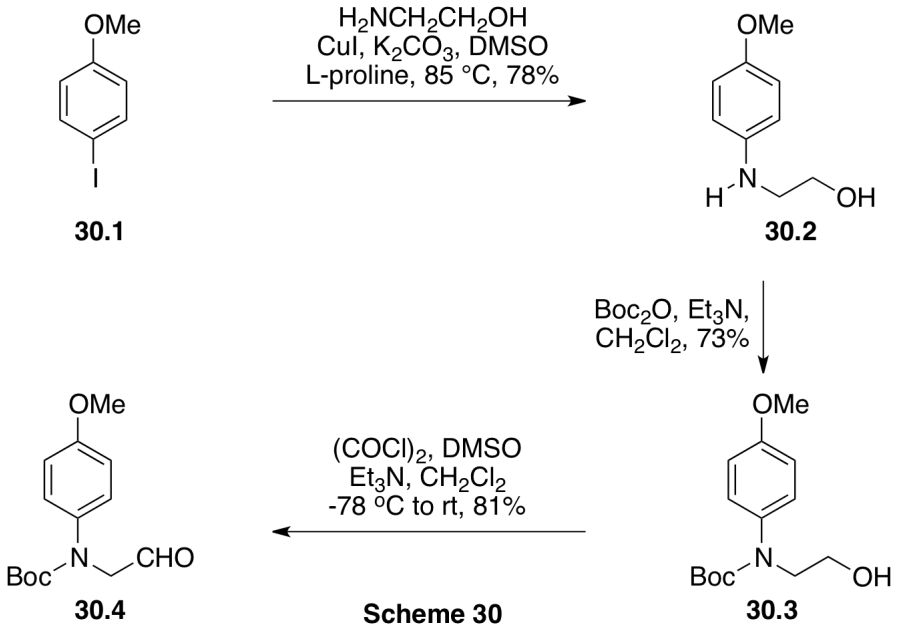
Scheme 28

Several acyclic *N*-protected amino aldehydes were used as well. Starting from commercially available aminoethanol and *N*-methyl aminoethanol, protection of the amine with a Boc group and Swern oxidation gave the amino aldehydes **29.3**.[27]



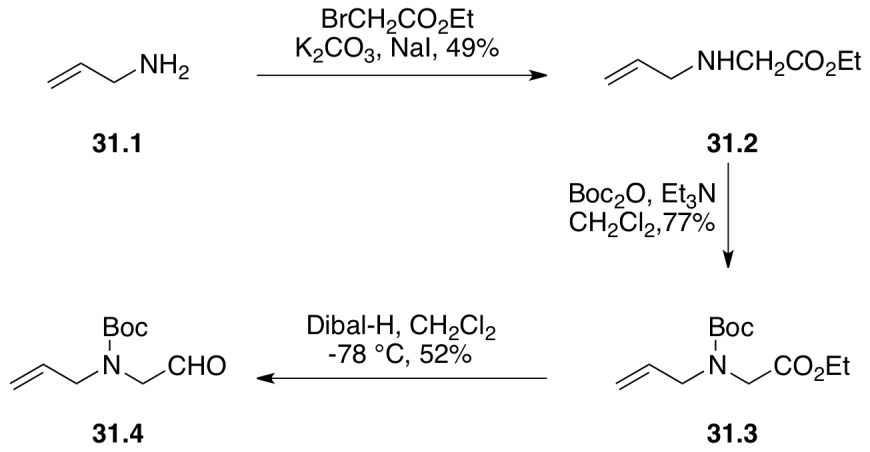
Scheme 29

Other *N*-substituted examples required more steps since the amino alcohols were not commercially available and needed to be synthesized individually. For an electronically rich aryl substituent, a copper-mediated coupling was carried out between aryl iodide **30.1** and aminoethanol. The reaction mixture was heated to 85 °C in DMSO and the desired *N*-aryl aminoethanol was obtained in 78% yield. Protection of the free amine with a Boc group and further oxidation of the primary alcohol provided amino aldehyde **30.4**.[28]



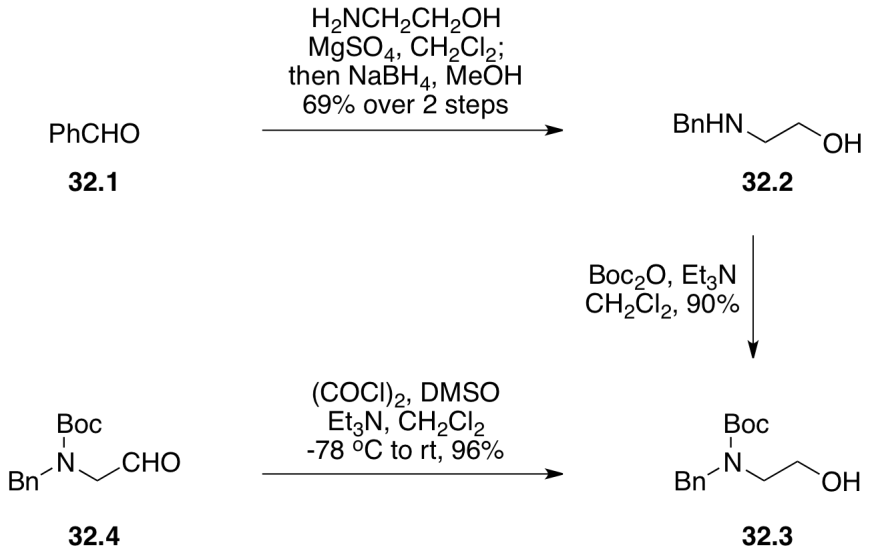
Scheme 30

An allyl substituted example was made via a 3-step sequence.[29] Alkylation of allylamine (**31.1**) with ethyl bromoacetate furnished secondary amine **31.2**, which was subsequently protected by a Boc group to afford carbamate **31.3**. Partial reduction of the ester functionality to an aldehyde was achieved by DIBAL-H reduction at -78 °C.



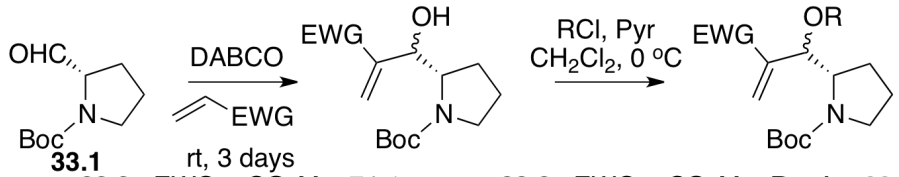
Scheme 31

N-Benzyl amino aldehyde **32.4** was synthesized via the following route: Condensation between benzaldehyde **32.1** and aminoethanol generated the expected imine which was then reduced to *N*-benzyl aminoethanol (**32.2**). Similar to the previous cases, protection of the amine and Swern oxidation afforded *N*-Boc amino aldehyde **32.4**.[30]



Scheme 32

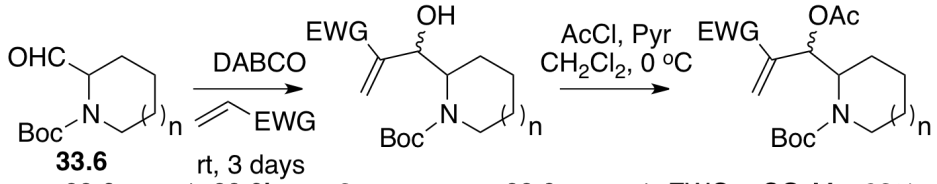
With the amino aldehydes in hand, we subjected all of them to the standard Morita-Baylis-Hillman conditions. Addition of methyl acrylate and acrylonitrile was very successful, although some self-dimerized side product from acrylonitrile was isolated. Subsequent acetylation with acetyl chloride and pyridine gave the desired MBH acetates.[22e] In order to study the effect of the leaving group, a carbonate was also synthesized for comparison.



33.1

33.2: EWG = CO_2Me, 74%

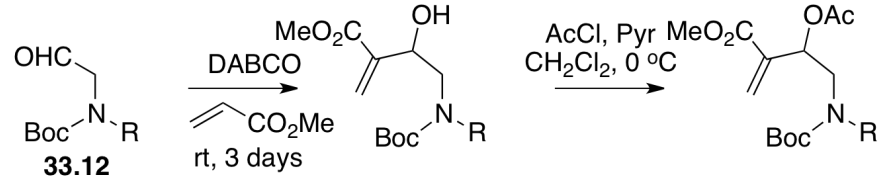
33.3: EWG = CO_2Me, R = Ac, 99%
33.4: EWG = CO_2Me, R = CO_2Et, 58%
33.5: EWG = CN, R = Ac, 72% for 2 steps



33.6

33.6: n = 1; **33.6'**: n = 2
33.7: n = 1, EWG = CO_2Me, 80%
33.8: n = 2, EWG = CO_2Me, 81%

33.9: n = 1, EWG = CO_2Me, 92%
33.10: n = 2, EWG = CO_2Me, 87%
33.11: n = 1, EWG = CN, 72% for 2 steps



33.12

33.12: R = H
33.12': R = Me
33.12'': R = Bn
33.12''': R = C_6H_4OMe-*p*
33.12'''': R = Allyl

33.13: R = H, 71%
33.14: R = Me, 86%
33.15: R = Bn, 69%
33.16: R = C_6H_4OMe-*p*, 86%

33.17: R = H, 73%
33.18: R = Me, 100%
33.19: R = Bn, 91%
33.20: R = C_6H_4OCMe-*p*, 83%
33.21: R = Allyl, 68% for 2 steps

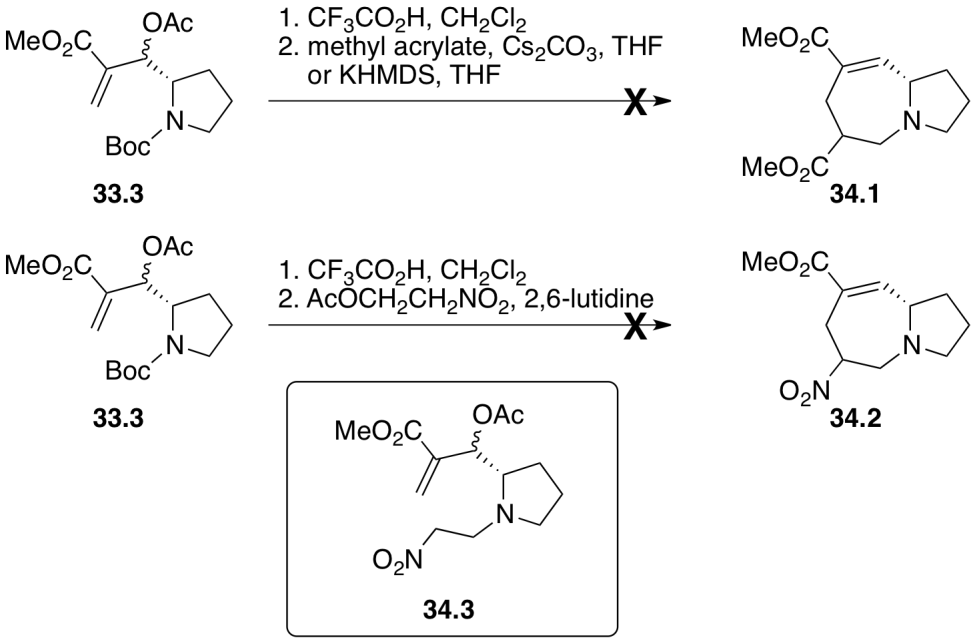
Scheme 33

Some naturally-occurring amino acids were converted into the corresponding amino aldehydes. Due to the fact that glycine-derived MBH

acetate gave very poor regioselectivity between 5-membered and 7-membered products (as discussed later), they were not investigated in detail.

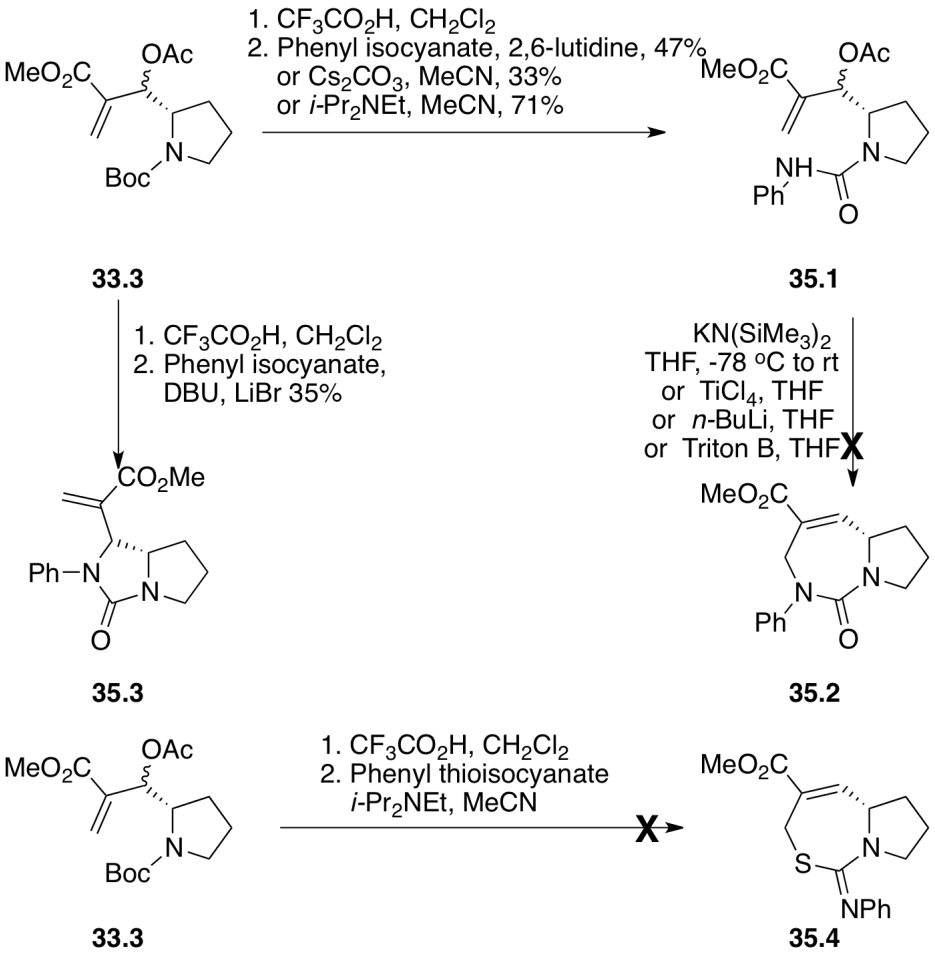
2.3 Cascade intramolecular conjugate displacement with various 1,2-dipoles

Several 1,2-dipoles were examined with **33.3** for screening of reaction conditions. Michael acceptors were chosen initially due to the fact that nitrogen-heterocycles are commonly present in natural products, medicines and drug candidates. Compound **33.3** was first deprotected with trifluoroacetic acid. The TFA salt of the amine and methyl acrylate were subjected to the standard intramolecular conjugate displacement conditions (Cs_2CO_3, THF).[15] No desired product **34.1** was obtained. Use of a strong base, $KN(SiMe_3)_2$, did not help the reaction at all. Another Michael acceptor, nitroethylene, was also investigated for the reaction, although it is known that the instability of nitroethylene limits its synthetic utility. We decided to generate nitroethylene *in situ* to minimize the possibility of polymerization.[31] After formation of the TFA salt of the amine, a solution of 2-nitroethyl acetate and 2,6-lutidine was added to the reaction mixture. However, only the Michael-type adduct **34.3** was isolated. The NO_2 electron-withdrawing group did enhance the addition of nitrogen onto the Michael acceptor, but the resulting highly stabilized carbanion did not undergo the ICD reaction and led to an acyclic product.



Scheme 34

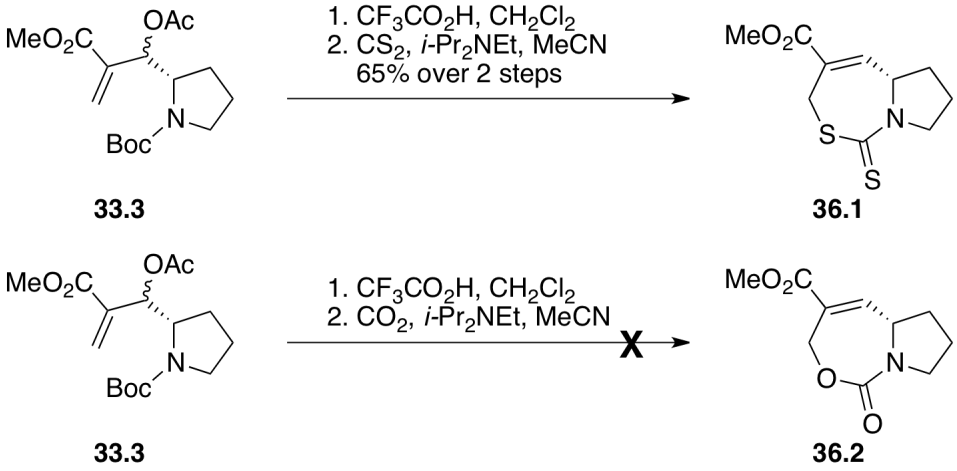
The second type of 1,2-dipole I tested was isocyanates. Applying similar reaction conditions to **33.3**, acidic deprotection of the Boc group gave the TFA salt of the free amine. Again, the crude compound was dissolved in THF and treated with phenyl isocyanate and 2,6-lutidine. None of the cyclized product was obtained. However, an acyclic urea **35.1** was isolated in 47% yield as the only product**.** Optimization of the reaction conditions by using different bases and solvents did not dramatically improve the reaction. Only the acyclic urea was obtained (71% yield). Subsequently, adding a base to **34.2** did not afforded any cyclic urea. Interestingly, using DBU as the base and LiBr as a Lewis acid, the 5-membered S_N2 type product **35.3** was the only isolated compound, instead of the expected 7-membered ICD product. On the other hand, using phenyl isothiocyanate as the 1,2-dipole, a complex mixture was produced, as judged by TLC examination of the reaction mixture.



Scheme 35

The third type of 1,2-dipole tested was carbon disulfide. Under the identical conditions to those used with phenyl isothiocyanate, the desired product (**36.1**) was isolated in an acceptable yield — 65% over 2 steps. Only the 7-membered compound was obtained. This type of heterocycle, a 2-thioxo-1,3-thiazepine derivative, is not well-known. As a closely related 1,2-dipole, carbon dioxide was also examined for this cascade intramolecular conjugate displacement. Under the standard conditions (acetonitrile, Hünig's base), carbon dioxide was bubbled into the reaction mixture for ca 12 hours. Unfortunately,

none of the desired carbamate was isolated. The low solubility of carbon dioxide in the organic solvent could be a major issue for trapping of the free amine.

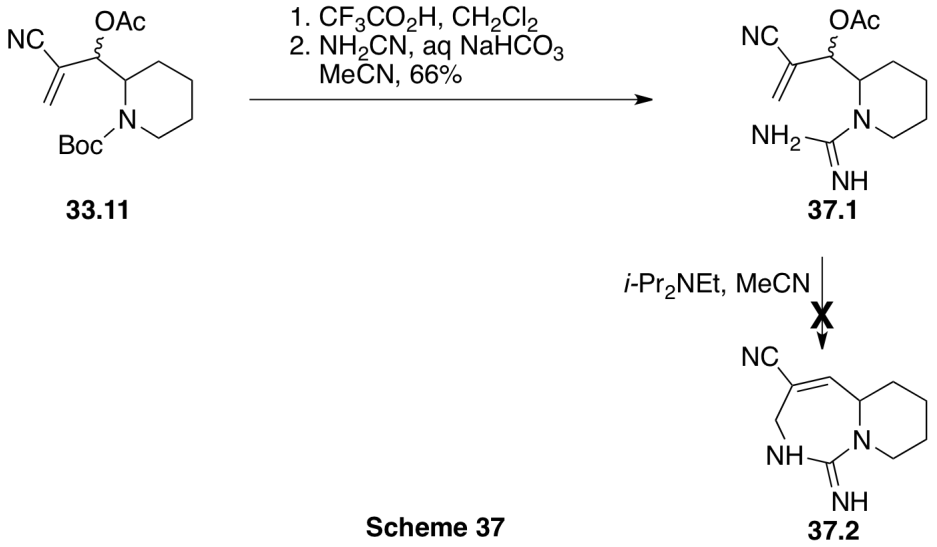


33.3 **36.1**

33.3 **36.2**

Scheme 36

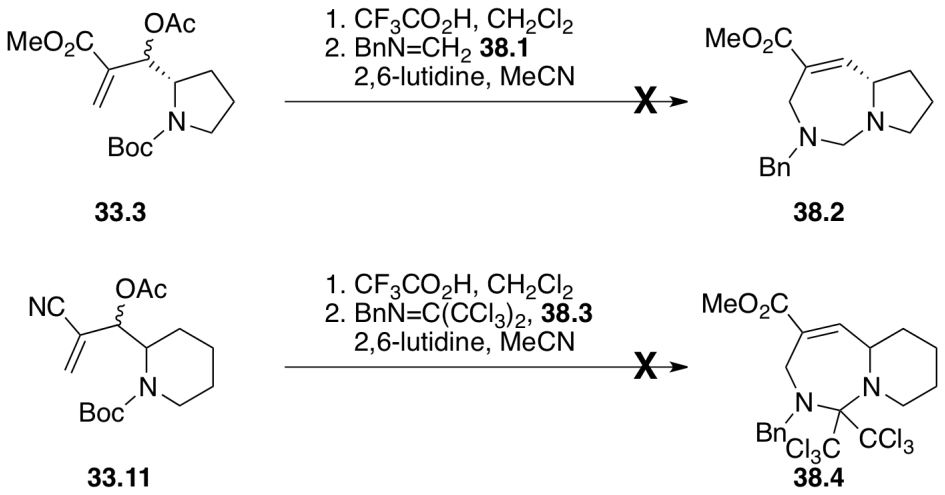
The next candidate in the list of 1,2-dipoles to be considered was cyanamide, since it could provide a general access to cyclic guanidines. After acid deprotection of the Boc group of **33.11**, the resulting TFA salt was dissolved in MeCN and treated with aqueous sodium bicarbonate and cyanamide. Like the isocyanate case, only the acyclic guanidine **37.1** was isolated. Compound **37.1** was subjected to basic conditions, but again none of the cyclized product was formed. This result, together with the isocyanate case, proved that the nitrogen atoms of guanidine and urea were poor nucleophiles for the ICD process.



33.11 **37.1** **37.2**

Scheme 37

I also considered the use of an imine as a 1,2-dipole; in this case a cyclic 1,1-diamino compound would be obtained. Starting from MBH acetate **33.3** (Scheme 38), the imine **38.1** was tried for the ICD reaction, but the experiment was unsuccessful and none of the cyclized product was isolated. Instead of simple imine **38.1**, imine **38.3**, which bears two electron deficient trichloromethyl groups, was examined as the trichloromethyl groups might enhance the first attack by the free amine. However, when **38.3** was used as the 1,2-dipole, the ICD product was again not formed. Based on results reported in previous publications from this laboratory, 7-*endo-trig* ICD processes are very successful with amines. The electron-withdrawing CCl_3 groups should facilitate attack by induction but this is offset by steric factors. The final outcome was that both reactions were unsuccessful.



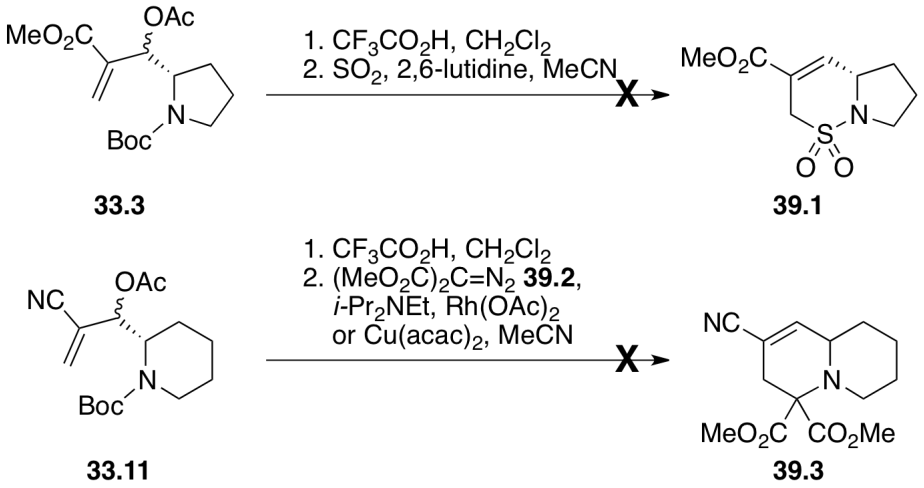
33.3 **38.2**

33.11 **38.4**

Scheme 38

Using a formal 1,1-dipole, which could be attacked by the free amine might also yield a 6-membered ICD product. The first example of this possibility we have examined was sulfur dioxide. However, treatment of the free amine derived from **33.3** did not afford any of the desired product. We believe that the electrophile was simply not strong enough to be attacked by the nitrogen nucleophile.

The second type of 1,1-dipole we examined was a stabilized carbene. Diazo compound **39.2**, which could be quickly synthesized via a diazo-transfer between tosyl azide and dimethyl malonate, was chosen as the precursor of the carbene. The reason for using a diazo compound is to avoid dimerization of the carbene itself. After acidic deprotection of the Boc group, the TFA salt of the free amine was treated with diazo compound **39.2**, *i*-Pr_2NEt and $Rh(OAc)_2$ as a catalyst.[32a] Unfortunately, we did not isolate any 6-membered product. Instead, only the carbene dimerized product and free amine were separated. Using $Cu(acac)_2$ as a catalyst did not provide any better result.[32b]

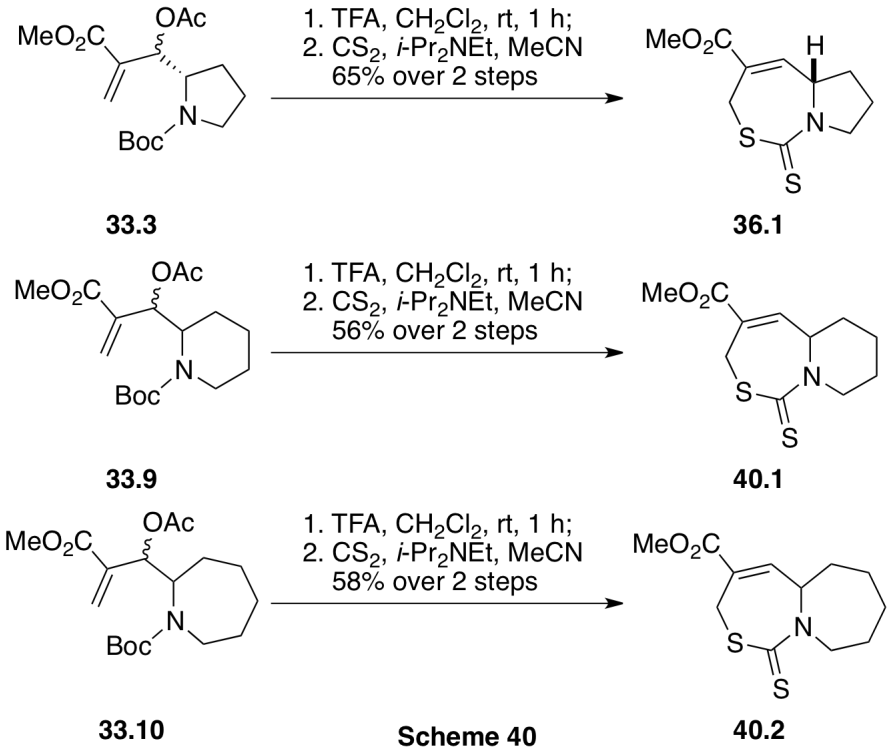


33.3 **39.1**

33.11 **39.3**

Scheme 39

After screening potential 1,1- and 1,2-dipoles, only carbon disulfide was a satisfactory choice for such a cascade intramolecular conjugate displacement, and we decided to test the substrate scope of the reaction. Cyclic amines were first



33.3 **36.1**

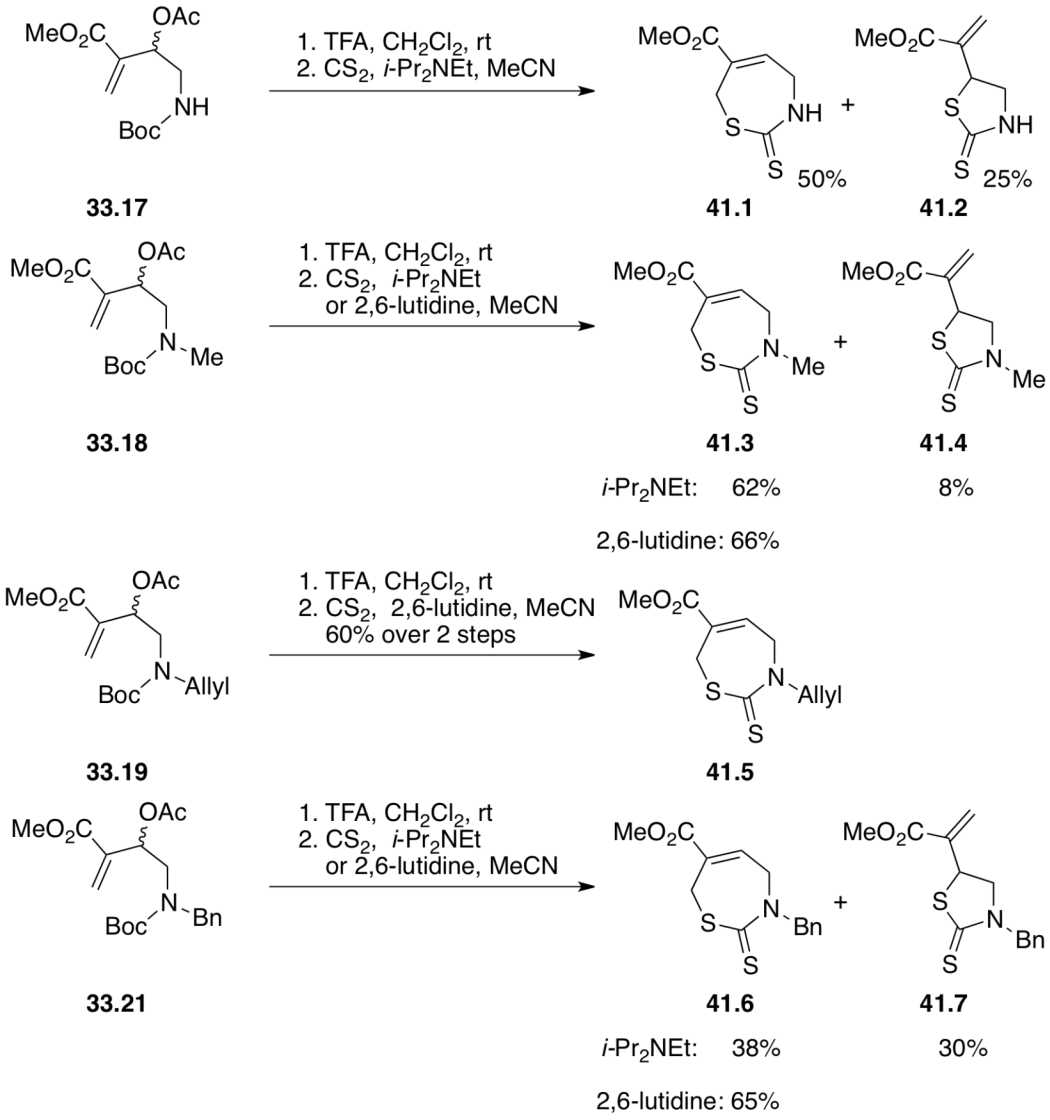
33.9 **40.1**

33.10 **40.2**

Scheme 40

tested. The 5-, 6- and 7-membered amino aldehydes were subjected to identical reaction conditions; in each case the 7-membered product from an S_N2' substitution was obtained and none of the 5-membered product arising by an S_N2 pathway was isolated.

Unlike the situation with cyclic amino aldehydes, which were of necessity, secondary amines, acyclic amines could be primary or secondary. The simplest example, the amino aldehyde made from glycine, was subjected to this 2-step sequence. What we found was that both the 7-membered ICD product and the 5-membered S_N2 product were isolated in a ratio of 2:1 in favor of the ICD compound (Scheme 41). Under the same reaction conditions, all cyclic cases gave only the 7-membered ICD products. In order to establish if secondary amines provided better regioselectivity, the *N*-substituted MBH acetates **33.17**, **33.18** and **33.19** were examined. When *i*-Pr_2NEt was used as the base, both compounds **33.17** and **33.19** gave mixtures of two products in favor of the ICD compound. If we switched the amine to 2,6-lutidine, a dramatic regioselectivity improvement was achieved. Compounds **33.18**, **33.19** and **33.21** were subjected to the reaction conditions, using 2,6-lutidine and the 7-membered ICD products were the only isolated products. Compared to the use of *i*-Pr_2NEt, 2,6-lutidine provided better yields. The aniline derivative **33.20** did not afford any cyclized product, probably due to the poor nucleophilicity of the aniline nitrogen.



33.17 41.1 41.2

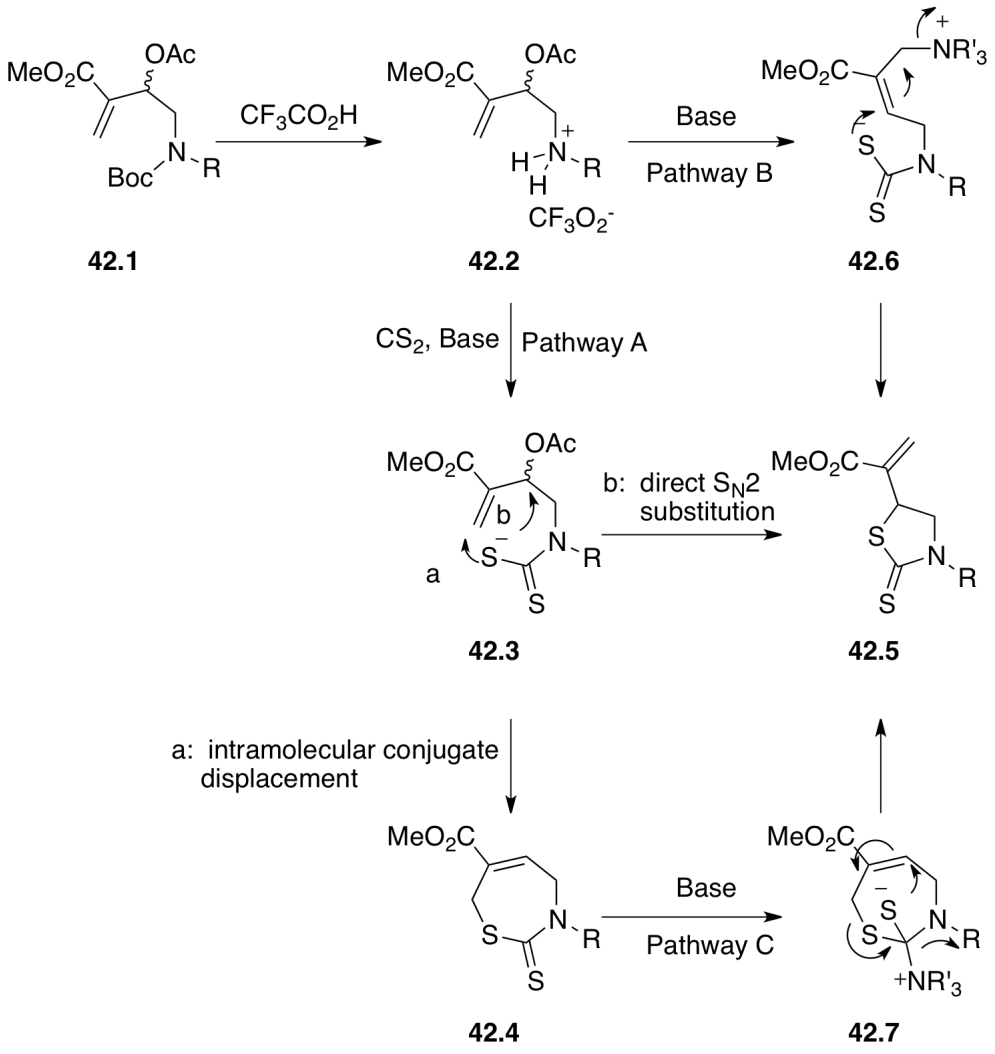
33.18 41.3 41.4

33.19 41.5

33.21 41.6 41.7

Scheme 41

As far as the reaction mechanism is concerned, formation of the 7-membered product was the desired cascade nitrogen trapping-intramolecular conjugate displacement reaction. On the other hand, the formation of the 5-membered S_N2 product could be the result of three different mechanisms. After trapping the 1,2-dipole (carbon disulfide), a direct S_N2 substitution will provide the 5-membered product, although, the soft sulfur nucleophile would have been expected to strongly favor conjugate attack.



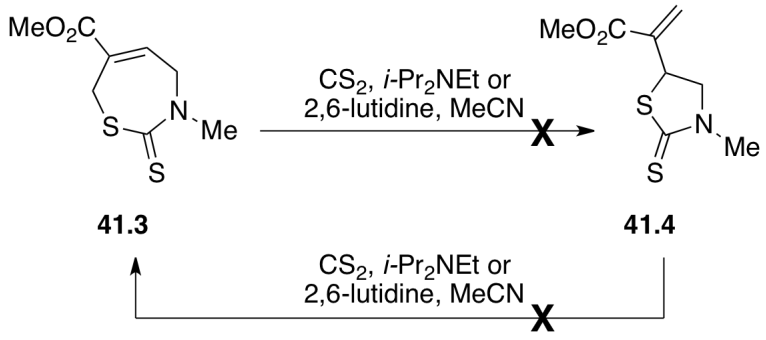
Scheme 42

Alternatively, if the base underwent the intermolecular conjugate displacement and the nitrogen of the free amine was trapped by carbon disulfide, the intermediate **42.6** could undergo intramolecular conjugate displacement and afford the 5-membered product.

The third pathway includes the formation of the 7-membered ICD product that is subsequently attacked by the base and rearranged into the 5-membered S_N2 type product.

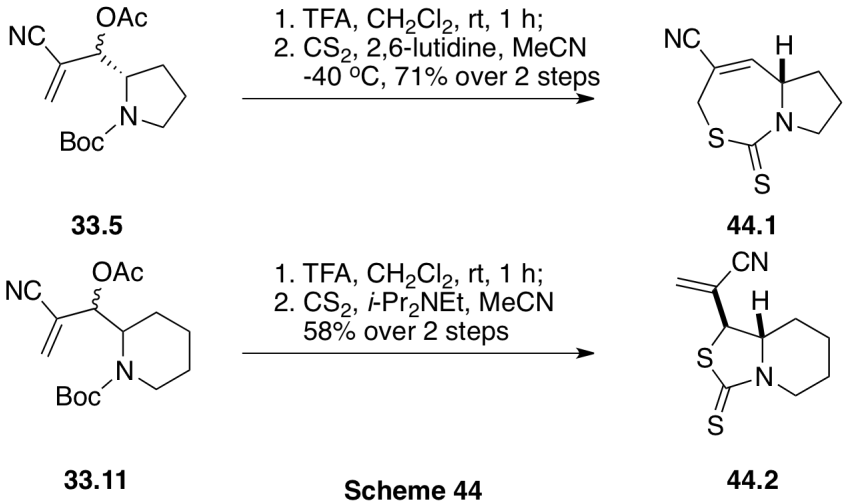
In contrast to *i*-Pr_2NEt, the better regioselectivity with 2,6-lutidine could be explained by the fact that lack of nucleophilicity of 2,6-lutidine reduces its ability to participate in intermolecular conjugate attack on the MBH acetate. It is highly likely that the 5-membered S_N2 type product was formed via pathway B.

However, we cannot rule out pathway C. A control experiment was carried out to check whether **41.3** and **41.4** could be converted into each other. Applying the standard ICD reaction conditions to **41.3**, after 24 hours, no **41.4** could be detected. The same situation happened with **41.4** and we believe that these two compounds are not interconvertable in our reaction.



Scheme 43

Another electron-withdrawing group that was tested was the nitrile group. Surprisingly, the 5-membered cyclic amine **33.5** and 6-membered cyclic amine **33.11** showed totally different results. In the 5-membered case, a regular ICD product was isolated (at -40 °C). The 6-membered cyclic amine predominately furnished the 5-membered S_N2 type product (room temperature).

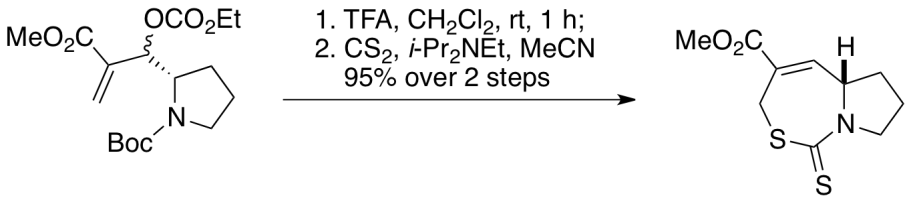


33.5 **44.1**

33.11 **44.2**

Scheme 44

In order to study the effect of the leaving group, carbonate **33.4** was synthesized. Subjecting **33.4** to the standard 2-step sequence, gave the desired 7-membered compound **36.1** as the only isolated product, which was obtained in a much better yield (95%).

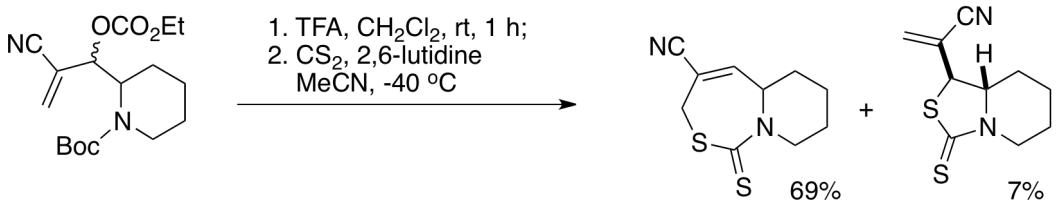


33.4 **36.1**

Scheme 45

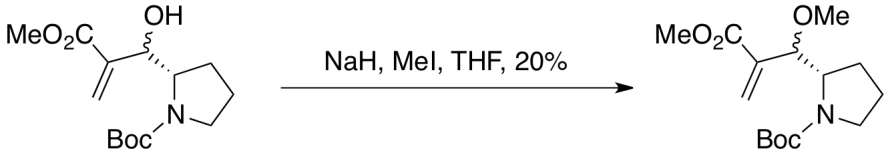
For comparison with the acetate **33.9**, the carbonate **46.1** was also synthesized to examine the regioselectivity. Interestingly, unlike the acetate starting material, in the carbonate case the 7-membered ICD product was the major isolated product (69% yield), as well as the 5-membered S_N2 type product (7%). A carbonate leaving group clearly favors the ICD process. The 7-

membered ICD product should be the kinetic product which is favored by the low reaction temperature used in that experiment (Scheme 46).

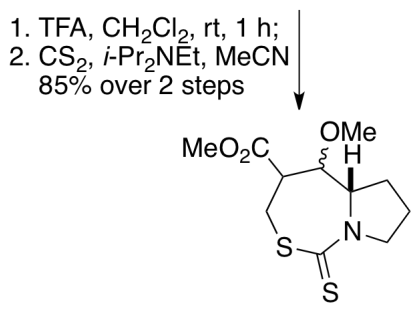


46.1 **46.2** **44.1**

Scheme 46



33.2 **47.1**

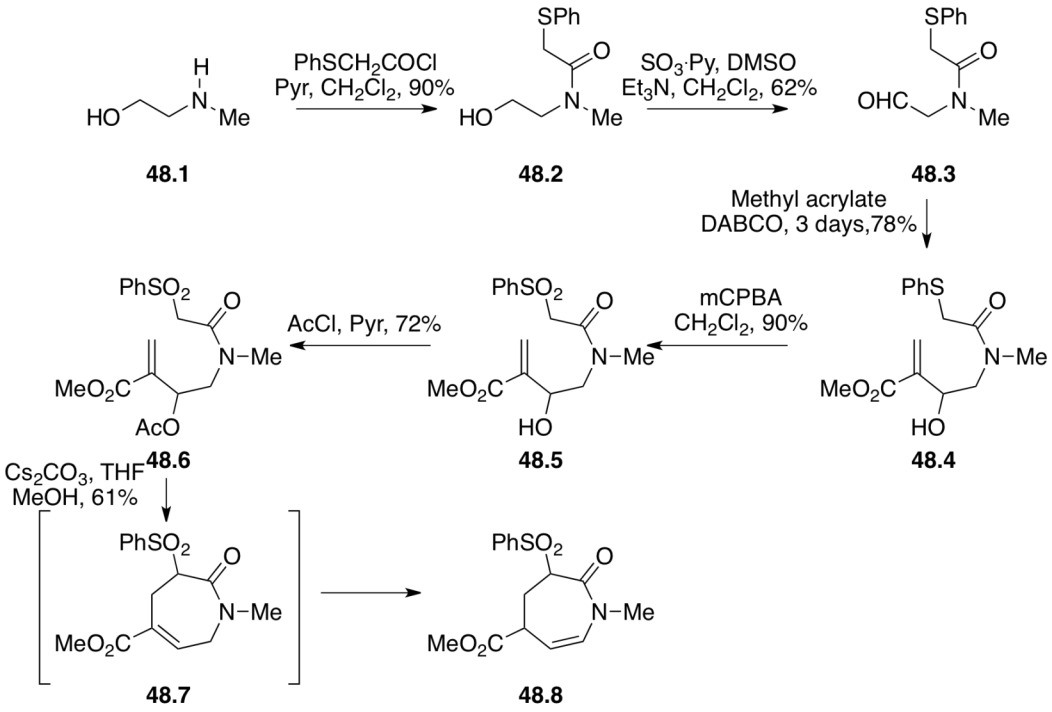


Scheme 47 **47.2**

In previous research in this laboratory, it was found that when a poor leaving group is used, instead of the exclusive formation of the ICD product, the standard Michael product is isolated as well. Applying the same idea, compound **47.1** was obtained via etherification of **33.3**. As expected, Michael addition compound **47.2** was isolated in 85% yield.

We next considered the situation in which we have an all-carbon tether on the nitrogen end; in this case a cyclic amide could be synthesized. *N*-methyl

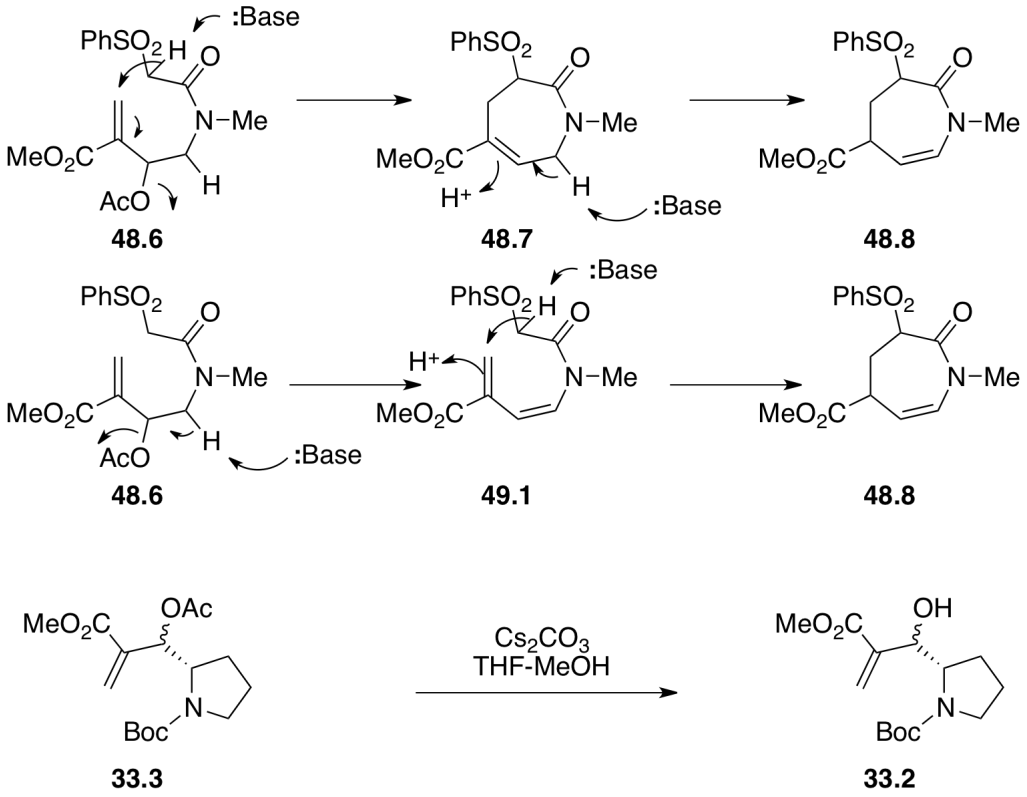
aminoethanol **48.1** was first acetylated and then oxidized to the amino aldehyde **48.3**. Morita-Baylis-Hillman reaction between **48.3** and methyl acrylate generated MBH alcohol **48.4**. Oxidation of the sulfide to sulfone and acetylation of the secondary alcohol provided the precursor for the ICD reaction — MBH acetate **48.6.** Instead of the expected product **48.7**, lactam **48.8** was the only isolated product.



Scheme 48

The formation of **48.8** could be explained in two different ways. The formation of the ICD product, followed by migration of the double bond to the more thermodynamically stable product is one possible pathway. Alternatively, elimination of the acetate could generate the *Z*-double bond and a Michael addition will give the same product **48.8**. In order to rule out the second pathway,

compound **33.3**, which served as a model, was subjected to the ICD reaction conditions. We did not obtain any elimination product. The hydrolyzed product **33.2** was the only isolated compound. From this result, it is most likely that lactam **48.8** was converted from **48.7** via a double bond migration.



Scheme 49

3. CONCLUSION

This section of this Ph.D. Thesis, describes a general type of reaction, intramolecular conjugate displacement, which was extended into a cascade process. Disfavored by Baldwin's rules, direct ICD processes of the 5-*endo*-*trig* type cannot proceed, but trapping a free amine with a 1,2-dipole, carbon disulfide, generates an intermediate bearing a negative charge on sulfur. Subsequent intramolecular conjugate displacement is a 7-*endo*-*trig* attack, which is a favored pathway. Many other 1,2-dipoles, as well as some formal 1,1-dipoles were also examined for the desired 7-*endo*-*trig* attack, but none of them proved to be successful. Several *N*,*S*-containing heterocycles were synthesized via this methodology. Cyclic secondary amines always produce 7-membered bicycles. However, for acyclic amines, a primary amine gave both 7-membered and 5-membered products. Upon optimization, secondary acyclic amines provide the 7-membered products when 2,6-lutidine was used as the base. Formation of 5-membered products was mainly due a S_N2'-S_N2' sequence, which was enhanced by nucleophilic amines. In contrast, when a poor leaving group was installed, the Michael type product was the only isolated compound.

In a subsequent experiment, we attempted to use carbon nucleophiles for intramolecular attack. When $PhSCH_2COCl$ was used to protect the secondary amine, a 7-membered lactam final product was produced. This result shows that further application of such a cascade intramolecular conjugate displacement may be worth examining.

4. EXPERIMENTAL

(2*S*)-β-Acetoxy-1-[(1,1-dimethylethoxy)carbonyl]-α-methylene-2-pyrrolidinepropanoic acid methyl ester (33.3).

33.2 **33.3**

AcCl (1.50 mL, 17.4 mmol) was added to a stirred mixture of **33.2** (1.66 g, 5.8 mmol) and pyridine (2.50 mL, 29.1 mmol) in CH_2Cl_2 (20 mL). Stirring was continued for 3.5 h and the mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (6 x 15 cm), using 4:1 hexane-EtOAc, gave **33.3** (1.84 g, 99%) as an oil: FTIR ($CDCl_3$, microscope) 2977, 2732, 2883, 1751, 1724, 1694, 1396, 1230, 1166 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44-1.51 (m, 9 H), 1.78-1.88 (m, 4 H), 2.10 (s, 3 H), 3.23-3.30 (m, 1 H), 3.54-3.60 (m, 1 H), 3.78 (s, 3 H), 4.14-4.30 (m, 1 H), 5.77 (s, 1 H), 6.18-6.30 (m, 1 H), 6.35 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0 (q), 21.1 (q), 23.6 (t), 26.2 (t), 28.4 (q), 46.6 (t), 47.0 (t), 52.0 (q), 52.1 (q), 58.0 (d), 71.6 (d), 80.1 (s), 126.0 (t), 137.8 (s), 154.3 (s), 165.3 (s), 169.1 (s) ; exact mass *m*/*z* calcd for $C_{16}H_{25}NNaO_6$ (M+Na) 350.1574, found 350.1575.

(2*S*)-1-[(1,1-Dimethylethoxy)carbonyl]-β-[(ethoxycarbonyl)oxy]-α-methylene-2-pyrrolidinepropanoic acid methyl ester (33.4).

33.2 **33.4**

EtOCOCl (71 μL, 0.75 mmol) was added to a stirred mixture of **33.2** (71 mg, 0.25 mmol), DMAP (30 mg, 0.25 mmol) and pyridine (0.11 mL, 1.25 mmol) in CH_2Cl_2 (5 mL) and stirring was continued for 3.5 h. The mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (2 x 15 cm), using 4:1 hexane-EtOAc, gave **33.4** (52 mg, 58%) as an oil: FTIR ($CDCl_3$, microscope) 2978, 2881, 1754, 1727, 1697, 1479, 1441, 1396, 1367, 1302, 1256, 1166 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.29 (t, *J* = 8 Hz, 3 H), 1.43-1.52 (m, 9 H), 1.73-1.78 (m, 2 H), 1.88-1.94 (m, 2 H), 3.25-3.30 (m, 1 H), 3.55 (s, 1 H), 3.78 (s, 3 H), 4.12-4.19 (m, 3 H), 5.66-5.87 (m, 1 H), 6.04 (s, 1 H), 6.38 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 23.5, 26.0, 28.3, 28.4, 47.0, 52.0, 58.1, 58.7, 64.3, 75.1, 80.1, 126.3, 127.6, 154.1, 154.3, 165.2; exact mass *m*/*z* calcd for $C_{17}H_{27}NNaO_7$ (M+Na) 380.1680, found 380.1680.

(2*S*)-2-(1-Acetoxy-2-cyano-2-propen-1-yl)-1-pyrrolidinecarboxylic dimethylethyl ester (33.5).

33.1 **33.5**

DABCO (1.29 g, 11.5 mmol) was added to a stirred mixture of **33.1** (766 mg, 3.85 mmol) and acrylonitrile (2.53 mL, 38.5 mmol) and stirring was continued for 3 days. The mixture was diluted with water and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated and the crude product was used directly for the ext step. AcCl (1.03 mL, 5.85 mmol) was added to a stirred mixture of the crude product and pyridine (1.68 mL, 19.3 mmol) in CH_2Cl_2 (10 mL). Stirring was continued for 3.5 h and the mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 4:1 hexane-EtOAc, gave **33.5** (811 mg, 72% over two steps) as an oil: FTIR ($CDCl_3$, microscope) 2977, 2934, 2226, 1754, 1696, 1479, 1456, 1394, 1368, 1224, 1167 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 1.49 (s, 9 H), 1.82-2.07 (m, 4 H), 2.12 (s, 3 H), 3.26- 3.34 (m, 1 H), 3.43-3.61 (m, 1 H), 4.07-4.16 (m, 1 H), 5.68-6.00 (m, 2 H), 6.04-6.07 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C) δ 20.7, 20.8, 24.0, 26.0, 28.2, 28.4, 28.6, 28.8, 47.0, 47.1, 58.9, 59.1, 59.4, 72.7, 73.0, 80.3,

116.3, 116.5, 120.9, 121.7, 131.7, 133.3, 154.3, 169.1; exact mass *m*/*z* calcd for $C_{15}H_{22}N_2NaO_4$ (M+Na) 317.1472, found 317.1473.

1-[(1,1-Dimethylethoxy)carbonyl]-β-hydroxy-α-methylene-2-piperidinepropanoic acid methyl ester (33.7).

33.6 **33.7**

DABCO (900 mg, 8.04 mmol) was added to a stirred mixture of **33.6** (572 mg, 2.68 mmol) and methyl acrylate (2.43 mL, 26.8 mmol) and stirring was continued for 4 days. The mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (4 x 15 cm), using 2:1 hexane-EtOAc, gave **33.7** (650 mg, 81%) as an oil: FTIR ($CDCl_3$, microscope) 3433, 2932, 2857, 1719, 1690, 1668, 1416, 1392, 1167 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 65 °C) δ 1.40-1.68 (m, 15 H), 2.21 (ddd, *J* = 2.4, 12, 12 Hz, 0.5 H), 2.76 (ddd, *J* = 2.4, 12, 12 Hz, 0.5 H), 2.97 (dd, *J* = 12, 12 Hz, 0.5 H), 3.44 (d, *J* = 9.2 Hz, 0.5 H), 3.81 (s, 3 H), 3.94-4.05 (m, 1 H), 4.32 (ddd, *J* = 2.4, 5.2, 10 Hz, 0.5 H), 4.40-4.43 (m, 0.5 H), 4.53 (dd, *J* = 10, 10 Hz, 0.5 H), 4.72 (dd, *J* = 8, 8 Hz, 0.5 H), 5.73 (s, 0.5 H), 5.87 (s, 0.5 H), 6.19 (s, 0.5 H), 6.33 (s, 0.5 H); ^{13}C NMR (125 MHz, $CDCl_3$, 65 °C) δ 19.3, 19.7, 24.5, 25.3, 25.5, 25.8, 27.9, 28.5, 28.6, 40.2, 51.8, 51.9, 54.3, 55.5, 71.1, 71.2, 79.6, 80.1, 126.8, 127.2, 141.8, 155.1, 166.7, 167.2; exact mass *m*/*z* calcd for $C_{15}H_{25}NNaO_5$ (M+Na) 322.1625,

found 322.1623. The ^{1}H NMR and ^{13}C NMR spectra indicated the presence of diastereoisomers and probably rotamers.

1-[(1,1-Dimethylethoxy)carbonyl]hexahydro-β-hydroxy-α-methylene-1*H*-azepine-2-propanoic acid methyl ester (33.8).

33.6' **33.8**

DABCO (591 mg, 5.28 mmol) was added to a stirred mixture of **33.6'** (400 mg, 1.76 mmol) and methyl acrylate (1.61 mL, 17.8 mmol), and stirring was continued for 3 days. The mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 2:1 hexane-EtOAc, gave **33.8** (440 mg, 80%) as an oil: FTIR ($CDCl_3$, microscope) 3434, 2928, 2854, 1722, 1689, 1676, 1478, 1441, 1414, 1391, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 1.26-2.16 (m, 17 H), 2.88-3.03 (m, 1 H), 3.48-3.77 (m, 1 H), 3.79 (s, 3 H), 4.13-4.40 (m, 2 H), 5.58-5.89 (m, 1 H), 6.22-6.27 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C) δ 25.4, 28.5, 29.0, 29.5, 30.3, 43.2, 44.5, 44.7, 51.7, 59.3, 60.6, 60.8, 74.5, 75.7, 79.6, 79.9, 125.8, 126.3, 140.3, 141.9, 155.5, 157.6, 159.8, 166.9, 167.3; exact mass *m*/*z* calcd for $C_{16}H_{27}NNaO_5$ (M+Na) 336.1781, found 336.1780. The ^1H NMR spectrum consisted of broad signals, and we attribute the extra signals in the ^{13}C NMR spectrum to the presence of rotamers and diastereoisomers.

β-Acetoxy-1-[(1,1-dimethylethoxy)carbonyl]-α-methylene-2-piperidinepropanoic acid methyl ester (33.9).

33.7 **33.9**

AcCl (0.13 mL, 1.53 mmol) was added to a stirred mixture of **33.7** (154 mg, 0.51 mmol) and pyridine (0.22 mL, 2.55 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3.5 h and the mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (3 x 15 cm), using 4:1 hexane-EtOAc, gave **2c** (159 mg, 92%) as an oil: FTIR ($CDCl_3$, microscope) 2935, 2860, 1744, 1724, 1692, 1413, 1391, 1229 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 1.35-1.77 (m, 15 H), 1.96 (s, 1.2 H), 2.01 (s, 1.8 H), 2.83 (ddd, *J* = 2.8, 13.2, 13.2 Hz, 1 H), 3.70 (s, 1.8 H), 3.75 (s, 1.2 H), 3.89-3.94 (m, 1 H), 4.47-4.48 (m, 1 H), 5.84-5.92 (m, 2 H), 6.26 (s, 0.6 H), 6.33 (s, 0.4 H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C) δ 19.2, 19.6, 20.8, 25.0, 25.5, 28.3, 28.4, 39.9, 51.6, 51.8, 53.3, 68.8, 70.1, 79.3, 79.5, 127.4, 127.7, 138.9, 139.5, 154.5, 155.1, 165.3, 165.6, 169.3, 169.4; exact mass *m*/*z* calcd for $C_{17}H_{27}NNaO_6$ (M+Na) 364.1731, found 364.1728.

β-Acetoxy-1-[(1,1-dimethylethoxy)carbonyl]hexahydro-α-methylene-1*H*-azepine-2-propanoic acid methyl ester (33.10).

33.8 **33.10**

AcCl (0.29 mL, 3.27 mmol) was added to a stirred mixture of **33.8** (341 mg, 1.09 mmol) and pyridine (0.47 mL, 5.45 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3.5 h, and the mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 4:1 hexane-EtOAc, gave **33.10** (355 mg, 87%) as an oil: FTIR ($CDCl_3$, microscope) 2929, 2855, 1751, 1725, 1692, 1440, 1366, 1232, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 1.16-2.16 (m, 20 H), 2.81-2.90 (m, 1 H), 3.56-3.70 (m, 1 H), 3.78-3.81 (m, 3 H), 4.29-4.51 (m, 1 H), 5.67-5.81 (m, 2 H), 6.28-6.32 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 20.9, 21.0, 24.8, 25.0, 28.5, 28.6, 28.8, 29.3, 29.7, 29.8, 30.1, 30.3, 43.4, 43.8, 51.9, 52.0, 56.8, 57.0, 51.6, 73.4, 74.0, 79.2, 79.3, 79.8, 80.0, 125.7, 126.0, 126.6, 138.6, 138.8, 155.4, 155.8, 156.2, 165.4, 165.6; exact mass *m*/*z* calcd for $C_{18}H_{29}NNaO_6$ (M+Na) 378.1887, found 378.1890.

2-(1-Acetoxy-2-cyano-2-propen-1-yl)-1-pyrrolidinecarboxylic acid 1,1-dimethylethyl ester (33.11).

33.6 **33.11**

DABCO (1.12 g, 9.96 mmol) was added to a stirred mixture of **33.6** (707 mg, 3.32 mmol) and acrylonitrile (2.20 mL, 33.2 mmol) and stirring was continued for 4 days. The mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated and the crude product was used directly for the next step. AcCl (0.89 mL, 9.96 mmol) was added to a stirred mixture of the crude product and pyridine (1.43 mL, 16.6 mmol) in CH_2Cl_2 (10 mL). Stirring was continued for 3.5 h and the mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (4 x 15 cm), using 4:1 hexane-EtOAc, gave **33.11** (732 mg, 72% over two steps) as an oil: FTIR ($CDCl_3$, microscope) 2935, 2866, 2228, 1750, 1694, 1449, 1475, 1367, 1223, 1168 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$ 60 °C) δ 1.46-1.53 (m, 11 H), 1.62-1.80 (m, 4 H), 2.07 (s, 1.31 H), 2.14 (s, 1.69 H), 2.73-2.75 (m, 1 H), 4.04-4.14 (m, 1 H), 4.48-4.62 (m, 1 H), 5.62 (d, J = 10 Hz, 0.56 H), 5.67 (d, J = 10 Hz, 0.44 H), 5.95 (s, 0.56 H), 6.00 (s, 0.56 H), 6.09 (s, 0.44 H), 6.12 (s, 0.44 H); ^{13}C NMR

(125 MHz, $CDCl_3$, 60 °C) δ 19.3, 19.4, 20.8, 20.9, 24.5, 24.9, 25.0, 28.4, 28.5, 29.8, 52.0, 52.1, 70.5, 70.9, 80.0, 80.7, 115.9, 116.2, 121.8, 132.8, 134.4, 154.7, 155.2, 169.4, 169.7; exact mass *m*/*z* calcd for $C_{16}H_{24}N_2NaO_4$ (M+Na) 331.1628, found 331.1628.

4-[[(1,1-Dimethylethoxy)carbonyl]amino]-3-hydroxy-2-methylene-butanoic acid methyl ester (33.13).

33.12 **33.13**

DABCO (1.05 g, 9.375 mmol) was added to a stirred mixture of **33.12** (500 mg, 3.125 mmol) and methyl acrylate (2.88 mL, 31.25 mmol) and stirring was continued for 4 days. The mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (3.5 x 15 cm), using 2:1 hexane-EtOAc, gave **33.13** (546 mg, 71%) as oil: FTIR ($CDCl_3$, microscope) 3385, 2978, 2934, 1716, 1522, 1440, 1393, 1278, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9 H), 3.26-3.29 (m, 1 H), 3.40-3.45 (m, 1 H), 3.76 (s, 3 H), 3.82-4.00 (m, 1 H), 4.57-4.56 (m, 1 H), 5.00 (br s, 1 H), 5.98 (s, 1 H), 6.34 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3 (q), 45.9 (t), 51.9 (q), 71.2 (q), 79.9 (s), 126.6 (t), 139.8 (s), 157.4 (s), 166.5 (s); exact mass *m*/*z* calcd for $C_{11}H_{19}NNaO_5$ (M+Na) 268.1155, found 268.1153.

4-[[(1,1-Dimethylethoxy)carbonyl]methylamino]-3-hydroxy-2-methylenebutanoic acid methyl ester (33.14).

33.12' **33.14**

DABCO (1.24 g, 11.10 mmol) was added to a stirred mixture of **31.12'** (640 mg, 3.70 mmol) and methyl acrylate (3.30 mL, 36.99 mmol) and stirring was continued for 3 days. The mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using 2:1 hexane-EtOAc, gave **33.13** (826 mg, 86%) as oil: FTIR ($CDCl_3$, microscope) 3432, 2977, 2953, 2933, 1791, 1697, 1672, 1483, 1395, 1155 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9 H), 2.86 (s, 3 H), 3.46 (s, 2 H), 3.76 (s, 3 H), 4.66 (m, 2 H), 5.89-6.07 (m, 1 H), 6.63 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3 (q), 36.4 (d), 51.8 (q), 55.3 (s), 71.0 (q), 80.5 (s), 126.5 (t), 140.2 (s), 158.4 (s), 166.5 (s); exact mass *m*/*z* calcd for $C_{12}H_{21}NNaO_5$ (M+Na) 282.1312, found 282.1313.

4-[[(1,1-Dimethylethoxy)carbonyl](phenylmethyl)amino]-3-hydroxy-2-methylene-butanoic acid methyl ester (33.15).

33.12'' **33.15**

DABCO (223 mg, 1.99 mmol) was added to a stirred mixture of **33.12''** (202 mg, 0.811 mmol) and methyl acrylate (0.59 mL, 6.44 mmol) and stirring was continued for 3 days. The mixture was diluted with water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (2 x 15 cm), using 2:1 hexane-EtOAc, gave **33.15** (189 mg, 69%) as an oil: FTIR ($CDCl_3$, microscope) 3437, 3066, 2954, 2925, 1717, 1695, 1669, 1464, 1415, 1366, 1247, 1167 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (hydroxyl H not observed) δ 1.47 (s, 9 H), 3.39-3.54 (m, 2 H), 3.76 (s, 3 H), 4.34-4.70 (m, 3 H), 6.09 (s, 1 H), 6.34 (s, 1 H), 7.22-7.34 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3 (q), 51.8 (d), 52.4 (t), 53.3 (t), 71.2 (q), 81.1 (s), 126.6 (t), 127.3 (d), 127.4 (d), 128.5 (d), 137.9 (s), 140.2 (s), 158.4 (s), 166.5 (s); exact mass *m*/*z* calcd for $C_{18}H_{25}NNaO_5$ (M+Na) 358.1625, found 358.1623.

4-[[(1,1-Dimethylethoxy)carbonyl](4-methoxyphenyl)amino]-3-hydroxy-2-methylenebutanoic acid methyl ester (33.16).

33.12''' **33.16**

DABCO (479 mg, 4.278 mmol) was added to a stirred mixture of **33.12'''** (378 mg, 1.426 mmol) and methyl acrylate (1.30 mL, 14.26 mmol) and stirring was continued for 3 days. The mixture was diluted with water and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 2:1 hexane-EtOAc, gave **33.16** (428 mg, 86%) as oil: FTIR ($CDCl_3$, microscope) 3438, 2977, 2953, 2935, 2838, 1716, 1698, 1669, 1513, 1441, 1367, 1220 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9 H), 3.61 (s, 3 H), 3.78-3.83 (m, 4 H), 3.91 (dd, J = 3.2, 6.4 Hz, 1 H), 4.65 (s, 1 H), 6.05 (s, 1 H), 6.34 (s, 1 H), 6.81-6.85 (m, 2 H), 7.26-7.27 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2 (q), 51.6 (q), 55.4 (q), 71.3 (d), 81.0 (s), 113.9 (d), 126.7 (t), 128.1 (d), 135.7 (s), 140.3 (s), 157.7 (s), 166.2 (s); exact mass m/z calcd for $C_{18}H_{25}NNaO_6$ (M+Na) 374.1574, found 374.1576.

3-Acetoxy-4-[[(1,1-dimethylethoxy)carbonyl]amino]-2-methylene-butanoic acid methyl ester (33.17).

33.13 **33.17**

AcCl (0.22 mL, 2.571 mmol) was added to a stirred mixture of **33.13** (210 mg, 0.857 mmol) and pyridine (0.37 mL, 4.285 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3.5 h and the mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (2 x 15 cm), using 4:1 hexane-EtOAc, gave **33.17** (179 mg, 73%) as an oil: FTIR ($CDCl_3$, microscope) 3378, 2978, 2934, 1718, 1521, 1440, 1368, 1233 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 9 H), 2.11 (s, 3 H), 3.48 (s, 2 H), 3.80 (s, 3 H), 4.68 (s, 1 H), 5.69 (s, 1 H), 5.85 (s, 1 H), 6.37 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9 (q), 28.2 (q), 43.2 (t), 52.0 (q), 71.1 (q), 79.3 (s), 126.7 (t), 137.0 (s), 155.7 (s), 165.2 (s), 169.6 (s); exact mass *m*/*z* calcd for $C_{13}H_{21}NNaO_6$ (M+Na) 310.1261, found 310.1259.

3-Acetoxy-4-[[(1,1-dimethylethoxy)carbonyl]methylamino]-2-methylenebutanoic acid methyl ester (33.18).

33.14 **33.18**

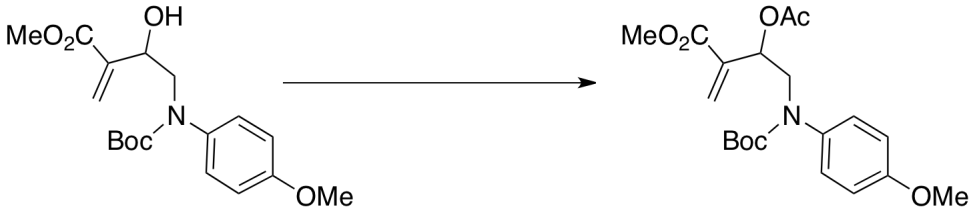
AcCl (0.82 mL, 9.498 mmol was added to a stirred mixture of **33.14** (820 mg, 3.166 mmol) and pyridine (1.36 mL, 15.83 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3.5 h and the mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (4 x 15 cm), using 4:1 hexane-EtOAc, gave **33.18** (953 mg, 100%) as an oil: FTIR ($CDCl_3$, microscope) 2976, 2932, 1794, 1722, 1698, 1482, 1441, 1393, 1368, 1232, 1152 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 1.41 (s, 9 H), 2.03 (s, 3 H), 2.87 (s, 3 H), 3.35-3.70 (m, 2 H), 3.75 (s, 3 H), 5.81-5.80 (m, 2 H), 6.36 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 28.2, 35.5, 51.6, 51.9, 70.7, 79.7, 126.5, 138.0, 155.7, 165.3, 169.4; exact mass *m*/*z* calcd for $C_{14}H_{23}NNaO_6$ (M+Na) 324.1418, found 324.1413.

4-[[(1,1-Dimethylethoxy)carbonyl](phenylmethyl)amino]-3-hydroxy-2-methylenebutanoic acid methyl ester (33.19).

33.15 **33.19**

DABCO (223 mg, 1.99 mmol) was added to a stirred mixture of **33.15** (202 mg, 0.811 mmol) and methyl acrylate (0.59 mL, 6.44 mmol) and stirring was continued for 3 days. The mixture was diluted with water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (2 x 15 cm), using 2:1 hexane-EtOAc, gave **33.19** (189 mg, 69%) as an oil: FTIR ($CDCl_3$, microscope) 3437, 3066, 2954, 2925, 1717, 1695, 1669, 1464, 1415, 1366, 1247, 1167 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (hydroxyl H not observed) δ 1.47 (s, 9 H), 2.04 (s, 3H), 3.39-3.54 (m, 2 H), 3.76 (s, 3 H), 4.34-4.70 (m, 3 H), 6.09 (s, 1 H), 6.34 (s, 1 H), 7.22-7.34 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.3 (q), 51.8 (d), 52.4 (t), 53.3 (t), 71.2 (q), 81.1 (s), 126.6 (t), 127.3 (d), 127.4 (d), 128.5 (d), 137.9 (s), 140.2 (s), 158.4 (s), 166.5 (s); exact mass *m*/*z* calcd for $C_{18}H_{25}NNaO_5$ (M+Na) 358.1625, found 358.1623.

3-Acetoxy-4-[[(1,1-dimethylethoxy)carbonyl](4-methoxyphenyl)-amino]-2-methylenebutanoic acid methyl ester (33.18).



33.16 **33.20**

AcCl (0.50 mL, 5.85 mmol) was added to a stirred mixture of **33.16** (411 mg, 1.17 mmol) and pyridine (0.30 mL, 3.51 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3.5 h and the mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (2 x 15 cm), using 4:1 hexane-EtOAc, gave **33.20** (380 mg, 83%) as an oil: FTIR ($CDCl_3$, microscope) 2976, 2934, 2839, 1746, 1700, 1513, 1440, 1392, 1368, 1293, 1236, 1150 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.38 (s, 9 H), 1.90 (s, 3 H), 3.72 (s, 3 H), 3.77 (s, 3 H), 3.80- 4.07 (m, 2 H), 5.81 (s, 1 H), 5.87 (s, 1 H), 6.35 (s, 1 H), 6.85-6.85 (m, 2 H), 7.07-7.09 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9 (q), 28.2 (q), 52.0 (q), 52.5 (t), 55.4 (q), 70.9 (d), 113.9 (d), 114.7 (s), 127.0 (t), 128.3 (d), 135.5 (s), 137.5 (s), 154.9 (s), 157.6 (s), 165.2 (s), 169.6 (s); exact mass *m*/*z* calcd for $C_{20}H_{27}NNaO_7$ (M+Na) 416.1680, found 416.1681.

3-Acetoxy-4-[[(1,1-dimethylethoxy)carbonyl]-2-propen-1-ylamino]-2-methylenebutanoic acid methyl ester (33.21).

33.12'''' **33.21**

DABCO (115 mg, 1.029 mmol) was added to a stirred mixture of **33.12''''** (68 mg, 0.343 mmol) and methyl acrylate (0.31 mL, 3.43 mmol) and stirring was continued for 3 days. The mixture was diluted with water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated and the crude product was used directly for the next step. Pyridine (0.11 mL, 1.29 mmol) and AcCl (70 μL, 0.77 mmol) were added to a stirred solution of crude product from the above experiment in CH_2Cl_2 (5 mL) and stirring was continued for 3.5 h. The mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (2 x 15 cm), using 4:1 hexane-EtOAc, gave **33.21** (76 mg, 68% over two steps) as an oil: FTIR ($CDCl_3$, microscope) 2978, 2954, 1749, 1698, 1458, 1408, 1367, 1231, 1170 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 1.50 (s, 9 H), 2.11 (s, 3 H), 3.51-3.70 (m, 2 H), 3.83 (s, 3 H), 3.86-3.99 (m, 2 H), 5.15-5.18 (m, 2 H), 5.78-5.89 (m, 3 H), 6.37 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 21.0, 28.4, 49.6, 50.4, 51.9, 70.8, 80.1, 116.5, 126.7, 134.0, 138.3, 155.5, 165.5, 169.5;

exact mass *m*/*z* calcd for $C_{16}H_{25}NNaO_6$ (M+Na) 350.1574, found 350.1575.

(5a*S*)-5a,6,7,8-Tetrahydro-1-thioxo-*3H*-pyrrolo[1,2-*c*][1,3]thiazepine-4-carboxylic acid methyl ester (36.1).

33.3 **36.1**

CF_3CO_2H (0.22 mL, 2.9 mmol) was added to a stirred solution of **33.3** (96 mg, 0.29 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3.5 h and the mixture was evaporated. The residue was dissolved in MeCN (5 mL) and CS_2 (88 μL, 1.47 mmol) and *i*-Pr_2NEt (0.25 mL, 1.47 mmol) were added. Stirring was continued overnight and the mixture was evaporated. Flash chromatography of the residue over the silica gel (2 x 15 cm), using 2:1 hexane-EtOAc, gave **36.1** (46 mg, 65%) as an oil: FTIR ($CDCl_3$, microscope) 2972, 2874, 1716, 1436, 1328, 1257, 1192, 1136 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.96-2.03 (m, 2 H), 2.10-2.15 (m, 1 H), 2.37-2.44 (m, 1 H), 3.41 (dd, *J* = 1, 14 Hz, 1 H), 3.80 (s, 3 H), 3.96 (ddd, *J* = 7.5, 7.5, 15 Hz, 1 H), 4.12 (m, 1 H), 4.35 (ddd, *J* = 1.5, 1.5, 15 Hz, 1 H), 4.99 (ddd, *J* = 3, 7.5, 7.5 Hz, 1 H), 6.81 (ddd, *J* = 1.5, 1.5, 7.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8 (t), 32.0 (t), 32.7 (t), 52.6 (d), 55.2 (t), 57.6 (q), 132.9 (s), 140.7 (d), 164.9 (s), 190.6 (s); exact mass *m*/*z* calcd for $C_{10}H_{13}NNaO_2S_2$ (M+Na) 266.0280, found 266.0280.

6,7,8,9-Tetrahydro-1-thioxo-3*H*,5a*H*-pyrido[1,2-*c*][1,3]thiazepine-4-carboxylic acid methyl ester (40.1).

33.9 **40.1**

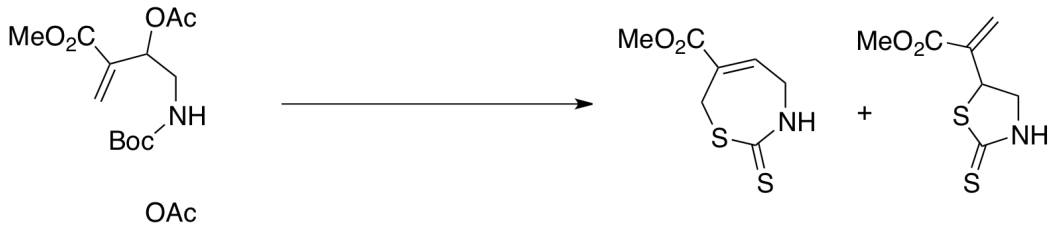
CF_3CO_2H (0.16 mL, 1.96 mmol) was added to a stirred solution of **33.9** (67 mg, 0.196 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3.5 h and the mixture was evaporated. The residue was dissolved in MeCN (5 mL) and CS_2 (48 μL, 0.784 mmol) and *i*-Pr_2NEt (0.13 mL, 0.980 mmol) were added. Stirring was continued overnight and the mixture was evaporated. Flash chromatography of the residue over the silica gel (2 x 15 cm), using 2:1 hexane-EtOAc, gave **40.1** (28 mg, 56%) as an oil: FTIR ($CDCl_3$, microscope) 2948, 2864, 1716, 1475, 1421, 1317, 1194, 1117 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.71-2.05 (m, 6 H), 3.62-3.70 (m, 2 H), 3.80 (s, 3 H), 4.14 (dd, *J* = 2, 15 Hz, 1 H), 4.73 (ddd, *J* = 5, 5, 14 Hz, 1 H), 5.15 (ddd, *J* = 5, 5, 8.5 Hz, 1 H), 7.05 (dd, *J* = 2, 8.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.2 (t), 22.1 (t), 26.3 (t), 34.1 (t), 47.4 (t), 52.6 (d), 56.7 (q), 120.6 (s), 139.9 (d), 165.2 (s), 195.9 (s); exact mass *m*/*z* calcd for $C_{11}H_{15}NNaO_2S_2$ (M+Na) 280.0436, found 280.0432.

5a,6,7,8,9,10-Hexahydro-1-thioxo-3*H*-azapino[1,2-*c*][1,3]thiazepine-4-carboxylic acid methyl ester (40.2).

33.10 **40.2**

CF_3CO_2H (0.18 mL, 2.36 mmol) was added to a stirred solution of **33.10** (79 mg, 0.236 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3.5 h, and the mixture was evaporated. The residue was dissolved in MeCN (5 mL), and CS_2 (72 μL, 0.944 mmol) and *i*-Pr_2NEt (0.13 mL, 0.980 mmol) were added. Stirring was continued overnight, and the mixture was evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 2:1 hexane-EtOAc, gave **40.2** (37 mg, 58%) as an oil: FTIR ($CDCl_3$, microscope) 2928, 2854, 1716, 1466, 1437, 1408, 1233, 1173 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.39-2.18 (m, 8 H), 3.21 (dd, J = 12, 13.5 Hz, 1 H), 3.62(d, J = 14 Hz, 1 H), 3.79(s, 3 H), 4.15(dd, J = 2, 14 Hz, 1 H), 4.89(ddd, J = 5, 9, 12 Hz, 1 H), 4.97(dd, J = 5, 14 Hz, 1 H), 6.91 (dd, J = 2, 9 Hz, 1 H); ^{13}C NMR(125 MHz, $CDCl_3$) δ 26.3 (t), 28.6 (t), 28.7 (t), 32.7 (t), 34.8 (t), 50.7 (t), 52.5 (d), 61.3 (q), 129.2 (s), 141.4 (d), 165.2 (s), 195.3 (s); exact mass *m*/*z* calcd for $C_{12}H_{17}NNaO_2S_2$ (M+Na) 294.0593, found 294.0593.

4,7-Dihydro-2(3*H*)-thioxo-1,3-thiazepine-6-carboxylic acid methyl ester (41.1) and α-Methylene-2-thioxo-5-thiazolidineacetic acid methyl ester (41.2).



33.17 **41.1** **41.2**

CF_3CO_2H (0.14 mL, 1.78 mmol) was added to a stirred solution of **33.17** (51 mg, 0.178 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3.5 h and the mixture was evaporated. The residue was dissolved in MeCN (5 mL) and CS_2 (43 μL, 0.712 mmol) and 2,6-lutidine (0.10 mL, 0.890 mmol) were added. Stirring was continued overnight and the mixture was evaporated. Flash chromatography of the residue over the silica gel (2 x 15 cm), using 2:1 hexane-EtOAc, gave **41.2** (9 mg, 25%) as oil and **41.1** (18 mg, 50%) as oils. Compound **41.1** had: FTIR ($CDCl_3$, microscope) 3143, 2999, 2982, 1711, 1530, 1452, 1281, 1167 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3 H), 3.93 (s, 2 H), 4.13 (d, J = 7.5 Hz, 2 H), 7.08 (t, J = 7.5 Hz, 1 H), 8.29 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.0 (t), 44.2 (t), 53.7 (q), 135.0 (d), 135.4 (s), 164.8 (s), 199.0 (s); exact mass m/z calcd for $C_7H_8NO_2S_2$ (M-H) 202.0002, found 201.9999. Compound **41.2** had: FTIR ($CDCl_3$, microscope) 3284, 3166, 2951, 1714, 1628, 1500, 1438, 1280, 1148 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (NH signal not observed) δ 3.81 (s, 3 H), 3.86 (dd, J

= 11.5, 4.5 Hz, 1 H), 4.26 (dd, *J* = 11.5, 8 Hz, 1 H), 4.95 (dd, *J* = 8, 4.5 Hz, 1 H), 6.09 (d, *J* = 1 Hz, 1 H), 6.50 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.9 (s), 52.5 (q), 55.6 (q), 127.3 (t), 137.4 (s), 165.7 (s), 200.6 (s); exact mass *m*/*z* calcd for $C_7H_8NO_2S_2$ (M-H) 202.0002, found 201.9999.

4,7-Dihydro-3-methyl-2(3*H*)-thioxo-1,3-thiazepine-6-carboxylic acid methyl ester (41.3).

33.18 **41.3**

CF_3CO_2H (0.30 mL, 11.10 mmol) was added to a stirred solution of **33.10** (120 mg, 0.399 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3.5 h and the mixture was evaporated. The residue was dissolved in MeCN (5 mL) and CS_2 (96 μL, 1.595 mmol) and 2,6-lutidine (0.23 mL, 1.994 mmol) were added. Stirring was continued overnight and the mixture was evaporated. Flash chromatography of the residue over the silica gel (2 x 15 cm), using 2:1 hexane-EtOAc, gave **41.3** (57 mg, 66%) as oil: FTIR ($CDCl_3$, microscope) 2949, 2926, 2851, 1714, 1649, 1498, 1456, 1319, 1258 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.58 (s, 3 H), 3.80 (s, 3 H), 3.87 (s, 2 H), 4.36 (d, J = 7.8 Hz, 2 H), 7.16(t, J = 7.8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.4(t), 45.3 (q), 51.3 (t), 52.6 (q), 133.7 (s), 134.9 (d), 165.0 (s), 195.3 (s); exact mass m/z calcd for $C_8H_{11}NNaO_2S_2$ (M+Na) 240.0123, found 240.0122.

4,7-Dihydro-3-(2-propen-1-yl)-2(3*H*)-thioxo-1,3-thiazepine-6-carboxylic acid methyl ester (41.5).

33.19 **41.5**

CF_3CO_2H (0.10 mL, 1.22 mmol) was added to a stirred solution of **33.19** (18 mg, 0.055 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3.5 h and the mixture was evaporated. The residue was dissolved in MeCN (5 mL) and CS_2 (30 μL, 0.508 mmol) and 2,6-lutidine (80 μL, 0.635 mmol) were added. Stirring was continued for 1.5 h and the mixture was evaporated. Flash chromatography of the residue over the silica gel (2 x 15 cm), using 2:1 hexane-EtOAc, gave **41.5** (8 mg, 60%) as an oil: FTIR ($CDCl_3$, microscope) 3079, 2950, 2849, 1717, 1486, 1451, 1408, 1288, 1263, 1225, 1168 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.82 (s, 3 H), 3.89 (s, 2 H), 4.28 (d, J = 8 Hz, 2 H), 4.73 (d, J = 5.5 Hz, 2 H), 5.31-5.35 (m, 2 H), 5.83-5.90 (m, 1 H), 7.08 (t, J = 8 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.4 (t), 48.3 (t), 52.7 (q), 58.7 (t), 119.9 (t), 131.0 (d), 134.0 (s), 135.5 (s), 165.0 (s), 195.9 (s); exact mass m/z calcd for $C_{10}H_{13}NNaO_2S_2$ (M+Na) 266.0280, found 266.0281.

4,7-Dihydro-3-(phenylmethyl)-2(3*H*)-thioxo-1,3-thiazepine-6-carboxylic acid methyl ester (41.6) and α-Methylene-3-(phenylmethyl)-2-thioxo-5-thiazolidineacetic acid methyl ester (41.7).

33.21 **41.6** **41.7**

CF_3CO_2H (0.10 mL, 1.27 mmol) was added to a stirred solution of **33.21** (48 mg, 0.127 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3 h and the mixture was evaporated. The residue was dissolved in MeCN (5 mL) and CS_2 (32 μL, 0.508 mmol) and 2, 6-lutidine (84 μL, 0.635 mmol) were added. Stirring was continued for 1.5 h and the mixture was evaporated. Flash chromatography of the residue over the silica gel (2 x 15 cm), using 4:1 hexane-EtOAc, gave **41.6** (24 mg, 65%) as an oil: FTIR ($CDCl_3$, microscope) 3060, 2950, 2922, 2851, 1717, 1495, 1485, 1449, 1436, 1260, 1137 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3 H), 3.89 (s, 2 H), 4.24 (d, J = 7.5 Hz, 2 H), 5.36 (s, 2 H), 6.82 (t, J = 7.5 Hz, 1 H), 7.26-7.38 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.4 (t), 48.1 (t), 52.6 (q), 58.9 (t), 128.3 (d), 128.4 (d), 129.0 (d), 134.1 (s), 135.0 (s), 135.6 (d), 164.9 (s), 196.4 (s); exact mass *m*/*z* calcd for $C_{14}H_{15}NNaO_2S_2$ (M+Na) 316.0440, found 316.0436.

In a similar experiment, in which the reaction time was longer (overnight)

and a different base (*i*-Pr_2NEt) was used, both **41.6** (38%) and **41.7** (30%) were isolated: CF_3CO_2H (0.16 mL, 2.06 mmol) was added to a stirred solution of **33.21** (76 mg, 0.21 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3 h and the mixture was evaporated. The residue was dissolved in MeCN (5 mL) and CS_2 (50 μL, 0.82 mmol) and *i*-Pr_2NEt (0.17 mL, 1.03 mmol) were added. Stirring was continued overnight and the mixture was evaporated. Flash chromatography of the residue over the silica gel (2 x 15 cm), using 4:1 hexane-EtOAc, gave **41.6** (23 mg, 38%) and **41.7** (18 mg, 30%) as oils: Compound **41.7** had: FTIR ($CDCl_3$, microscope) 3028, 2951, 2850, 1715, 1677, 1485, 1437, 1307, 1280, 1176, 1144 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.75 (s, 3 H), 3.80 (dd, *J* = 4, 12 Hz, 1 H), 4.19 (dd, *J* = 8, 12 Hz, 1 H), 4.56 (ddd, *J* = 1, 4, 8 Hz, 1 H), 5.10 (d, *J* = 15 Hz, 1 H), 5.80 (d, *J* = 1 Hz, 1 H), 6.36 (s, 1 H), 7.32-7.37 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.8 (d), 52.4 (q), 52.6 (t), 60.1 (t), 126.9 (t), 128.4 (d), 128.9 (d), 134.8 (s), 137.8 (s), 165.7 (s), 195.7 (s); exact mass *m*/*z* calcd for $C_{14}H_{15}NNaO_2S_2$ (M+Na) 316.0436, found 316.0441.

(5a*S*)-4-Cyano-5a,6,7,8-tetrahydro-*3H*-pyrrolo[1,2-*c*][1,3]thiazepine-1-thione (44.1).

33.5 **44.1**

CF_3CO_2H (0.20 mL, 2.69 mmol) was added to a stirred solution of **33.5** (79 mg, 0.269 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3.5 h and the mixture was evaporated. The residue was dissolved in MeCN (5 mL) and cooled to -40 °C. CS_2 (69 μL, 1.076 mmol) and 2,6-lutidine (0.16 mL, 1.345 mmol) were added. The cold bath was left in place but not recharged and stirring was continued overnight. The mixture was evaporated and flash chromatography of the residue over the silica gel (2 x 15 cm), using 2:1 hexane-EtOAc, gave **44.1** (40 mg, 71%) as an oil: FTIR ($CDCl_3$, microscope) 2973, 2951, 2875, 2222, 1749, 1630, 1435, 1456, 1357, 1327, 1280, 1135 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.95-2.20 (m, 4 H), 2.39-2.47 (m, 1 H), 3.03 (d, *J* = 15.5 Hz, 1 H), 3.98 (ddd, *J* = 7, 8.5, 12.5 Hz, 1 H), 4.12 (ddd, *J* = 4.5, 7, 12.5 Hz, 1 H), 4.37 (dd, *J* = 1, 15.5 Hz, 1 H), 5.02 (ddd, *J* = 3.5, 7.5, 7.5 Hz, 1 H), 6.55 (dd, *J* = 2, 7.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.0 (t), 32.6 (d), 34.3 (t), 55.2 (t), 57.3 (q), 114.9 (s), 116.5 (s), 146.3 (d), 189.9 (s); exact mass *m*/*z* calcd for $C_9H_{11}N_2S_2$ (M+H) 211.0358, found 211.0363.

1-(1-Cyanoethenyl)hexahydro-3*H*-thiazolo[3,4-*a*]pyridine-3-thione (44.2).

33.11 **44.2**

CF_3CO_2H (0.25 mL, 3.31 mmol) was added to a stirred solution of **33.11** (102 mg, 0.331 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3.5 h and the mixture was evaporated. The residue was dissolved in MeCN (5 mL) and CS_2 (85 μL, 1.324 mmol) and *i*-Pr_2NEt (0.28 mL, 1.665 mmol) were added. Stirring was continued overnight and the mixture was evaporated. Flash chromatography of the residue over the silica gel (2 x 15 cm), using 2:1 hexane-EtOAc, gave **44.2** (43 mg, 58%) as an oil: FTIR ($CDCl_3$, microscope) 2941, 2856, 2225, 1471, 1436, 1352, 1328, 1310, 1163, 1144 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 1.45-1.63 (m, 3 H), 1.82-2.08 (m, 3 H), 2.89 (ddd, *J* = 3.6, 13.2, 13.2 Hz, 1 H), 3.96 (ddd, *J* = 3.6, 8, 10.8 Hz, 1 H), 4.12 (d, *J* = 10 Hz, 1 H), 4.79 (ddd, *J* = 2, 2, 13.2 Hz, 1 H), 6.10 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.5 (t), 23.9 (t), 31.5 (t), 47.8 (t), 52.7 (d), 70.9 (d), 115.8 (s), 120.1 (s), 134.3 (t), 193.5 (s); exact mass *m*/*z* calcd for $C_{10}H_{13}N_2S_2$ (M+H) 225.0515, found 225.0513.

(5a*S*)-5a,6,7,8-Tetrahydro-1-thioxo-*3H*-pyrrolo[1,2-*c*][1,3]thiazepine-4-carboxylic acid methyl ester (36.1).

33.4 **36.1**

CF_3CO_2H (30 μL, 0.39 mmol) was added to a stirred solution of **33.4** (14 mg, 0.039 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3.5 h and the mixture was evaporated. The residue was dissolved in MeCN (5 mL) and CS_2 (10 μL, 0.156 mmol) and *i*-Pr_2NEt (35 μL, 0.195 mmol) were added. Stirring was continued overnight and the mixture was evaporated. Flash chromatography of the residue over the silica gel (1.5 x 15 cm), using 4:1 hexane-EtOAc, gave **36.1** (9 mg, 95%) as an oil identical to material made from **33.3**.

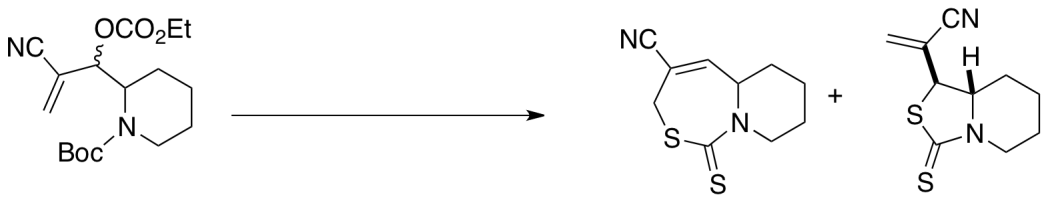
2-[2-Cyano-1-[(ethoxycarbonyl)oxy]-2-propen-1-yl]-1-piperidine-carboxylic acid 1,1-dimethylethyl ester (46.1).

33.6 **46.1**

DABCO (677 mg, 5.96 mmol) was added to a stirred mixture of **33.6** (423 mg, 1.99 mmol) and acrylonitrile (1.32 mL, 19.86 mmol) and stirring was continued for 3 days. The mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated and the crude product was used directly for the next step. EtOCOCl (0.44 mL, 4.6 mmol) was added to a stirred mixture of crude product from last step and pyridine (0.88 mL, 9.93 mmol) in CH_2Cl_2 (5 mL) and stirring was continued for 3.5 h. The mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (2.5 x 15 cm), using 2:1 hexane-EtOAc, gave **46.1** (288 mg, 43% over two steps) as an oil: FTIR ($CDCl_3$, microscope) 3115, 2980, 2940, 2869, 2228, 1753, 1687, 1476, 1449, 1412, 1369, 1334, 1310, 1257, 1168, 1148 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.2 Hz, 3 H), 1.47 (s, 9 H), 1.42-1.66 (m, 5 H), 1.83-1.87 (m, 1 H), 2.71 (br s, 1 H), 4.08-4.15 (m, 1 H), 4.24 (q, *J* = 7.2 Hz, 2 H), 4.47-4.58 (m, 1 H), 5.41 (d, *J* = 9.9 Hz, 1 H), 6.02-6.05 (m, 2 H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 14.6, 19.6, 24.7, 25.3, 28.7, 52.4, 65.4, 74.3, 81.2, 116.4, 121.5, 133.9, 154.4, 154.9; exact mass *m*/*z* calcd for $C_{17}H_{26}N_2NaO_5$ (M+Na) 361.1734, found 361.1732.

4-Cyano-6,7,8,9-tetrahydro-3*H*,5a*H*-pyrido[1,2-*c*][1,3]thiazepine-1-thione (46.2) and 1-(1-Cyanoethenyl)hexahydro-3*H*-thiazolo[3,4-*a*]pyridine-3-thione (44.1).



46.1 **46.2** **44.1**

CF_3CO_2H (50 μL, 0.65 mmol) was added to a stirred solution of **46.1** (22 mg, 0.065 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 3.5 h and the mixture was evaporated. The residue was dissolved in MeCN (5 mL) and cooled to -40 °C. CS_2 (16 μL, 0.26 mmol) and 2,6-lutidine (48 μL, 0.33 mmol) were added. The cold bath was left in place but not recharged and stirring was continued overnight. The mixture was evaporated and flash chromatography of the residue over the silica gel (1.5 x 15 cm), using 2:1 hexane-EtOAc, gave a 10:1 inseparable mixture (11 mg , 76%) of **46.2** (69%) and **44.1** (7%) as an oil. (The assignment to **44.1** is based on the presence of a characteristic ^{1}H NMR signals at δ 2.9, 4.1, 4.8, 6.1 and we assume that **44.1** from this experiment has the same stereochemistry as material prepared from **33.11**.) The material had: FTIR ($CDCl_3$, microscope) 2945, 2863, 2221, 1716, 1635, 1474, 1421, 1353, 1239, 1171, 1116 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74-2.05 (m, 6 H), 3.42 (dd, *J* = 1.5, 16 Hz, 1 H), 3.69 (ddd, *J* = 4.5, 9, 14 Hz, 1 H), 3.99 (dd, *J* = 1.5, 16 Hz, 1 H),

4.59 (ddd, J = 5, 6, 14 Hz, 1 H), 5.31-5.34 (m, 1 H), 6.72 (dd, J = 1.5, 7.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9 (t), 21.8 (t), 26.4 (t), 35.7 (t), 47.7 (t), 56.2 (d), 112.7 (s), 116.9 (s), 145.7 (d), 195.3 (t); exact mass m/z calcd for $C_{10}H_{12}N_2NaS_2$ (M+Na) 247.0334, found 247.0336.

(2*S*)-1-[(1,1-Dimethylethoxy)carbonyl]-β-methoxy-α-methylene-2-pyrrolidinepropanoic acid methyl ester (47.1).

33.2 **47.1**

NaH (20 mg, 60% $^{w}/_{w}$, 0.489 mmol) was added to a stirred solution of **33.2** (93 mg, 0.326 mmol) in THF (5 mL). Stirring was continued for 15 min, MeI (40 μL, 0.625 mmol) was then added and stirring was continued overnight. The mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatograph of the residue over silica gel (2 x 15 cm), using 4:1 hexane-EtOAc, gave **47.1** (20 mg, 20%) as an oil: FTIR ($CDCl_3$, microscope) 2977, 2933, 2883, 1725, 1695, 1438, 1394, 1366, 1263, 1166 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.43-1.52 (m, 9 H), 1.62- 1.73 (m, 2 H), 1.81-1.95 (m, 2 H), 3.13-3.31 (m, 4 H), 3.41-3.55 (m, 1 H), 3.74-3.76 (m, 3 H), 3.93-4.03 (m, 1 H), 4.50-4.62 (m, 1 H), 5.78-5.86 (m, 1 H), 6.24-6.36 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.5, 24.1, 25.4, 26.0, 28.4, 28.6, 47.0, 51.8. 51.9, 57.5, 58.2, 59.4, 79.4, 80.1, 126.0, 138.4, 154.4, 166.5; exact mass *m*/*z* calcd for $C_{15}H_{25}NNaO_5$ (M+Na) 322.1625, found 322.1627.

(5a*S*)-4,5,5a,6,7,8-Hexahydro-5-methoxy-1-thioxo-*3H*-pyrrolo[1,2-*c*][1,3]thiazepine-4-carboxylic acid methyl ester (47.2).

47.1 **47.2**

CF_3CO_2H (33 μL, 0.43 mmol) was added to a stirred solution of **47.1** (13 mg, 0.043 mmol) in CH_2Cl_2 (3 mL). Stirring was continued for 3.5 h and the mixture was evaporated. The residue was dissolved in MeCN (5 mL) and CS_2 (11 μL, 0.172 mmol) and *i*-Pr_2NEt (37 μL, 0.215 mmol) were added. Stirring was continued overnight and the mixture was evaporated. Flash chromatography of the residue over the silica gel (1.5 x 15 cm), using 2:1 hexane-EtOAc, gave **47.2** (10 mg, 85%) as an oil: FTIR ($CDCl_3$, microscope) 2949, 2878, 1732, 1434, 1357, 1330, 1205, 1174 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.03-2.18 (m, 4 H), 3.14-3.31 (m, 3 H), 3.59- 3.63 (m. 3 H), 3.75-3.91 (m, 6 H), 4.22-4.50 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.5, 24.1, 25.4, 26.0, 28.4, 28.6, 47.0, 51.8. 51.9, 57.5, 58.2, 59.4, 79.4, 80.1, 126.0, 138.4, 154.4, 166.5; exact mass *m*/*z* calcd for $C_{11}H_{17}NNaO_3S_2$ (M+Na) 298.0542, found 298.0546.

***N*-(2-Hydroxyethyl)-*N*-methyl-2-(phenylthio)acetamide (48.2).**

48.1 **48.2**

A solution of $PhSCH_2COCl$ (1.51 g, 8.11 mmol) in CH_2Cl_2 (5 mL) was added to a stirred and cooled (0 °C) solution of **48.1** (5.33 g, 81.1 mmol) and pyridine (0.84 mL) in CH_2Cl_2 (20 mL). The ice bath was left in place but not recharged and stirring was continued for 4 h, by which time the mixture had reached room temperature. The mixture was quenched with water (15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (4 x 15 cm), using EtOAc, gave **48.2** (1.647g, 90%) as an oil: FTIR ($CDCl_3$, microscope) 3405, 3056, 2935, 2879, 1632, 1481, 1439, 1402, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.62-2.66 (m, 1 H), 2.98-3.12 (m, 3 H), 3.50-3.90 (m, 5 H), 7.22-7.48 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.8, 36.9, 37.2, 37.4, 51.8, 52.2, 59.8, 61.5, 126.8, 127.2, 129.0, 129.1, 130.1, 130.8, 134.6, 135.2, 169.3, 170.3; exact mass *m*/*z* calcd for $C_{11}H_{15}NNaO_2S$ (M+Na) 248.0716, found 248.0715.

***N*-Methyl-*N*-(2-oxoethyl)-2-(phenylthio)acetamide (48.3).**

48.2 **48.3**

Pyridine-SO_3 complex (110 mg, 0.693 mmol) was added to a stirred and cooled (0 °C) mixture of **48.2** (52 mg, 0.231 mmol), Et_3N (0.29 mL, 2.079 mmol) and DMSO (0.13 mL, 2.310 mmol) in CH_2Cl_2 (20 mL). Stirring at 0 °C was continued for 4.5 h and the mixture was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (1.5 x 15 cm), using 1:1 hexane-EtOAc, gave **48.3** (32 mg, 62%) as an oil: FTIR ($CDCl_3$, microscope) 3057, 2920, 2834, 2722, 1730, 1645, 1583, 1481, 1439, 1395, 1113 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.98 (s, 0.5 H), 3.12 (s, 2.5 H), 3.63 (s, 0.4 H), 3.81 (s, 1.6 H), 4.17 (s, 1.6 H), 4.25 (s, 0.4 H), 7.22-7.47 (m, 5 H), 9.52 (s, 0.8 H), 9.67 (s, 0.2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.5, 36.6, 37.4, 58.3, 60.1, 127.2, 127.3, 129.1, 129.2, 130.3, 130.6, 134.2, 134.6, 168.6, 169.3, 196.7, 196.8; exact mass *m*/*z* calcd for $C_{11}H_{13}NNaO_2S$ (M+Na) 246.0559, found 246.0559.

3-Hydroxy-2-methylene-4-[methyl[2-(phenylthio)acetyl]amino]-butanoic acid methyl ester (48.4).

48.3 **48.4**

DABCO (310 mg, 2.77 mmol) was added to a stirred mixture of **48.3** (206 mg, 0.923 mmol) and methyl acrylate (1.66 mL, 18.48 mmol) and stirring was continued for 3 days. The mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 1:1 hexane-EtOAc, gave **48.4** (223 mg, 78%) as oil: FTIR ($CDCl_3$, microscope) 3388, 357, 2994, 2951, 2926, 2854, 1713, 1632, 1482, 1439, 1402, 1313, 1270, 1196 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.01-3.08 (m, 3 H), 3.51-3.95 (m, 7 H), 4.53-4.72 (m, 2 H), 6.05-6.06 (m, 1 H), 6.32-6.36 (m, 1 H), 7.17-7.45(m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.9, 36.8, 37.0, 38.0, 51.9, 52.0, 55.7, 56.0, 69.2, 70.8, 126.7, 126.8, 126.9, 127.2, 128.9, 129.1, 129.3, 130.1, 130.6, 134.5, 135.4, 139.7, 140.2, 166.3, 166.5, 169.5, 171.5; exact mass *m/z* calcd for $C_{15}H_{19}NNaO_4S$ (M+Na) 332.0927, found 332.0924.

3-Hydroxy-2-methylene-4-[methyl[2-(phenylsulfonyl)acetyl]amino]-butanoic acid methyl ester (48.5).

48.4 **48.5**

MCPBA (70%$^{w}/_{w}$, 188 mg, 0.764 mmol) was added to a stirred and cooled solution of **48.4** (118 mg, 0.382 mmol) in CH_2Cl_2 (5 mL). Stirring at 0 °C was continued for 2 h and the mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:2 hexane-EtOAc, gave **48.5** (117 mg, 90%) as oil: FTIR ($CDCl_3$, microscope) 3419, 3066, 3003, 2953, 2926, 2854, 1712, 1645, 1481, 1447, 1404, 1321, 1155 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.02 (s, 1.2 H), 3.23 (s, 1.8 H), 3.52-3.72 (m, 2 H), 3.78 (s, 1.8 H), 3.82 (s, 1.2 H), 4.22-4.57 (m, 2 H), 4.68-4.73 (m, 1 H), 6.07-6.10 (m, 1 H), 6.37-6.42 (m, 1 H), 7.54-7.95 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.2, 38.7, 52.0, 52.2, 55.5, 56.2, 59.7, 60.0, 69.3, 70.4, 126.9, 127.1, 128.5, 129.1, 129.2, 134.1, 134.3, 138.6, 139.1, 139.4, 139.8, 162.3, 164.0, 166.2, 166.5; exact mass *m*/*z* calcd for $C_{15}H_{19}NNaO_6S$ (M+Na) 364.0820, found 364.0825.

3-Acetoxy-2-methylene-4-[methyl[2-(phenylsulfonyl)acetyl]amino]-butanoic acid methyl ester (48.6).

48.5 **48.6**

AcCl (31 μL, 0.36 mmol) was added to a stirred mixture of **48.4** (41 mg, 0.12 mmol) and pyridine (50 μL, 0.60 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 1.5 h and the mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (1.5 x 15 cm), using 1:2 hexane-EtOAc, gave **48.6** (33 mg, 72%) as an oil: FTIR ($CDCl_3$, microscope) 3064, 3003, 2954, 2925, 2853, 1744, 1657, 1481, 1447, 1403, 1372, 1311, 1230, 1155 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.08 (s, 1.4 H), 2.10 (s, 1.6 H), 3.01 (s, 1.6 H), 3.26 (s, 1.4 H), 3.47-3.98 (m, 5 H), 4.14-4.45 (m, 2 H), 5.70-5.88 (m, 1 H), 5.90-5.93 (m, 1 H), 6.38-6.41 (m, 1 H), 7.45-7.69 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ20.9, 21.0, 35.3, 37.8, 51.1, 52.1, 52.4, 53.7, 59.6, 59.8, 69.8, 70.8, 127.2, 127.5, 128.5, 128.5, 129.1, 129.1, 134.1, 134.1, 136.4, 136.8, 138.9, 139.1, 161.9, 162.0, 165.2, 165.3, 169.1, 169.8; exact mass *m*/*z* calcd for $C_{17}H_{21}NNaO_7S$ (M+Na) 406.0931, found 406.0924.

4,5,6,7-Tetrahydro-1-methyl-7-oxo-6-(phenylsulfonyl)-1*H*-azepine-4-carboxylic acid methyl ester (48.8).

48.6 **48.8**

Cs_2CO_3 (63 mg, 0.197 mmol) was added to a stirred solution of **48.6** (37 mg, 0.097 mmol) in THF-MeOH (10:1, 5.5 mL) and stirring was continued for 20 min. The mixture was filtered through a pad of Celite (2.5 x 4 cm) and evaporated. Flash chromatography of the residue over the silica gel (1.5 x 15 cm), using 1:2 hexane-EtOAc, gave **48.8** (19 mg, 61%) as an oil, containing slight impurities (^{1}H NMR): FTIR ($CDCl_3$, microscope) 2956, 2924, 2853, 1738, 1690, 1463, 1448, 1379, 1309, 1247, 1207, 1149 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.79 (ddd, *J* = 8, 12, 13 Hz, 1 H), 2.87 (ddd, *J* = 7, 11.5, 13.5 Hz, 1 H), 2.97 (s, 3 H), 3.44 (dddd, *J* = 2, 5.5, 7.5, 13.5 Hz, 1 H), 3.73 (s, 3 H), 4.36 (dd, 6.5, 12 Hz, 1 H), 5.82 (dd, *J* = 6, 8 Hz, 1 H), 6.06 (dd, *J* = 2.5, 8 Hz, 1 H), 7.55-8.09 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.1 (d), 35.2 (t), 39.6 (q), 52.6 (q), 66.7 (d), 118.0 (d), 128.7 (d), 130.3 (d), 131.5 (d), 134.0 (d), 137.8 (s), 165.8 (s), 171.8 (s); exact mass *m*/*z* calcd for $C_{15}H_{17}NNaO_5S$ (M+Na) 346.0720, found 346.0714.

5. References

1 Bordwell, F. G.; Schexnayder, D. A. *J. Org. Chem.* **1963,** *33*, 3249-3246.

2 (a) Knochel, P.; Seebach, D. *Nouv. J. Chim.* **1981**, *5*, 75-77. (b) Knochel, P.; Seebach, D. *Tetrahedron Lett.* **1981**, *22*, 3223-3226. (c) Seebach, D.; Knochel, P. *Helv. Chim. Acta* **1984**, *67*, 261-283. (d) Seebach, D.; Calderari, G.; Knochel, P. *Tetrahedron* **1985**, *41*, 4861-4872.

3 (a) Baylis, A. B.; Hillman, M. E. D. Ger. 2155113, 1972; (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001-8062. (c) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811-891. (d) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581-1588. (e) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447-5674.

4 (a) Chamakh, A.; M'Hirisi, M.; Villieras, J.; Lebreton, J.; Amri, H. *Synthesis* **2000**, 295-299. (b) Chen, C.-Y.; Chang, M.-Y.; Hsu, R.-T.; Chen, S.-T.; Chang, N.-C. *Tetrahedron Lett.* **2003**, *44*, 8627-8630. (c) Roy, A. K.; Batra, S. *Synthesis* **2003**, 1347-1356. (d) Basavaiah, D.; Aravindu, K. *Org. Lett.* **2007**, *9*, 2453-2456. (e) Singh, V.; Batra, S. *Eur. J. Org. Chem.* **2007**, 2970-2976. (f) Nayak, M.; Batra, S. *Eur. J. Org. Chem.* **2009**, 3505-3507. (g) Ravinder, M.; Sadhu, P. S.; Rao, V. J. *Tetrahedron Lett.* **2009**, *50*, 4229-4232. (h) Reddy, C. R.; Kiranmai, N.; Johny, K.; Pendke, M.; Naresh, P. *Synthesis* **2009**, 399-402. (i) Baidya, M.; Remennikov, G. Y.; Mayer, P.; Mayr, H. *Chem. Eur. J.* **2010**, *16*, 1365-1371. (j) Basavaiah, D.; Aravindu, K.; Kumar, K. S.; Reddy, K. R.

Eur. J. Org. Chem. **2010**, 1843-1848. (k) Huang, C.-C.; Chang, N.-C. *Org. Lett.* **2008**, *10*, 673-676.

5 (a) Eagen, M. C.; Cromwell, N. H. *J. Org. Chem.* **1974**, *39*, 911-914. (b) Rebman, R. P.; Cromwell, N. H. *Tetrahedron Lett.* **1965**, *6*, 4833-4836. (c) Cromwell, N. H.; Matsumoto, K.; George, A. D. *J. Org. Chem.* **1971**, *36*, 272-274.

6 Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736.

7 (a) Takahashi, T.; Hori, K.; Tsuji, J. *Tetrahedron Lett.* **1981**, *22*, 119-122. (b) Takagi, R.; Miwa, Y.; Nerio, T.; Inoue, Y.; Matsumura, S.; Ohkata, K. *Org. Biomol. Chem.* **2007**, *5*, 286-300. (c) Takagi, R.; Inoue, Y.; Ohkata, K. *J. Org. Chem.* **2008**, *73*, 9320-9325.

8 Ramachandran, P. V.; Madhi, S.; Bland-Berry, L.; Reddy, M. V. R.; O'Donnell, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 13450-13451.

9 Chen, C.-G.; Hou, X.-L.; Pu, L. *Org. Lett.* **2009**, *11*, 2073-2075.

10 Cho, C.-W.; Krische, M. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 6689-6691.

11 Jiang, Y.-Q.; Shi, Y.-L.; Shi, M. *J. Am. Chem. Soc.* **2008**, *130*, 7202-7203.

12 Gomez-Bengoa, E.; Landa, A.; Lizarraga, A.; Mielgo, A.; Oiarbide, M.; Palomo, C. *Chem. Sci.* **2011**, *2*, 353-357.

13 Shafiq, Z.; Liu, L.; Liu, Z.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2007**, *9*, 2525-2528.

14 Qi, J.; Porco, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 12682-12683.

15 (a) Prabhudas, B.; Clive, D. L. J. A*ngew. Chem*. *Int. Ed*. **2007**, *46*, 9295-9297. (b) Wang, L.; Prabhudas, B.; Clive, D. L. J. *J. Am. Chem. Soc.* **2009**, *131*, 6003-6012.

16 (a) Eagen, M. C.; Cromwell, N. H. *J. Org. Chem.* **1974**, *39*, 911-914. (b) Eagen, M. C.; Cromwell, N. H. *J. Org. Chem.* **1974**, *39*, 3863-3866. (c) Zhong, W.; Zhao, Y.; Guo, B.; Wu, P.; Su, W. *Synth. Commun.* **2008**, *38*, 3291-3302. (d) Li, J.; Wang, X.; Zhang, Y. *Tetrahedron Lett.* **2005**, *46*, 5233-5237. (e) Kwon, S. H.; Cho, C. W. *Bull. Korean Chem. Soc.* **2008**, *29*, 1835-1838. (f) Cui, H.-L.; Feng, X.; Peng, J.; Lei, J.; Jiang, K.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2009**, *48*, 5737-5740. (g) Patra, A.; Roy, A. K.; Batra, S.; Bhaduri, A. P. *Synlett* **2002**, *2002*, 1819-1822. (h) Kotti, S. R. S. S.; Xu, X.; Li, G.; Headley, A. D. *Tetrahedron Lett.* **2004**, *45*, 1427-1431. (i) Ciclosi, M.; Fava, C.; Galeazzi, R.; Orena, M.; Sepulveda-Arques, J. *Tetrahedron Lett.* **2002**, *43*, 2199-2202. (j) Kim, J. N.; Lee, H. J.; Gong, J. H. *Tetrahedron Lett.* **2002**, *43*, 9141-9146. (l) Cho, C.-W.; Kong, J.-R.; Krische, M. J. *Org. Lett.* **2004**, *6*, 1337-1339. (m) Park, H.; Cho, C.-W.; Krische, M. J. *J. Org. Chem.* **2006**, *71*, 7892-7894.

17 (a) Kenmoku, H.; Sassa, T.; Kato, N. *Tetrahedron Lett.* **2000**, *41*, 4389-4393. (b) Watanabe, H.; Takano, M.; Umino, A.; Ito, T.; Ishikawa, H.; Nakada, M. *Org. Lett.* **2006**, *9*, 359-362.

18 Du, Y.; Han, X.; Lu, X. *Tetrahedron Lett.* **2004**, *45*, 4967-4971.

19 (a) Bauchat, P.; Foucaud, A. *Tetrahedron Lett.* **1989**, *30*, 6337-6338. (b) Bauchat, P.; Le Bras, N.; Rigal, L.; Foucaud, A. *Tetrahedrn* **1994**, *50*, 7815-7826.

20 (a) Bode, M. L.; Kaye, P. T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2612-2613. (b) Bode, M. L.; Kaye, P. T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1809-1813.

21 Song, Y. S.; Lee, K.-J. *Synthesis* **2007**, *2007*, 3037-3043.

22 (a) Yu, M.; Clive, D. L. J.; Yeh, V. S. C.; Kang, S.; Wang, J. *Tetrahedron Lett.* **2004**, *45*, 2879-2881. (b) Clive, D. L. J.; Yu, M.; Li, Z. J. *Chem. Soc., Chem. Commun.* **2005**, 906-908. (c) Clive, D. L. J.; Wang, J.; Yu, M. *Tetrahedron Lett.* **2005**, *46*, 2853-2855. (d) Clive, D. L. J.; Yu, M.; Wang, J.; Yeh, V. S. C.; Kang, S. *Chem. Rev.* **2005**, *105*, 4483-4514. (e) Clive, D. L. J.; Li, Z.; Yu, M. *J. Org. Chem*. **2007**, *72*, 5608-5617. (f) Liu, D.; Acharya, H. P.; Yu, M.; Wang, J.; Yeh, V. S. C.; Kang, S.; Chiruta, C.; Jachak, S. M.; Clive, D. L. J. *J. Org. Chem*. **2009**, *74*, 7417-7428.

23 Reviews on the Morita-Baylis-Hillman reaction: (a) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653-4670. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8011-8062. (c) Ciganek, E. *Org. React*. **1997**, *51*, 201-350. (d) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Re*v. **2003**, *103*, 811-891.

24 (a) Weichert, A.; Hoffmann, H. M. R. *J. Org. Chem.* **1991**, *56*, 4098-4112. (b) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron* **1988**, *44*, 6095-6106. (c) Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.*

2003, *68*, 692-700.

25 (a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc*. **1973**, *95*, 2697-2699; (b) Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049-1132.

26 (a) Sato, T.; Yamazaki, T.; Nakanishi, Y.; Uenishi, J.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1438-1443. (b) (12) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109–1117.

27 (a) White, J. D.; Hansen, J. D. *J. Org. Chem.* **2005**, *70*, 1963-1977. (b) Chabra, S. R.; Mahajan, A.; Chan, W. C. *J. Org. Chem*. **2002**, *67*, 4017-4029. (c) Kato, S.; Harada, H.; Morie, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3219-3226.

28 Yang, M.; Liu, F. *J. Org. Chem*. **2007**, *72*, 8969-8971.

29 Schleich, S.; Helmchen, G. *Eur. J. Org. Chem*. **1999**, 2515-2521.

30 (a) Mapitse, R.; Hayes, C. J. *Tetrahedron Lett*. **2002**, *43*, 3541-3542. (b) Bender, W.; Kinast, G.; Knorr, A.; Stasch, J. P. Eur. Pat. Appl. **1991**, EP 412350 A2.

31 Clark, D. C.; Weinhardt, K. K.; Berger, J.; Fisher, L. E.; Brown, C. M.; MacKinnon, A. C.; Kilpatrick, A. T.; Spedding, M. *J. Med. Chem.* **1990**, *33*, 633–641.

32 (a) Shi, W.; Jiang, N.; Zhang, S.; Wu, W.; Du, D.; Wang, J. *Org. Lett.* **2003**, *5*, 2243-2246. (b) Maier, T. C.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 4594–4595.

Chapter 3

Synthetic studies on marinopyrroles A and B

1. INTRODUCTION

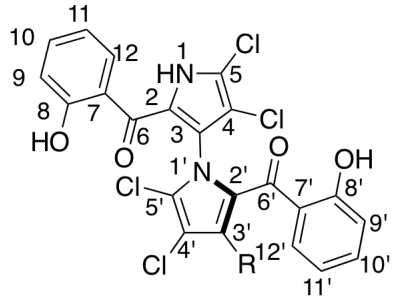
1.1 General

Historically, the majority of drugs have been discovered and developed from natural products, as well as their derivatives, metabolites and mimics.[1] Natural-product-based drug discovery reached its peak during the 1970s and 1980s.[2] In the past 20 years, over 50% of new chemical entities (NCEs) were natural products, synthetic or semisynthetic natural product derivatives.[2,3]

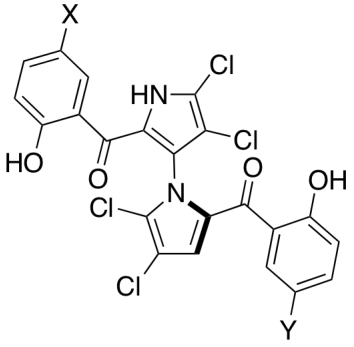
Ever since the discovery of penicillin, bacteria were considered primary sources for structurally and functionally diverse secondary metabolites.[4] Many of these compounds show interesting structural features and remarkable biological activities that may lead to potential drug candidates. Traditionally, the majority of bacteria studied in the past came from soil samples and marine habitats did not draw enough attention due to the difficulty of obtaining samples. Recent advances in deep water sampling tools, unlike the previously used scuba diving techniques, provide a new method of access to biologically active marine natural products.[5] Nowadays, more and more researchers have been attracted to this area.

In 2008 Fenical and coworkers reported a new family of natural products, named marinopyrroles, which were originally separated from the actinomycete strain CNQ-418.[6] Two members of this family, marinopyrrole A (**1.1**) and B (**1.2**) were initially found and four other members were isolated in 2010.[7] Both marinopyrrole A and B show significant activities against methicillin-resistant *S. aureus* (MRSA) with MIC_{90} values of less than 1 $\mu g/mL^{-1}$. In addition, both of also show interesting anticancer properties against human colon cancer cell line

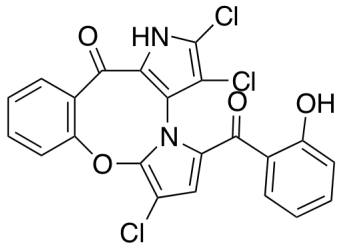
(HCT-166) with IC_{50} values around 5 $\mu g/mL^{-1}$. Fenical and coworkers believe that the unique bispyrrole core structure would provide a new type of antibiotic at a time when there is an urgent need for such substances for clinical use.[5] Marinopyrrole A-E exist as atropo-enantiomers.[5,7]



(-)-marinopyrrole A (1.1), R = H
(-)-marinopyrrole B (1.2), R = Br



(-)-marinopyrrole C (1.3), X = Cl, Y = H
(-)-marinopyrrole D (1.4), X = H, Y = Cl
(-)-marinopyrrole E (1.5), X = H, Y = Br



(±)-marinopyrrole F (1.6)

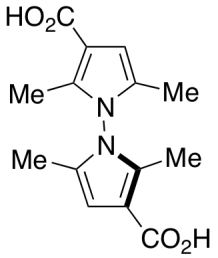
Scheme 1

1.2 Isolation and structure determination of the marinopyrroles

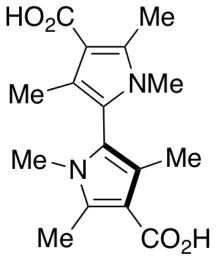
The initial isolation of **1.1** and **1.2** started with the cultivation of the actinomycetes strain CNQ-418. This bacterium was cultivated in a seawater-based medium for 7 days with vigorous shaking. Solid phase extraction of the broth using Amberlite resin (XAD-16), filtration through cheesecloth, 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 as marinopyrrole A and B. Upon optimization of the culturing conditions, another four members of the family were isolated via similar processes.

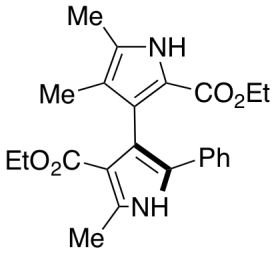
The structure determination of **1.1** and **1.2** began with both 1D and 2D NMR experiments. Along with COSY, HMQC and HMBC spectra, two independent benzoyl groups were identified. However, the bispyrrole core was very difficult to assign due to the lack of correlation in 2D NMR measurements. X-ray crystallographic analysis was used as the last option for structure determination. Both of the phenolic hydroxyl groups of **1.1** were acetylated to provide the corresponding acetates, *p*-bromobenzoates and *p*-nitrobenzoates. Methylation of nitrogen with CH_2N_2 furnished the corresponding *N*-methyl derivative. Unfortunately, none of the above compounds yielded X-ray crystallographic quality crystals. Luckily, **1.2** itself gave fine crystals by slow evaporation from PhMe. The structural assignment to **1.1** was made by comparing its spectra (both 1D and 2D NMR spectra) with those of **1.2**. Both of these compounds had similar optical rotations, which suggested that both members of this new family should be related atropo-enantiomers. Later, an X-ray experiment further confirmed these compounds have the *M*-configuration. The marinopyrroles **1.3**, **1.4**, and **1.5** were also assigned by comparison of the NMR and circular dichroism spectra with those of **1.2**, and the structure of **1.6** was determined by X-ray crystallography.



2.1



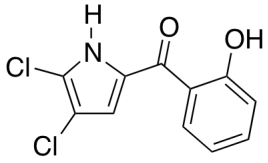
2.2



2.3

Scheme 2

Except for the marinopyrroles, there were only three examples of axially chiral bispyrrole units reported in the literature (Scheme 2).[8] All of those compounds were synthetic and required resolution to obtain single enantiomers. Interestingly, of the three possible bispyrroles that involve bonding through nitrogen, only the achiral 1,2'-bispyrrole had been previously found in nature.[9] The chirality along the C,N single bond in naturally occurring bispyrroles could be induced by an enzymatic coupling process.[6,7] A structural subunit of marinopyrrole A, monodeoxypyoluteorin (**3.1**), was also isolated from actinomycete strain CNQ-418. Compound **3.1** and the related pyrrolomycins[10] are known to have antibacterial activities.[11]



monodeoxypyoluteorin (3.1)

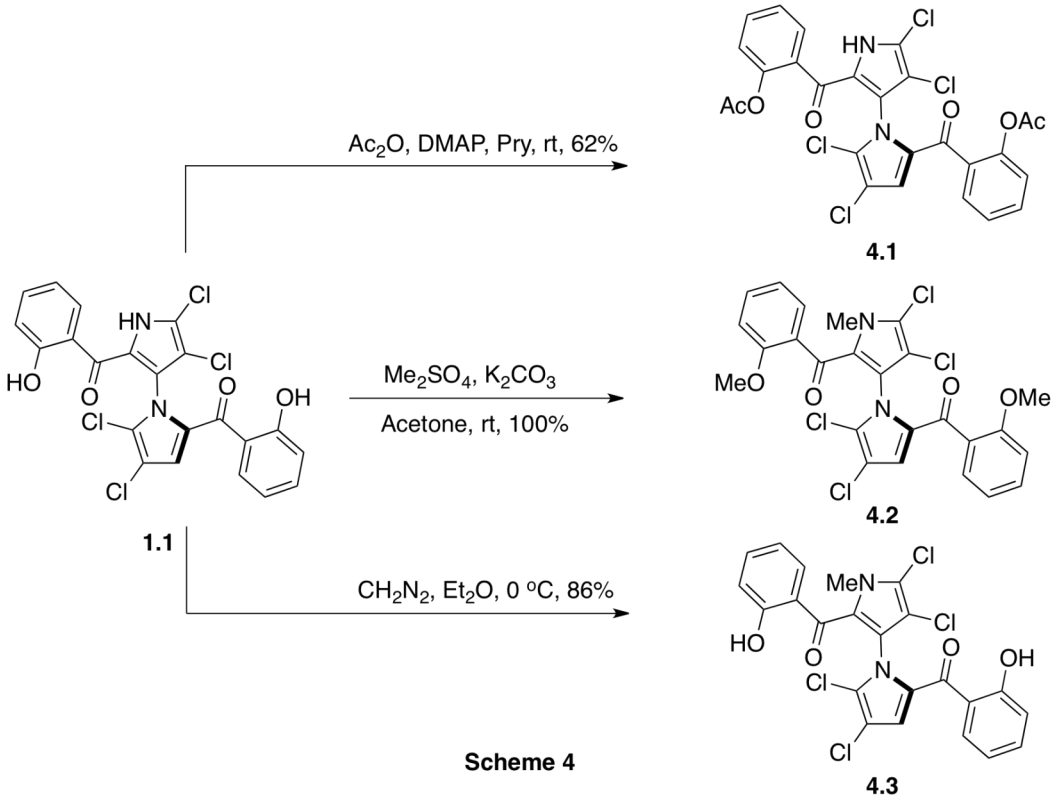
Scheme 3

Although marinopyrroles A-E are fashioned by nature in enantiopure from, racemization occurs at elevated temperature. Upon heating at 120 °C in PhMe, **1.1** and **1.2** were completely racemized. In comparison, the racemization of **1.3** required a higher temperature (150 °C in $ClCH_2CH_2Cl$), and **1.4** and **1.5** did not racemize even at 180 °C. It is believed that the halogens at C-11 and C'-11 increase the energy barriers for the rotation along the C,N axis.

Compound **1.6** was obtained as a racemate, presumably because the energy barrier of rotation about the C,N axis is significantly reduced after cyclization. An enantioenriched sample of **1.6**, collected by using chiral HPLC, was completely racemized in MeOH after 6 h at room temperature. Notably, the absolute configuration of the marinopyrroles may not be critical for biological activity since the non-natural atropo-enantionmer of **1.1** showed very similar potency to the natural form.

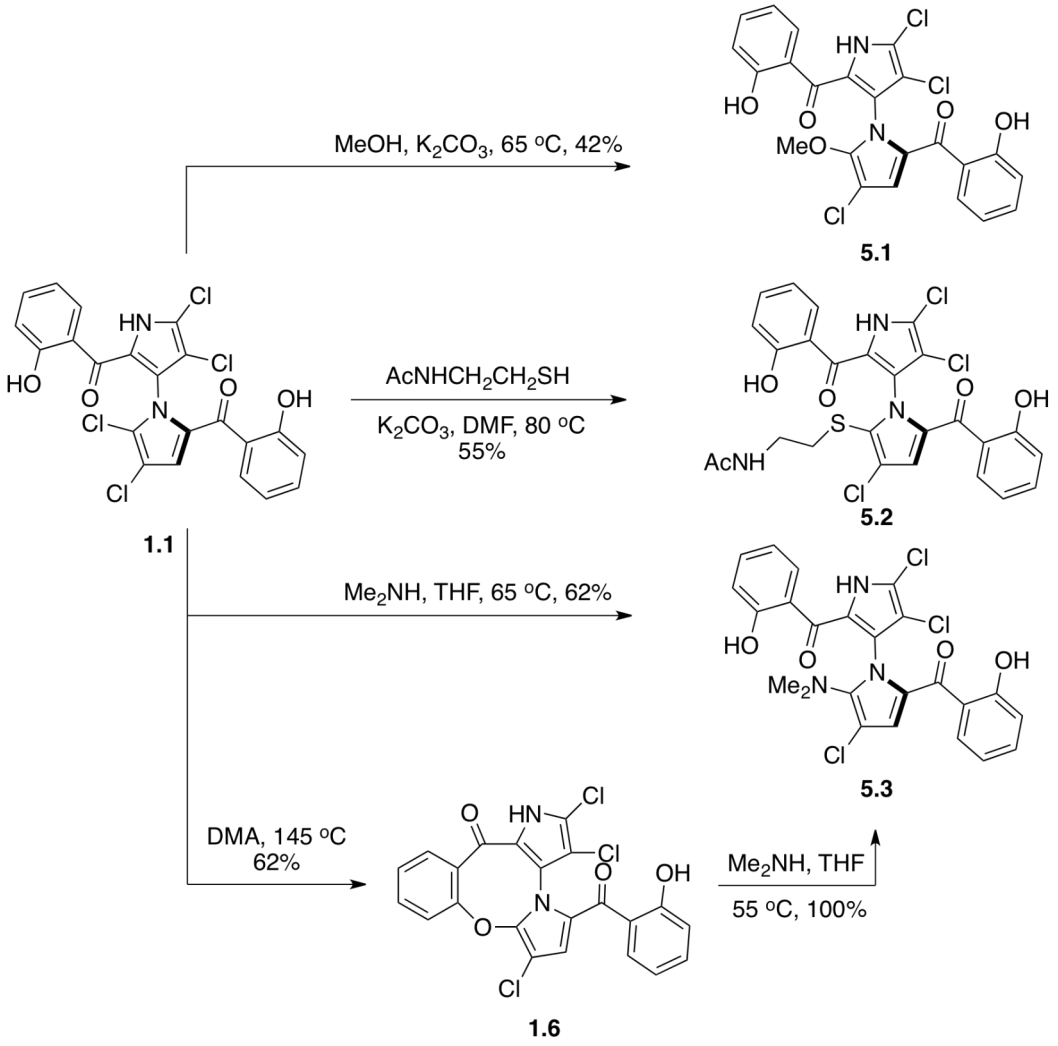
1.3 Reactivity of marinopyrroles

Fenical and coworkers also studied the reactivity[7] of marinopyrroles in order to explore the reasons for their antibiotic activities. To begin with, the phenolic hydroxyl groups of **1.1** were acetylated (**4.1**) and methylated (**4.2**). The pyrrole nitrogen was also methylated (**4.3**). Interestingly, the potency of **4.1** against MRSA was dramatically lowered (ca 5-fold). The derivatives **4.2** and **4.3** were devoid of biological activity. These observations show that the polar functionalities are required for activity MRSA.



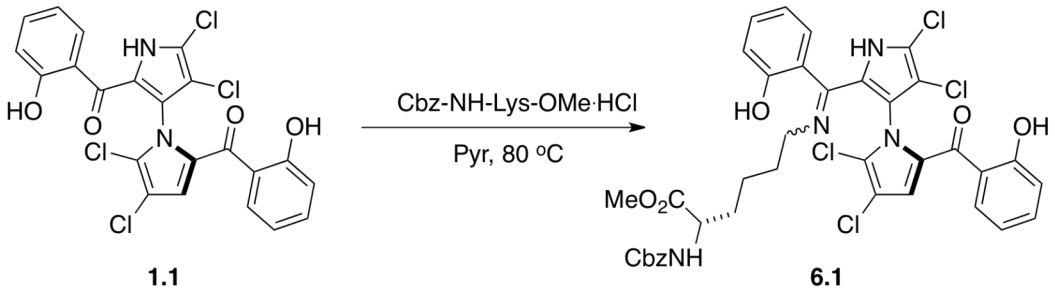
Scheme 4

Multiple halogenation of bispyrroles strongly lowers their electrophilicity. Marinopyrrole A (**1.1)** was treated with various heteroatom-containing nucleophiles (oxygen, sulfur and nitrogen) to yield derivatives. In all cases, the chlorine at the C-5' position was displaced by the nucleophile. When **1.1** was heated at 145 °C in DMA it was converted into **1.6**. Subsequent treatment of **1.6** with Me_2NH yielded **5.3** in quantitative yield. The methoxy derivative **5.1** retained similar potency toward MRSA as the parent marinopyrrole A. While **5.2** and **5.3** are 5 to 20-fold less potent for the same inhibition process. Another interesting observation was the loss of optical purity after substitution at the C-5' position. Both **5.1** and **5.3** were isolated as racemates and **5.2** had an ee of 76%.



Scheme 5

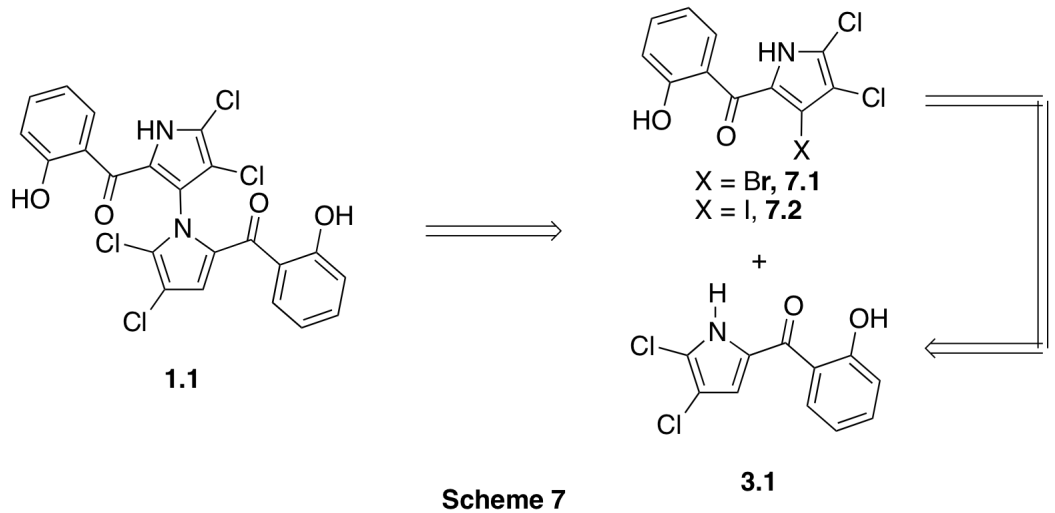
When **1.1** was heated in pyridine, it reacted with a protected lysine to give the corresponding imine **6.1** as two conformers. Previous studies in the Fenical group showed that cytotoxicity in eukaryotic cells was triggered when **1.1** targeted actins via the formation of corresponding imines.[12]



Scheme 6

1.4 Synthetic studies towards marinopyrroles in the Fenical group

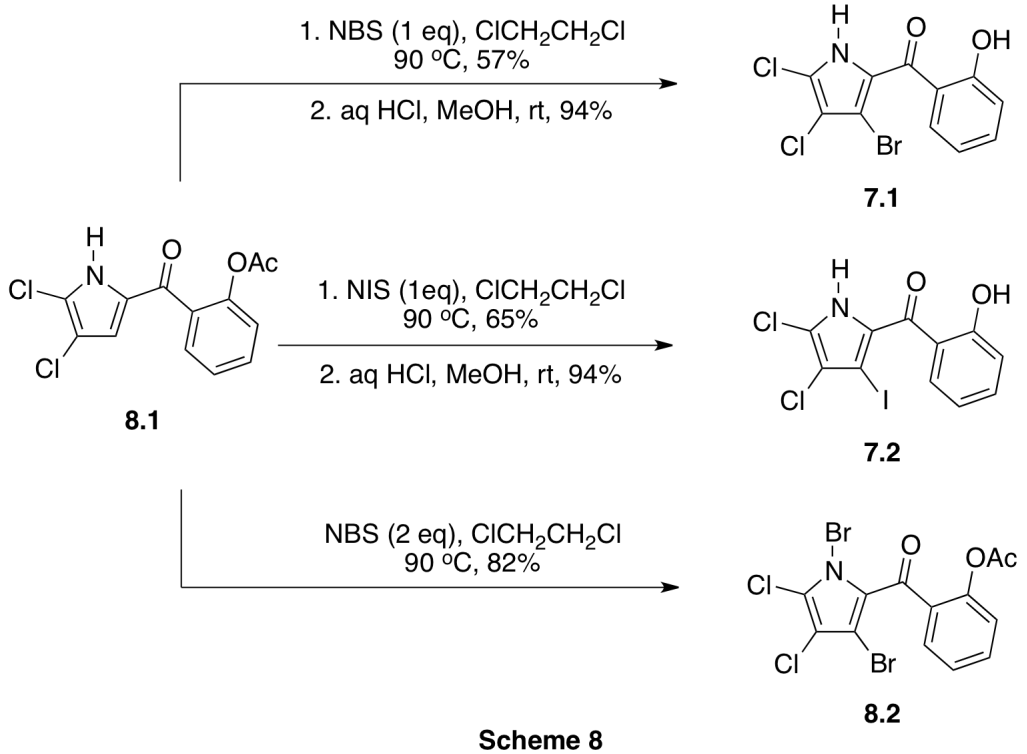
Fenical's retrosynthetic plan started with a direct disconnection of the C,N axis via an Ullmann type coupling, which quickly lead to two subunits: monodeoxypyoluteorin (**3.1**) and 3-iodo- or 3-bromomonodeoxypyoluteorin (**7.1** and **7.2**). Compound **3.1** was convertible into **7.1** and **7.2** via functionality manipulations.



Scheme 7

Although Ullmann coupling between aryl halides and azoles is well established,[13] direct construction of a C,N axis had never previously been

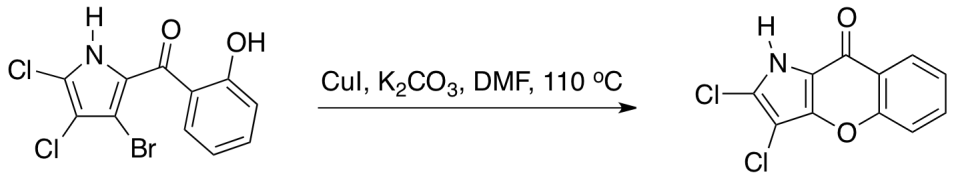
demonstrated in the formation of bispyrroles. In order to test such an approach, **7.1** and **7.2** were synthesized from *O*-acetyl monodeoxypyoluteorin (**8.1**) via electrophilic substitution. An excess of NBS (2 equiv) in the bromination step gave the *N*-brominated product **8.2**.



Scheme 8

Unfortunately, all attempts at coupling between 3-halopyrroles and monodeoxypyoluteorins were unsuccessful. Several modern methods[13] were applied but none of them provided significant amounts of the desired products. Unfavorable steric interactions between the substituents ortho to the site of required bond formation were suggested to strongly inhibit the transition metal-catalyzed Ullmann coupling. Such steric effects had been reported and it is known that the difficulty of forming biaryls dramatically increases in the presence

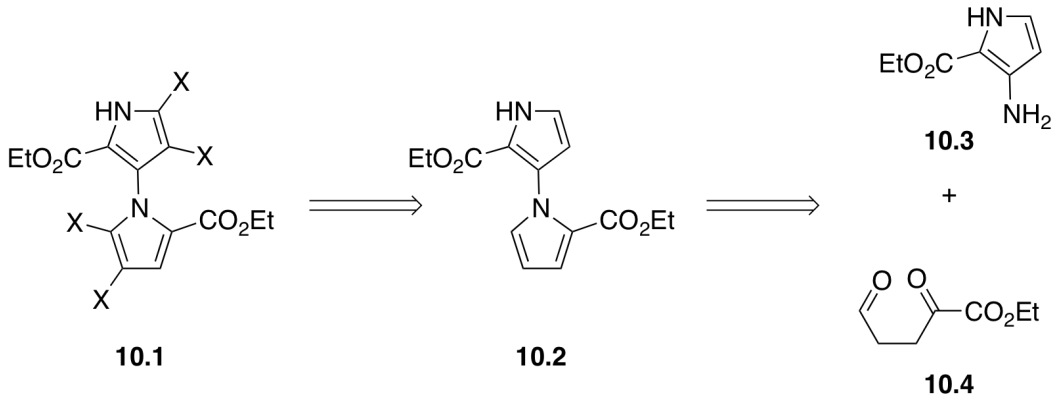
of di-ortho substitution of the parent aryl.[13a] Instead of undergoing intermolecular coupling, the 3-halo pyrrole substrates underwent an intramolecular coupling involving the pendant phenols, even when the phenolic hydroxyls were first acetylated. When **8.2** was subjected to coupling conditions, **9.1** was formed and tested for biological activities. Disappointedly, **9.1** was inactive against MRSA and HCT-116.



8.2 **9.1**

Scheme 9

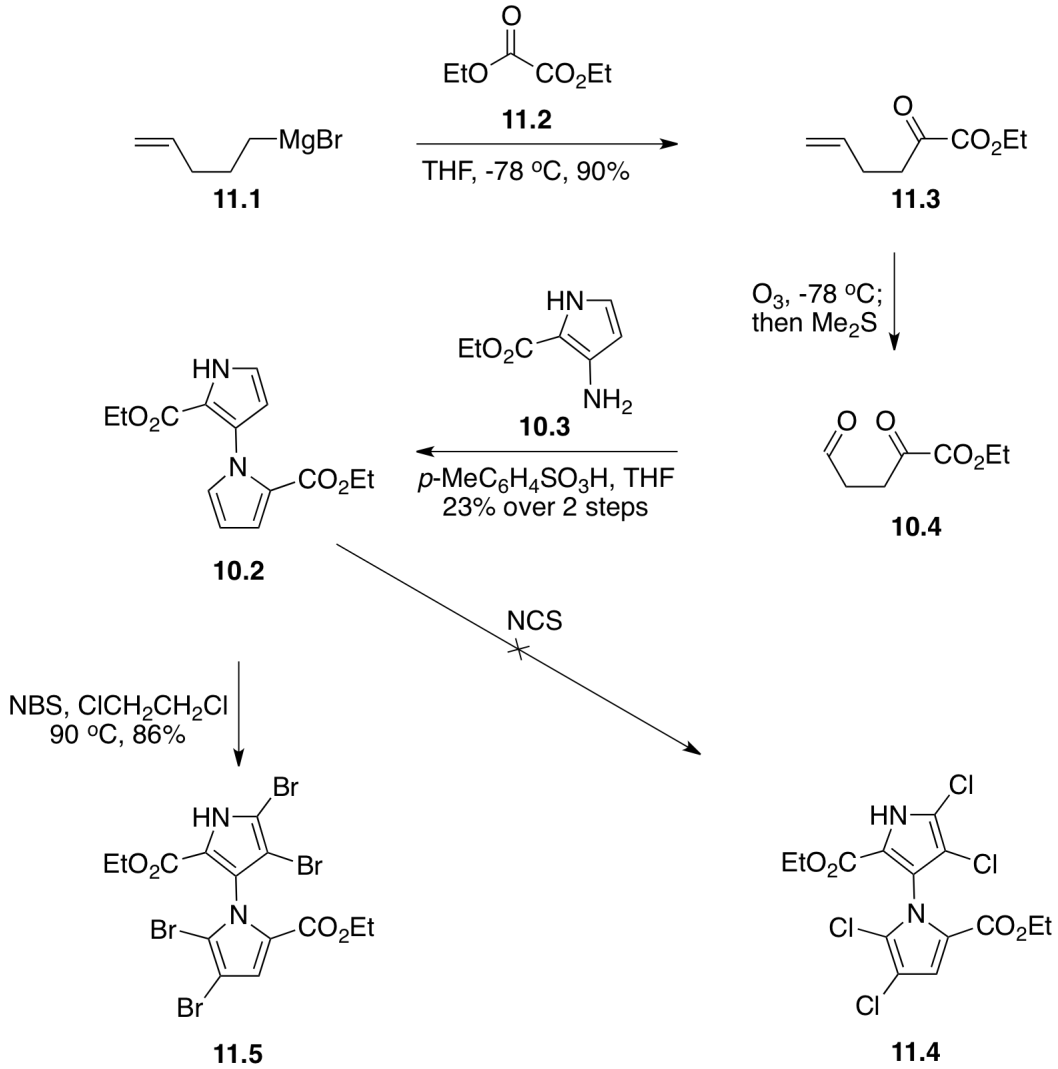
Another attempt to make the core structure was based on halogenation of the parent bispyrrole which was expected to be available by Paal-Knorr reaction between 3-aminopyrrole and a 1,4-diketo compound (Scheme 10).



10.1 **10.2** **10.3** **10.4**

Scheme 10

Homoallylic Grignard reagent **11.1** was treated with diethyl oxalate (**11.2**) at -78 °C to yield the monoaddition product **11.3**, and ozonolysis gave the 1,4-dicarbonyl compound **10.4**. Standard Paal-Knorr reaction readily occurred between **10.4** and 3-aminopyrrole **10.3** to furnish **10.2**. Tetrachlorination of **10.2** failed when an excess of NCS was used. In contrast, tetrabromination of **10.2** proceeded to give the corresponding brominated bispyrrole **11.5**. Interestingly, bromination at the C'-3 position did not occur; this reduced reactivity of C'-3



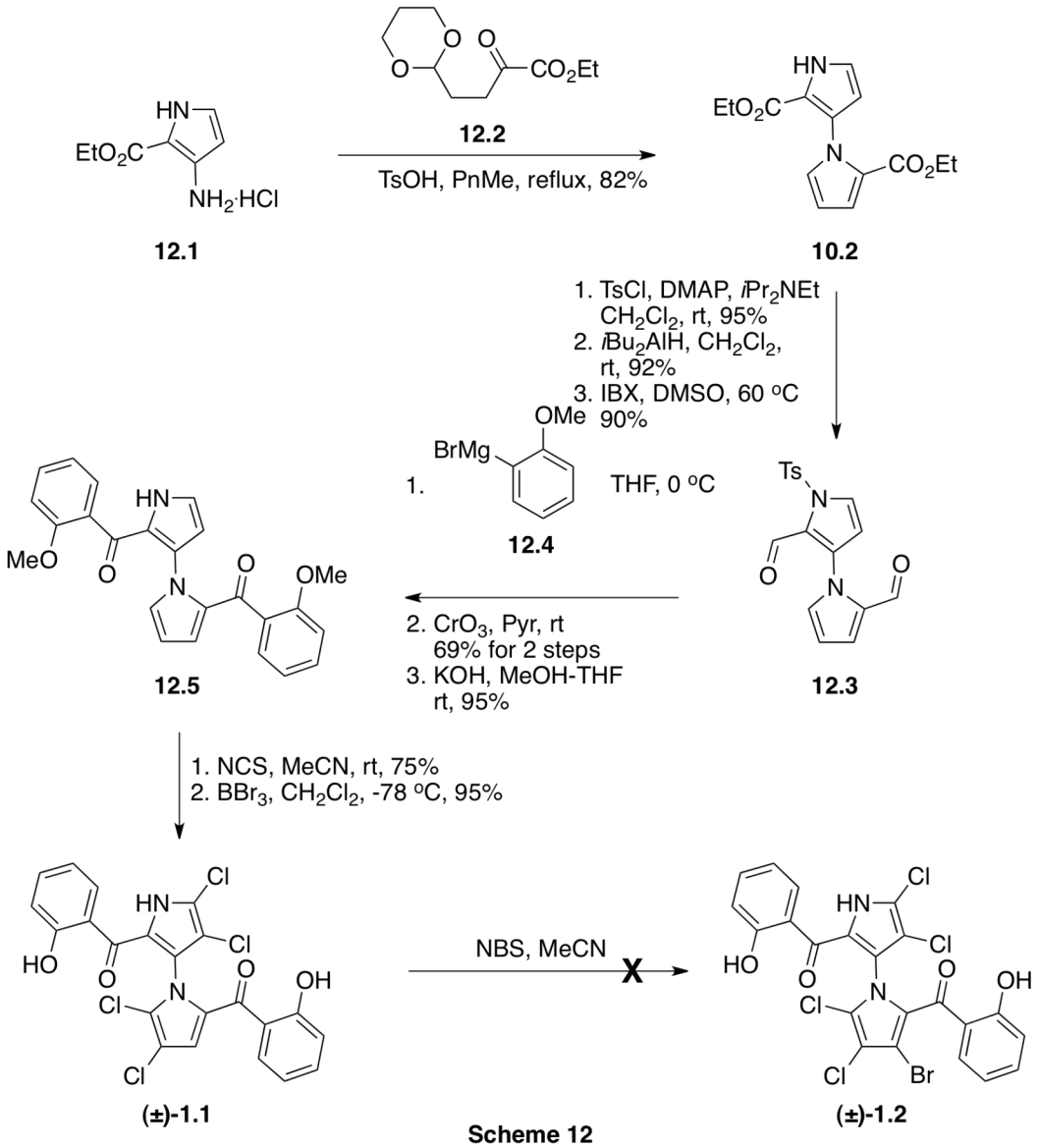
Scheme 11

towards electrophilic halogenation was also observed in later synthetic studies.[1] The mimic **11.5** of marinopyrrole A was synthesized as a racemate in five steps with an overall yield of 17.8%. The structure of tetrabromide **11.5** was confirmed by X-ray crystallographic analysis. Both **10.2** and **11.5** were also tested for antimicrobial activity and cytotoxicity. A dramatic loss of potency was observed and so the salicyloyl subunits must play an important role in inhibition.

1.5 First total synthesis of marinopyrrole A and a library of analogs for antibiotic and anticancer evaluation

In 2010, Li and coworkers reported the first total synthesis of (±)-marinopyrrole A (**1.1**).[1] As the key access to the bispyrrole core, Li and coworkers were inspired by the work of the Fenical group and decided to carry out a Paal-Knorr reaction between 3-aminopyrrole **12.1** and the protected 1,4-dicarbonyl compound **12.2**. Acid-catalyzed condensation readily occurred to produce the bispyrrole core. After protecting (tosyl group) the nitrogen on the pyrrole ring, the diester was reduced to the corresponding diol using *i*-Bu_2AlH at room temperature. The resulting hydroxyl groups were then oxidized with IBX in DMSO to give dialdehyde **12.3**. Addition of the aryl Grignard reagent **12.4** to both aldehydes provided a diol, which was rapidly oxidized to a diketone using the Collins reagent in CH_2Cl_2. Removal of the tosyl group with KOH in MeOH-THF gave **12.5**, as the bispyrrole core. Chlorination of the bispyrrole and liberation of the phenolic hydroxyl groups by treatment with BBr_3 provided racemic marinopyrrole A (**1.1**). Unfortunately, direct bromination of

marinopyrrole A to yield marinopyrrole B was unsuccessful. NBS was applied under various reaction conditions but none of them furnished any of the desired product. This is probably due to the electron deficiency of the multiply-halogenated bispyrrole and also the steric hindrance to introduction of a (large) bromine atom.



Scheme 12

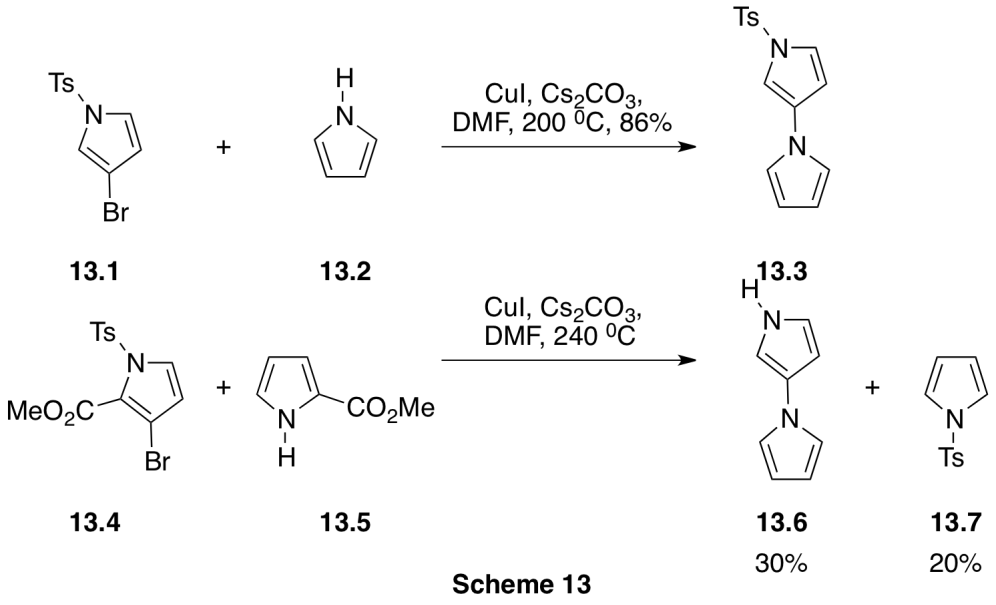
The total synthesis of marinopyrrole A was accomplished by Li and coworkers in 9 steps and 30% overall yield. Marinopyrrole B remained as an unsolved problem which probably requires a chemoselective and efficient bromination process to be used in the early stages of the synthesis.

A library of analogs of marinopyrrole A was synthesized by using different aryl Grignard reagents, but no screening for biological activity was reported. All the compounds were racemates. Although both naturally occurring marinopyrrole A and B and their (unnatural) racemates provide similar potency, an enantioselective synthesis of marinopyrrole A is still needed for modeling the bonding site of target protein.

1.6 Second total synthesis of marinopyrrole A

In late 2010, Sarli and coworkers reported the second total synthesis of (±)-marinopyrrole A.[14] As in Fenical's work, direct Ullmann coupling between 3-halopyrrole **8.2** and monodeoxypyoluteorin **3.1** was unsuccessful. However, Ullmann coupling remained still the most attractive disconnection since it could rapidly deliver the core from readily available and simple starting materials. In order to investigate such a possibility, Sarli and coworkers started to screen various conditions for C-N coupling. *N*-Protected 3-bromopyrrole **13.1** and pyrrole (**13.2**) were subjected to the screening conditions and it was found that when microwaves were applied to the Fukuyama modification (CuI, Cs_2CO_3, DMF)[15] of the Ullmann coupling conditions, a dramatic improvement was achieved. Two equivalents of CuI were required to give a satisfactory yield since

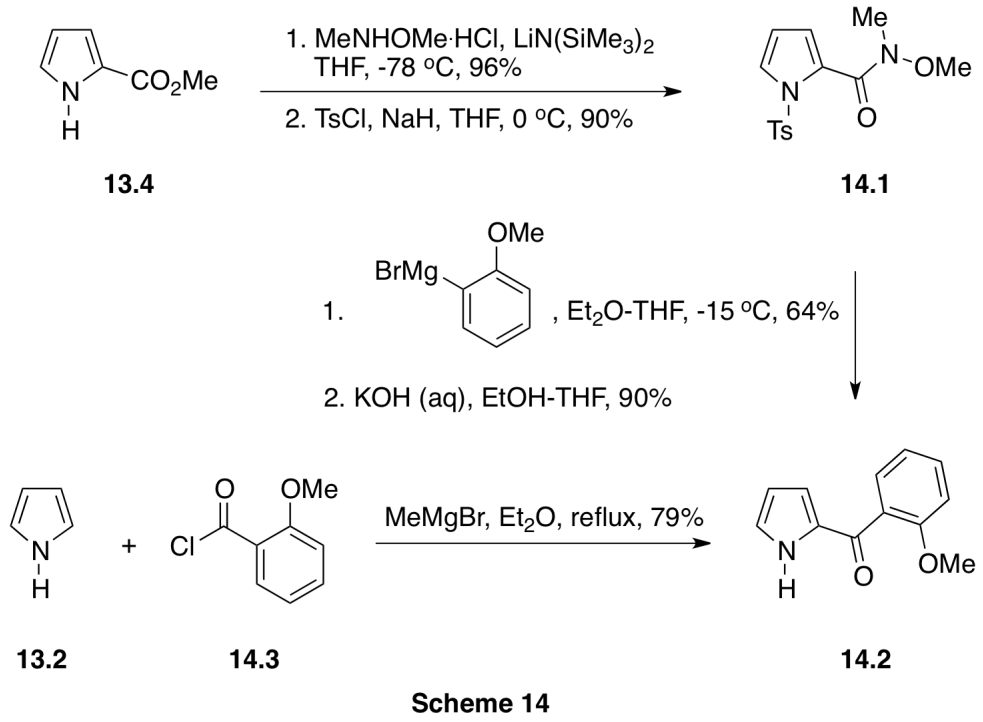
a catalytic process gave poor yields. Ortho substituents generally reduced the efficiency of such coupling reactions. When these conditions were used with *N*-protect 3-bromopyrrole **13.4** and ester **13.5** at elevated temperature, coupling along the C,N axis did proceed, as well as unwanted hydrolysis, decarboxylation and deprotection, and **13.6** was isolated in 30% yield. The reduced product **13.7** was also isolated (20%). Several different attempts at the coupling were made, but all of them failed.



Scheme 13

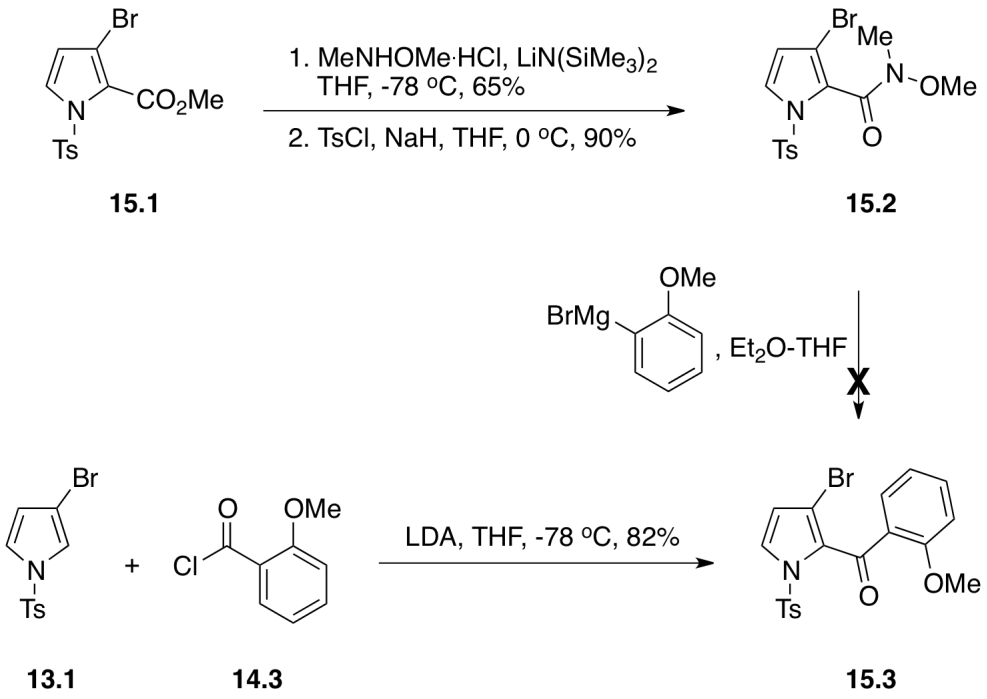
Instead of ester functionalities, ketones were subjected to similar reaction conditions. Pyrrole ester **13.4** was treated with *N*,*O*-dimethylhydroxylamine (Scheme 14) to produce the corresponding Weinreb amide and the nitrogen of the pyrrole was protected with a tosyl group to give sulfonamide **14.1**. This was treated with anisoylmagnesium bromide, and then removal of the tosyl protecting group gave dechloropyoluteorin **14.2**, which represents the bottom part of

marinopyrrole A. A more convenient one-step procedure was then developed by the addition of the dianion of pyrrole to the carbonyl of anisoyl chloride **14.3**.



Scheme 14

For the top unit of marinopyrrole A, a similar sequence of reactions was applied to the *N*-tosylpyrrole **15.1** which was first converted into the corresponding Weinreb amide. The tosyl protecting group was removed in the same step and had to be replaced, as protection of nitrogen was required. Direct addition of the *o*-anisoyl Grignard reagent to **15.2** failed to give the desired product (**15.3**). Fortunately, when **13.1** was treated with LDA the corresponding aryllithium reagent was formed and reaction with anisoyl chloride **14.3** readily occurred to provide **15.3**, which was easily made in this way on a large scale.

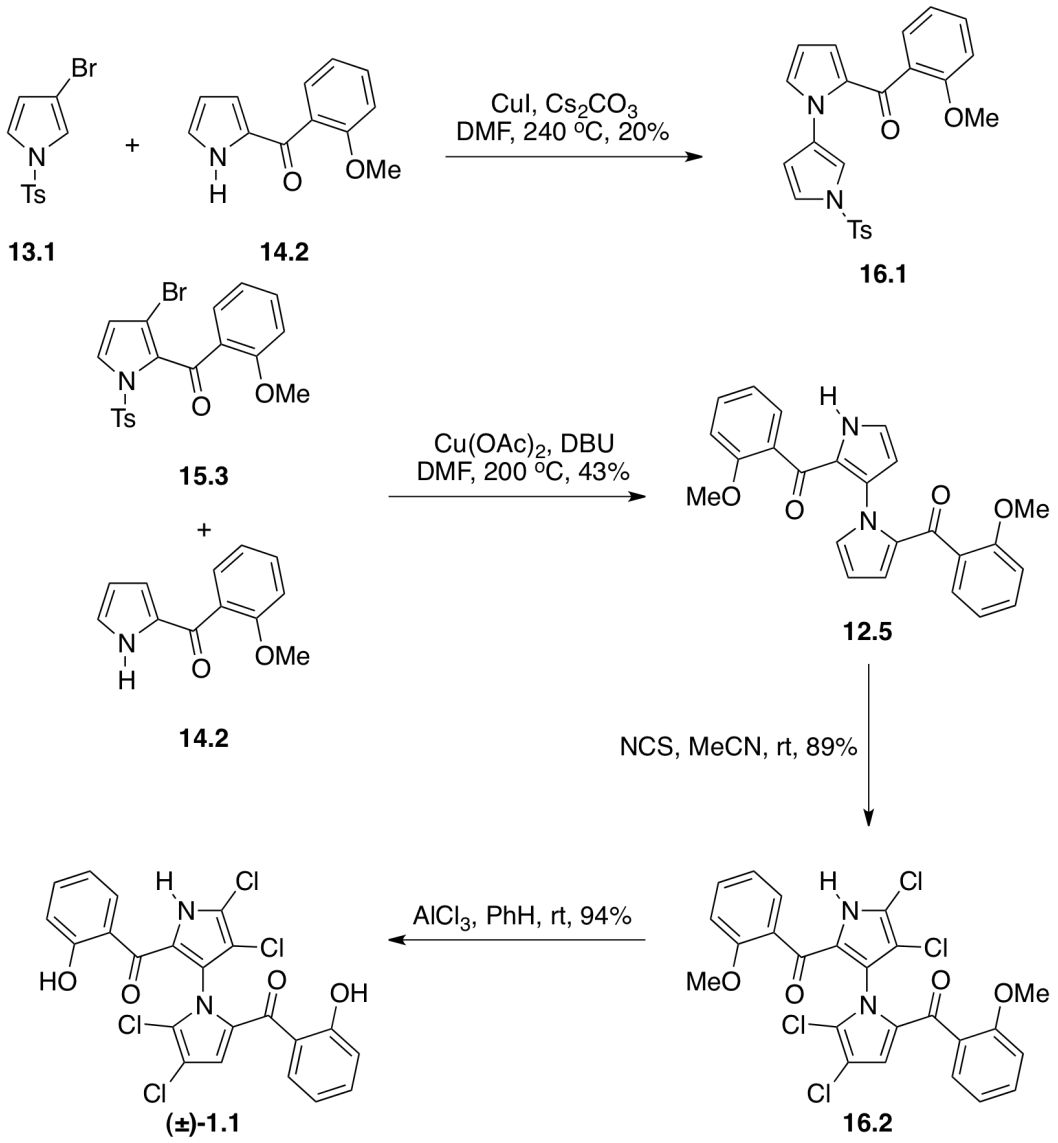


15.1 **15.2**

13.1 **14.3** **15.3**

Scheme 15

A brief model study was undertaken to test the efficiency of the Ullmann coupling reaction. When **13.1** and **14.2** were subjected to the optimized conditions that had been established, the *N*-tosyl protected bispyrrole **16.1** was obtained, but only 20% yield. A significant amount of starting material was recovered and prolonging the reaction time did not improve the yield.



Scheme 16

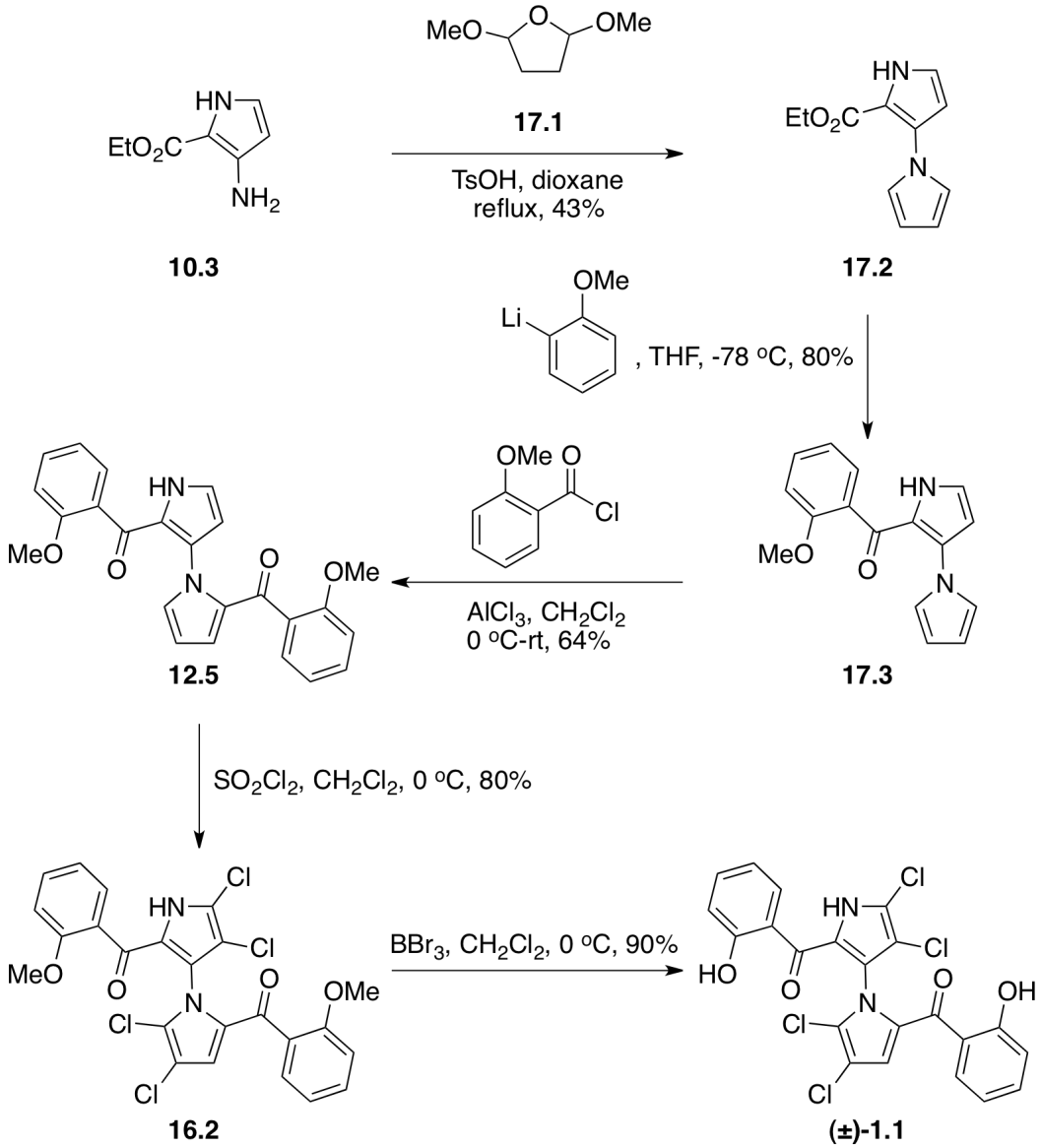
When **15.3** and **14.2** were subjected to the optimized reaction conditions [$Cu(OAc)_2$, DBU, DMF, 200 °C, microwaves] the desired bispyrrole **12.5** was obtained in 19% isolated yield (43% based on recovery of starting material). The subsequent functionality manipulation is closely related to the approach used by Li and coworkers. Two steps: tetrachlorination by NCS and Lewis acidic demethylation with $AlCl_3$, completed the total synthesis of (±)-marinopyrrole A

(**1.1**) in 17% yield over the 6 steps. (This yield is corrected for recovered starting material in the Ullmann coupling.) Again, no progress towards marinopyrrole B was reported. Attempted bromination at the C'-3 position of the bispyrrole was problematic. Early stage bromination at C'-3 of **14.2** may lead to polymerization as a competing reaction and so this is not a useful route. Although this second synthesis was shorter, low yields in some steps leaves room for future improvements.

1.7 Third total synthesis of marinopyrrole A

In 2011, Nicolaou and coworkers reported the third total synthesis of marinopyrrole A and also the preparation of some analogs.[16] Although a direct, late-stage linkage of two fully elaborated pyrrole subunit via Ullmann coupling would be the most obvious disconnection, this process could be limited in terms of substrate scope and coupling efficiency. Such results were fully described by the Sarli group, as described above. An alternative approach via construction of the bottom azole structure would give access to various derivatives. This idea was very similar to the approach of Li and coworkers. The commercially available compounds **10.3** and **17.1** were condensed to generate bispyrrole **17.2** via acid-catalyzed Paal-Knorr reaction. Successful *monoaddition* of the *o*-anisoyllithium reagent (large excess) to **17.2** occurred so as to install one of the anisoyl unit. The second anisoyl subunit was added onto the core via a Friedel-Crafts reaction. In the presence of $AlCl_3$, *o*-anisoyl chloride reacted with bispyrrole **17.3** to yield intermediate **12.5**, which was previously synthesized by

both Li's and Sarli's groups. Tetrachlorination, using SO_2Cl_2 in CH_2Cl_2, and demethylation with BBr_3 provided (±)-marinopyrrole A (**1.1**).



Scheme 17

Numerous synthetic derivatives were also synthesized. Except for the *O*-diacetylated marinopyrrole A, which showed identical inhibition against MRSA,

all the other compounds had a significantly lower antibacterial activity. Interestingly, the racemate of marinopyrrole A (**1.1**) was less potent compared to each of its atropo-enantiomers. Again, the synthesis of marinopyrrole B was not reported and a better strategy for construction of other members of the marinopyrrole family is clearly needed.

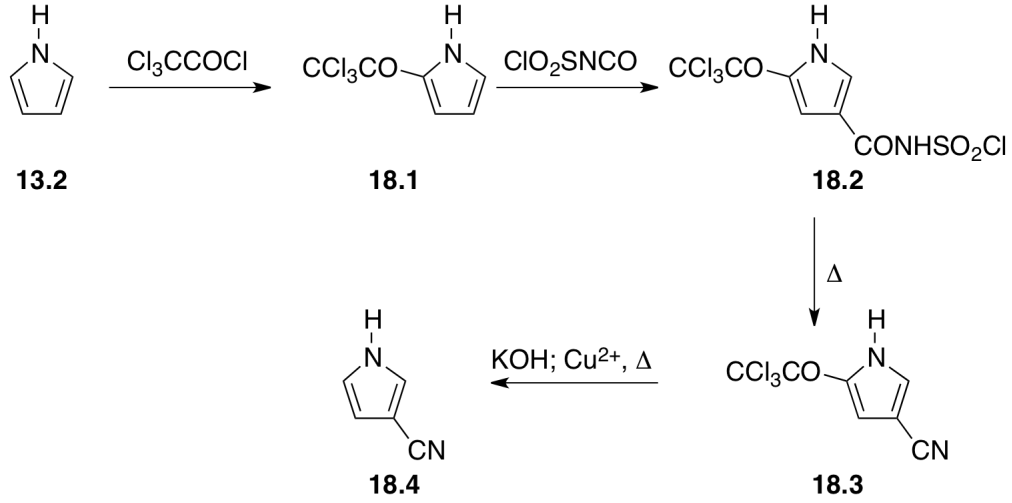
1.8 Electrophilic substitution and halogenation of pyrroles

The presence of several halogens in the marinopyrroles requires a sophisticated retrosynthetic analysis because the order of halogenation is a crucial factor. Kinetic electrophilic substitution at the α-position of pyrrole is well known and it was found to be the most predominant and often exclusive pathway.[17] One exception is the silylation of *N*-alkylated (methyl or benzyl) pyrrole, which undergoes silylation at the β-position ($Me_3SiO_3SCF_3$ and Et_3N).[18,19] Based on theoretical calculations, the β-positions of pyrrole has the highest net negative charge density. This position is extremely hard and has a high tendency to react with hard electrophiles.[20] Soft electrophiles react at the α-positions. Direct substitution at the β-positions has attracted attention in recent years and numerous investigations (see next section) have been carried out to effect β-substitution.

In terms of reactivity, the order of substitution with soft electrophiles is 2(α)>4(γ)>5(δ)>3(β). In general, three types of methods were discussed herein:

1.8.1 Directed β-substitution using a removable group at the α-position

In 1981, Anderson and coworker reported that β-substituted pyrroles could be prepared by introduction of a directing group at the α-position, followed by removal at a later stage.[21] For example, α-trichloroacetylation of **13.2** gave 2-trichloroacetylpyrrole **18.1** via a Friedel-Crafts reaction. Compound **18.1** was then reacted with chlorosulfonyl isocyanate to provide **18.2** and, upon heating, desulfonylation and dehydration readily occurred to give nitrile **18.3**. Removal of the trichloroacetyl moiety via basic hydrolysis and decarboxylation furnished the desired β-substituted pyrrole **18.4**.

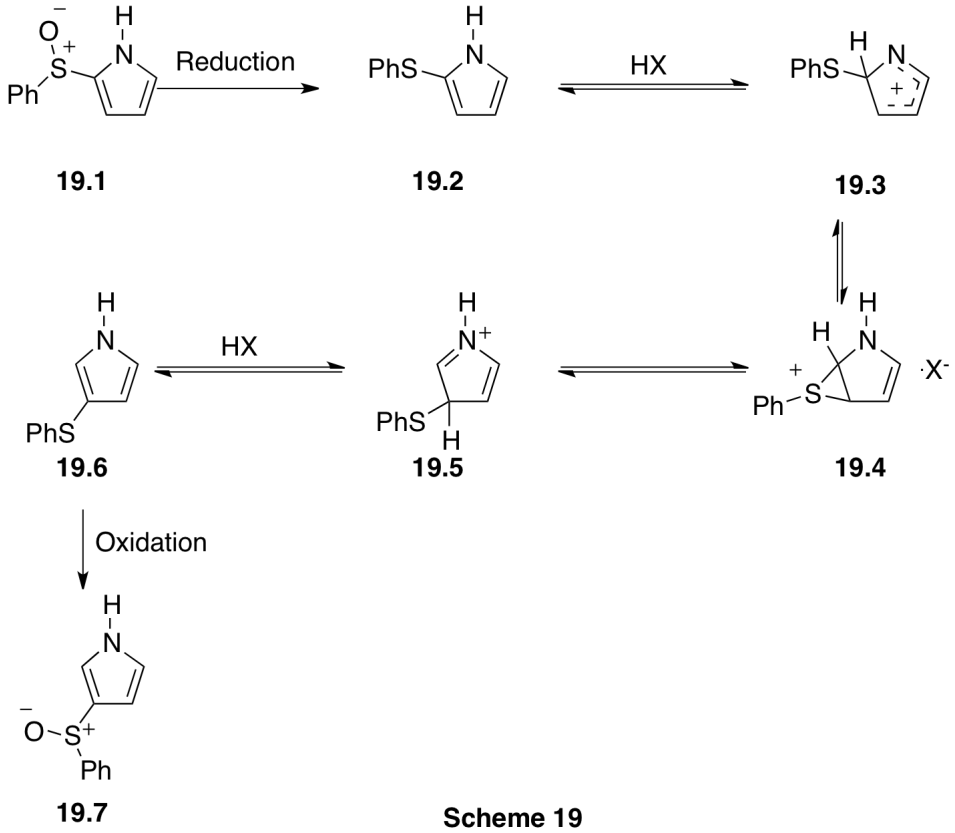


Scheme 18

1.8.2 Acid mediated isomerization of α isomers

In 1983, Muchowski and coworkers reported that α-sulfinyl pyrrole could undergo a three-step sequence to provide the corresponding β-isomer.[22] Initially the sulfinyl group of **19.1** was reduced and the resulting sulfide **19.2** was then treated with acid. An acid-catalyzed rearrangement readily occurred and the

corresponding β-isomer **19.6** was formed via the mechanism Shown in Scheme 19. Sulfide **19.6** was then oxidized to form sulfoxide **19.7**.

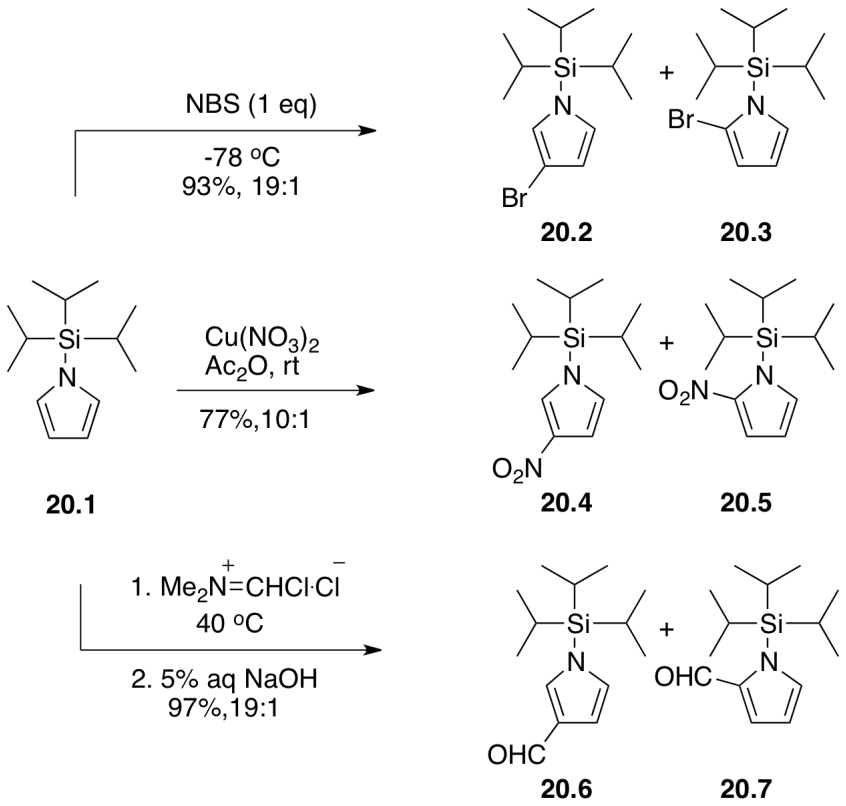


Scheme 19

1.8.3 Introduction of a sterically large group on the nitrogen

In 1990 Muchowski and coworkers reported that *N*-triisopropylsilyl-protected pyrroles underwent β-substitution predominantly, due to significant steric hindrance around the α-position.[23] Upon deprotection, β-substituted pyrroles were obtained by this extremely short sequence. Bromination, nitration and formylation were applied to *N*-triisopropylsilyl-protected pyrroles and all reactions successfully provided the β-substituted pyrroles. Under various

conditions, chlorination gave predominately α-chlorinated products. This method was efficient, although careful screening of reaction conditions was recommended.



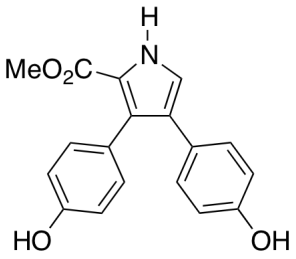
Scheme 20

1.9 Multiply halogenated pyrroles: their biological activity and synthetic utility

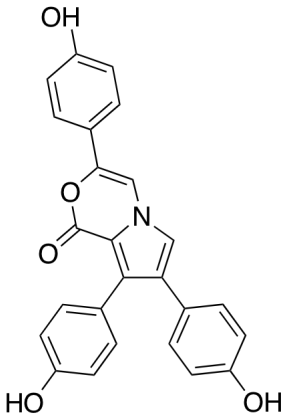
Halogenation is a not uncommon pathway in the biosynthesis of secondary metabolites.[24] In the absence of appropriate enzymatic methods, highly efficient and selective halogenation processes are often difficult to achieve via standard chemical reactions. In comparison to other halogenated natural products, halogenated pyrroles show strong antimicrobial activities, especially against Gram-positive bacteria.[25] Due to electronic and steric factors in pyrroles, it is

difficult to prepare multiply halogenated pyrroles and several syntheses of halogenated pyrroles will be compared in this part of the introduction.

In 2006 Smith and coworkers reported the synthesis of multiply halogenated pyrroles, which were considered as synthetic precursors to lamellarin Q (**21.1**) and lukinol A (**21.2**).[26]



lamellarin Q
21.1

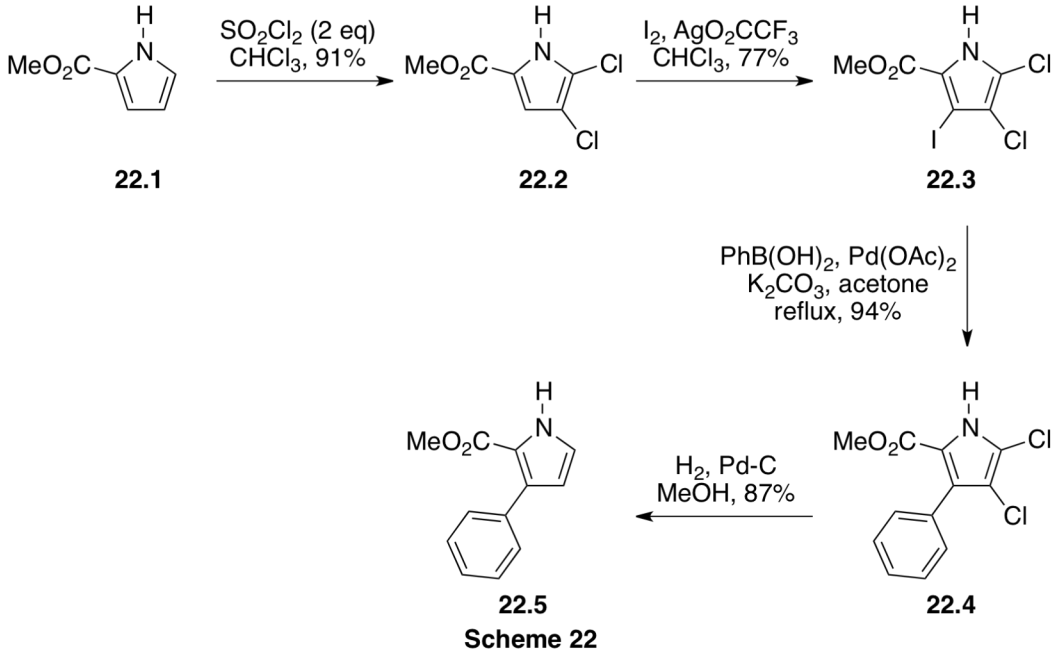


lukinol A
21.2

Scheme 21

As previously mentioned, the ranking of reactivity indicates that regioselective halogenation at the C-3 and C-4 positions is problematic since the reactivity of C-5 is higher than C-3. In order to obtain a C-3 arylated product, a four-step sequence was developed (Scheme 22). Methyl 2-pyrrolecarboxylate (**22.1**) was chlorinated by SO_2Cl_2 to yield **22.2**. The least reactive C-3 position was then iodinated with I_2 in the presence of $AgOCOCF_3$. Arylation of **22.3** was achieved via a standard Suzuki-Miyaura coupling reaction. Hydrogenation of the

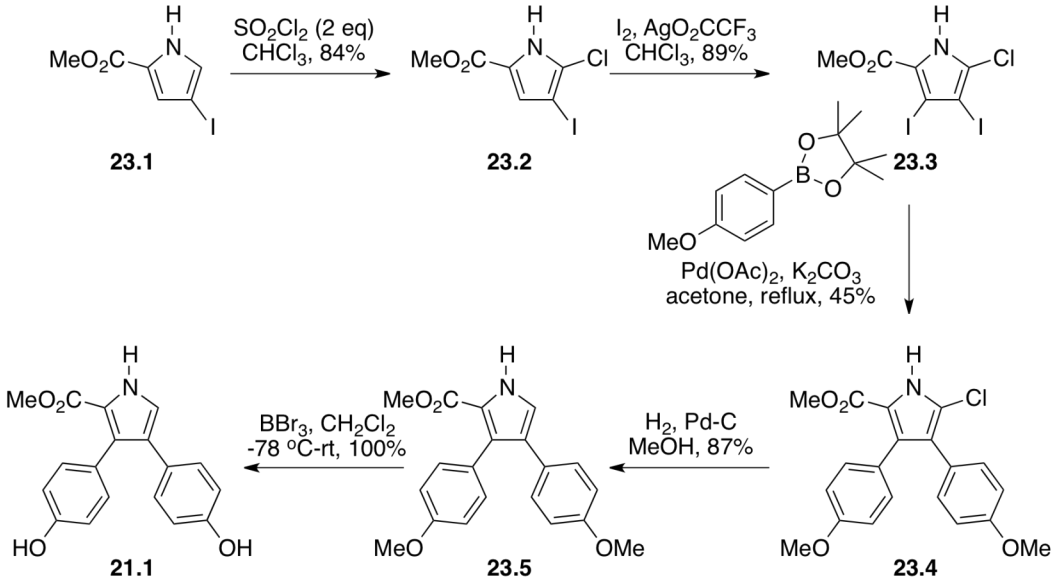
resulting 3-arylated pyrrole **22.4** removed unwanted chlorines at the C-4 and C-5 positions.



22.1 **22.2** **22.3** **22.4** **22.5**

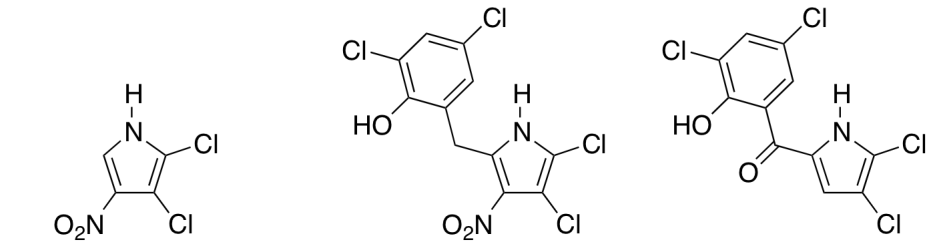
Scheme 22

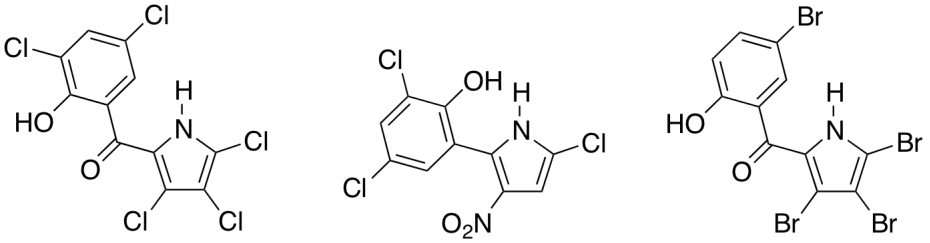
In order to synthesis lamellarin Q (**21.1)**, the problem was how to regioselectively halogenate the less reactive C-4 position. Starting from the known pyrrole **23.1**, chlorination at the C-5 position, followed by iodination at C-4, furnished diiodide **23.3**. With this diiodide in hand, Pd-mediated Suzuki-Miyaura coupling was smoothly effected to produce the diarylated pyrrole core **23.4**. As described above, removal of the chlorine was achieved by hydrogenation, and then demethylation of the resulting pyrrole furnished the final product, lamellarin Q (**21.1**).

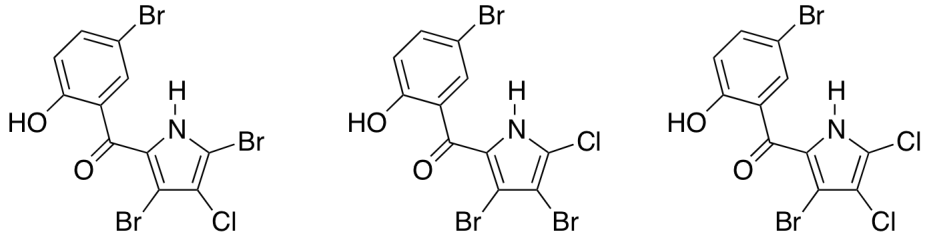


Scheme 23

As mentioned before, pyrrolomycins are a family of several natural products which show remarkable potency against Gram-positive bacteria. They were originally isolated from the culture broth of *Actinosporangium vitaminophilum* SF-2080. When bromide ion was introduced into the fermentation medium of *A. vitaminophilum* SF-2080, a new group of brominated pyrrolomycins, PM-F_x, was also been generated. Among these compounds, PM-D and PM-F_{2a} showed relatively high potency against Gram-positive bacteria. Due to the highly halogenated nature of the pyrrolomycins, it is important to study the order of halogenation in order to address the synthesis of these natural products and their derivatives. Easy access to this type of compound could lead to potential drug candidates for a new type of antibiotic.

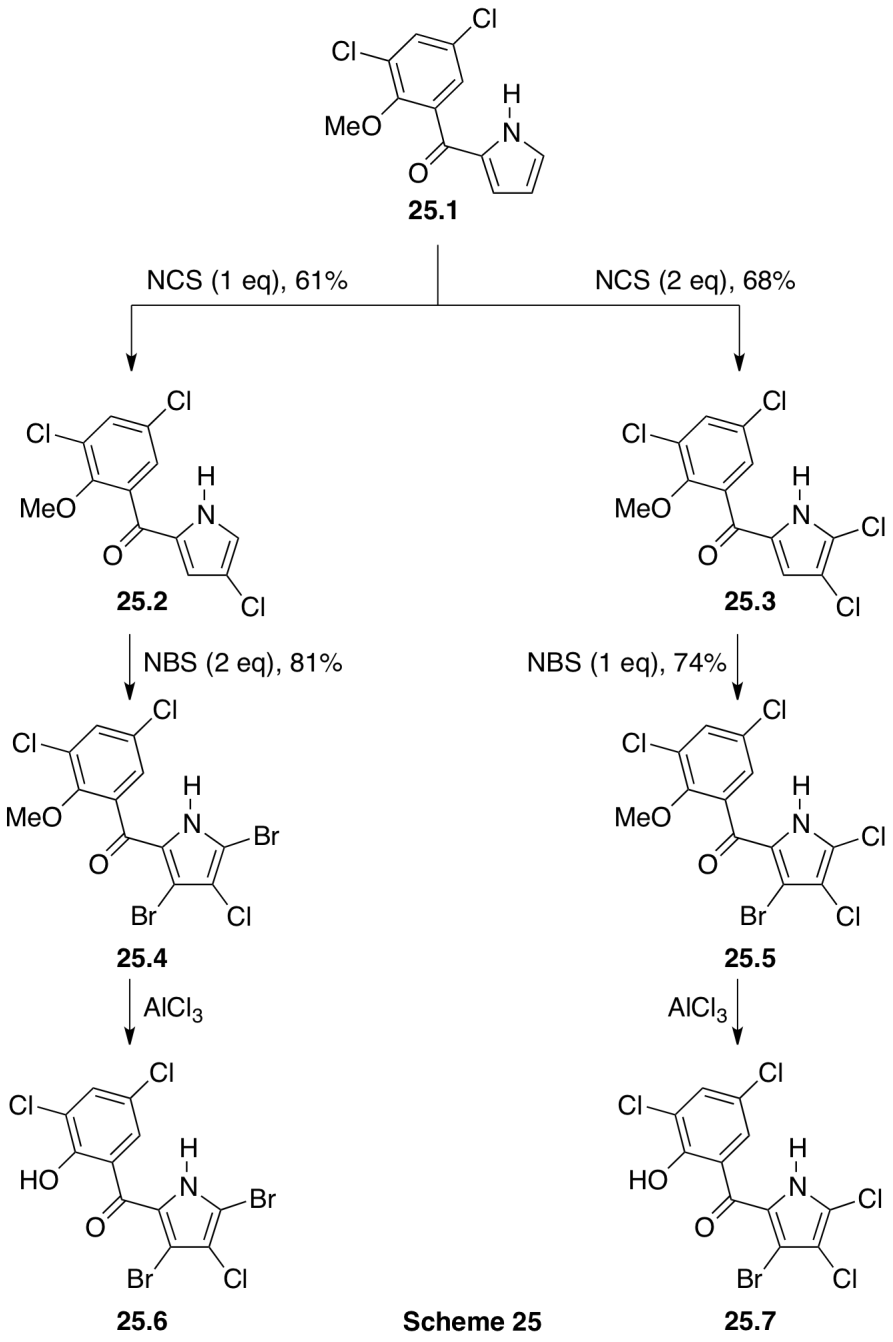






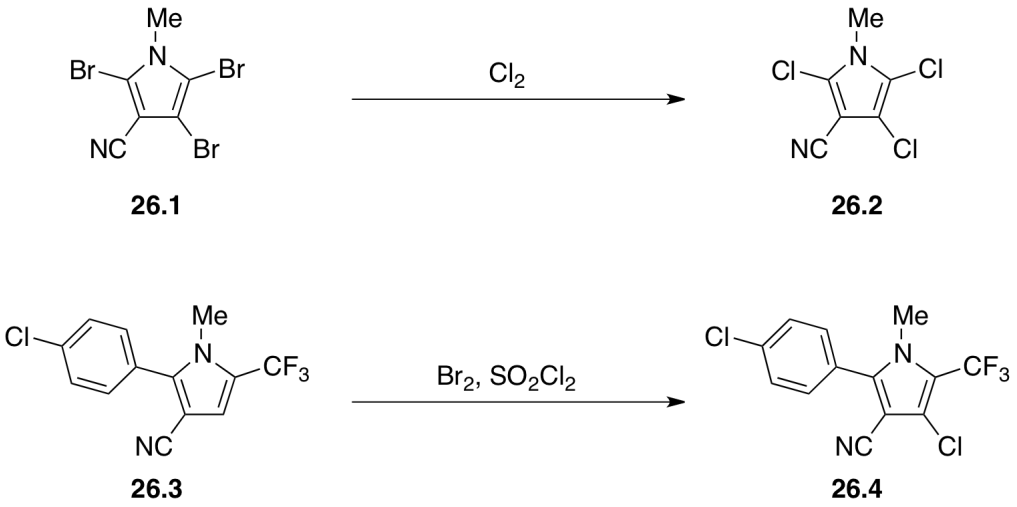
Scheme 24

In 2007 Raimondi and coworkers reported the synthesis of a class of compounds which is closely related to the pyrrolomycins.[27] Based on the reactivity of each different carbon, manipulation of the amount of electrophile generated a general method of access to multiply-halogenated pyrroles. Notably, the synthetic analogs were more potent than the parent natural products against Gram-positive bacteria.



Scheme 25

In 1993 Kameswaron reported that pyrroles bearing electron withdrawing groups can be chlorinated via so call debrominative chlorination.[28] Treatment with chlorine or sulfuryl chloride causes the originally attached bromines to be displaced by chlorines.



26.1 **26.2**

26.3 **26.4**

Scheme 26

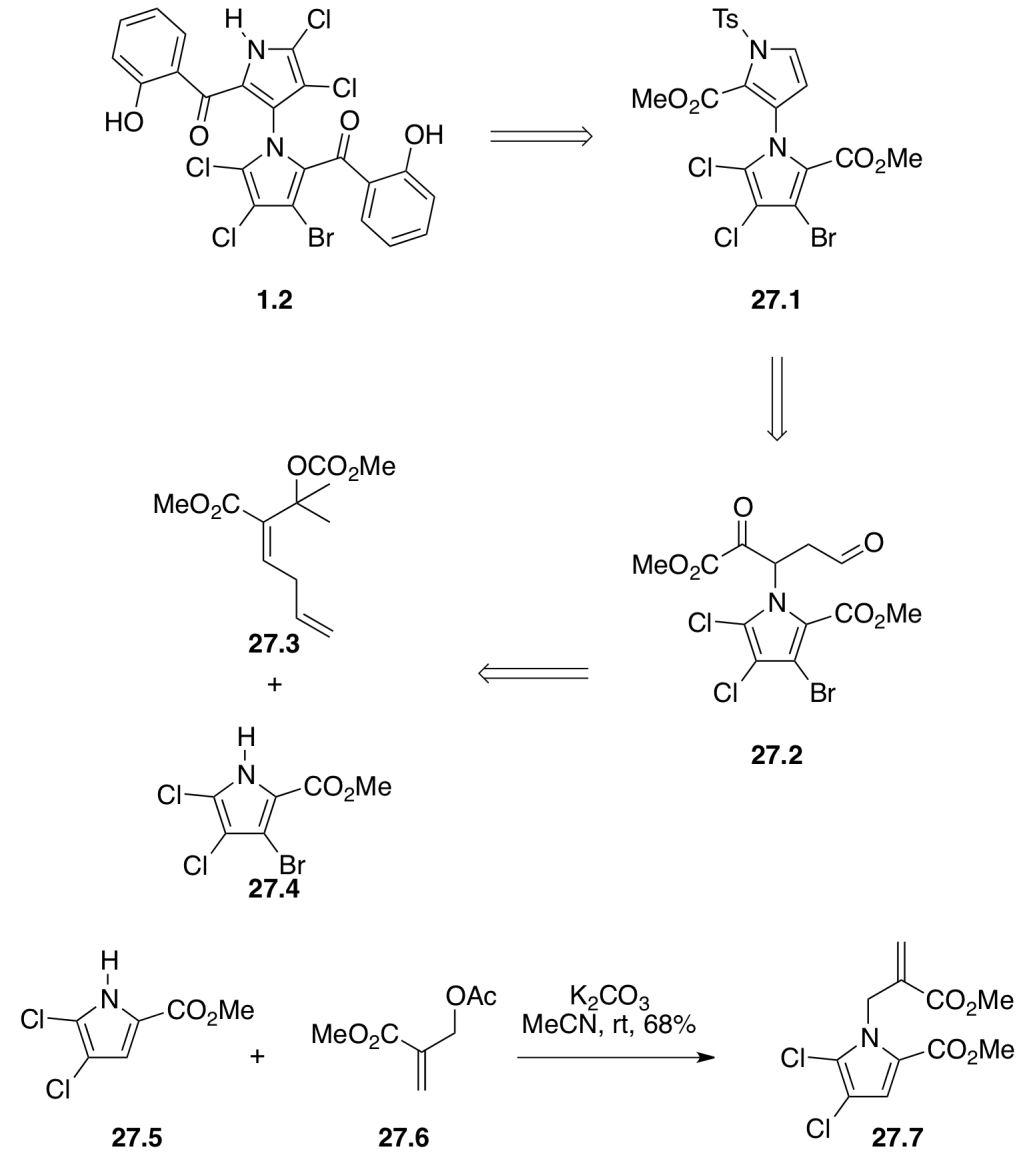
2. RESULTS AND DISCUSSION

2.1 Research objective

Marinopyrrole A and B are highly halogenated bispyrroles which show high potency against MRSA. The major goal of this project was the synthesis of marinopyrrole B since it had never been synthesized and, since late stage bromination of marinopyrrole A was unsuccessful, a new synthetic strategy was required to solve the problems posed by marinopyrrole B.

2.2 Synthetic studies on marinopyrrole B

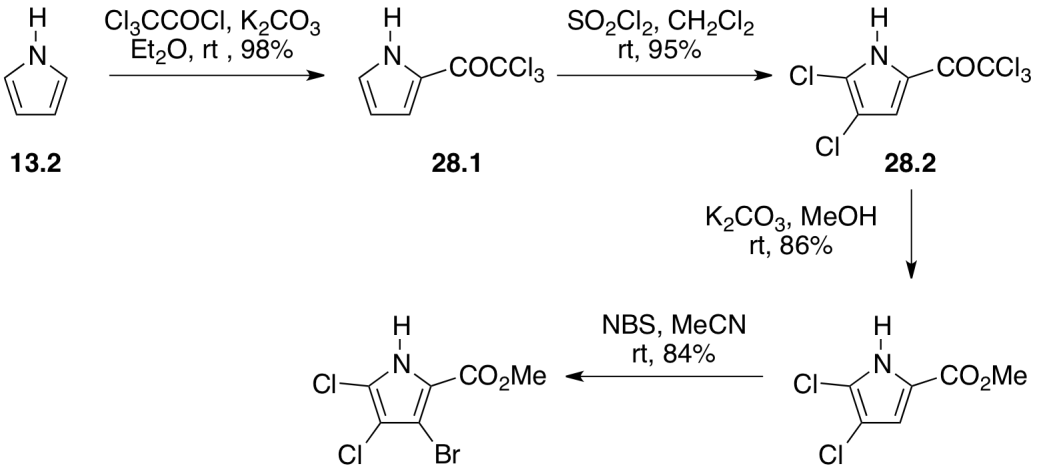
Based on the work of Dr. Fernandopulle, a former member of this group who had prepared **27.7**, a retrosynthetic proposal was developed along the following lines: The plan was to introduce bromine at the C'-3 position at an early stage so that it would not be necessary to try late stage bromination, which appeared to be difficult. We choose **27.1** as the key intermediate which already has the bromine at C'-3 and should be easily converted to marinopyrrole B via several functionality manipulations. Unlike other approaches, we decided to construct the top pyrrole ring via a Paal-Knorr reaction, which would require the keto aldehyde **27.2**. An intermolecular conjugate displacement between **27.3** and **27.4**, followed by several standard functionality transformations should allow the construction of **27.2**.



Scheme 27

Preparation of the bottom pyrrole piece was achieved in the following way (Scheme 28): pyrrole (**13.2**) was converted to trichloromethyl ketone **28.1** by reaction with trichloroacetyl chloride in the presence of a base.[29] Regioselective chlorination was carried out by using SO_2Cl_2 to yield the dichlorinated pyrrole **28.2**.[30] The C-3 position was untouched even with a prolonged reaction time

under these conditions. The trichloromethyl ketone was then converted into the corresponding ester **28.3** by treatment with K_2CO_3 in MeOH. Direct bromination at C-3 (NBS, MeCN) then yielded **28.4**. Bromodichloropyrrole **28.4** was synthesized in large quantity for screening reaction conditions for the intermolecular conjugate displacement.

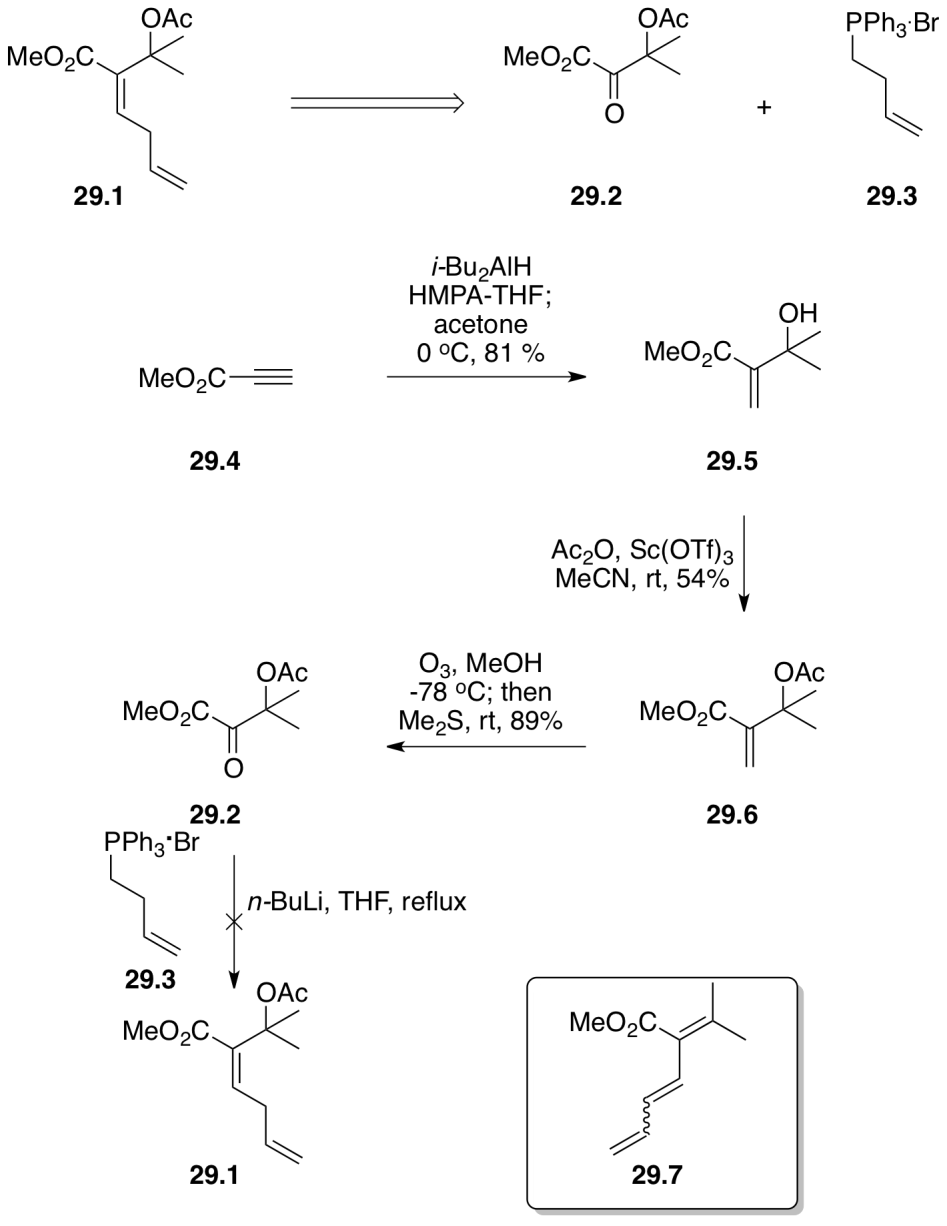


13.2 **28.1** **28.2** **28.4** **28.3**

Scheme 28

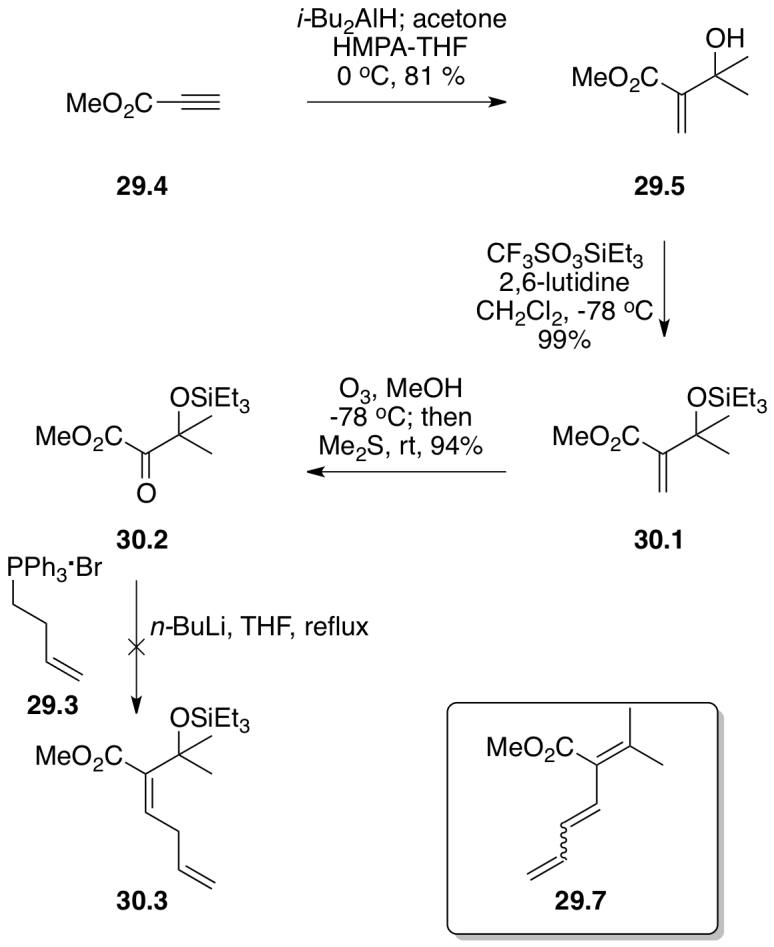
Instead of using the carbonate **27.3**, the acetate **29.1** was first considered, but the synthesis of **29.1** was problematic. The original plan included a disconnection at the conjugated double bond of the α,β-unsaturated ester (see **29.1**), which led to α-keto ester **29.2** and known Wittig salt **29.3.**[31] The keto ester **29.2** was synthesized via a 3-step sequence: methyl propiolate **29.4** was treated with DIBAL-H in the presence of HMPA in THF at 0 °C to give an enolate which was subsequently trapped by acetone.[32] The resulting alcohol (**29.5**) was acetylated to give **29.6**.[33] Ozonolysis of the double bond of the α,β-unsaturated ester then gave the desired α-keto ester **29.1**. When the Wittig reaction was

applied to **29.2**, disappointedly the desired product **29.1** was not obtained. Easy elimination from **29.1** gave the undesired product **29.7**. Reducing the amount of ylide did not improve the reaction, indicating that the second reaction (the elimination) was fast and irreversible.



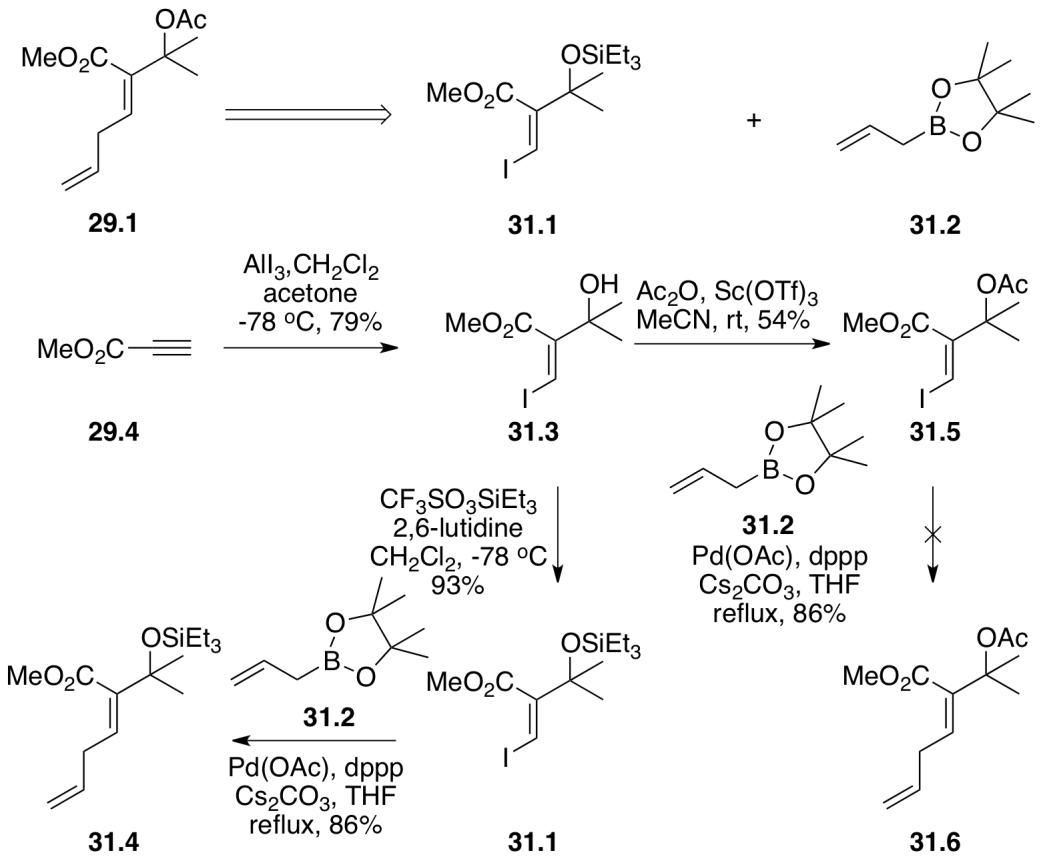
Scheme 29

In order to avoid this unwanted elimination, we then examined the Wittig reaction with a poor leaving group. A similar sequence to that we had used to try to make **29.1** was applied to the synthesis the new precursor **30.2**. Silylation of the allylic alcohol **29.5** was achieved by using $CF_3SO_3SiEt_3$ and 2,6-lutidine in CH_2Cl_2. Ozonolysis of the resulting silyl ether **30.1** gave **30.2** as the desired α-keto ester. We subjected this compound to standard Wittig conditions, but again, only an elimination product (in this case, **29.7**) could be isolated.



Scheme 30

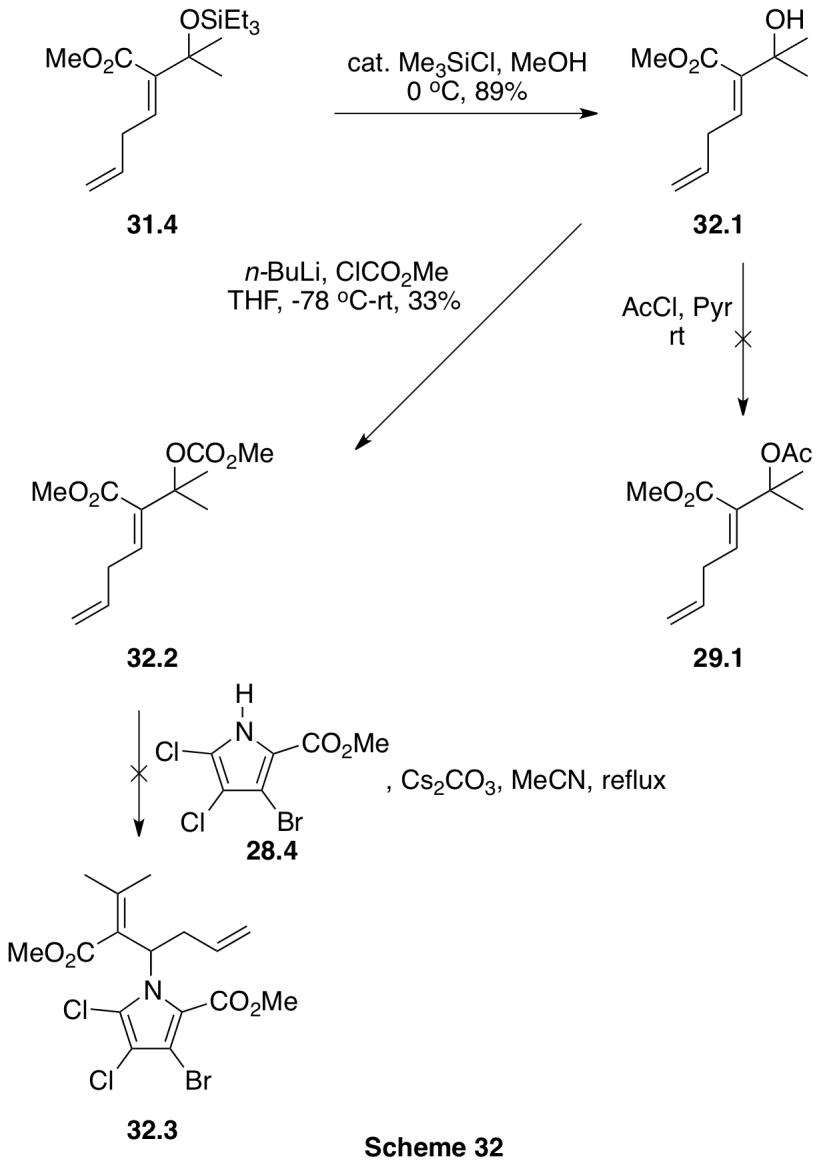
Due to the facility of the elimination, we needed to find an alternative disconnection for these α,β-unsaturated esters. A different disconnection would be between the allyl unit **31.2** and the α,β-unsaturated unit **31.1**. Since Suzuki-Miyaura coupling of vinyl halides and allyl boronic acids or esters are well established in the literature, it was likely that such a disconnection would furnish the desired product.



Scheme 31

Starting from methyl propiolate (**29.4**), Michael addition of iodide, followed by trapping the newly formed carbanion with acetone, generated allylic alcohol **31.3**.[34] This was then acetylated with Ac_2O in the presence of $Sc(OTf)_3$.[32]

However, Suzuki-Miyaura coupling between **31.5** and **31.2** failed to give the desired allyl acetate.[35] Presumably, Pd inserted into the allyl acetate to generate an allyl palladium complex, which underwent various transformations and led to a complex mixture. The tertiary alcohol **31.3** was then protected by a triethylsilyl group. When **31.1** was subjected to the Suzuki-Miyaura coupling conditions, reaction occurred readily to provide the expected diene in good yield.

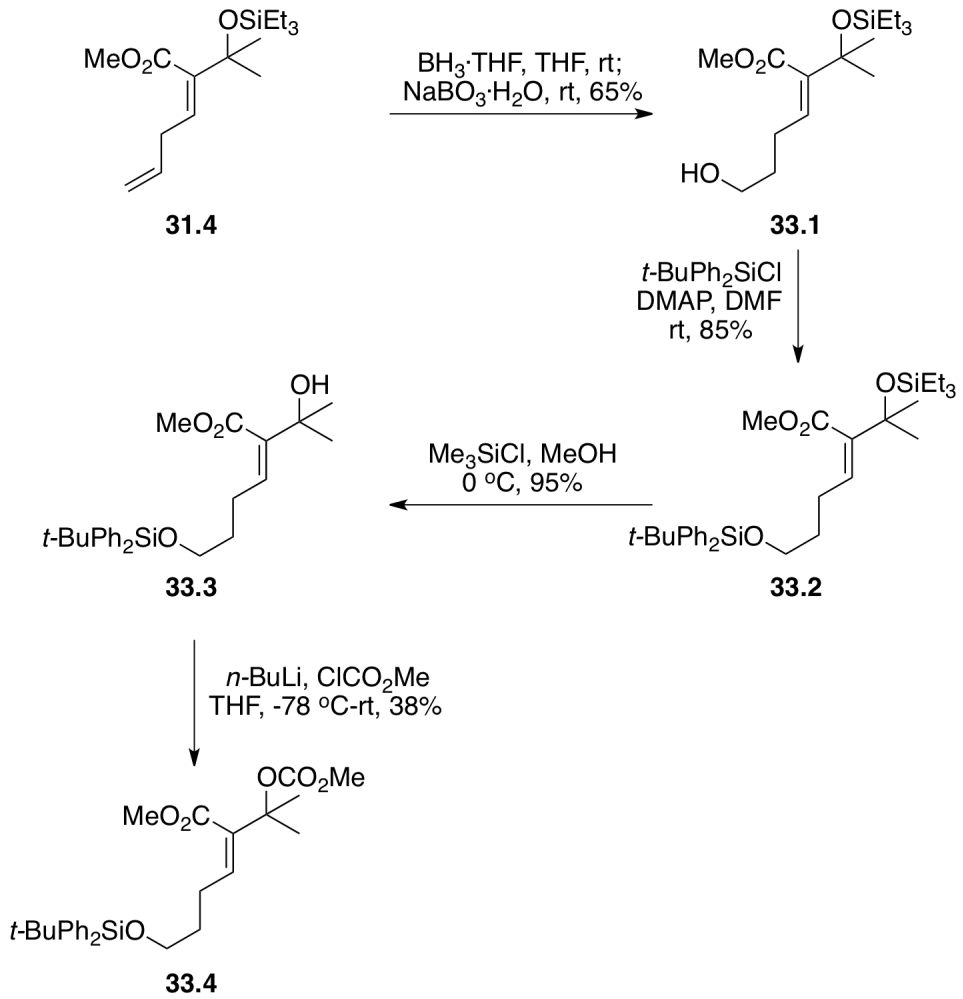


Scheme 32

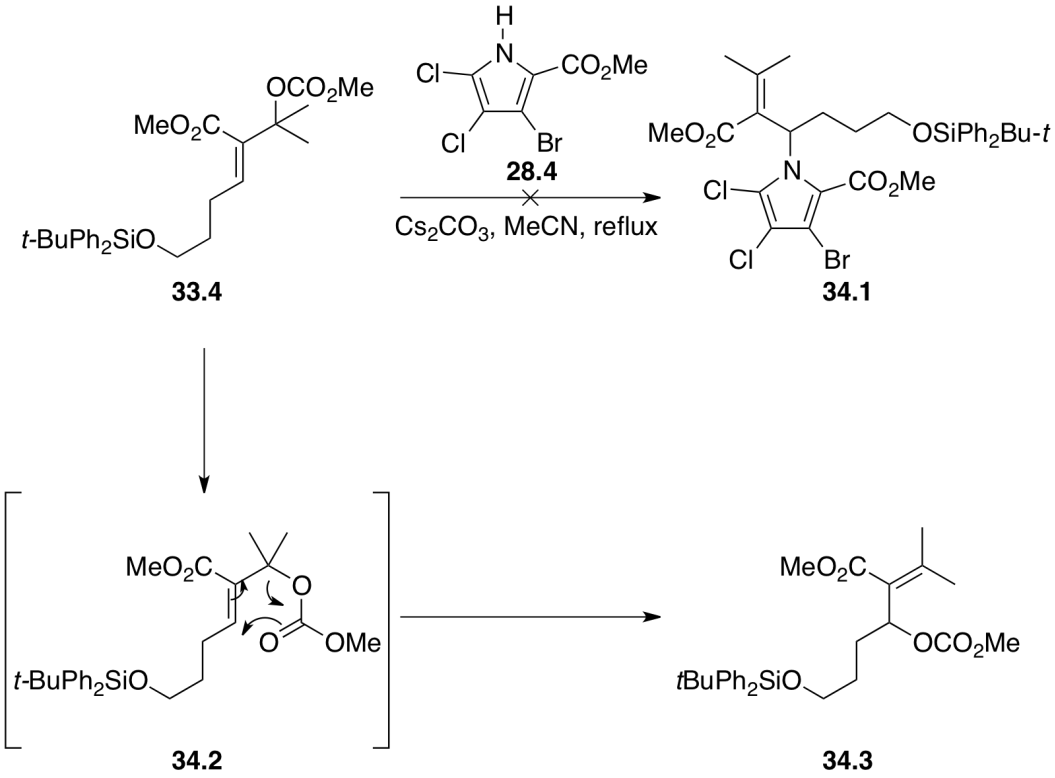
We then removed the silyl group and attempted to reprotect the hydroxyl to obtain the corresponding acetate **29.1** which would be used for examining the desired conjugate displacement reaction.[36] The silyl group was removed in acidic methanol, but reprotection of the hydroxyl group with AcCl and pyridine was fruitless. After some optimization, we found that the allylic alcohol **32.1** could be converted to the allylic carbonate **32.2** (*n*-BuLi, $ClCO_2Me$). Allylic carbonates had previously been used for conjugate displacement reactions. We then subjected the newly obtained allylic carbonate **32.2** to the reaction conditions optimized by Dr. Fernandopulle for making **27.7** but, unfortunately, we were unable to obtain any of the desired product. Due to the electron deficient nature of the pyrrole ring, the nucleophilicity of the nitrogen is dramatically reduced and the reactivity of the pyrrole is insufficient for conjugate displacement. Probably, unfavorable steric factors also play a role. Only **28.4** was recovered from the reaction mixture. It is possible that **32.2** undergoes elimination of the type mentioned above, to form a triene.

In order to suppress such elimination, we decided to replace the terminal double bond by a terminal alcohol, as in **33.1**. The hydroxyl would then be protected. In the absence of the terminal double, the lower extent of conjugation may suppress elimination and allow the desired conjugate displacement process. Hydroboration of the terminal double of **31.4**, using BH_3·THF complex, followed by oxidation of the resulting borane with $NaBO_3·H_2O$, avoided basic hydrolysis of the ester group[37] and gave **33.1**. This was then protected by a *t*-butyldiphenylsilyl group to give **33.2**. Selective deprotection of the triethylsilyl

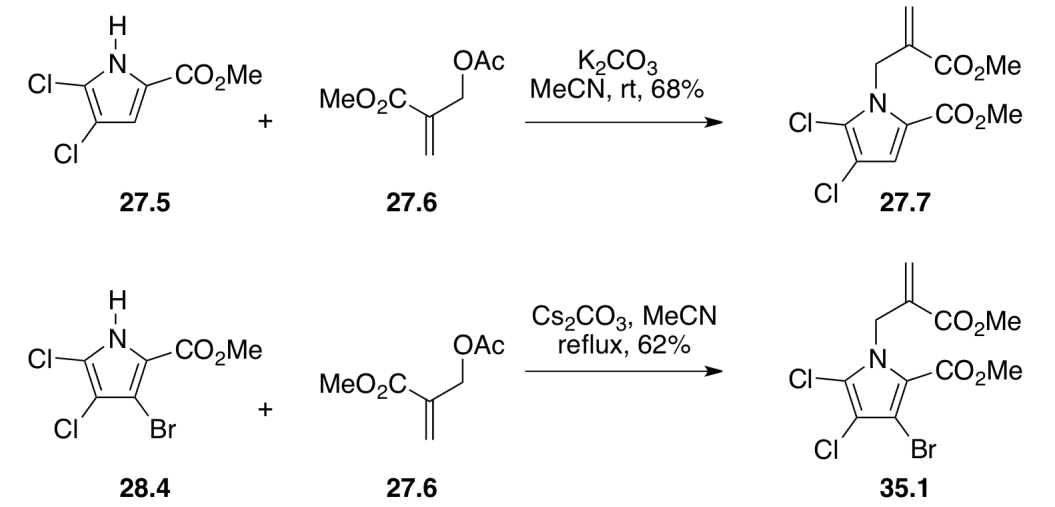
group in the presence of the *t*-butyldiphenylsilyl group under acidic methanolic conditions was successful and the resulting tertiary alcohol **33.3** was then converted to the allylic carbonate **33.4** under conditions used previously. However, the conjugate displacement process was again unsuccessful. No significant conversion was detected when the reaction was carried out at room temperature. When elevated temperatures were used, instead of the conjugate displacement product, the only isolated product was **34.3**, the result of a 3,3-sigmatropic rearrangement.[38]



Scheme 33



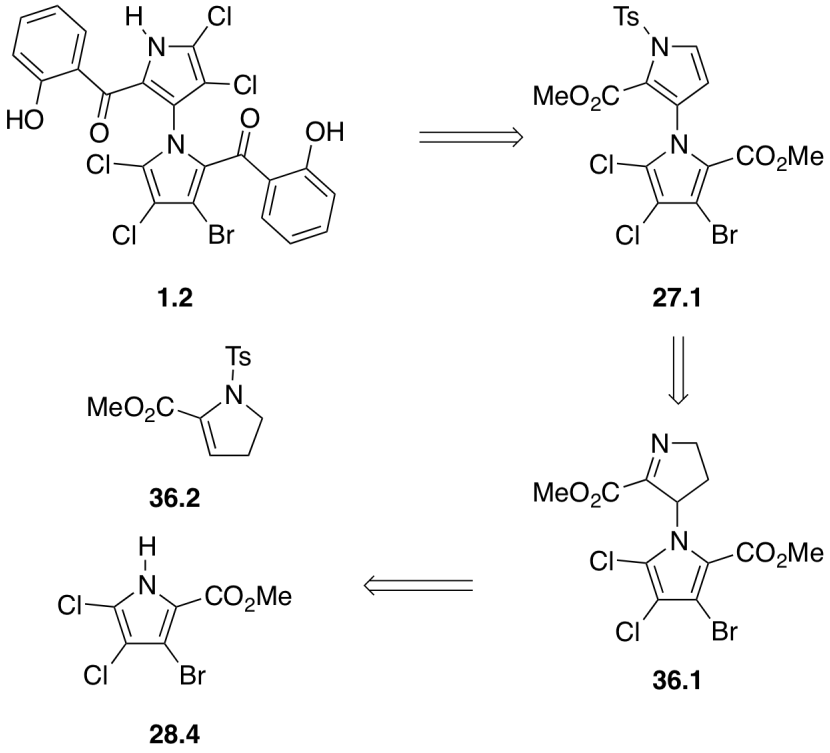
Scheme 34



Scheme 35

The reduced nucleophilicity of multiply-halogenated pyrroles could be responsible for the failure of the intermolecular conjugate addition reaction. It was found that the reaction between **27.5** and **27.6** occurred at room temperature

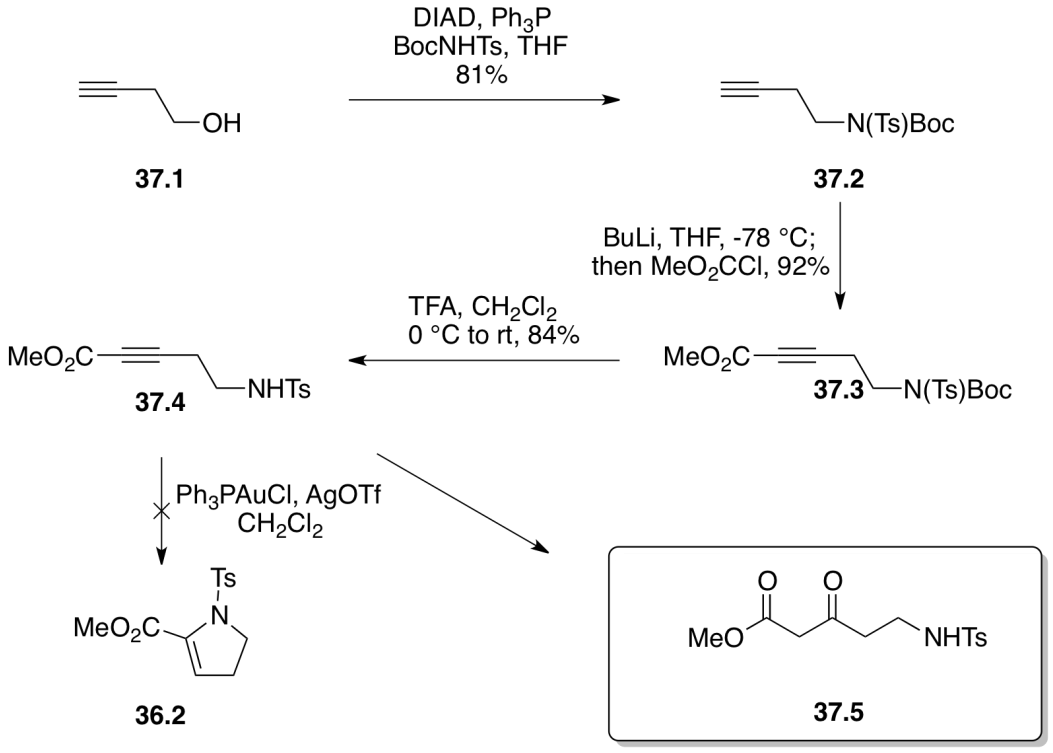
smoothly to give the product **27.7** (68%). However, when **28.4** and **27.6** were subjected to the identical reaction conditions, only a trace amount of the desired product was isolated. An elevated reaction temperature (MeCN, reflux) significantly improved the yield and the desired conjugate displacement adduct **35.1** was isolated in 62% yield.



Scheme 36

At this point we considered another retrosynthetic disconnection. The intermediate **27.1** was considered as the precursor of **1.2**. Bispyrrole **27.1** should be accessible from **36.1** by oxidation. Formation of the linkage via the C,N axis was again planned by way of a conjugate displacement, in this case between **36.2** and **28.4**.

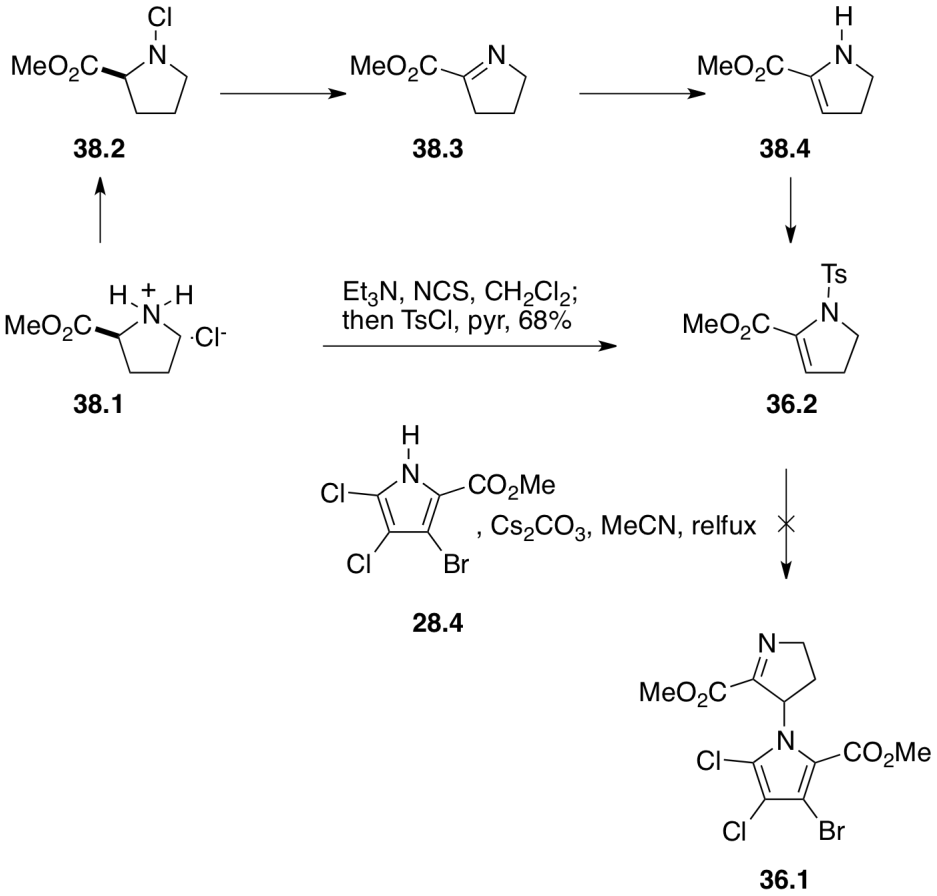
The synthesis of **36.2** was first carried out via a gold catalyzed synthesis of 2,3-dihydropyrrole.[39] The homopropargylic alcohol **37.1** was subjected to a Mitsunobu reaction to give the *N*-protected homopropargylic amine **37.2**.[40] This was treated with *n*-BuLi and MeO_2CCl and the resulting ester **37.3** was then deprotected under acidic conditions to provide **37.4**, which was subjected to cyclization conditions reported for a simpler case.[38] Unfortunately, only the hydration product, the β-keto ester **37.5** was isolated.



Scheme 37

Based on the observations of Schmalz and coworkers,[41] proline methyl ester hydrochloric acid salt (**38.1**) was converted into **38.2** by a three-step, one-pot sequence: chlorination of the amine under basic conditions rapidly generated the

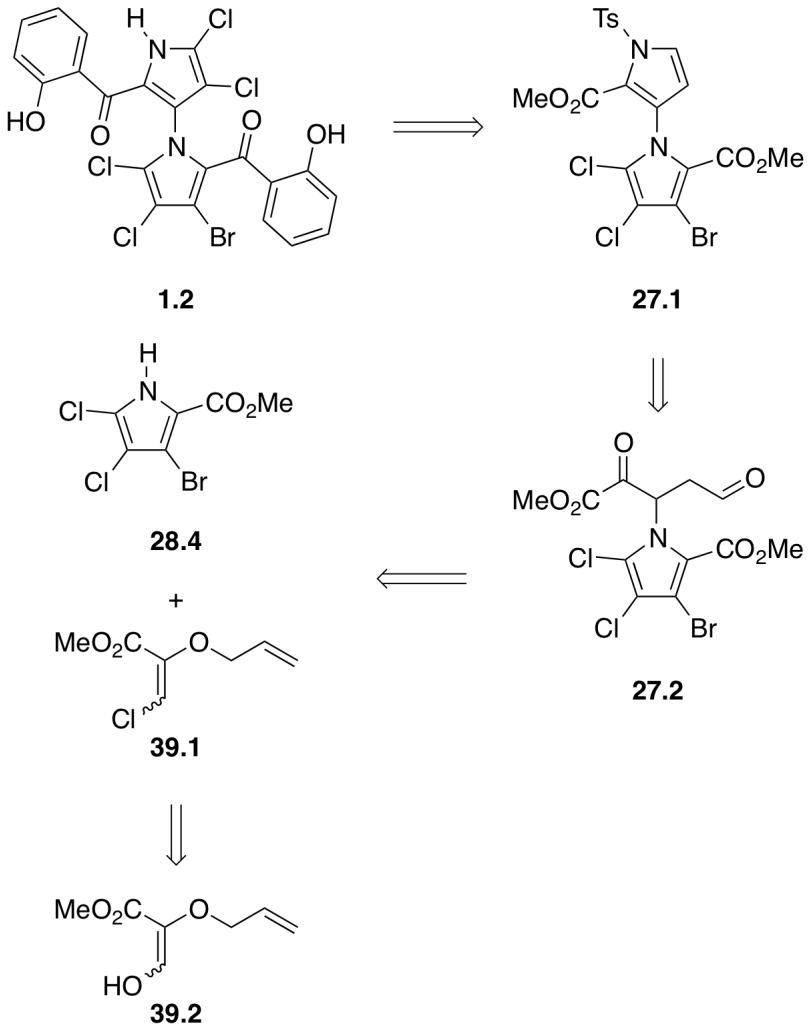
N-chloro compound **38.2** and elimination of HCl produced imine **38.3**. Tosylation of nitrogen and migration of the double bond provided **36.2**. With **36.2** in hand, it was subjected to conditions for intermolecular conjugate displacement. Experiments at room temperature and at elevated temperature (MeCN, reflux) both failed. Again, this outcome might be due to the poor nucleophilicity of pyrrole **28.4**.



Scheme 38

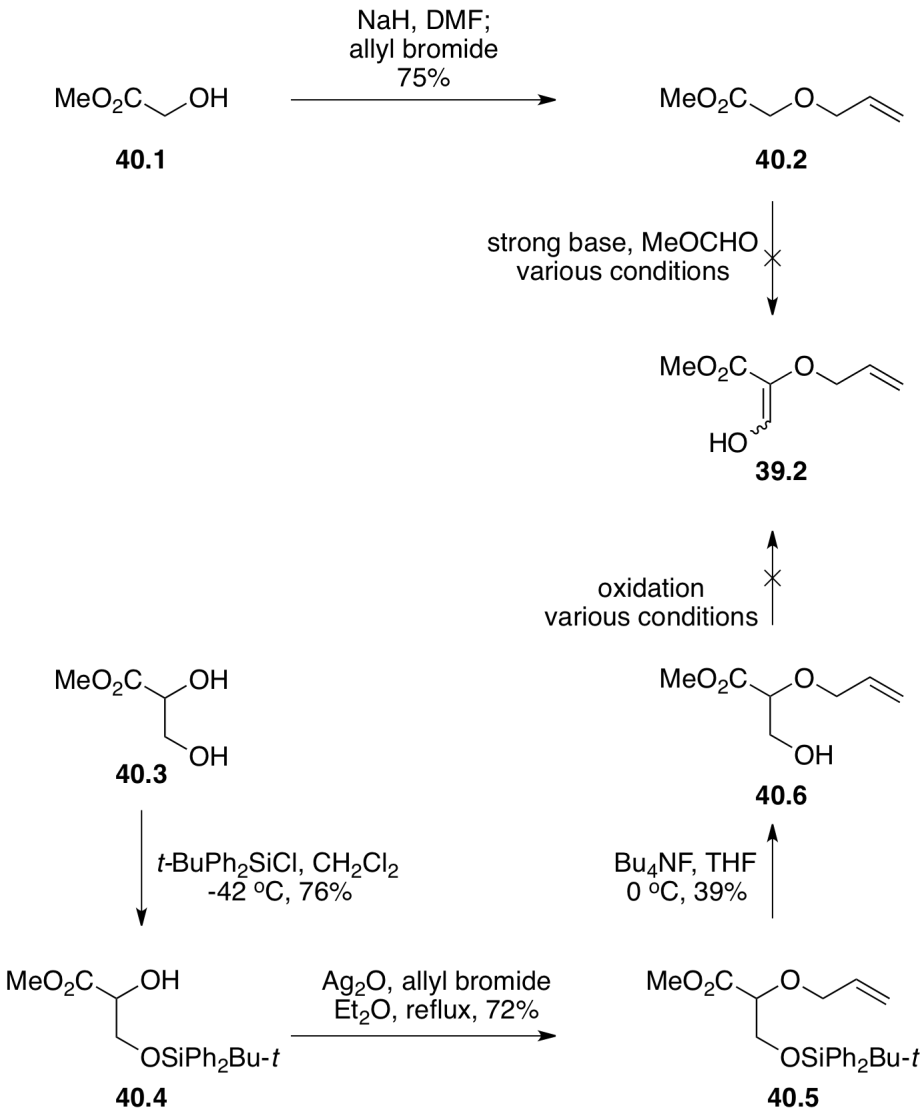
The third approach to marinopyrrole B that we tried involved the following disconnection: Like the previous cases, the common intermediate **27.2** was again the initial target. We hoped it could be reached via an addition-

elimination between **28.4** and **39.1**, followed by [3,3]-sigmatropic rearrangement and double bond cleavage. The vinyl chloride **39.1** would be elaborated from alcohol **39.2** by replacing the hydroxyl at the β-position by chlorine.



Scheme 39

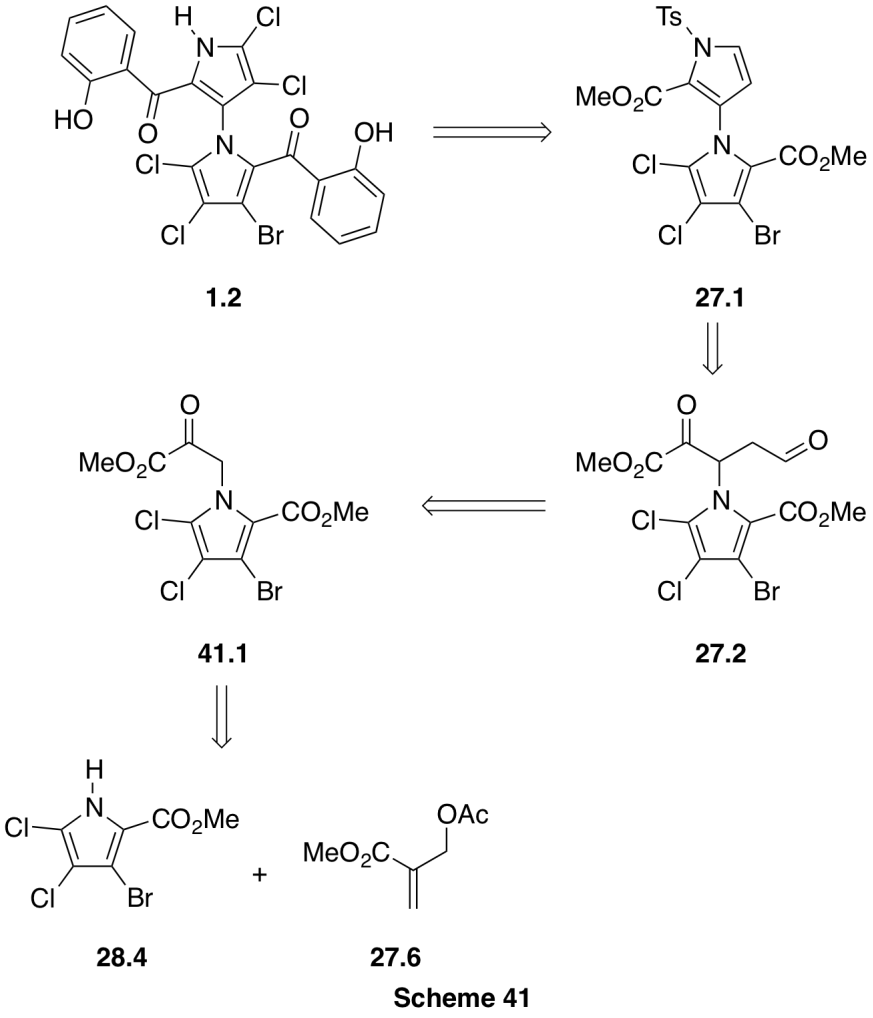
Starting from methyl 2-hydroxyacetate (**40.1**), the hydroxyl was protected by allylation.[42] The resulting allyl ether **40.2** was then treated with strong base and methyl formate. Unfortunately, even though I screened various reaction conditions, none of them provided the desired product **39.2**.



Scheme 40

An alternative route was also tested. In the hope of introducing the double bond via oxidation of a terminal alcohol, diol **40.3** was used as the starting point for the synthesis. The less sterically hindered primary hydroxyl of **40.3** was first protected by silylation.[43] The resulting secondary alcohol **40.4** was protected by allylation, and then desilylation of **40.5** gave **40.6**, but in poor yield. Various

oxidation conditions for conversion of **40.6** into **39.2** were tried, but none of the desired product was produced. Clearly, a different disconnection was required.

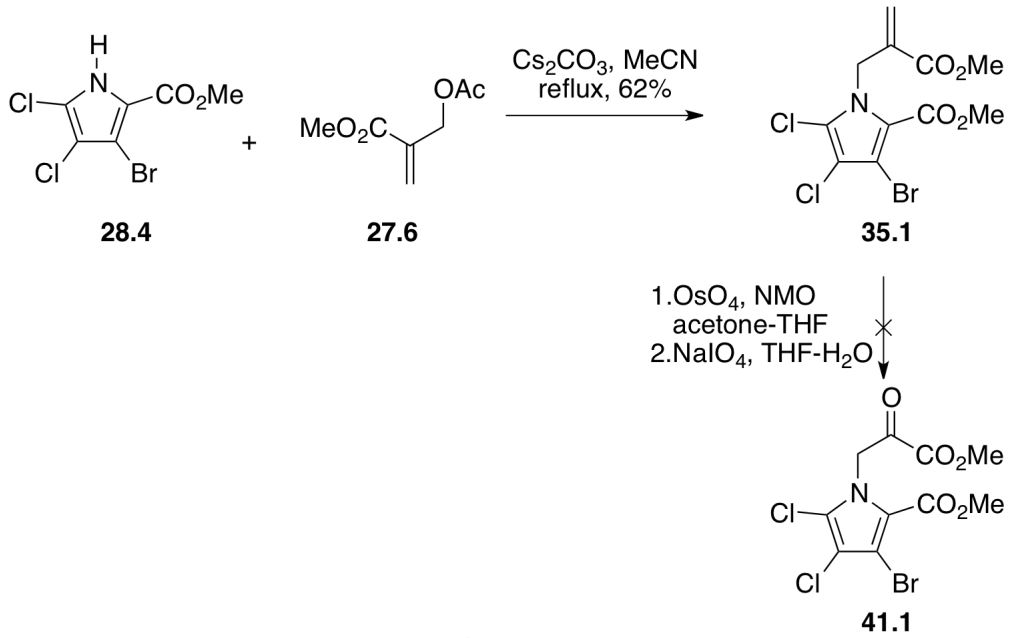


Scheme 41

Our observations thus far suggested that the nucleophilic reactivity of pyrrole **28.4** is low and that this pyrrole unit should be introduced at an early stage. We felt it would be more economical to try yet another route, and the new plan (Scheme 41) involved the intermediate **27.1**. Allylation of **41.1** and cleavage of the double bond of the product should provide **27.2**. An intermolecular conjugate displacement between **28.4** and **27.6** should serve to alkylate the nitrogen atom of

the pyrrole. Subsequent oxidative cleavage of the carbon-carbon double bond will then afford the desired α-keto ester.

As mentioned before, the reaction between **28.4** and **27.6**[44] was successful, and in refluxing MeCN, the desired product was produced in 62% yield. Using a two-step sequence, first with OsO_4, NMO and then $NaIO_4$, oxidative cleavage of the double bond of **35.1** failed to furnish compound **41.1**.

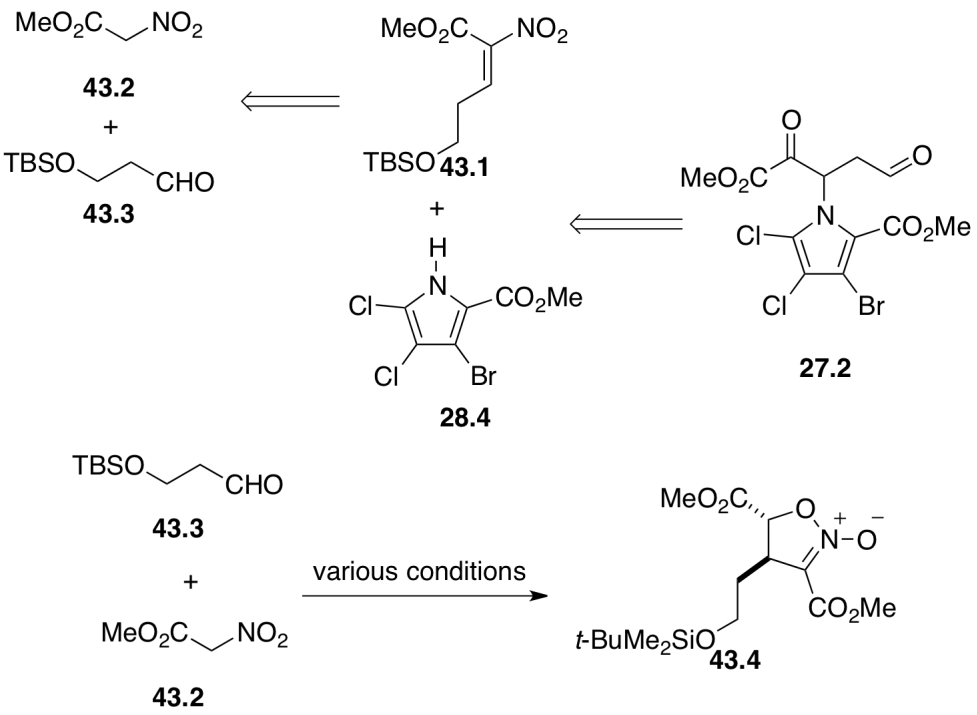


28.4 **27.6** **35.1** **41.1**

Scheme 42

At the same time, one additional route was explored for the synthesis: we considered that the common intermediate **27.2** might be obtained via a Michael addition between **43.1** and **28.4**, followed by several functionality manipulations. The Michael acceptor **43.1** should be available by the condensation between **43.2** [45] and **43.3**. However, many reaction conditions were tested for the condensation of **43.2** and **43.3**, but none of them gave any of the desired product.[46]

Interestingly, a cyclized product **43.4** was obtained, which was identified by single crystal X-ray analysis.

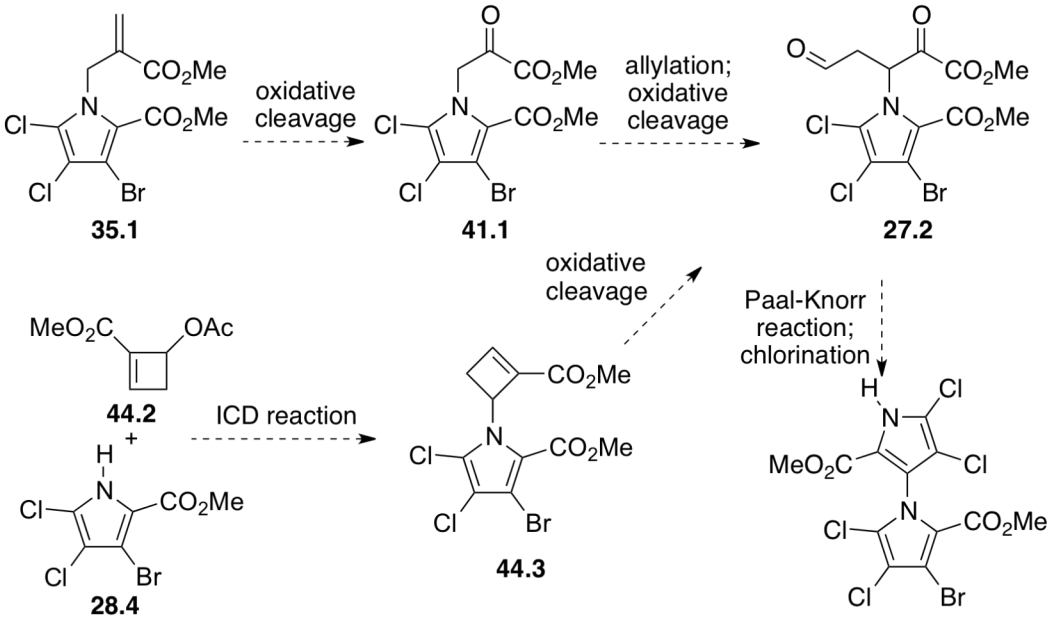


Scheme 43

3. CONCLUSION

The marine natural products marinopyrrole A and B provide significant biological activity against methicillin-resistant *S. aureus* (MRSA) and a human colon cancer cell line (HCT-166). These properties made them potential candidates as antibiotic or anticancer agents. Their potency and unique structural features require a practical synthetic route.

In our approach, the top pyrrole ring was to be constructed by a Paal-Knorr reaction. Direct conjugate displacement on the α,β-unsaturated ester (**32.2** and **33.4**) by **28.4** was unsuccessful but did work when there was no substitution on the β-position as in **27.6** (see Scheme 35). The apparently low nucleophilic reactivity of the multiply-substituted pyrrole **28.4** could be the main reason for the lack of addition.



Scheme 44

Future research on this project will involve applying the route via allylation of **41.1** (see Scheme 44). Cleavage of the resulting allyl ether should set the stage for a Paal-Knorr reaction to provide the desired bispyrrole core.

Alternatively, a better ICD acceptor, like **44.2** should facilitate the attack of the pyrrole subunit. 3,3-Sigmatropic rearrangement of **44.2** would be degenerate. Elimination of the acetate to form a cyclobutadiene would be unlikely because such a compound is antiaromatic. Reduced steric hindrance in the case of **44.2** compared with open-chain analogs should also facilitate the ICD attack. These studies will be continued by current group members.

4. Experimental Section

Methyl 3-methyl-2-methylidene-3-[(triethylsilyl)oxy]butanoate (30.1).

29.5 **30.1**

$Et_3SiOSO_2CF_3$ (0.36 mL, 1.67 mmol) was added to a stirred and cooled (–78 °C) solution of **29.5** (198 mg, 1.39 mmol) and 2,6-lutidine (0.29 mL, 2.50 mmol) in CH_2Cl_2 (3 mL). Stirring at –78 °C was continued for additional 3.5 h and the mixture was quenched with water (10 mL), and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (2.5 x 15 cm), using 8:1 hexane-EtOAc, gave **30.1** (354 mg, 99%) as oil: FTIR ($CDCl_3$, microscope) 2955, 2913, 2878, 1723, 1621, 1314, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.62 (q, J = 8 Hz, 6 H), 0.95 (t, J = 8 Hz, 9 H), 1.51 (s, 6 H), 3.73 (s, 3 H), 5.95 (d, J = 2 Hz, 1 H), 6.02 (d, J = 2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.8 (t), 7.1 (q), 29.9 (q), 51.5 (q), 74.6 (s), 122.7 (t), 148.5 (s), 167.4 (s); exact mass m/z calcd for $C_{13}H_{26}NaO_3Si$ (M+Na) 281.1543, found 281.1544.

Methyl 3-methyl-2-oxo-3-[(triethylsilyl)oxy]butanoate (30.2).

30.1 **30.2**

A solution **30.1** (334 mg, 1.31 mmol) in MeOH (6 mL) was added to a three necked round-bottomed flask which was equipped with a drying tube, a septum and an inlet for O_3. The solution was cooled to –78 °C and O_3 was bubbled into the solution. Stirring was continued for an additional 30 min (by which time all starting material had reacted, TLC control) at –78 °C and Me_2S (0.92 mL, 12.6 mmol) was then added. The cold bath was left in place bur not recharged and stirring was continued overnight. Evaporation of the solvent and flash chromatography of the residue over the silica gel (2.5 x 15 cm), using 10:1 hexane-EtOAc, gave **30.2** (354 mg, 99%) as oil: FTIR ($CDCl_3$, microscope) 2957, 2915, 1749, 1734, 1459, 1293, 1199 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.60 (q, J = 8 Hz, 6 H), 0.94 (t, J = 8 Hz, 9 H), 1.48 (s, 6 H), 3.83 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.5 (t), 6.8 (q), 27.2 (q), 51.9 (q), 78.5 (s), 167.4 (s), 200.9 (s); exact mass m/z calcd for $C_{12}H_{24}NaO_4Si$ (M+Na) 283.1336, found 283.1331.

Methyl (2*Z*)-3-hydroxy-2-(iodomethylidene)-3-methylbutanoate (31.3).

29.4 **31.3**

AlI_3 (2.24 g, 5.5 mmol) was diluted with CH_2Cl_2 (50 mL) and the solution was cooled to –78 °C. Stirring was continued for 5 min and methyl propiolate **29.4** (0.51 mL, 6 mmol) and acetone (0.37 mL, 5 mmol) were added. Stirring at –78 °C was continued for 5 h. The mixture was quenched with water (10 mL), and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (15 cm x 3 cm), using 8:1 hexane-EtOAc, gave **31.1** (1.074g, 79%) as oil: FTIR ($CDCl_3$, microscope) 3443, 3076, 2979, 2951, 1729, 1605, 1434, 1298 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 6 H), 2.36 (s, 1 H), 3.86, (s, 3 H), 6.88 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.1 (q), 52.1 (q), 74.3 (s), 79.3 (d), 153.4 (s), 168.5 (s); exact mass *m*/*z* calcd for $C_{11}H_{11}INaO_3$ (M+Na) 292.9645, found 292.9644.

Methyl (2*Z*)-2(iodomethylidene)-3-methyl-3-[(triethylsilyl)oxy]-butanoate (31.1).

31.3 **31.1**

$Et_3SiOSO_2CF_3$ (0.15 mL, 0.68 mmol) was added to a stirred and cooled (–78 °C) solution of **31.3** (152 mg, 0.56 mmol) and 2,6-lutidine (0.12 mL, 1.01 mmol) in CH_2Cl_2 (3 mL). Stirring at –78 °C was continued for 3.5 h and the mixture was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (1.5 x 15 cm), using 8:1 hexane-EtOAc, gave **31.1** (200 mg, 93%) as oil: FTIR ($CDCl_3$, microscope) 3082, 2954, 2912, 2877, 1735, 1606, 1458, 1294, 1174 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.60 (q, *J* = 8 Hz, 6 H), 0.94 (t, *J* = 8 Hz, 9 H), 1.44 (s, 6 H), 3.81 (s, 3 H), 6.64 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.6 (t), 7.0 (q), 30.2 (q), 52.0 (q), 76.5 (d), 155.7 (s), 168.7 (s); exact mass *m*/*z* calcd for $C_{13}H_{25}INaO_3Si$ (M+Na) 407.0510, found 407.0511.

Methyl (2*Z*)-3-(acetoxy)-2-(iodomethylidene)-3-methylbutanoate (31.5).

31.3 **31.5**

$Sc(OSO_2CF_3)_3$ (1 mg, 0.002 mmol) was added to a stirred mixture of **31.3** (39 mg, 0.144 mmol) and Ac_2O (20 μL, 0.202 mmol) in MeCN (1 mL). Stirring was continued for 5 h and the mixture was quenched with saturated aqueous $NaHCO_3$, and extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (0.5 x 15 cm), using 4:1 hexane-EtOAc, gave **31.5** (23 mg, 54%) as an oil: FTIR ($CDCl_3$, microscope) 2957, 2915, 1749, 1734, 1459, 1293, 1199 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.64 (s, 6 H), 1.99 (s, 3 H), 3.84 (s, 3 H), 6.72 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9 (q), 26.5 (q), 52.2 (q), 79.1 (d), 81.5 (s), 150.6 (s), 167.6 (s), 169.4 (s); exact mass *m*/*z* calcd for $C_9H_{13}INaO_4$ (M+Na) 283.1336, found 283.1331.

Methyl (2*Z*)-2-[2-[(triethylsilyl)oxy]propan-2yl]hexa-2,5-dienoate (31.4).

31.1 **31.4**

$Pd(OAc)_2$ (54 mg, 0.24 mmol), dppp (198 mg, 0.48 mmol) and Cs_2CO_3 (1.57 g, 4.80 mmol) were added to a stirred solution of **31.1** (921 mg, 2.40 mmol) and allylboronic acid pinacol ester (1.61 g, 9.60 mmol) in THF (50 mL). The mixture was refluxed for 24 h, cooled and quenched with water (25 mL). The mixture was extracted with Et_2O (3 x 25 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.5 x 15 cm), using 8:1 hexane-EtOAc, gave **31.4** (617 mg, 86%) as oil: FTIR ($CDCl_3$, microscope) 3081, 2954, 2913, 2877, 1729, 1653, 1638, 1458, 1209, 1186 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.59 (q, *J* = 8 Hz, 6 H), 0.94 (t, *J* = 8 Hz, 9 H), 1.45 (s, 6 H), 2.80-2.84 (m, 2 H), 3.74 (s, 3 H), 4.00-5.06 (m, 2 H), 5.79 (ddt, *J* = 6.5, 10, 16.5 Hz, 1 H), 5.82 (t, *J* = 10 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.7 (t), 7.0 (q), 30.6 (q), 33.6 (t), 51.2 (q), 74.2 (s), 115.6 (t), 127.4 (d), 135.9 (d), 143.6 (s), 169.4 (s); exact mass *m*/*z* calcd for $C_{16}H_{30}NaO_3Si$ (M+Na) 321.1856, found 321.1856.

Methyl (2*Z*)-2-(2-hydroxypropan-2-yl)hexa-2,5-dienoate (32.1).

31.4 **32.1**

Me_3SiCl (1 drop, 50 μL syringe) was added to a stirred and cooled (0 °C) solution of **31.4** (20 mg, 0.07 mmol) in MeOH (3 mL). Stirring was continued for 10 min and the mixture was evaporated. Flash chromatography of the residue over silica gel (0.5 x 15 cm), using 4:1 hexane-EtOAc, gave **32.1** (11 mg, 89%) as an oil: FTIR ($CDCl_3$, microscope) 3447, 3081, 2926, 2854, 1726, 1638, 1458, 1210 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.42 (s, 6 H), 2.94-2.98 (m, 3 H), 3.80 (s, 3 H), 5.02-5.08 (m, 2 H), 5.80 (ddt, J = 6.5, 10, 17 Hz, 1 H), 6.01 (t, J = 7.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.3 (q), 33.9 (t), 51.6 (q), 71.7 (s), 116.0 (t), 131.9 (d), 135.4 (d), 140.3 (s), 169.4 (s); exact mass *m*/*z* calcd for $C_{10}H_{16}NaO_3$ (M+Na) 207.0992, found 207.0994.

Methyl (2*Z*)-2-[2-[(methoxycarbonyl)oxy]propan-2-yl]hexa-2,5-dienoate (32.2).

32.1 **32.2**

n-BuLi (2.5 M in hexane, 0.46 μL, 0.114 mmol) was added to a stirred and cooled (–78 °C) solution of **32.1** (21 mg, 0.114 mmol) in THF (1 mL). Stirring was continued for 15 min and MeOCOCl (11 μL, 0.137 mmol) was added. The cooling bath was left in place but not recharged and stirring was continued for 2 h. The mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 8:1 hexane-EtOAc, gave **33.2** (9 mg, 33%) as an oil: FTIR ($CDCl_3$, microscope) 3081, 2987, 2955, 2851, 1754, 1730, 1440, 1386, 1372, 1275, 1214 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.66 (s, 6 H), 2.87-2.91 (m, 2 H), 3.71 (s, 3 H), 3.72 (s, 3 H), 3.77 (s, 3 H), 5.02-5.09 (m, 2 H), 5.79 (ddt, *J* = 6, 10, 16.5 Hz, 1 H), 5.88 (t, *J* = 7.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) 26.9 (q), 33.6 (t), 51.7 (q), 54.2 (q), 81.9 (s), 116.3 (s), 130.9 (d), 135.1 (d), 138.1 (s), 153.6 (s), 167.9 (s); exact mass *m*/*z* calcd for $C_{12}H_{18}NaO_5$ (M+Na) 265.1046, found 265.1045.

Methyl (2*Z*)-6-hydroxy-2-[2-[(triethylsilyl)oxy]propan-2-yl]hex-2-enoate (33.1).

31.4 **33.1**

9-BBN (0.5 M, 5.74 mL, 2.87 mmol) was added to a stirred solution of **31.4** (214 mg, 0.72 mmol) in THF (15 mL) and stirring was continued for 5 h. The mixture was cooled to 0 °C, a solution of $NaBO_3 \cdot H_2O$ (431 mg, 4.31 mmol) in water (30 mL) was added, and stirring was continued overnight. The mixture was diluted with water (25 mL) and extracted with Et_2O (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (2 x 15 cm), using 4:1 hexane-EtOAc, gave **33.1** (148 mg, 65%) as an oil: FTIR ($CDCl_3$, microscope) 3438, 2953, 2914, 2877, 1728, 1459, 1434, 1214, 1167 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.61 (q, *J* = 8 Hz, 6 H), 0.96 (t, *J* = 8 Hz, 9 H), 1.46 (s, 6 H), 1.66-1.71 (m, 2 H), 2.19 (dt, *J* = 7.5, 7.5 Hz, 2 H), 2.28 (br s, 1 H), 3.64 (t, *J* = 6.0 Hz, 2 H), 3.78 (s, 3 H), 5.78 (t, *J* = 7.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.7 (t), 7.0 (q), 25.7 (t), 30.7 (q), 31.6 (t), 51.5 (q), 61.3 (t), 74.2 (s), 129.4 (d), 144.1 (s), 170.2 (s); exact mass *m/z* calcd for $C_{16}H_{32}NaO_4Si$ (M+Na) 339.1962, found 339.1956.

Methyl (2*Z*)-6-[(*tert*-butyldiphenylsilyl)oxy]-2-[2-[(triethylsilyl)oxy]-propan-2-yl]hex-2-enoate (33.2).

33.1 **33.2**

DMAP (84 mg, 0.69 mmol) and *t*-$BuPh_2SiCl$ (0.12 mL, 0.48 mmol) were added to a stirred solution of **33.1** (145 mg, 0.46 mmol) in DMF (3 mL). Stirring was continued overnight and the mixture was quenched with water (10 mL) and extracted with Et_2O (3 x 15 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 8:1 hexane-EtOAc, gave **33.2** (216 mg, 85%) as an oil: FTIR ($CDCl_3$, microscope) 3438, 2953, 2914, 2877, 1728, 1459, 1434, 1214, 1167 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.61 (q, *J* = 8 Hz, 6 H), 0.96 (t, *J* = 8 Hz, 9 H), 1.07 (s, 9 H), 1.45 (s, 6 H), 1.65-1.70 (m, 2 H), 2.19 (dt, *J* = 7.5, 7.5 Hz, 2 H), 2.28 (br s, 1 H), 3.67 (t, *J* = 6.5 Hz, 2 H), 3.72 (s, 3 H), 5.80 (t, *J* = 7.5 Hz, 1 H), 7.38-7.46 (m, 6 H), 7.68-7.70 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.7 (t), 7.1 (q), 19.2 (t), 26.1 (t), 26.9 (q), 30.6 (q), 32.3 (t), 51.2 (q), 61.4 (t), 74.2 (s), 127.6 (d), 129.5 (d), 129.6 (d), 134.0 (s), 135.6 (d), 143.0 (s), 169.6 (s); exact mass *m*/*z* calcd for $C_{32}H_{50}NaO_4Si_2$ (M+Na) 577.3140, found 577.3138.

Methyl (2*Z*)-6-[(*tert*-butyldiphenylsilyl)oxy]-2-(2-hydroxypropan-2-yl)hex-2-enoate (33.3).

33.2 **33.3**

Me_3SiCl (1 drop, 50 μL syringe) was added to a stirred and cooled (0 °C) solution of **33.2** (44 mg, 0.08 mmol) in MeOH (2 mL). Stirring was continued for an additional 5 min and the mixture was evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:4 hexane-EtOAc, gave **33.3** (33 mg, 95%) as an oil: FTIR ($CDCl_3$, microscope) 3455, 3071, 2953, 2858, 1725, 1590, 1472, 1256, 1210 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 9 H), 1.41 (s, 6 H), 1.68-1.73 (m, 2 H), 2.34 (dt, *J* = 7.5, 7.5 Hz, 2 H), 3.69 (t, *J* = 6.5 Hz, 2 H), 3.78 (s, 3 H), 6.00 (t, *J* = 7.5 Hz, 1 H), 7.39-7.47 (m, 6 H), 7.68-7.70 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3 (t), 26.4 (t), 26.9 (q), 29.3 (q), 32.2 (t), 51.5 (q), 63.3 (t), 71.7 (s), 127.6 (d), 129.6 (d), 133.9 (s), 134.5 (d), 135.6 (d), 139.8 (s), 169.7 (s); exact mass *m*/*z* calcd for $C_{26}H_{36}NaO_4Si$ (M+Na) 463.2275, found 463.2271.

Methyl (2*Z*)-6-[(*tert*-butyldiphenylsilyl)oxy]-2-[2-[(methoxycarbonyl)-oxy]propan-2-yl]hex-2-enoate (33.4).

33.3 **33.4**

n-BuLi (2.5 M in hexane, 0.11 mL, 0.268 mmol) was added to a stirred and cooled (–78 °C) solution of **33.3** (118 mg, 0.268 mmol) in THF (3 mL). Stirring was continued for 15 min and methyl chloroformate (25 μL, 0.322 mmol) was added. The cooling bath was left in place but not recharged and stirring was continued overnight. The mixture was quenched with saturated aqueous NH_4Cl (15 mL) and extracted with Et_2O (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 8:1 hexane-EtOAc, gave **33.4** (51 mg, 38%) as an oil: FTIR ($CDCl_3$, microscope) 3072, 2953, 2858, 1753, 1730, 1472, 1429, 1385, 1275, 1218 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 9 H), 1.63 (s, 6 H), 1.66-1.68 (m, 2 H), 2.25 (dt, *J* = 7.5, 7.5 Hz, 2 H), 3.66 (t, *J* = 6.5 Hz, 2 H), 3.70 (s, 3 H), 3.72 (s, 3 H), 5.85 (t, *J* = 7.5 Hz, 1 H), 7.36-7.43 (m, 6 H), 7.65-7.66 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3 (t), 26.3 (t), 26.9 (q), 29.3 (q), 32.1 (s), 51.6 (q), 54.1 (q), 63.3 (t), 81.9 (s), 127.6 (d), 129.6 (d), 133.2 (d), 133.9 (s), 135.6 (d),

153.5 (s), 168.2 (s); exact mass *m*/*z* calcd for $C_{28}H_{38}NaO_6Si$ (M+Na) 521.2330, found 521.2329.

Methyl 6-[(*tert*-butyldiphenylsilyl)oxy]-3-[(methoxycarbonyl)-oxy]-2-(propan-2-ylidene)hexanoate (34.3).

33.4 **34.3**

NaH (8.4 mg, 60% $^{w}/_{w}$, 0.212 mmol) was added to a stirred solution of pyrrole **28.4** (29 mg, 0.106 mmol) in dioxane (2 mL). Stirring was continued for additional 1 h and a solution of **33.4** (30 mg, 0.060 mmol) in dioxane (1 mL) was added. The mixture was refluxed for 24 h, cooled, quenched with water (15 mL), and extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 10:1 hexane-EtOAc, gave **34.3** (21 mg, 70%) as an oil: FTIR ($CDCl_3$, microscope) 3072, 3048, 2999, 2954, 2932, 2858, 1748, 1727, 1473, 1442, 1429, 1269 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.56-1.68 (m, 2 H), 1.87-1.93 (m, 7 H), 2.02-2.10 (m, 1 H), 3.66-3.75 (m, 2 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 5.55 (dd, *J* = 6.5 Hz, 8.5 Hz, 1 H), 7.38-7.45 (m, 6 H), 7.67-7.69 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2 (t), 20.7 (q), 23.3 (q), 26.9 (q), 28.7 (t), 30.0 (s), 51.6 (q), 54.7 (q), 63.3 (t), 75.6 (d),127.6 (d), 127.7 (s). 129.6 (d), 133.9 (s), 135.6 (d), 142.0 (s), 155.3 (s), 168.5 (s); exact mass *m*/*z* calcd for $C_{28}H_{38}NaO_6Si$(M+Na) 521.2330, found 521.2328.

Methyl 3-bromo-4,5-dichloro-1-(3-methoxy-2-methylidene-3-oxopropyl)-1*H*-pyrrole-2-carboxylate (35.1).

28.4 **35.1**

A solution of **27.6** (0.32 mg, 0.20 mmol) in MeCN (0.5 mL) was added to a stirred suspension of **28.4** (27 mg, 0.10 mmol) and K_2CO_3 (167 mg, 1 mmol) in MeCN (0.2 mL) and the mixture was refluxed overnight, cooled, diluted with water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (0.5 x 15 cm), using 10:1 hexane-EtOAc, gave **35.1** (23 mg, 62%) as a semisolid: FTIR ($CDCl_3$, microscope) 3001, 2956, 2854, 1714, 1439, 1272, 1147 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.82 (s, 3 H), 3.85 (s, 3 H), 4.92-4.93 (m, 1 H), 5.29-5.30 (m, 1 H), 6.23-6.24 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.5 (t), 51.7 (q), 52.2 (q), 105.3 (s), 113.4 (s), 119.7 (s), 121.7 (s), 124.6 (s), 135.7 (t), 159.3 (s), 165.2 (s); exact mass *m*/*z* calcd for $C_{11}H_{10}{}^{79}Br^{35}Cl_2NNaO_4$ (M+Na) 391.9067, found 391.9062.

Methyl 1-[(4-methylbenzene)sulfonyl]-4,5-dihydro-1*H*-pyrrole-2-carboxylate (36.2).

38.1 **36.2**

Et_3N (0.31 mL, 2.2 mmol) and NCS (147 mg, 1.1 mmol) were added to a stirred and cooled (0 °C) solution of **38.1** (167 mg, 1 mmol) in CH_2Cl_2 (2.5 mL). Stirring at 0 °C was continued for 3 h and pyridine (0.19 mL, 2.3 mmol) was added at a slow dropwise rate. Stirring at 0 °C was continued for 15 min, and TsCl (419 mg, 2.2 mmol) was added. The cold bath was left in place but not recharged and stirring was continued overnight. The mixture was wash with 1*N* HCl and saturated aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (2.5 x 15 cm), using 3:1 hexane-EtOAc, gave **36.2** (190 mg, 68%) as oil: FTIR ($CDCl_3$, microscope) 3095, 2954, 2924, 1742, 1438, 1355, 1316, 1165 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.03 (dt, *J* = 3, 8 Hz, 2 H), 2.35 (s, 3 H), 3.77 (s, 3 H), 3. 79 (t, *J* = 8.5 Hz, 2 H), 6.11-6.12 (m, 1 H), 7.24-7.26 (m, 2 H), 7.65-7.66 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5 (q), 28.9 (t), 52.2 (q), 50.8 (t), 52.3 (q), 127.9 (d), 128.5 (d), 129.6 (d), 133.7 (s), 137.4 (s), 144.2 (s), 162.2(s); exact mass *m*/*z* calcd for $C_{13}H_{15}NNaO_4S$ (M+Na) 304.0614, found 304.0614.

Methyl 3-[(*tert*-butyldiphenylsilyl)oxy]-2-(prop-2-en-1-yloxy)propanoate (40.6).

40.5 **40.6**

Bu_4NF (1.0 M in THF, 0.92 mL, 0.92 mmol) was added to a stirred and cooled (0 °C) solution of **40.5** (365 mg, 0.114 mmol) in THF (10 mL). Stirring was continued for 2 h. The mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 6:1 hexane-EtOAc, gave **40.6** (58 mg, 39%) as an oil: FTIR ($CDCl_3$, microscope) 3447, 3082, 2954, 2927, 2879, 1748, 1437, 1207, 1129, 1054 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.17 (br s, 1 H), 3.77 (s, 3 H), 3.81 (dd, *J* = 4, 11 Hz, 1 H), 3.89 (dd, *J* = 3.5, 11.5 Hz, 1 H), 4.01 (dd, *J* = 6, 12.5 Hz, 1 H), 4.05 (dd, *J* = 3.5, 6 Hz, 1 H), 4.27 (dd, *J* = 6. 12.5 Hz, 1 H), 5.23 (dd, *J* = 1.5, 10 Hz, 1 H), 5.30 (dd, *J* = 1.5, 17 Hz, 1 H), 5.92 (ddt, *J* = 6,10, 17 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) 52.1 (q), 63.4 (t), 71.9 (s), 78.4 (d), 118.4 (t), 133.7 (d), 171,1 (s); exact mass *m*/*z* calcd for $C_7H_{12}NaO_4$ (M+Na) 183.0627, found 183.0628.

Dimethyl *trans*-4-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4,5-dihydro-isoxazole-3,5-dicarboxylate 2-oxide (43.4).

43.2 **43.4**

A solution of **43.2** (0.31 mL, 2.2 mmol) in DMF (0.1 mL) was added dropwise to a stirred mixture of NH_4OAc (0.31 mL, 2.2 mmol) and **43.3** (167 mg, 1 mmol) in DMF (0.2 mL) and stirring was continued overnight. The mixture was washed with water and extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over the silica gel (0.5 x 15 cm), using 3:1 hexane-EtOAc, gave **43.4** (18 mg, 29%) as a semi solid: FTIR ($CDCl_3$, microscope) 2930, 2857, 1744, 1707, 1634, 1472, 1249, 1106 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.84 (s, 6 H), 0.91 (s, 9 H), 2.03-2.17 (m, 2 H), 3.83-3.88 (m, 9 H), 5.16 (d, J = 2.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.7 (q), -5.6 (q), 18.2 (s), 25.8 (q), 33.6 (t), 46.0 (d), 52.6 (q), 52.9 (q), 60.5 (t), 76.2 (d), 109.0 (s), 159.0 (s), 169.1 (s); exact mass m/z calcd for $C_{15}H_{27}NNaO_7Si$ (M+Na) 384.1449, found 384.1448.

5. References

1 Cheng, C.; Pan, L.; Chen, Y.; Song, H.; Qin, Y.; Li, R. *J. Comb. Chem.* **2010**, *12*, 541-547.

2 Abou-Gharbia, M. *J. Med. Chem.* **2009**, *52*, 2-9.

3 Ojima, I. *J. Med. Chem.* **2008**, *51*, 2587-2588.

4 Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461-477.

5 von Nussbaum, F.; Brands, M.; Hinzen, B.; Weigand, S.; Haebich, D. *Angew. Chem. Int. Ed.* **2006**, *45*, 5072-5129.

6 Hughes, C. C.; Prieto-Davo, A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2008**, *10*, 629-631.

7 Hughes, C. C.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *J. Org. Chem.* **2010**, *75*, 3240-3250.

8 (a) Chang, C.; Adams, R. *J. Am. Chem. Soc.* **1931**, *53*, 2353–2357. (b) Webb, J. L. A. *J. Org. Chem.* **1953**, *18*, 1423–1427. (c) Dey, S.; Pal, C.; Nandi, D.; Giri, V. S.; Zaidlewicz, M.; Krzeminski, M.; Smentek, L.; Hess, B. A.; Gawronski, J.; Kwit, M.; Babu, N. J.; Nangia, A.; Jaisankar, P. *Org. Lett.* **2008**, *10*, 1373–1376.

9 Wu, J.; Vetter, W.; Gribble, G. W.; Schneekloth, J. S., Jr.; Blank, D. H.; Gorls, H. *Angew. Chem. Int. Ed.* **2002**, *41*, 1740–1743.

10 (a) Kaneda, M.; Nakamura, S.; Ezaki, N.; Iitaka, Y. *J. Antibiot.* **1981**, *34*, 1366–1368. (b) Ezaki, N.; Koyama, M.; Shamura, T.; Tsuruoka, T.; Inouye, S. *J. Antibiot.* **1983**, *36*, 1263–1267. (c) Ezaki, N.; Koyama, M.;

Kodama, Y.; Shomura, T.; Tashiro, K.; Tsuruoka, T.; Inouye, S. *J. Antibiot.* **1983**, *36*, 1431–1438.

11 (a) Takeda, R. J. *J. Am. Chem. Soc.* **1958**, *80*, 4749-4750. (b) Takeda, R. J. *Bull. Agr. Chem. Soc. Jpn.* **1959**, *23*, 126-130. (c) Birch, A. J.; Hodge, P.; Rickards, R. W.; Takeda, R.; Watson, T. R. *J. Chem. Soc.* **1964**, 2641-2644. (d) Kaneda, M.; Nakamura, S.; Ezaki, N.; Iitaka, Y. *J. Antibiot.* **1981**, *34*, 1366-1368. (e) Ezaki, N.; Koyama, M.; Shamura, T.; Tsuruoka, T.; Inouye, S. *J. Antibiot.* **1983**, *36*, 1263-1267. (f) Ezaki, N.; Koyama, M.; Kodama, Y.; Shomura, T.; Tashiro, K.; Tsuruoka, T.; Inouye, S. *J. Antibiot.* **1983**, *36*, 1431-1438.

12 Hughes, C. C.; Yang, Y.-L.; Liu, W.-T.; Dorrestein, P. C.; La Clair, J. J.; Fenical, W. *J. Am. Chem. Soc.* **2009**, *131*, 12094-6.

13 For Ullman coupling reactions for the synthesis of aryl azoles: (a) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428-2439. (b) Antilla, J, C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578-5587. (c) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607-5622. (d) Cai, Q.; Zhu, W.; Zhang, H.; Zhang, Y.; Ma, D. *Synthesis* **2005**, 496-499. (e) Taillefer, M.; Xia, N.; Ouali, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 934-936. (f) Correa, A.; Bolm, C. *Angew. Chem. Int. Ed.* **2007**, *46*, 8862-8865. (g) Mino, T.; Harada, Y.; Shindo, H.; Sakamoto, M.; Fujita, T. *Synlett* **2008**, 614-620.

14 Kanakis, A. A.; Sarli, V. *Org. Lett.* **2010**, *12*, 4872-4874.

15 Yamada, K.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Synlett* 2002, 231-234.

16 Nicolaou, K. C.; Simmons, N. L.; Chen, J. S.; Nina, M. Haste, N. M.; Nizet, V. *Tetrahedron Lett.* **2011**, *52*, 2041-2043.

17 Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: London, 1977.

18 Majchrzak, M. W.; Simchen, G. *Tetrahedron* **1986**, *42*, 1299-1304.

19 Frick, V.; Simchen, G. *Synthesis* **1984**, 929-930.

20 Catalan, J.; Yanez, M. *J. Am. Chem. Soc.* **1984**, *106*, 421-422.

21 Loader, C. E.; Anderson, H. J. *Can. J. Chem.* **1981**, *59*, 2673-2686.

22 DeSales, J.; Greenhouse, R.; Muchowski, J. M. *J. Org. Chem.* **1982**, *47*, 3668-3672.

23 Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 6317-6328.

24 Morrison, M. D.; Hanthorn, J. J.; Pratt, D. A. *Org. Lett.* **2009**, *11*, 1051-1054.

25 Schillaci, D.; Petruso, S.; Cascioferro, S.; Raimondi, M. V.; Haagenson, J. A. J.; Molin, S. *Int. J. Antimicrob. Agents* **2008**, *31*, 380-384.

26 Smith, J. A.; Ng, S.; White, J. *Org. Biomol. Chem.* **2006**, *4*, 2477-2482.

27 Raimondi, M. V.; Schillaci, D.; Petruso, S. *J. Heterocycl. Chem.* **2007**, *44*, 1407-1416.

28 Kameswaran, V. EP 0 600 157 A1, 1993.

29 Bailey, D. M.; Johnson, R. E.; Albertson, N. F. *Org. Synth. Coll. Vol.* **1988**, *6*, 618-620.

30 Durham, D. G.; Hughes, C. G.; Rees, A. H. *Can. J. Chem.* **1972**, *50*, 3223-3238.

31 Okuro, K.; Gurnham, J.; Alper, H. *J. Org. Chem*. **2011**, *76*, 4715-4720.

32 Xu, L.; Kündig, E. P. *Helv. Chim. Acta* **1994**, *77*, 1480-1484.

33 Qi, J.; Porco, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 12682-12683.

34 Lee, S. I.; Hwang, G,; Ryu, D. H. *Synlett* **2007**, 59-62.

35 Espino, G.; Kurbangalieva, A.; Brown, J. M. *Chem. Common.* **2007**, 1742-1744.

36 (a) Clive, D. L. J.; Li, Z.; Yu, M. *J. Org. Chem*. **2007**, *72*, 5608-5617. (b) Wang, L.; Prabhudas, B.; Clive, D. L. J. *J. Am. Chem. Soc.* **2009**, *131*, 6003-6012. (c) Chen, Z.; Clive, D. L. J. *J. Org. Chem.* **2010**, *75*, 7014-7017.

37 Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930-5933.

38 Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3021-3024.

39 Zhang, X.; Xamena, F. X. L.; Corma, A. *J. Catal.* **2009**, *265*, 155-160.

40 Teichert, J. F.; Zhang, S.; van Zijl, A. W.; Slaa, J. W.; Minnaard, A. J.; Fernga, B. L. *Org. Lett.* **2010**, *12*, 4658-4660.

41 Huy, P.; Neudorfl, J.; Shmalz, H. *Org*. *Lett*. **2011**, *13*, 216-219.

42 Sato, Y.; Fujisawa, H.,; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1275-1287.

43 Goubert, M.; Toupet, L.; Sinibaldi, M.; Canet, I. *Tetrahedron* **2007**, *63*, 8255-8266.

44 Villieras, J.; Rambaud, M. *Org. Synth., Coll. Vol.* **1993**, *8*, 265-267.

45 Zen, S.; Koyama, M.; Koto, S. *Org. Synth.* **1976**, 55, 7779-7782.

46 (a) Dorey, G.; Poissonnet, G.; Potier, M. C.; De Carvalho, L. P.; Venault, P.; Chapouthier, G.; Rossier, J.; Potier, P.; Dodd, R. H. *J. Med. Chem.* **1989**, 32, 1799-1804. (b) Aubry, S.; Razafindrabe, C. R.; Bourdon, B.; Pellet-Rostaing, S.; Lemaire, M.; *Tetrahedron Lett.* **2007**, *48*, 9163-9166. (c) Soengas, R. G.; Estevez, J. C.; Estevez, R. J. *Tetrahedron* **2003**, *59*, 6285-628.