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Indium-Mediated Allylations in Aqueous Media: An Expansion of the Scope and a Demonstration of the Synthetic Utility of the Reaction.

Submitted to the Faculty of Graduate Studies and Research in
partial fulfillment of the requirements of the degree of

Doctor of Philosophy

By

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To the loving memory of Jane Mathilda Gumbs (Ma Jane).

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Abstract

The scope of the indium-mediated allylations in aqueous media has been successfully expanded and an improved understanding of the synthetic utility of the reaction has been developed. The range of useful functionalities that can be efficiently produced by the methodology has been increased and the concise construction of naturally occurring and/or biologically significant substrates has been undertaken.

We have demonstrated how N-acylimidazoles could be allylated under controlled temperature conditions, in aqueous media furnishing predominantly 4-alkyl-1,6-heptadien-4-ols. The intermediate α-alkyl-β,γ-unsaturated ketones were present in significant amounts only when the bulk of the acyl or α substituents were such that it interfered with a subsequent allylation. An investigation into the efficient production of the homo allylic ketone, independent of bulk was also performed. Success in this light was effected with the introduction of infrequently used, N-acylpyrazoles in a unique Wienreb-amide type role. These substrates also proved useful for the generation of β-keto esters in a direct manner via a indium-mediated Reformatsky-type reaction in THF.

A successful extension of the methodology into the realms of intramolecular carbocylizations proved to be high yielding and exclusive in terms of γ-regio and *cis*-diastereoselectivity. The high utility of the reaction was shown with the synthesis of oxygen heterocyles fused with α-methylene-γ-butyrolactones, substrates, which were revealed to be cytotoxic against several cancer cell lines. An easy incorporation of chiral auxiliaries to the cyclization reactions was also introduced, and a path to possibly produce these important compounds in an enantioselective manner, revealed.

Indium-mediated allylations in aqueous media also proved useful as a tool for the general construction of paraconic acids, which are naturally occurring, densely functionalized and biologically active 5-membered lactones. A facile route free of labor-intensive tasks was designed and utilized in the production of naturally occurring methylenolactocin and protolichesterinic acid. A further extension to include the synthesis of a related *bis*-fused lactone, canadensolide, encountered serious problems. Here it was discovered that the reaction of an enolizable allylic indium species with water occurred more quickly than the intended reaction of this species with an aldehyde in an intramolecular cyclization. This, coupled with other results observed throughout our research, revealed that though very useful, the indium-mediated allylation is negatively affected by the presence of γ-carboxylate groups. While the C-In bond appears to have a low propensity to react with the aqueous media and react quantitatively with appropriate electrophiles, the presence of a γ-carboxylate group offers the possibility of enol formation leading to the generation of an O-In species that is rapidly protonated. We were therefore able to successfully use the methodology in this circumstance, only for the production of a deoxy analog while canadensolide remained illusive.

Résumé

La compréhension des applications synthétiques de diverses réactions d'allylation assitées par l'indium a été grandement améliorée par une étude approfondie de divers paramètres réactionnels. Le nombre de groupements fonctionnels accessibles par ce type de réaction a été augmenté et la synthèse symplifiée de plusieurs produits naturels et de substances ayant une activité biologique a pu ainsi être entreprise.

Nous avons démontré que des N-acylimidazoles pouvaient être facilement allylés en milieu aqueux et à des températures controlables pour donner le 4-alkyl-1,6-heptadien-4-ols comme produit majoritaire. Les produits intermédiaires α-alkyl-β,γ-cétones insaturées étaient obtenues en abondance dans le milieu réactionnel seulement quand l'encombrement stérique favorisait une interférence avec l'allylation subséquente. Le succés de cette méthode nous a permis d'introduire ou d'utiliser le N-acylpyrazole comme amide de Wienreb. Ces substrats se sont révélés très utiles dans la synthèse abrégée de cétoesters par la réaction du type Reformatsky assistée par l'indium dans le THF.

La réaction se prête bien à la carbocyclisation qui, comme nous l'avons observé, produit un très haut rendement, une régiosélectivité γ et une diastéréosélectivité *cis* presque exclusives. L'importance de la reaction s'est réaffirmée dans la synthèse d'hétérocycles oxygénés fusionnés en α-méthylène-γ-butyrolactone qui ont démontré une activité cytotoxique significative sur des cellules de cancer. Grâce à l'introduction facile d'auxilliaires chiraux une nouvelle voie de synthèse de ces importants composés a été découverte.

L'allylation assitée par l'indium s'est révélée également utile dans la synthèse d'acides paraconiques des produits naturels à 5-membres, hautement funtionalisés et biologiquement actifs. De la même manière, de nouvelles méthodes simplifiées ont été mises au point pour effectuer la synthèse de méthylènolactocine et d'acide protolichestérinique. L'adaptation de la méthode à la synthèse d'une lactone bicyclique s'est révélée plus difficile. Il a été ainsi découvert que l'énolisation aqueuse de l'espèce indium allyle était plus rapide que la cyclisation impliquant une fonction aldéhyde. Cette cyclisation ainsi que d'autres résultats au cours de ces travaux ont démontré que malgré sa très grande utilité, la réaction assitée par l'indium est inefficace en présence de groupements γ-carboxylatés.

Bien que la liason C-In soit apparemment résistante à l'hydrolyse et se comporte comme un excellent nucléophile, la présence d'un groupement γ-carboxylate conduit à la formation d'un énol suivie de la génération d'une espèce O-In facilement protonée. Cette limite nous a permis de ne réussir que la synthèse de l'anologue déoxy du canadensolide.

List of abbreviations

Aq	aqueous
Ac	acetyl
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad spectral signal
Bu (Bu^n)	*n*-butyl
Bz	benzoyl
CI	chemical ionization
CSA	camphor sulphonic acid
δ	chemical shift
d	doublet
dabco	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCB	2,6-dichlorobenzyl
DHP	dihydropyran
DIBAL-H	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethylformamide
DMS	dimethyl sulfide (also called methyl sulfide)
DMSO	dimethylsulfoxide
EI	electron impact

Eqn	equation
Et	ethyl
EWG	electron withdrawing group
eV	electron volt
hr	hour
Hz	hertz
IR	infrared spectroscopy
KDO	3-Deoxy-D-manno-octulosonic acid
KDN	3-deoxy-D-glycero-D-galacto-nonulosonic acid
LAH	lithium aluminium hydride
LDA	lithium disopropylamide
m	multiplet
Me	methyl
mp	melting point
MS	mass spectroscopy
NBS	N-bromosuccinimde
NMR	nuclear magnetic resonance spectroscopy
PCC	pyridinium chlorochromate
q	quartet
RT (rt)	room temperature
s	singlet
t	triplet
TBDMS	tert-butyldimethylsilyl

TEA	triethyl amine
TFA	triflouroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC (tlc)	thin layer chromatography
TMS	trimethylsilyl
UV	ultra violet spectroscopy

CHAPTER 1

The emergence of water as a solvent in conventional organic synthetic methodologies.

1.0 Introduction

As we progress towards the dawn of a new millenium we no doubt collectively recognize that, the manner in which essential tasks are performed, is as essential as the tasks themselves. A tremendous increase in an understanding of our world and the delicate balance under which it thrives, has led to a more thorough knowledge of how easily we impact on its well being. In this light, the manner in which chemistry is performed has undergone and continues to undergo necessary changes. No longer is the focus limited only to performing a specific transformation but rather it has expanded into performing the desired transformation in a cost-effective manner under as environmentally friendly conditions as is possible. We now are highly aware of carcinogens, mutagens, and /or toxic compounds. Biohazards are increasingly targeted for elimination and proper solvent disposal is a costly necessity. Consequently water has recently acquired much attention in methodological and synthetic studies. The scope of useful reactions performed in water is ever increasing and there exists a continuous search for the development of water-based, reaction mediators and/or reacting species. There is also a desire to illustrate the synthetic utility of the presently existing techniques, specifically as they apply to the synthesis of biologically significant compounds.

In 1980, Breslow initiated a flurry of studies on pericyclic reactions in aqueous media with a rate enhancing water based Diels-Alder reaction.[1] By the mid 1980's, it had not only become clear that water was a suitable system for the performance of organic reactions but it quickly became apparent that water was a missing ingredient from the reacting environment of many otherwise sluggish or failing transformations.[2] One impressive feat in advancing aqueous based organic chemistry, occurred during that decade in the field of Barbier-type reactions, approximately 85 years after Barbier had performed his work.[3] The *in situ* generation of organic species capable of coupling to carbonyl functionalities via metal mediation in water was performed successfully for the first time.[4]

Traditional Organometallic reagents such as alkyl-lithium and -magnesium reagents have been of utmost importance to numerous chemists as tools for C-C bond formation.[5] The complete exclusion of water from the reagents, solvents and flasks are often, time-consuming and tedious tasks which are well associated with these reactions. The discovery of Barbier-type reactions in aqueous media went contrary to the normal expectations and represented a significant development. Since then, a small but growing number of metals have been found for mediating such reactions. Tin, zinc and bismuth are three such metals which are often used but arguably the most intriguing metal was one previously not much explored, indium.[6] Indium proved easy to use, and very efficient for reactions which were very slow or did not work at all when the other metals were employed. It allowed for the facile generation of homoallylic alcohols in very good yields in short reaction times and proved very valuable in carbohydrate synthesis.[6,7] After much study, a good understanding of the high chemoselectivity,

regioselectivity, and diastereoselectivity of the indium-mediated reaction has been gathered.[8]

With some understanding of the indium-mediated allylation with aldehydes in aqueous media it is the goal of this dissertation to further develop the scope of chemistry surrounding the use of this methodology.

Prior to the discussion of the specific areas of research however, a literature survey will be provided. This chapter will focus on recent developments in aqueous chemistry with a significant proportion dedicated to organometallic-type reactions in aqueous media. In addition, within each subsequent chapter, a relevant brief literature survey will be provided on the target group of compounds being studied using the indium-mediated allylation.

1.1 Recent advances in using water as a solvent in organic chemistry

Owing to the inherent problems of insolubility and incompatibility of many organic reagents and intermediates in water, it had for the most part been previously ignored in chemistry as a useful solvent for synthetic purposes. Indeed, it is often considered as a hindrance to the progress of many reactions. Alkyl-lithium and -magnesium reagents, for example, are two frequently used synthetic tools for carbon-carbon bond formation. They are employed in large number of reactions, but can only be used effectively in completely anhydrous surroundings. Water however possesses many significant qualities which makes it a very attractive candidate as a solvent for synthesis. Easily the most abundant naturally occurring liquid on earth, it is readily available at a very low cost. In addition, water can be used freely in large amounts without the danger

of toxicity. It possesses a unique structure as a liquid, where its molecules are held together by strong directional hydrogen bonding (a maximum of 4/molecule in ice). It has a high heat capacity, the highest cohesive energy density, and therefore a very large surface tension. These properties give rise to the special effect known as the hydrophobic effect that for example is essential to the folding of nucleic acids and proteins and the binding of enzymes to substrates in biological systems. It is an entropy-governed aggregation of non-polar species in water. This is a process which not only aids in the reaction between two hydrophobic reactants but also in affecting stereochemical reaction outcome through the favoring of compressed transition states.[2,6c,9] In addition, if we were to consider that, central to our very existence, is the fact that on a continuous basis, multitudes of biochemical reactions are being performed *in vivo* in an aqueous environment, the potential of this widely abundant substance as a solvent would be revealed. Nature had made water its choice as a solvent but with few exceptions it was ignored or purposefully avoided by organic chemists. Though ignored its favorable qualities have meant that water could never be erased from the arsenal of potential solvents. Indeed the past two decades have seen a renaissance in efforts into investigating this potential.[6,7,8]

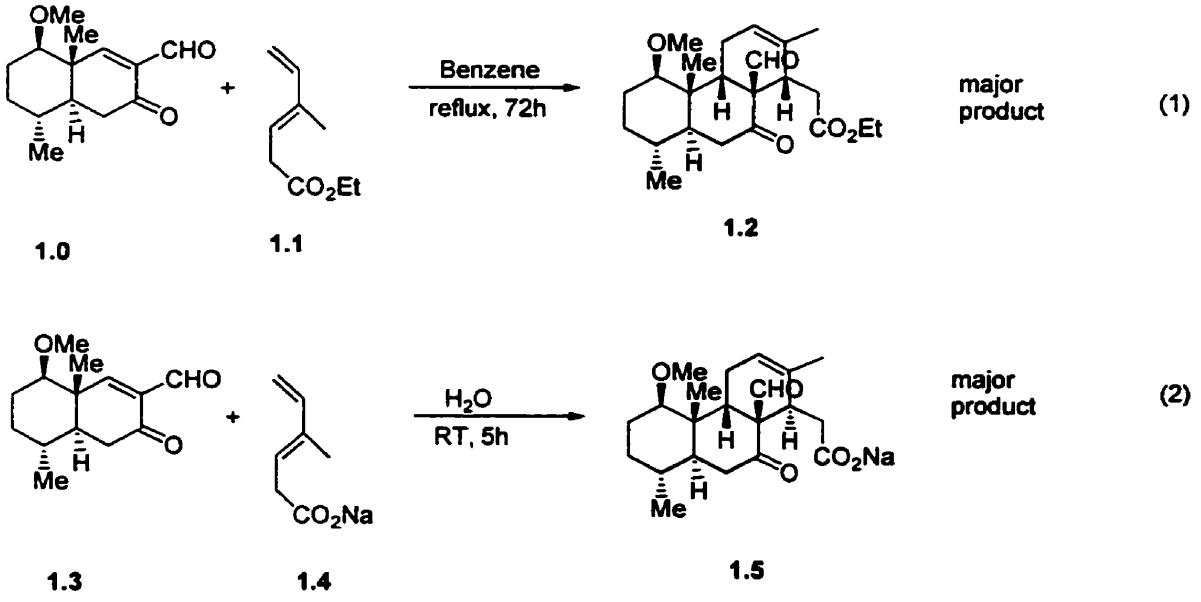
1.1.1 Water as a solvent in the Diels Alder reaction

The resurgence began in 1980 at Columbia University, when Breslow reported that a significant rate enhancement in the Diels-Alder reaction shown in Scheme 1.0, had occurred. The cycloaddition progressed 12-fold faster in methanol and 730-fold

faster in water than in isooctane,[1] a result that was primarily attributed to the *hydrophobic effect*.

Scheme 1.0

An even more striking effect was reported in 1995, when with 5-methoxy-1,4-naphthoquinone as the dienophile the reaction was found to be 12,780 times faster in water than hexanes.[10] Since the initial work of Breslow, the Diels-Alder reaction in water has found application in numerous biologically significant syntheses.[6] Particularly intriguing have been not only the rate enhancements but also the dramatic alteration in the stereochemical outcome that is often observed. For example, Grieco *et al.* has reported, that after extensive experimentation in organic media to react **1.0** and **1.1,** they obtained compound **1.2** possessing undesirable stereochemistry as the major



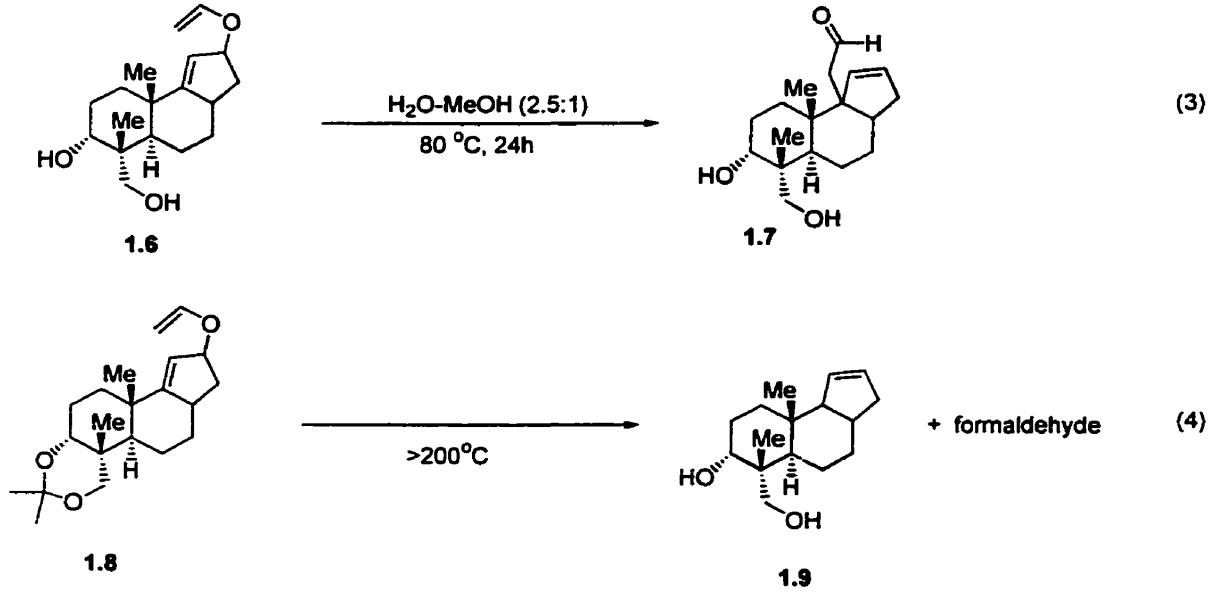
Scheme 1.1

product. It was only when aqueous conditions were employed for the reaction (Eq. 2) that the correct stereochemistry was obtained.[11] Indeed other similar effects of water on the stereochemical outcome from the reaction of varying dienes and dienophiles have been reported.[12] Very recently, Engberts *et al.* reported an extension to the benefits achieved by using water as the reaction medium.[13] They found that by employing the use of copper (II) complexes of chiral amino acids they could induce significant enantiomeric excesses in the Diels-Alder reaction in water compared to the same reaction in organic solvents. This represented a significant achievement as the first example of enantiomeric excesses in a Lewis-acid catalyzed reaction in water. The authors also pointed out, that the reaction is very significant for mechanistic studies because ion-pairing and clustering of the catalyst species, two factors which normally complicate such studies, would normally not be present in water.

1.1.2 Water as a solvent in the Claisen rearrangement.

An equally clear rate altering effect has been demonstrated in the Claisen rearrangement. Though the cause is still being debated, the results have also been used on numerous occasions for important synthetic constructions.[2,6] It had been well established throughout the 1980's that the rate of the Claisen rearrangement was improved with increased solvent polarity.[14] This, coupled with the results obtained in the aqueous Diels-Alder reaction, probably were the determining factors that led researchers to attempt the rearrangement in water.[15] Numerous examples of the rate enhancing abilities of water on the sigmatropic rearrangement now exists.[2,6,16] In many

cases the reaction proceeded at conditions much milder than organic solvents would permit. One prime example was the vinylether **1.6** which cyclized readily at 80 °C in aqueous media to the desired aldehyde **1.7**.[16] In the absence of the aqueous solvent, however, its diol protected counterpart **1.8**, required temperatures in excess of 200°C to effect the desired transformation. Such high temperatures however caused serious side reactions such as the degradation product **1.9**.[17] The inclusion of water as a solvent for the Claisen rearrangement has meant that products deemed inaccessible due to the harsh conditions necessary to effect the desired rearrangement are now possible.

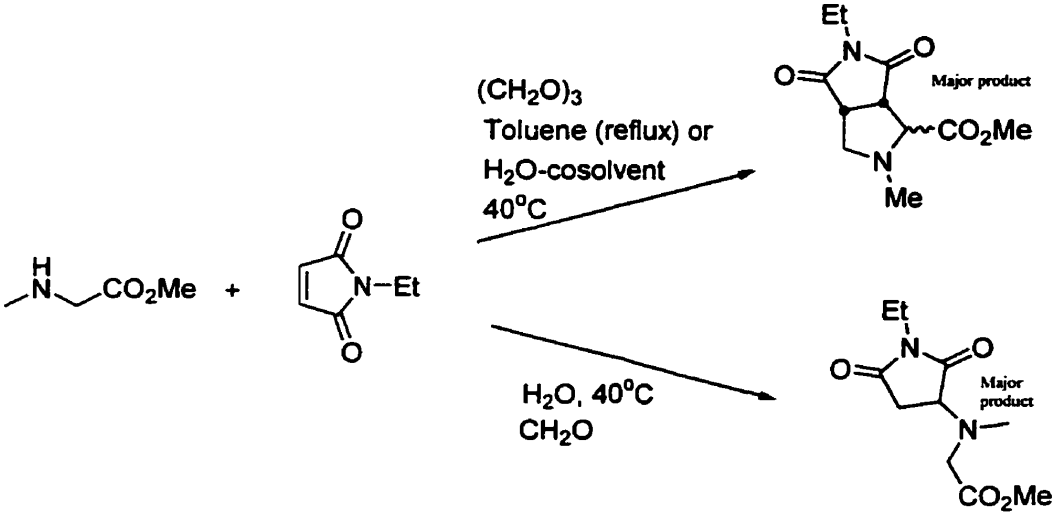


Scheme 1.2

1.1.3 Other pericyclic reactions in water:

Water as a solvent in the Diels-Alder reaction and Claisen rearrangement has furnished numerous benefits to chemists desirous of using these reactions for synthetic purposes. There have been other pericyclic reactions that have also been performed

successfully in aqueous media. The hetero Diels-Alder reaction, for example, has been used in an admirable fashion to synthesize biologically significant molecules such as 2-deoxy-KDO and KDO (3-deoxy-D-manno-2-octulosonic acid), a sugar found in the outer membrane lipopolysaccharide of all gram negative bacteria.[18] In addition the retro Diels-Alder reaction[9a,19] and 1,3-dipolar cycloadditions have undergone successful performances in aqueous media.[6a,c] In the latter case one interesting study was reported by Lubineau *et al*[20] with the reaction of azomethine ylides and N-ethylmaleimide. They found that pure water promoted the Michael addition product whereas the cycloaddition product could be produced in very good yields with the inclusion of cosolvents (Scheme 1.3).



Scheme 1.3

More recently, Engberts *et al.*[21] have further demonstrated the significant rate enhancement caused by having water as solvent in the 1,3 cycloaddition, when electron rich dipolarophiles were used.

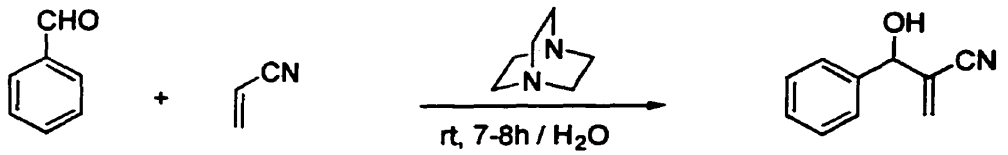
1.1.4 Water as a solvent in aldol condensations.

The aldol condensation, which involves the addition of the α-position of a carbonyl compound to the carbonyl center of another compound, can occur in either a self or cross coupling fashion. This reaction is often conducted in aqueous solution of either an acidic or basic nature. It, for example, has been used for the one pot synthesis of flavanols by employing the use to surfactants for dehydrating purposes.[22] A variation of the aldol reaction, the Mukaiyama reaction,[23] involves the coupling of a silyl enol ether with an aldehyde in the presence of a Lewis acid. In organic solvents this reaction occurs only under high pressure if a Lewis acid is absent. In 1986 Lubineau *et al.* however performed the reaction successfully in water without additives, though in relatively long periods of time.[24] Since their work, the reaction rate has been enhanced by the addition of lanthanide triflates (water stable Lewis acids) and surfactants.[25]

1.1.5 Michael additions in water

It had long been believed that Michael additions could not occur without the addition of a catalyst. Indeed, in organic solvents this remains the case, conversely however the reaction can occur spontaneously under totally neutral conditions when water is used as the solvent. Many examples exists of the utility of the reaction in water.[6] A related reaction, the 1,4-diazabicyclo[2.2.2]octane (dabco) catalyzed addition of an activated methylene to an aldehyde in what is known as the Baylis-Hillman reaction,[26] is a valuable reaction which has suffered from the one drawback of requiring

a relatively long completion time.[27] In 1994, it was shown that the reaction of acrylonitrile with benzaldehyde was greatly accelerated by using water as a solvent (Scheme 1.4).[28] The reaction that normally required several days was reduced to a matter of hours.



Scheme 1.4

1.1.6 Other nucleophilic reactions accelerated by water.

The performance of organic reactions in water has necessarily altered the way chemistry has developed in the past twenty years. In addition to aldol condensations and Michael additions there are several other examples of C-C bond forming nucleophilic additions in water. Benzoin condensations (200 times faster in water than ethanol)[29] and Wittig-Horner reactions [30] are two noteworthy examples.

1.2 Organometallic - type reactions in aqueous media

Organometallic-type reactions constitute an area of organic chemistry that has and continues to attract much interest as a useful tool for the generation of varied

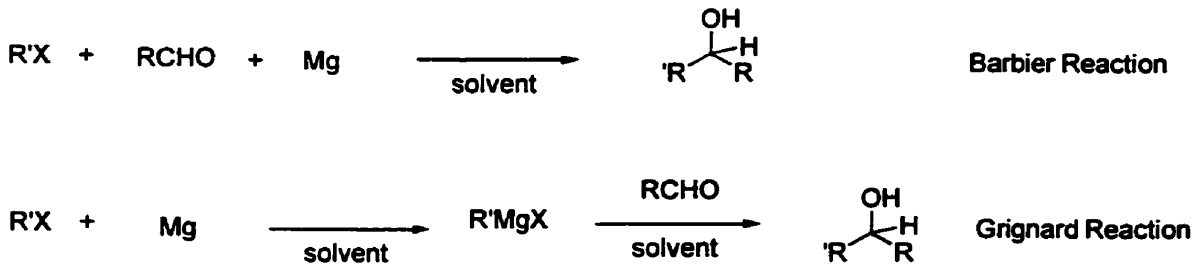
functionalities in a very selective manner. The field encompasses all reactions in which organometallic reagents are generated *in situ* from a direct reaction of the metal with organic substrates. The reactions can be considered single step processes, although some manipulation of the starting metal is sometimes required either in an activating or pacifying manner. This is in direct contrast to conventional organometallic reactions which involves the initial generation of the organometallic species in sometimes lengthy, sensitive processes prior to the addition of an electrophile.

Organometallic compounds have been utilized extensively for the foundation of organic synthesis: carbon-carbon bond formation. Of the large variety of these reactions that exist, Reformatsky type reactions and allylations, comprise a significant proportion. Often performed in organic solvents, such reactions usually necessitate great effort to ensure the complete exclusion of water from the reacting environment. Being of such importance it would be a significant disadvantage if such useful reactions could only be optimized in the absence of water.

1.2.1 The Barbier & Grignard Reaction: In the beginning...

The addition of organometallic species to carbonyl compounds was developed initially in a one-step sequence by Barbier [3] and subsequently in a more successful two-step sequence by Grignard (Scheme 1.5).[31] These reactions employed the use of magnesium which superceded the earlier use of zinc in the Wagner-Saytzeff reaction.[32] The Grignard reaction was advantageous primarily for two reasons. Firstly the reaction proved easier to start if the halide and magnesium were reacted previously, and

secondly by-product formation was reduced under the more controlled conditions. The Grignard reaction initially suffered great difficulties however, when the use of allylic

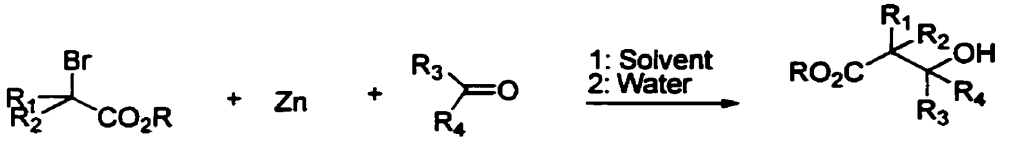


Scheme 1.5

halides was desired. It was here that the Barbier reaction proved most beneficial. Although the allylic magnesium species was later successfully prepared by careful experimental control, the Barbier reaction continued to develop in a comprehensive manner for the allylation of a variety of aldehydes and ketones.[33] These reactions are beneficial but have the disadvantage of often requiring great effort to avoid the presence of acidic hydrogens in reacting substrates as well as avoid any moisture from the reacting vessels, solvents and atmosphere. This limitation became the focus of a tremendous amount of research at about the same time that water emerged as a valuable solvent for the pericyclic reactions mentioned previously.[4] Through the substitution for magnesium of a variety of metals, chemists have developed an exploding field of allylations, where equivalent transformations not only occur in the presence of acidic funtionalities but thrive best in an aqueous environment. The metals used are varied, with the use predominantly of zinc, tin and more recently indium.[6, 7, 8]

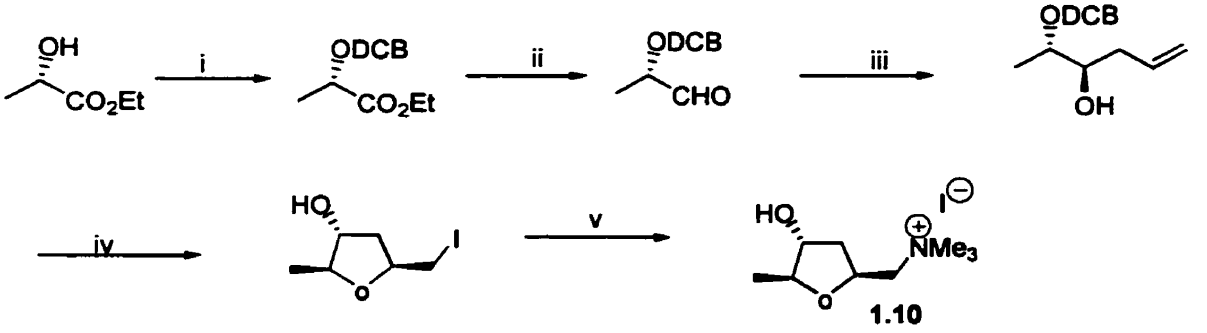
1.2.2 Zinc mediated organometallic type reactions in aqueous media

As the precursor to magnesium in the organometallic reaction as described above, zinc has had a long life in the hands of organic chemists. The Reformatsky reaction is one such example where it has found much use.



Scheme 1.6

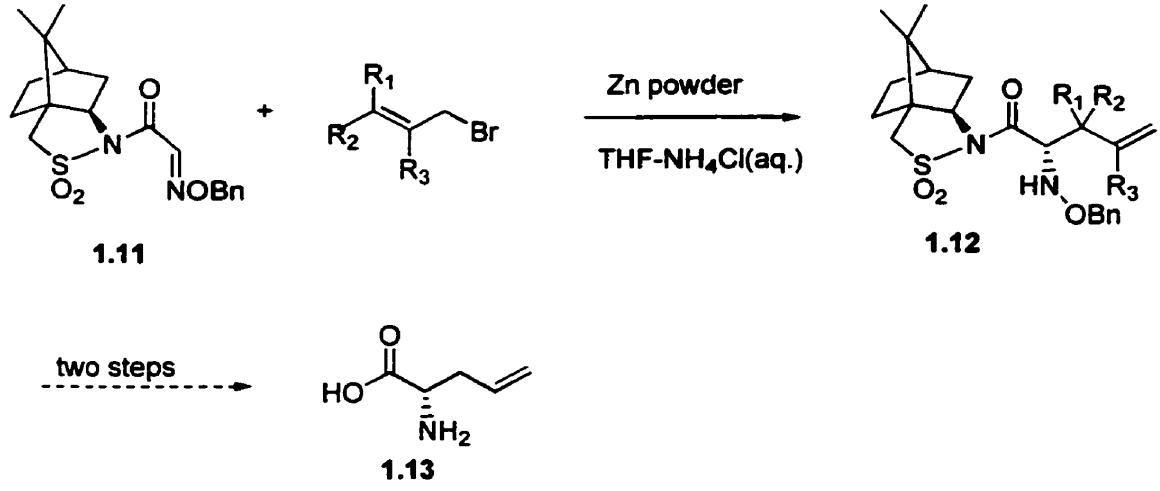
More recently the Reformatsky reaction mediated by zinc has been performed successfully in aqueous media, albeit in modest yields with the aid of catalytic amounts of benzoyl peroxide or peracids.[34] Zinc has gained much use in the allylation of carbonyl compounds. In its presence, allylic halides react efficiently with carbonyl compounds in water, usually with the aid of co-solvents such as THF or reverse-phase C-18 and/or additives such as ammonium chloride.[6] Its usefulness has been illustrated



(i) DCBBr/ Ag_2O/ET_2O/reflux/6h; (ii) DIBAL-H/Et_2O/-78°C/ 2h; (iii) Allylbromide/Zn/H_2O/NH_4Cl/3h (iv) I_2/CH_3CN/0°C/3h; (v) NMe_3/EtOH/80°C/4h.

Scheme 1.7

quite nicely with the synthesis of (+)-muscarine, **1.10** according to Scheme 1.7.[35] More recently, Hanessian *et al.* at the University of Montreal have reported an asymmetric synthesis of allylglycine **1.13** and other unnatural α-aminoacids using the zinc mediated Barbier type allylation of chiral oximes in aqueous solution.[36] When allylated, (1S)-(-)-2-10-camphorsultam-oximes **1.11,** produce product **1.12** with diastereomeric ratios as high as 99:1. Zinc has also been used to couple benzylic halides to aromatic aldehydes utilizing silver salts as catalyst at 30 °C.[37]

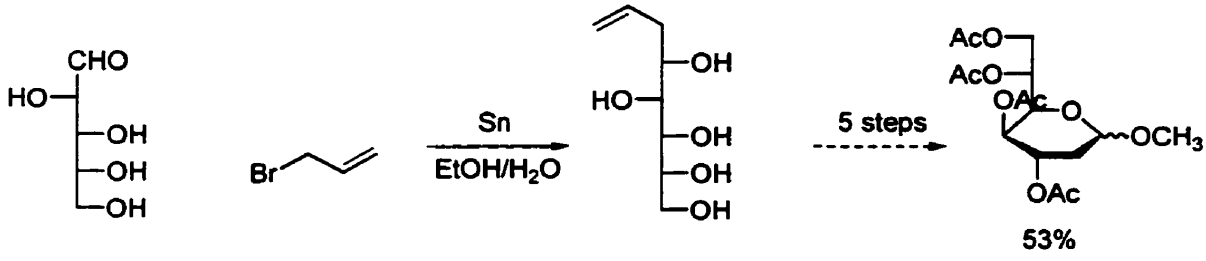


Scheme 1.8

1.2.3 Tin mediated organometallic type reactions in aqueous media

In aqueous media, allyltin reagents have enjoyed some success and with the aid of Lewis acids have been used in both a regioselective and stereoselective manner. The exploration of the effect of aqueous media on the tin mediated reaction also began in the early eighties when it was observed that a significant rate enhancement was

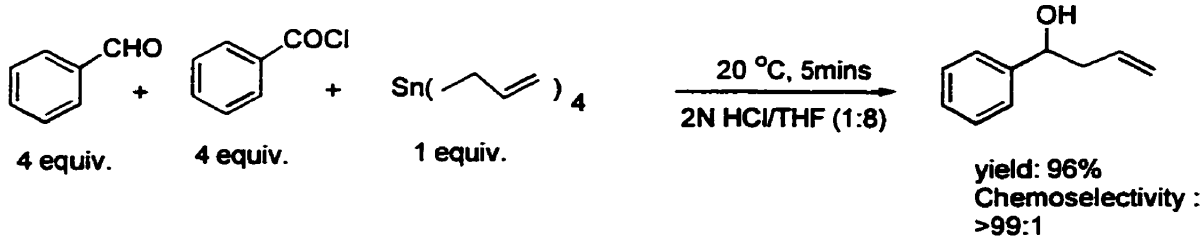
observed by the addition of water to the ether in which the reaction was being performed.[38] Since then tin has been used successfully in aqueous media usually with the aid of additives such as aluminium and/or HBr to allylate a wide variety of substrates. It was found however that the employment of sonication obviated the need of such additives and that under such conditions in a saturated NH_4Cl/THF medium the reaction proceeded efficiently.[39] Whitesides *et al.* demonstrated that a heated solution of allyl bromide, tin powder and aldoses (preferentially pentoses) reacted well in a series of organic-solvent/water systems (Scheme 1.9).[40] They found that the reaction showed limited diastereoselectivity-dependence on the solvent system used with the major isomer being that corresponding to the threo configuration.



Scheme 1.9

Such valuable transformations are primary reasons why the aqueous based reaction is of such importance. Functionalized allylic as well as allenylic and propargylic tin compounds have been successfully coupled to varying aldehydes though often with modest selectivity.[6, 40] In addition to performing the reaction in a Barbier-type manner, organotin reagents can be separately prepared usually from the allyl halide and the corresponding lithiated organotin and used in coupling reactions. Kobayashi *et al.* illustrated how such reactions can be enhanced with the use of water stable lanthanide

triflates.[41] In so doing a wide variety of ketones and aldehydes including 2-deoxy-D-glucose could be allylated in good yields. Yamamoto has further shown how tetraallyltin serves to allylate aldehydes at room temperature in aq. HCl/THF in a



Scheme 1.10

chemoselective manner in the presence of esters, ketones, and even acid chlorides (Scheme 1.10).[42] Earlier work performed by Li and Chan found that tin was also capable of mediating a low yield Reformatsky-type reaction between α-bromo esters and aromatic aldehydes in water.[43]

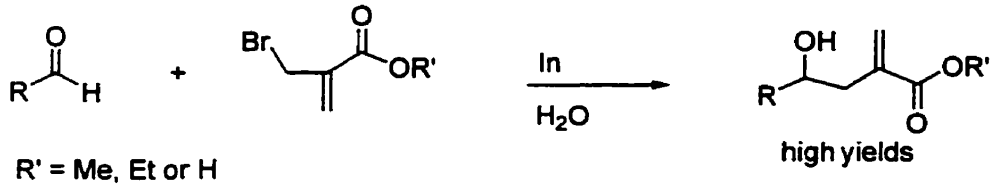
1.2.4 Indium mediated organometallic type reactions in aqueous media

Arguably the most attractive of the metals capable of mediating reactions in aqueous media, indium, has received a tremendous amount of attention in the last decade. Familiarizing oneself with this Group III metal is necessary to acquire an understanding of why it was a treasure waiting to be revealed. Named by F. Reich (1799-1882) & H. T. Richter (1824-1898), German metallurgists, indium is a rare metal of 0.1 ppm natural occurrence. It is a soft, ductile, silver-white solid, which melts at a relatively low temperature of 157 °C. At ordinary temperatures, indium is stable to air and oxygen. Though soluble in mineral acids, indium is unaffected by boiling water and

very resistant to alkaline conditions. Its first ionization potential of 5.79eV compares favorably with those of Group 1 elements (sodium 5.12eV and lithium 5.39eV) and is much lower than metals such as zinc (9.39eV), tin (7.43eV) and magnesium (7.65) each of which have well established lives in organometallic chemistry. Indium by comparison is therefore properly suited to effect metal mediated reactions in aqueous media. It allylates a variety of aldehydes and ketones in water at room temperature without the need for additives. It exhibits high degrees of chemo-, regio- and diastereoselectivity in reactions that are generally high yielding and occur in a short period of time.

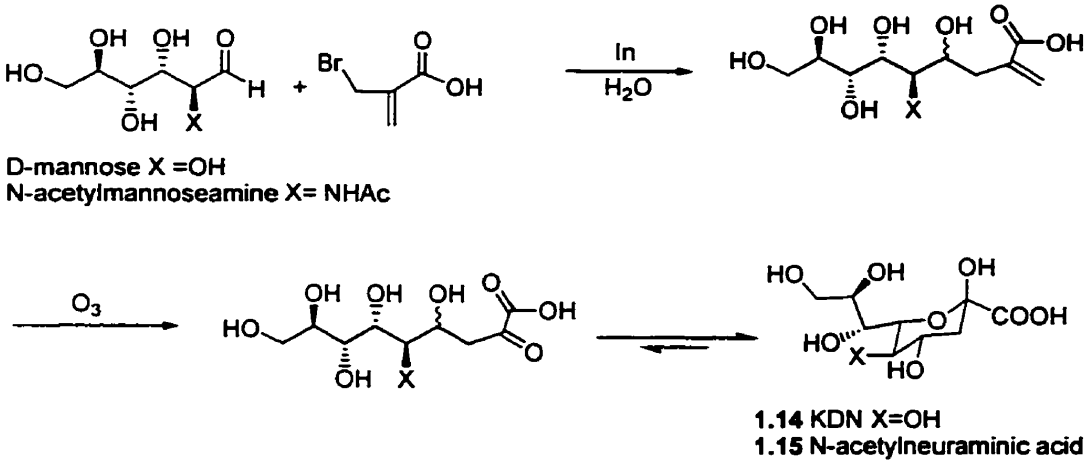
1.2.4a Chemoselectivity

Indium activates allylic chlorides, bromides and iodides in increasing reactivity with allylic bromides being the species most often used. Aldehydes thus far have shown the highest degree of reactivity under the allylating conditions with ketones reacting much more slowly.[43,44] Owing to the chemoselectivity of the reaction carboxylic acids and esters are not at all affected by the allylating conditions and their incorporation into allylic bromides have served as an efficient method of producing acrylic esters and acids (Scheme 1.11).[6,7,8,43,44]



Scheme 1.11

In such reactions the dangers of Wurtz-type coupling or pinacol coupling which sometimes complicate zinc and tin mediated reactions are not present. Since the reaction itself occurs in water, it therefore stands to reason that, hydroxyl groups, when present, do not require protection. This advantage has been combined with bromoacrylic acids in the synthesis of biologically significant carbohydrates such as 3-deoxy-D-glycero-D-galacto-nonulosonic acid (KDN) **1.14** and N-acetylneuraminic acid **1.15** in a relatively simple manner.[7b]

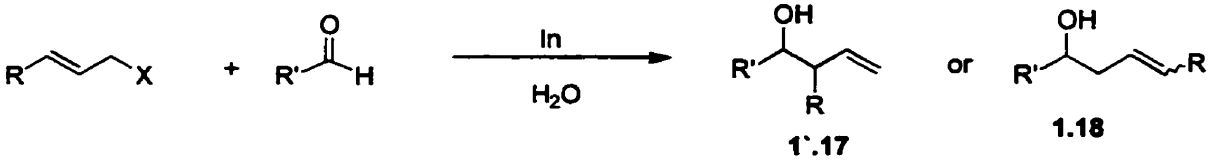


Scheme 1.12

Though tolerated by a variety of functional groups, the indium-mediated reaction is affected by the presence of "nitro" functionalities. Nitrobenzaldehyde, for example, reacted with allyl bromide and indium to produce an orange polymer rather than the desired homoallylic alcohol. This limitation of indium was overcome with the use of bismuth metal.[6a,44] In addition α-haloesters are known to be reduced to a large extent to dehalogenated esters when treated with indium in water.[43]

1.2.4b Regioselectivity

γ-Substituted allylic halides, theoretically possess the ability to couple with carbonyl compounds in either the α or γ positions. Extensive research by Chan and Isaac[8] as well as others[6a,b,7] have shown that the reaction occurs exclusively in the γ position (product **1.17**) with the only exceptions reported being species containing the bulky t-butyl and trialkylsilyl groups as the γ-substituents which give the α-coupled product **1.18**.

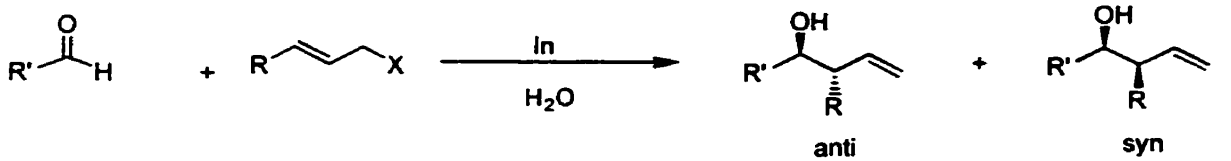


1`.17 **1.18**

Scheme 1.13

1.2.4c Diastereoselectivity

Exhaustive studies were performed in an effort to understand the diastereoselectivity associated with the indium-mediated reaction.[44] The insights gathered have led to a more thorough knowledge of the reaction and have enabled a better ability to predict its outcome. γ-Regioselective coupling as shown in Scheme 1.14, leads usually to an *anti* dominated mixture of isomers. The stereochemistry observed is independent of the geometry of the starting halide and relies highly on the substituents of the aldehyde and bromide in question.



R'	R	anti:syn
		96:4
	"	90:10
$n\text{-}C_8H_{17}\text{-}CHO$	"	69:31
	CO_2Me	84:16
"	CH_3	50:50

Scheme 1.14

Chan and Isaac proposed the following mechanistic outline (Figure 1.0) to account for the observed regioselectivity and the dominant *anti*-diastereoselectivity. The allylic halide reacts with indium to generate the allylic indium species **1.19**, which equilibrates with its configurational isomer **1.21** via its constitutional isomer **1.20.** These species are each capable of reacting with the aldehyde in a coordinated manner as illustrated (species **1.22-1.25**), If R_1 or R_2 are sterically significantly encumbered, **1.24** and **1.25** are favored leading to a mixture of *cis* and *trans* alkenes. Otherwise, species **1.22** and **1.23** are preferred and the discriminating factor then becomes the size of R_3 and unfavorable interactions created by its proximity to R_1 or R_2.

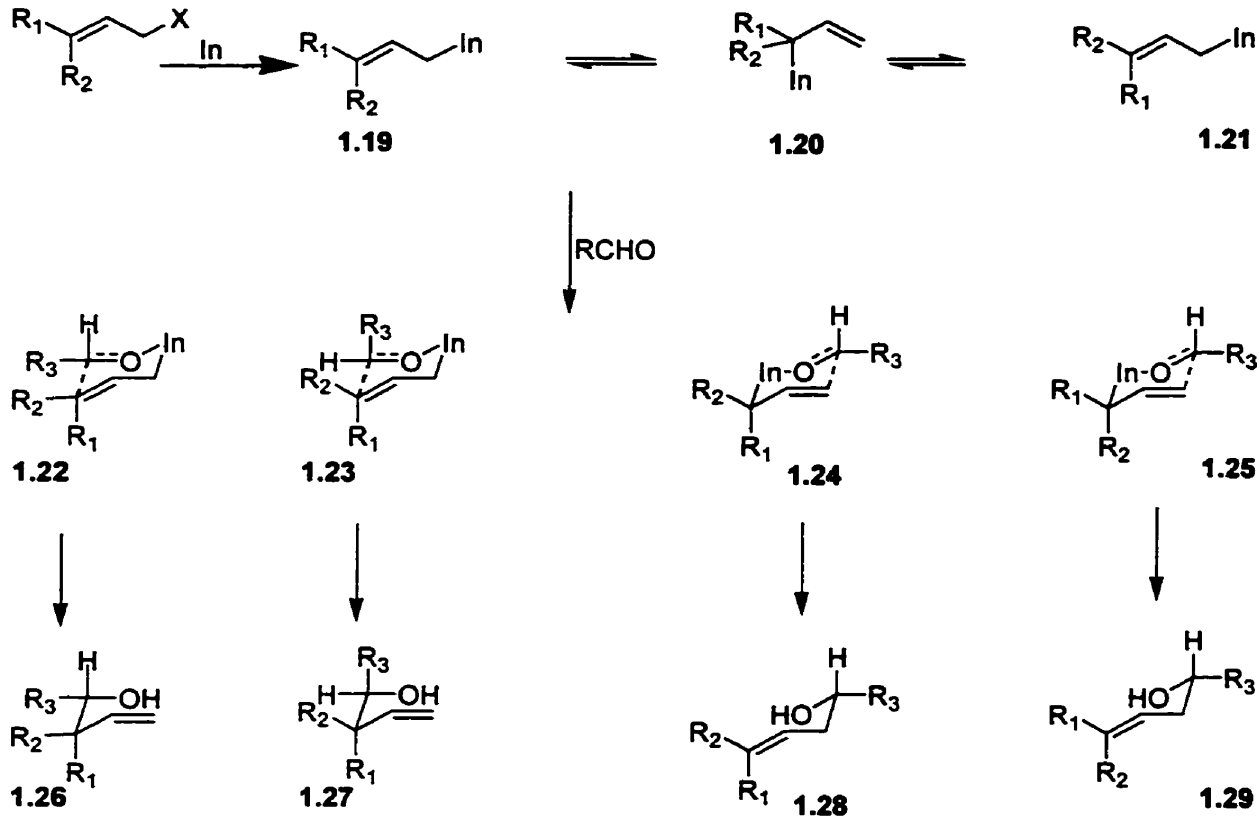


Figure 1.0[8]

The situation becomes more interesting when the aldehyde possesses a substituent in the α-position. Paquette *et al.* demonstrated that α-hydroxy aldehydes **1.30** are allylated with a strong preference for the *syn* diastereomer **1.31** in aqueous media.[45] He further showed that if the hydroxyl group is shifted to the β position **1.32** the *anti* diastereomer **1.33** dominates the product mixture. This can be explained according to the Cram-chelate model that if true infers that indium can chelate to the organic molecule in a manner strong enough such that disruptive solvation forces do not override it. Chan and Isaac further illustrated (Scheme 1.15) with the use of aldoses,

that with γ-substituted allylic halides, 3-contiguous stereocenters can be generated in a predictable manner giving *syn-syn*, *syn-anti* products dependant on the factors

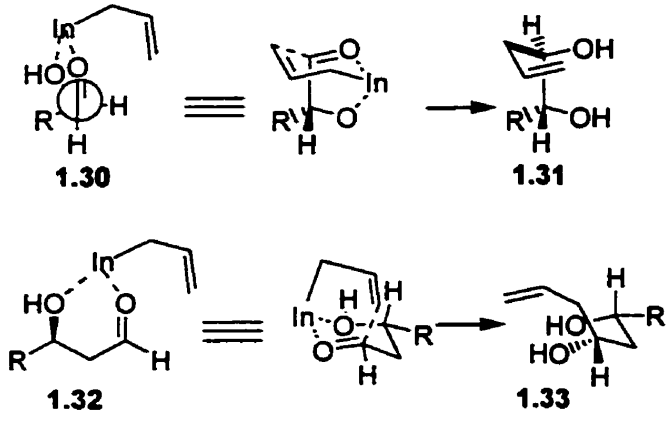
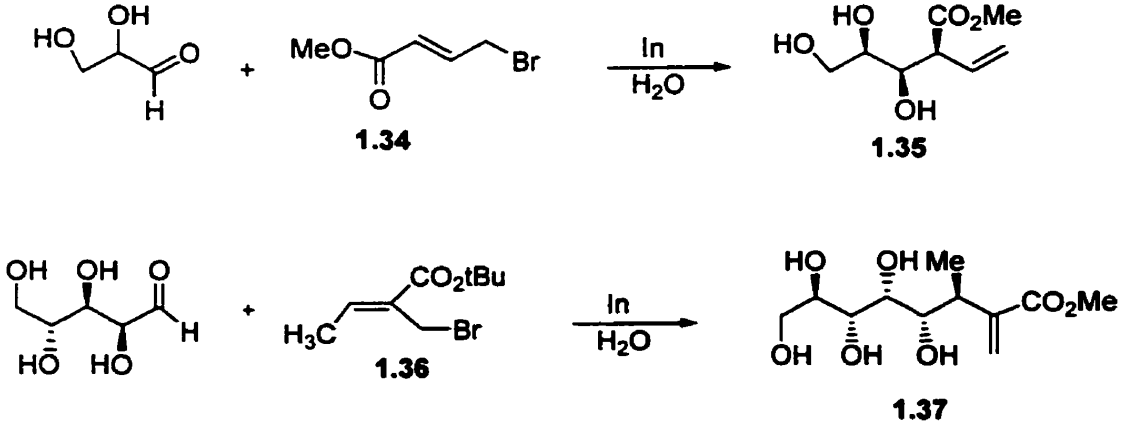


Figure 1.1[45]

shown in Figure 1.1 as well as the geometry of the allylic species.[44] They found that methyl bromocrotonate **1.26**, which is expected to prefer the transoid geometry after activation, reacts to generate the syn-syn diastereomer **1.27** as the major product. When however, a bromide that maintains the cisoid configuration as is the case when *t*-butyl 2-bromomethylbut-2-enoate **1.28** was used, the *syn-anti* diastereomer **1.29** then dominated. Very similar results were later published by Paquette and Isaac.[46]



Scheme 1.15

1.3 Research Outline

With some knowledge of the indium-mediated allylation, we embarked on our endeavors of expanding the scope of the reaction and in so doing further demonstrate its synthetic utility. The advantages associated with increasing the range encompassed by this reaction are numerous. The mild conditions coupled with low cost and low levels of toxicity makes the methodology very attractive. The exclusive regioselectivity, high diastereoselectivity, chemoselectivity and productivity are all characteristics that are desirable in any synthetic scheme. In this light, we sought to apply the methodology to the synthesis of fused carbocycles via intramolecular carbocyclizations. We were interested in an investigation of the feasibility of the reaction and the diastereoselectivity associated with any closure obtained. An expansion was then undertaken with the synthesis of functionalized oxygen-heterocycles, analogs of important cembranolides. These substrates were then subjected to cytotoxity assays with breast cancer, renal cancer, and two types of melanoma cell lines. Attempts at performing the intramolecular cyclizations in an enantiomerically selective manner were also made (**Chapter 3**). Following this study the methodology was applied to the construction of densely functionalized 5-membered systems including the synthesis of (±)-methylenolactocin, (±)-protolichesterinic acid, and attempted synthesis of (±)-canadensolide (**Chapter 4**). Prior to all this however, we focused our study on investigating the feasibility of using the methodology for the efficient production of homoallylic ketones. This required a search for the appropriate derivative that could be allylated in a controlled manner, a task with some difficulty

considering the level of chemoselectivity associated with the reaction. Upon finding such a derivative, a suppression of the propensity of such reactions to proceed further to give di-addition products represented the focal point of our research and consequently a unique role for acylpyrazoles was introduced (**Chapter 2**).

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CHAPTER 2

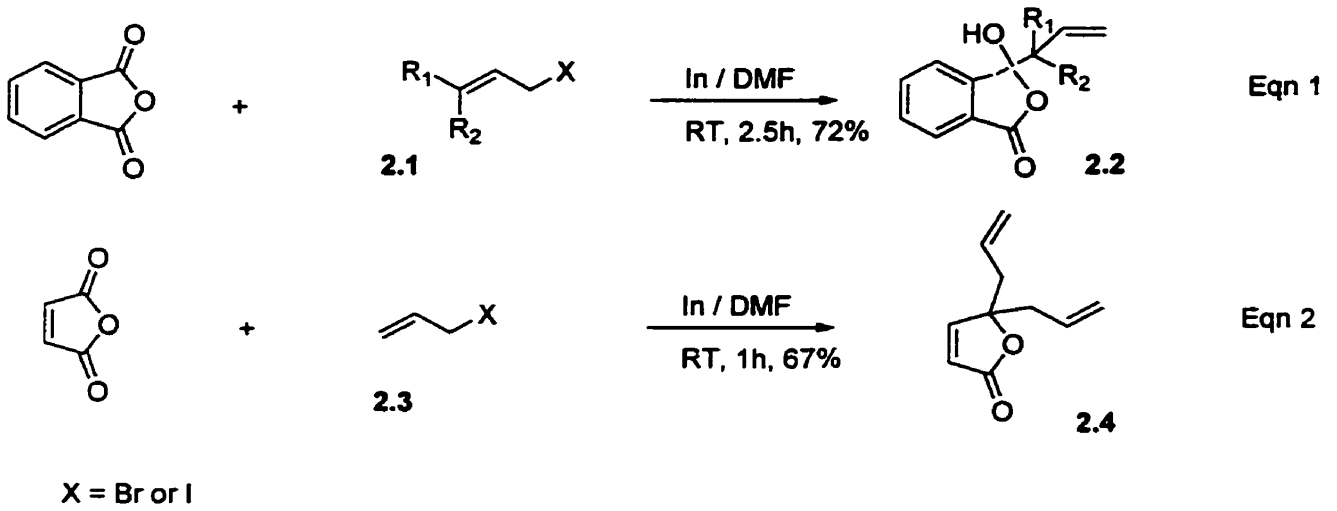
An expansion of the scope of the indium–mediated allylation reaction to include the controlled allylation of carboxylic acid derivatives in aqueous media: A unique role for acylpyrazoles in the construction of β,γ-unsaturated ketones and β-keto esters.

2.0 Introduction

Owing to the stability of an extensive variety of functional groups to the indium-mediated allylation conditions, very few variations on the theme of aldehydes/ketones and their nitrogen derivatives as substrates had been examined.[4] This being so, we were interested in further expanding the scope of this reaction to include the allylation of carboxylic acid derivatives in water. Particularly we sought to employ the mild methodology for the synthesis of homoallylic ketones in a direct manner.

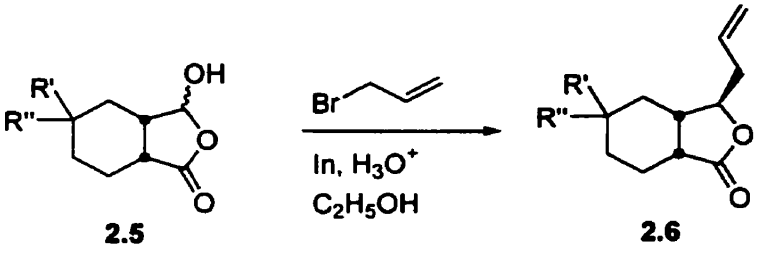
2.1 Carboxylic acid derivatives as substrates in Barbier-type allylations.

A limited number of carboxylic acid derivatives had previously been allylated successfully in Barbier-type reactions.[5] Cyclic anhydrides, for example, have been allylated to afford phthalides and butenolides in good yields (Scheme 2.1).[6] When reacted with simple allylic halides **2.3**, cyclic anhydrides furnished gem-diallylated



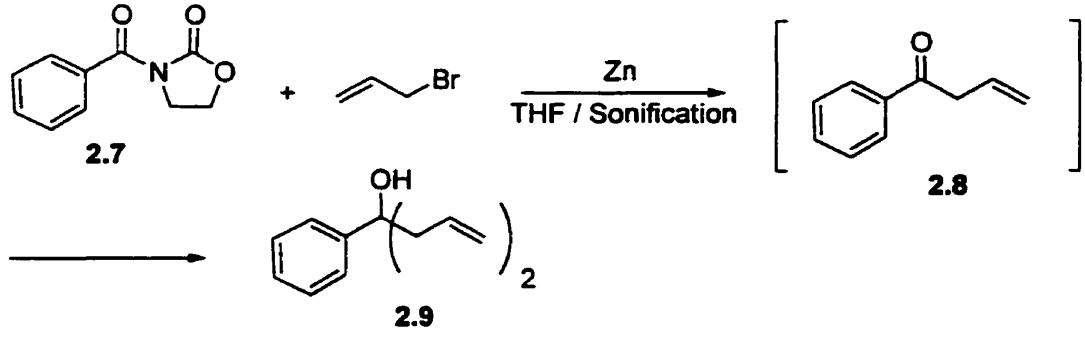
Scheme 2.1[5]

lactones **2.4** in reasonably good yields in less than three hours (Scheme 2.2, Eqn 2). γ-Substituted halides **2.1** due to their increased bulk, stopped at the mono-allylated derivative affording the γ-hydroxy-γ-lactones **2.2** (Scheme 2.1, Eqn 1). As substrates, acyclic anhydrides were much less productive giving very low yields of the desired allylated products. The reactions observed with cyclic imides were also much more complicated than those with cyclic anhydrides, yielding products in low amounts in an unpredictable manner.[7] Paquette *et al.*[8] has more recently shown that γ-hydroxy-γ-lactones **2.5** can be further allylated in acidic solution to give the corresponding γ-allyl-γ-lactones **2.6** in good yields (Scheme 2.2).



Scheme 2.2

Acyloyl-oxazolidinones have also been used as substrates under Barbier-type conditions employing zinc as the mediating agent in anhydrous THF.[8] When allylated, 3-benzoyl-oxazolidin-2-one **2.7** yielded 4-phenyl-1,6-heptadien-4-ol **2.9** (the diallylated product) in 91 % yield with full consumption of the intermediate ketone **2.8** (Scheme 2.3). Though the reaction was not useful for the production of the homoallylic ketone, the oxazolidinone derivatives were used in the successful construction of β-keto esters through the Reformatsky type coupling with α-halo esters.



2.7 **2.8** **2.9**

Scheme 2.3

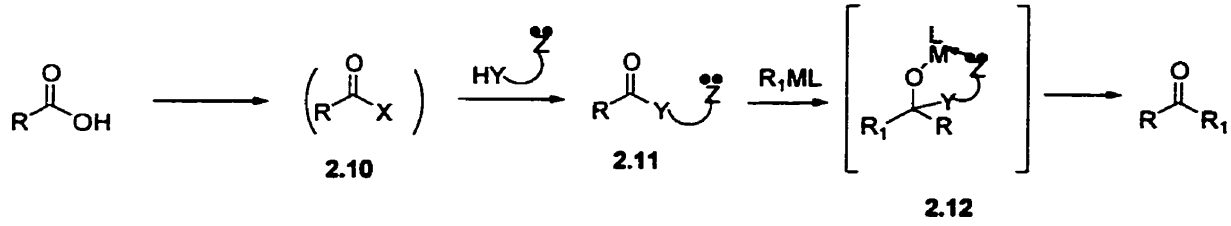
In an attempt to extend the scope of the indium-mediated allylation, we sought carboxylic acid derivatives that could be allylated in a controllable manner. Our endeavors were two-fold: the first being the introduction of substrates reactive enough to couple with the allylindium species, which are notoriously chemoselective. We were aware however that such reagents had to be stable enough to withstand the aqueous conditions if only for a brief period. Secondly, we wanted to control the outcome of the reaction such that the diallylated product as shown in Scheme 2.2, would be replaced by the homoallylic ketone as the major, if not the only reaction product.

2.1.1 Ketones via the addition of organometallic reagents to carboxylic acid derivatives: managing the problem of double versus single addition of organometallic reagents to carboxylic acid derivatives.

Ketones are abundant in nature, and are versatile functionalities capable of being easily transformed in a very useful manner in synthetic strategies. This and their utility in carbon-carbon bond formation, has necessarily meant that they have been the focus of much work and a large number of strategies for their convergent construction have been developed.[10] Exhaustive exploration of the generation of this fuctionality from organometallic reagents and carboxylic acids and their derivatives have been developed but methods possessing economical and physical efficiency, as well as ease of performance are continuously being sought.[10] The considerations for the most part must include the difficulty associated with the use of the mediating metal as well as the difficulty involved in the preparation of the needed acid derivatives. Organometallic species such as dialkylcopper and to a lesser extent cadmium reagents have been used with very reactive starting derivatives such as acid chlorides to give increased ketone yields.[10] Magnesium and lithium reagents are the most readily available reagents of the sort and though they generally produce the ketones upon addition to typical derivatives, the outcome is significantly complicated by a subsequent rapid reaction to yield the tertiary alcohol.[12,13]

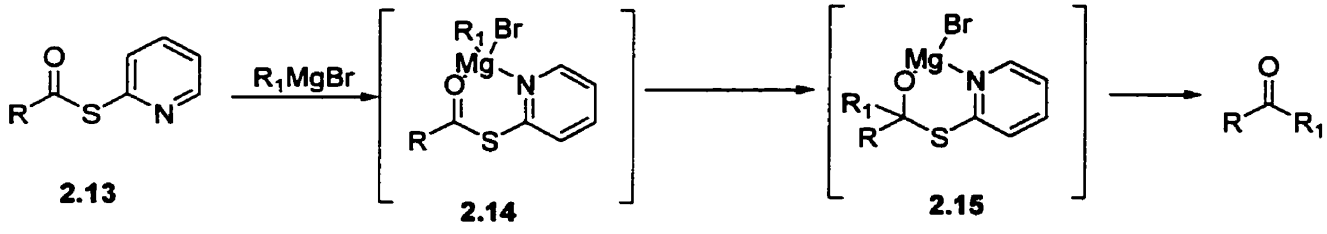
In a desire to reduce this problem, arguably the most significant development in this area occurred with the advent of hetero substituted esters (Scheme 2.4, **2.11**, Y = O,

S) and amides (Scheme 2.4, **2.11**, Y =NR) capable of chelating the initial tetrahedral intermediate **2.12** hence preventing premature release of the desired ketone.[10]



Scheme 2.4

N,O-Dialkylhydroxamates, introduced by Wienreb[14] are widely used for such purposes and are reliable at furnishing the desired ketones. A related S-(2-pyridyl) thiolate derivative **2.13** has also been shown by Mukaiyama *et al.*[15] to be effective in producing the ketone, though the reaction has tended to not be as general. Unlike N,O-dialkylhydroxamates, it was found that the ketone production was not a result of tetrahedral intermediate stabilization (Scheme 2.5, species **2.15**). Rather, it was a chemoselectivity arising from the superior activity of species **2.14** (Scheme 2.5) versus the product ketone toward the organometallic reagent.



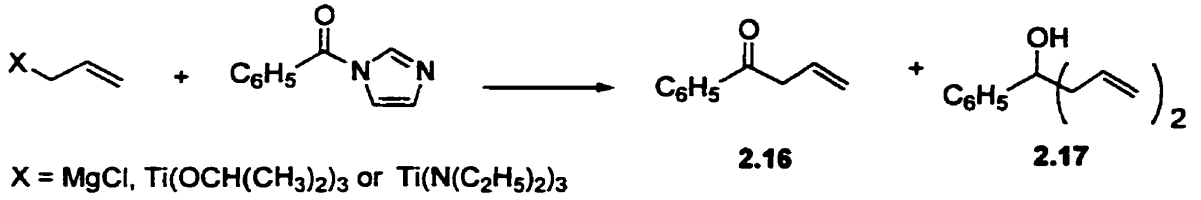
Scheme 2.5

It has been demonstrated,[16] that the outcome of this reaction is very much substrate dependent and therefore it has not found as wide an applicability as that of hydroxamates.

One problem associated with using the hyroxamate derivatives however is that often derivatization of the acid prior to formation of the hydroxamate is required and subsequent time-consuming purification may be a necessity. More recently acyl hemiacetals which are more easily prepared have been utilized successfully in a similar manner.[11]

2.2 An expansion of the scope of the indium-mediated allylation in water. The successful allylation of N-acylimidazoles.

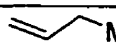
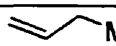
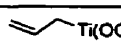
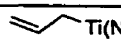
N-Acylimidazoles are very easily prepared via reaction of the acids with 1,1-carbonyldiimidazole or the acid chlorides directly with imidazole. Though often used as acylating agents for esterifications and amide formations, acylimidazoles have been reacted with Grignard reagents in the production of alkyl (low to moderate yields) and aryl ketones (good yields), 1,2-diketones, α-ketoesters and acids.[17, 18, 19] Reetz *et al.*[17b] found that N-acylimidazoles reacted with allyl Grignard reagents to give large amounts of the tertiary alcohols (Scheme 2.6, X = MgCl, **B**) even at -78 °C. They discovered however that the β,γ–unsaturated ketones (Scheme 2.6, **A**) could be produced almost exclusively if allyltitanium tris-amides were used (Table 1).



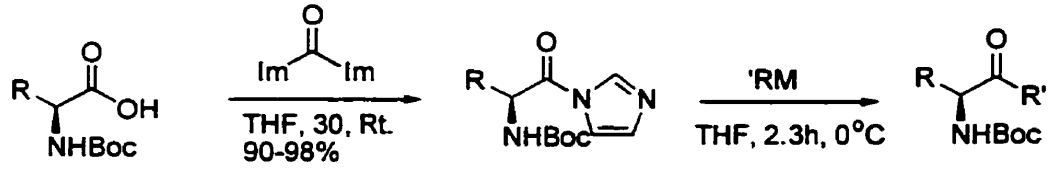
X = MgCl, $Ti(OCH(CH_3)_2)_3$ or $Ti(N(C_2H_5)_2)_3$

Scheme 2.6

Table 2.1: Reaction of benzoylimidazole with with allyl -magnesium and -titanium reagents (Scheme 2.6).[17b]

Allylating agent	Temp. (°C)	Reaction time (h)	Yield (%)	**2.16:2.17**
	-25	6	95	<2:>98
	-78	6	90	60:40
	-50	6	60	66:34
	-50	6	60	>98:<2
	-25	15	95	>98:<2

Subsequent to our work, Ricci *et al.*[17c] published results showing that with the aid of catalytic amounts of CuI, α-amino acids could be converted to α-amino ketones via imidazolides (Scheme 2.7).



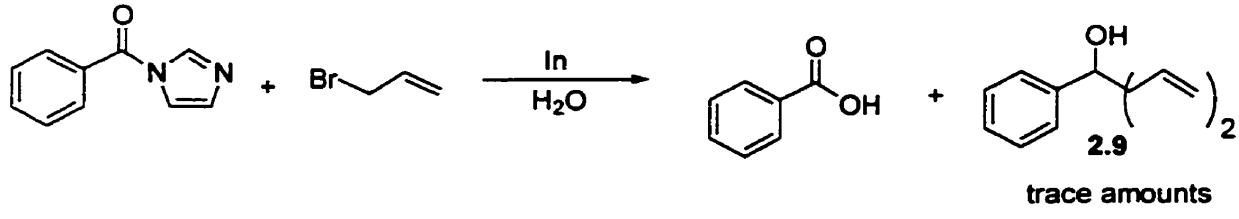
'RM = Grignard reagent + CuI

Scheme 2.7

We believed that N-acylimidazoles were sufficiently reactive to be allylated by allylindium species. We were uncertain however if in aqueous media, hydrolysis of the imidazolide to the corresponding carboxylic acid would compete significantly with the desired allylation. In addition, it was not obvious whether the allylation, if it were to occur, would give the allylic ketone or tertiary alcohol as the predominant product. The need to investigate this reaction therefore was evident.

2.2.1 Results and discussion of the reaction of imidazolides with allylic halides in water mediated by indium.

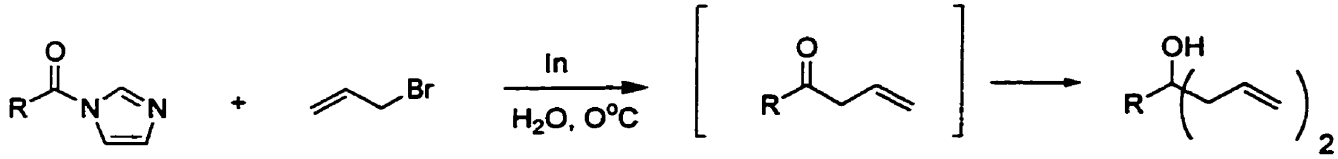
N-Benzoylimidazole was prepared by reacting the carboxylic acid chloride with imidazole in CH_2Cl_2. For the indium-mediated allylation, the allylic halide (1 mmol) and imidazolide (1.5 mmol) were mixed and water was added to the stirring mixture followed quickly by indium powder (3 mmol). An immediate exothermic reaction ensued which if left unchecked exceeded 50°C. An aliquot of the solution was taken and analyzed by ^1H NMR which showed a significant amount of hydrolysis of the starting imidazolide and the presence of a small amount of the diallylated product (Scheme 2.8).



Scheme 2.8

The outcome of the above reaction was undesired but a possible explanation quickly became apparent to us. We believed that initial indium-mediated allylation of the imidazolide was exothermic and that this exothermicity initiated hydrolysis of the starting imidazolide, a process which is itself exothermic, leading to the poor results observed. We were confident however that if we were to absorb the initial heat of the allylation the outcome of the reaction could be altered.

In this light therefore, we repeated the allylation at 0°C. Under these conditions benzoylimidazole was allylated in a quantitative and rapid fashion, giving predominantly the tertiary alcohol **2.20** and a small amount of the intermediate

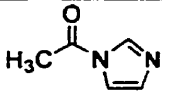
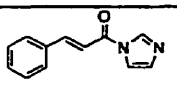
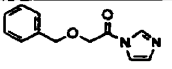
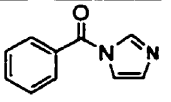
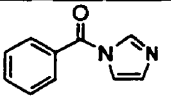
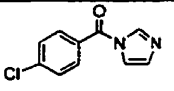
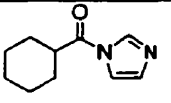
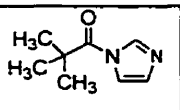


2.18 **2.19** **2.20**

Scheme 2.9

homoallylic ketone **2.19**. Several attempts were made at improving the ratio of the homoallylic ketone by altering the proportions of allyl bromide to the imidazolide as well as the order of addition and the slight lowering of temperature (-5°C) but in all cases the tertiary alcohol **2.20** dominated. After investigation with various N-acylimidazoles and substituted allylic bromides (Table 2), we found that the only factor

Table 2.2: The indium-mediated allylation of N-acylimidazoles in water

Entry	Imidazolide	Bromide	% Yield	% Ketone	% 3° Alcohol
1			>80	0	100
2			88	0	100
3			90	0	100
4			95	6	94
5			95	5	95
6			90	50	50
7			86	33	67
8			85	93	7

All reactions were performed at 0 °C on a mmol scale using imidazolide:allylbromide:indium, 1.5:1:3 respectively, in 2-3mls of water. The isolated yields are reported and the ratios were determined by ^{1}H NMR analysis of the crude. The organic materials were mixed and then added to water then immediately followed by the addition of indium powder in three portions to reduce clumping.

governing the production of the homoallylic ketone was steric hindrance. As shown (Table 2, entries 6-8), it was only when the bulk surrounding the reactive center of the intermediate ketone **2.7** was significant, that a decrease in **2.8** was observed. For example when crotyl bromide was used, 50 % of the desired ketone was obtained. In a similar manner pivaloylimidazole reacted to produce the corresponding ketone in 93 % yield (Entry 8).

The allylation of the imidazolides represented a significant expansion of the scope of the indium-mediated reaction. Even though it was previously known that such substrates could be reacted with Grignard reagents, the extension could not be trivially made to allylindium species as they have generally been much more discriminating. It represented the first example of the reaction of carboxylic acid derivatives in water with allyl halides mediated by indium, doing so in high yields in short reaction times.

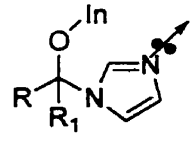
Having successfully entered a new realm of the aqueous based reaction, we were now eager to further pursue our aim at efficiently producing the homoallylic ketone independent of steric hindrance.

2.3 Solving the problem of tertiary alcohol formation: A unique role for N-acylpyrazoles in water in the convenient synthesis of homoallylic ketones.

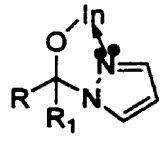
The complication of tertiary alcohol formation is one that often poses a problem in numerous other metal mediated additions to carboxylic acid derivatives.[12] To curtail this nuisance in lithium and magnesium mediated reactions, heterosubstituted esters and

amides capable of chelating with the mediating metal in the intermediary tetrahedral addition compound, have been used.[12,13] Having established that imidazolides (1,3-diazoles) were capable of being allylated via indium-mediated conditions we focused our search for a similar substrate that may be able to exhibit more control under the reaction conditions.

The chelating ability of a neighboring hydroxyl functionality, had been well demonstrated to govern the stereochemical outcome of the indium-mediated allylations.[20a, 20b] In addition Loh *et al.*[21] had demonstrated the effect of nitrogen chelation with 2-pyridinecarboxaldehyde, which when allylated by ethyl 4-bromocrotonate in the presence of indium and water, produced predominantly the *syn* diastereomer, the opposite of what was observed when benzaldehyde[20b] was used as the substrate. This was explained by implicating the chelation of the ring nitrogen and aldehyde oxygen with indium. Geometrically it was not possible for the 3-nitrogen of the imidazolides **2.21** to form a species capable of stabilizing the tetrahedral intermediate equivalent to **2.12**. We believed however that a nitrogen atom in the 2-position **2.22** would allow for the necessary participation (Figure 2.1) and therefore we turned our focus toward investigating the allylation of N-acylpyrazoles in water.



2.21

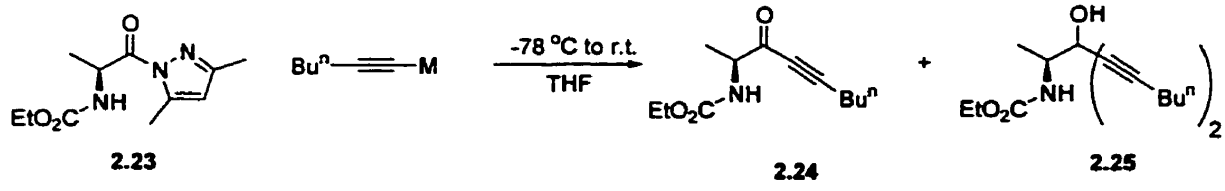


2.22

Figure 2.1

A brief survey of the literature did not reveal much on the use of N-acylpyrazoles in such a fashion. Their preparation however has been known for

sometime from the reaction of pyrazole with anhydrides or acid halides as well as their reduction with $LiAlH_4$ is known to proceed to the corresponding aldehyde.[22] Use of a dimethylpyrazolide **2.23** (Scheme 2.10), in an attempt to produce alkynic ketone **2.24** was also known to be ineffective, producing a product ratio of 1:10 in favor of **2.25**.[10]

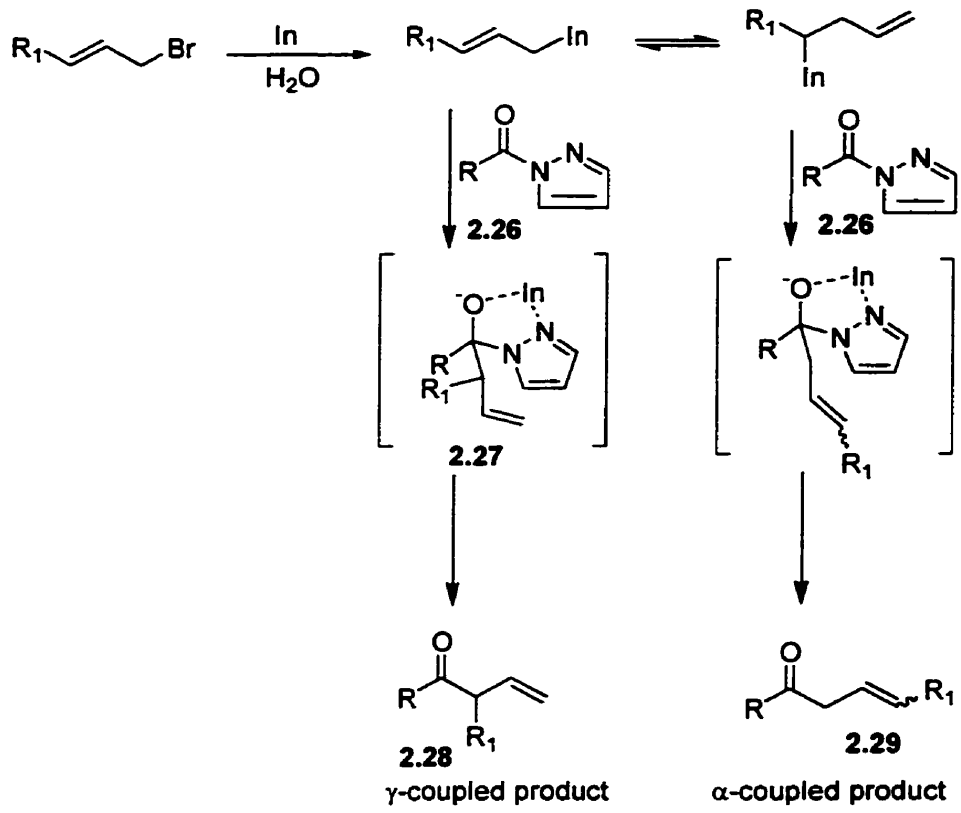


2.23 **2.24** **2.25**

Scheme 2.10[10]

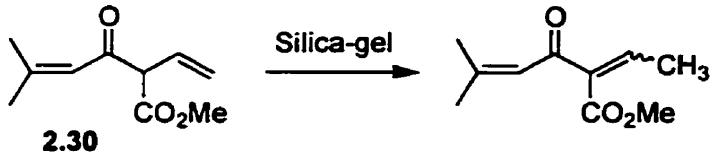
2.3.1 Results and discussion of the reaction of pyrazolides with allylic halides in water mediated by indium.

N-Acylpyrazoles were reacted using the same conditions as N-acylimidazoles with various allylic bromides (Scheme 2.11). With this new substrate, we observed an immediate alteration of the product ratios of the indium-mediated reaction. Where previously the tertiary alcohol was the major product, we had now obtained predominantly the homoallylic ketone in high yields (Table 3). Thus when benzoylpyrazole was treated with allyl bromide and indium under identical conditions to those used previously, the ratio of 4-phenyl-1,6-heptadien-4-ol (diallylation product) to allyl phenyl ketone was reversed from 94:6 to 25:75. In a similar manner the production of allyl cyclohexyl ketone increased from 33 % to 95% by substituting the 1,2- for the 1,3-diazole.



Scheme 2.11

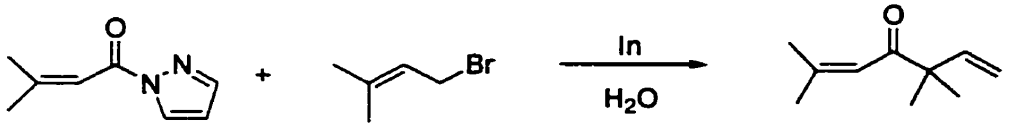
The results in Table 2.3 show that when γ-substituted allylic halides were employed, the homoallylic ketone was furnished exclusively. Coupling to the acylpyrazoles occurred only at the γ-position of the allylic halide with no α-coupling observed. In general, the reaction provided the β,γ-unsaturated ketones as the sole products without migration of the double bond. After purification via flash chromatography through silica gel, the ketones were isolated intact with the only exception being **2.30**, which isomerized completely as shown (Scheme 2.12).



2.30

Scheme 2.12

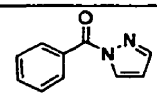
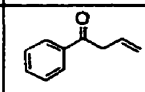
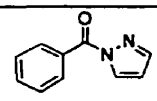
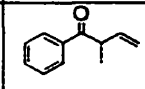
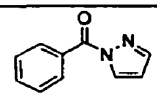
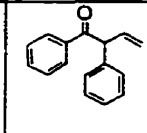
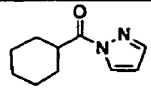
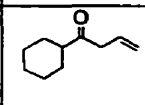
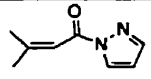
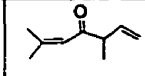
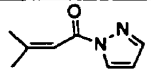
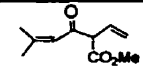
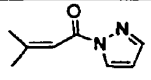
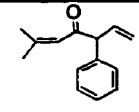
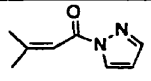
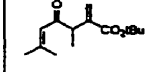
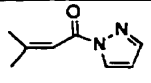
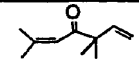
The synthetic usefulness of the reaction was demonstrated by a facile synthesis of artemisia ketone **2.31** which is a monoterpene isolated from the volatile oil *of Santolina chamaecyparissus L.* and *Artemisia annua L* (Scheme 2.12).[23] When treated with 3,3-dimethylallylbromide under the indium-mediated conditions 3,3-dimethylacryloyl pyrazole (derived from the corresponding acid), furnished the desired natural ketone in 65 % yield.



2.31

Scheme 2.13[24]

Table 2.3: Indium-mediated allylation of acyloyl-pyrazoles in aqueous media.[24]

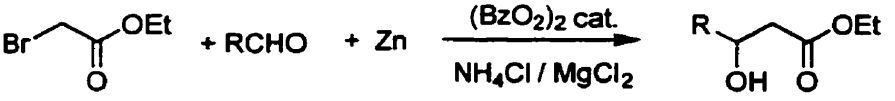
Entry	Pyrazolide	Bromide	%Yield	Major Product	% Ketone	% Alcohol
1			90		75	25
2			88		100	0
3			95		100	0
4			90		>95	<5
5			92		95	5
6			50	 **2.30**[a]	100	0
7			92		100	0
8			75		100	0
9			65		100	0

a) Observed in the ^{1}H NMR of the crude but after purification the isomerized product (not seen in the ^{1}H NMR) shown in Scheme 2.12, was the only isolated product.

We were particularly pleased that we had successfully developed a method for the synthesis of homoallylic ketones in aqueous media and in so doing we introduced a novel role for N-acylpyrazoles. These derivatives performed in a manner similar to Wienreb amides[14] furnishing much superior yields of the homoallylic ketone compared to when N-acylimidazoles were employed. To the best of our knowledge, such a role for these substrates in Barbier-type reactions is unprecedented.

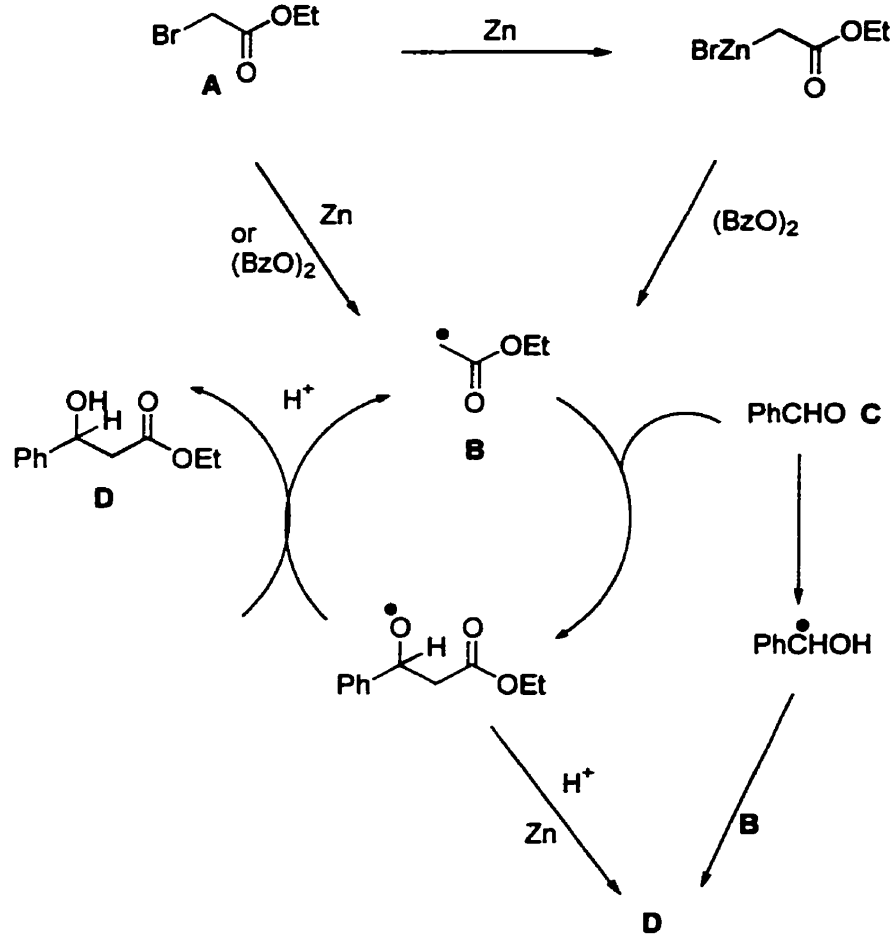
2.4 An investigation of the indium-mediated Reformatsky-type reaction: The synthesis of β-keto esters.

Having introduced a novel substrate for the production of homoallylic ketones in good yields, we then wanted to employ the same methodology to investigate the feasibility of producing β-ketoesters. β-Hydroxy esters have previously been synthesized in aqueous solvent with indium, zinc and tin as the mediating metals with low to moderate yields.[25] More recently[26] an improved reaction was reported in saturated aqueous solutions (ammonium chloride/magnesium chloride, or ammonium chloride/calcium chloride) with catalytic amounts of benzoyl peroxide using zinc as the mediator (Scheme 2.14).



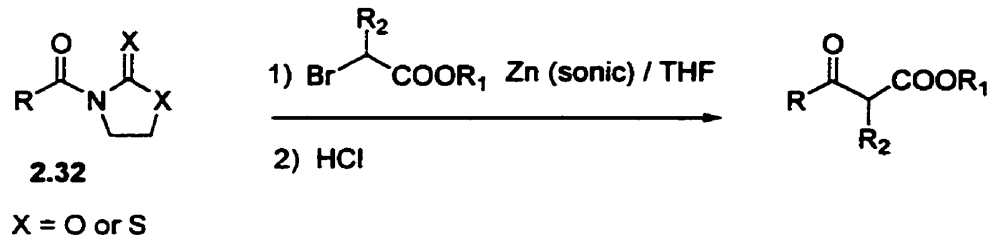
Scheme 2.14

Scheme 2.15 illustrates the radical chain mechanism, which the authors proposed to account for the catalytic effect observed by addition of the peroxide. They suggested that the chain pathway may compete with non chain pathways involving radicals



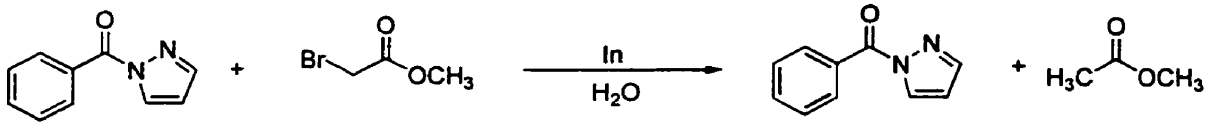
Scheme 2.15

produced on the metal surface as was previously described.[1] The direct synthesis of β-ketoesters in a similar manner has been much less explored. In 1993, Kashima *et al.*[9] reported a high yielding zinc mediated Reformatsky-type coupling of α-bromo esters to 3-acyloxazolidin-2-ones and thiazolidine-2-thiones in THF (Scheme 2.16, **2.32**). Rollin *et al.* [27] also demonstrated similar coupling to anhydrides with electrochemically activated zinc in acetonitrile producing the β-ketoesters in good yields.



Scheme 2.16

We initiated our studies without knowledge of the above reaction (Scheme 2.16) with the attempted coupling of methyl bromoacetate and benzoylpyrazole under the same conditions used for the allylation reactions (Schemes 2.9 and 2.11). Immediately after the addition of indium a very exothermic reaction occurred which had to be cooled to prevent destruction of the pyrazolide.[1]H NMR analysis of the product mixture did not reveal the presence of the β-ketoester. Instead, we found that the methyl bromoacetate had been rapidly converted to methyl acetate. Our attempts of altering the order of addition or changing the amounts of bromide or indium used or the use of saturated NH_4Cl solution did not change the fact that protodehalogenation of the halide occurred (Scheme 2.17).

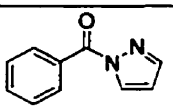
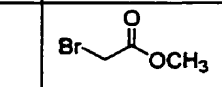
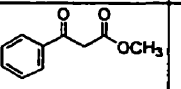
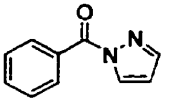
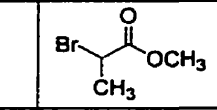
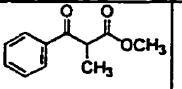
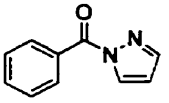
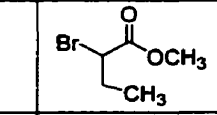
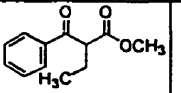
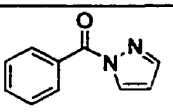
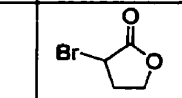
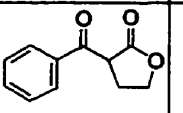
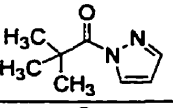
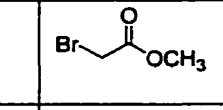
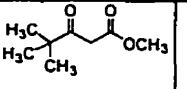
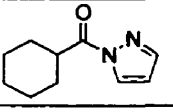
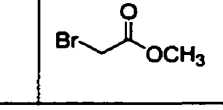
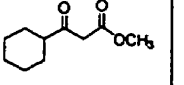


Scheme 2.17

The reaction however proceeded well when performed in THF solvent. Specifically we found that while the reaction was sluggish in distilled THF, it

proceeded smoothly when the solvent remained undistilled. After 6-12 hours we were able to obtain the β-ketoester of a variety of reactants (Table 2.3.)

Table 2.3: The indium-mediated reformatsky–type production of β-keto esters

Entry	Pyrazolide	α-Bromo Ester	Product	Solvent(s) (THF:H_2O)	% Yield
1				1:0 9:1 0:1	75[a] ~10[b] 0
2				1:0 9:1 0:1	33[a] 0[b] 0
3				1:0 9:1 0:1	0[a] 0[b] 0
4				1:0 9:1 0:1	88[a] ~15[b] 0
5				1:0 9:1 0:1	70[a] <10[b] 0[a]
6				1:0 9:1 0:1	85[a] ~12[b] 0

a) All the reactions were performed in undistilled THF at room temperature, with 2 fold excesses of both the bromide and indium relative to the pyrazolide. The yields determined were isolated and done so after 12 hrs of reaction. b) % Conversion based on ^{1}H NMR ($CDCl_3$).

We found that the 1° halides furnished the highest yields with the exception of 2-bromo-γ-butyrolactone, which gave very good results. The unreacted pyrazole was recovered intact while excess bromide was reduced.

The reaction served as a very useful manner for the production of β-ketoesters, but there remain some aspects that are not well explained. We have not fully uncovered the reason for the apparent sensitivity of reaction outcome to the purity of the THF

used. It maybe that small amount of peroxides and water present in the undistilled solvent aided the reaction in a manner similar to that explained in Scheme 2.12.

2.5 Conclusion

We have successfully expanded the scope of the indium-mediated allylation to include the allylation of carboxylic acid derivatives in aqueous media. We illustrated that in a reaction governed by steric bulk, acylimidazoles were allylated in a quantitative fashion furnishing predominantly the homoallylic alcohols. An even more significant contribution to the methodology was made with the introduction of acylpyrazoles, which performed in a manner reflective of Wienreb amides, furnishing the homoallylic ketones in good yields with unsubstituted allylic halides and exclusively with γ-subsituted halides. The use of pyrazoles in such a manner was unprecedented and represented an advancement of the utility of the indium-mediated aqueous based methodology. In addition, the acylpyrazoles were shown to be suitable substrates for the synthesis of β-ketoesters in good yields. The reaction mediated by indium was performed successfully in THF.

The range of useful functionalites that can be efficiently produced by the indium-methodology, which is characterized by low levels of toxicity, low cost and a truly mild nature, has been successfully expanded.

2.6 Experimental procedures

General procedure for the preparation of acyl-imidazoles and –pyrazoles:

In a typical experiment imidazole (20 mmol) was dissolved in distilled CH_2Cl_2 (20ml) containing TEA (20mmol) and cooled to 0 °C under a steady flow of argon. The requisite acid chloride (20 mmol) dissolved in 10ml of CH_2Cl_2 (distilled) was delivered dropwise over several minutes to the stirring solution imidazole solution at 0°C. The mixture was allowed to warm to 25°C and stirred at this temperature for 2 h to ensure completion. The reaction mixture was then diluted with 100ml of diethyl ether, filtered and evaporated under reduced pressure. Purification through silica gel with hexanes:ethyl acetate (3:1) furnished quantitive yields.

1-Acetylimidazole:[28] 2.0 g (93%); white solid; mp 99-103 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.42 (s, 1H), 7.04 (s, 1H), 2.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 135.6, 130.4, 115.6, 23.3.

1-Cinnamoylimidazole[29]**:** 3.6 g (92%); white powder; mp 129-130 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.08 (d, 1H, J = 15.4 Hz), 7.68-7.45 (m, 6H), 7.17 (d, 1H, J = 1.7 Hz), 7.07 (d, 1H, J = 15.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.7, 149.0, 135.6, 132.9, 131.0, 130.6, 128.6, 128.1, 115.9, 114.3.

1-(Benzyloxy)acetylimidazole: 3.7 g (88%); light brown solid; mp 99-100 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.29 (m, 6H), 6.86 (s, 1H), 4.57 (s, 2H), 4.12 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 137.3, 133.6, 128.3, 128.1, 127.8, 119.0, 73.0, 69.7.

1-Benzoylimidazole:[30] 3.4 g (98%); pale yellow liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.79 (d, 2H, J = 8.0 Hz), 7.68 (t, 1H, J = 8.0 Hz), 7.56 (t, 2H, J = 7.5 Hz), 7.54 (s, 1H), 7.17 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 138.2 136.8, 130.2, 129.2 128.0, 126.4

1-p-Chlorobenzoylimidazole:[17b] 4.0 g (97%); white solid; mp 82-84 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.74 (d, 2H, J = 8.3 Hz), 7.53 (d, 2H, J = 8.3 Hz), 7.50 (s, 1H), 7.16 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 139.3, 137.1, 130.3, 129.4, 128.5, 117.3

1-Cyclohexanoylimidazole: 3.5 g (98%); pale yellow solid; mp 74-75 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.44 (s, 1H), 7.06 (s, 1H), 2.86 (m, 1H), 1.92 (d, 2H, J = 13.0 Hz), 1.83 (d, 2H, J = 13.0 Hz), 1.73-1.21 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 136.0, 130.6, 116.0, 43.6, 29.2, 25.3, 25.2.

1-Pivaloylimidazole: 2.7 g (90%); white solid; mp 49-50 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.50 (d, 1H, 1.2 Hz), 7.00 (d, 1H, 1.0 Hz), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 137.5, 129.9, 117.9, 42.3, 29.4.

1-Benzoylpyrazole: 2.7 g (89%); colorless crystal; mp 35-36 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.43 (d, 1H, J = 3.0 Hz), 8.10 (d, 1H, J = 8.0 Hz), 7.80 (s, 1H), 7.60 (t, 1H, J = 8.3 Hz), 7.50 (t, 1H, J = 8.0 Hz), 6.51 (dd, 1H, J = 1.5 Hz and J = 3.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 144.4, 132.9, 131.4, 130.3, 128.0, 109.4.

1-Cyclohexanoylpyrazole: 3.5 g (98%); slightly yellow oil;^{1}H NMR (200 MHz, $CDCl_3$) δ 8.24 (d, 1H, J = 2.2 Hz), 7.72 (s, 1H), 6.43 (d, 1H, J = 2.4 Hz), 3.64 (tt, 1H, J = 3.5 Hz, J = 11.3 Hz), 2.04-1.30 (m, 10H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 174.9, 143.8, 128.7, 109.9, 42.9, 30.6, 27.3, 26.9.

3-Methyl-2-butenoylpyrazole: 2.7 g (90%); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, 1H, J = 2.5 Hz), 7.70 (s, 1H), 7.10 (s, 1H), 6.42 (d, 1H, J = 1.5 Hz), 2.32 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 163.0, 143.2, 128.4, 114.0, 109.2, 28.4, 21.3.

General procedure for the allylation of N-acylimidazoles in water, mediated by indium: The acylimidazole (1.5 mmol)) was mixed with the allylic bromide (1 mmol) and cooled to 0°C (If both reactants were solid a minimum amount of THF was used to create a solution). To the stirring mixture was added 2ml of H_2O and the resulting mixture agitated at high speed. Indium powder (99.99% with Mg 1% as anti-caking agent, commercially available from ALDRICH®; 3mmol) was added in 3 portions over a period of approximately 5 minutes. A vigorous rate of stirring and the low temperature was maintained until the starting material was judged to be fully consumed (generally 1 h -2 h; monitored by tlc: starting imidazoles were UV active but unlike the products, did not stain with the anisaldehyde/H_2SO_4/EtOH/AcOH stain). The milk colored solution was then saturated with NaCl, and extracted with 3 X 10 ml of diethyl ether, dried with $MgSO_4$, filtered through celite and evaporated under reduced pressure. All products were purified by elution through silica gel with hexanes:ethyl acetate (49:1).

4-Phenyl-1,6-heptadien-4-ol: 194 mg (95 %); colorless liquid; ^{1}H NMR (200 MHz $CDCl_3$) δ 7.41-7.22 (m, 5H), 5.61 (m, 2H), 5.11 (d, 2H, J = 16.0 Hz), 5.08 (d, 2H, J = 8.0 Hz), 2.69 (dd, 2H, J = 6.0 Hz and J = 14.0 Hz), 2.52 (dd, 2H, J = 8.5 Hz, and J =14.0 Hz). ^{13}C NMR (200 MHz, $CDCl_3$) δ 146.1, 132.7, 127.5, 126.0, 124.7, 118.7,

4-Methyl-1,6-heptadien-4-ol: 101 mg (80%); colorless liquid; ^{1}H NMR (500 MHz $CDCl_3$) δ 5.84 (m, 2H), 5.11 (d, 2H, J = 10.0 Hz), 5.09(d, 2H, J = 17.0 Hz), 2.21 (m, 4H), 1.15 (s, 3H). ^{13}C NMR (50 MHz $CDCl_3$) δ 133.8, 118.5, 71.9, 46.0, 26.1. IR 3545 cm^{-1} (OH)

4-(2-Phenylethene)-1,6-heptadien-4-ol: 189 mg (88%); slightly yellow liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.24 (m, 5H), 6.62 (d, 1H, J = 20.0 Hz), 6.25 (d, 1H, J = 20.0 Hz), 5.85 (m, 2H), 5.19 (m, 4H), 2.41 (m, 4H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 136.1, 134.0, 132.6, 127.9, 126.8, 125.8, 118.7, 73.8, 45.9. IR ($CHCl_3$), 3557 cm^{-1} (OH), 3066cm^{-1}, 1639cm^{-1}, 1254cm^{-1}.

4-(Benzyloxymethyl)-1,6-heptadien-4-ol: 210 mg (90%); colorless liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40 (m, 5H), 5.83 (m, 2H), 5.10 (m, 4H), 4.55 (s, 2H), 3.35 (s, 2H), 2.4 (m, 4H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 138.1, 133.5, 128.4, 127.7, 127.6, 74.9, 73.4, 73.2, 41.4. MS CI (NH_3) m/z 250 (M + NH_4, 2.2), 232 (M, 12.0), 215 (M-OH, 100.0) .

2,6-Dimethyl-4-pheny-1,6-heptadien-4-ol: 180 mg (95%); colorless liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.83 (d, 2H, 1.4 Hz), 4.69 (d, 2H, 1.6 Hz), (m, 4H), 1.41 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.0, 142.9, 127.7, 126.2, 125.3, 115.4, 74.5, 51.1, 24.1. IR ($CHCl_3$) 3533 cm^{-1}, 3007 cm^{-1}, 2397 cm^{-1}, 1187 cm^{-1}.

4-Cyclohexyl-1,6-heptadien-4-ol: 101 mg (52%); colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$), 5.89 (m, 2H), 5.13 (d, 2H, J = 10.5 Hz), 5.10 (d, 2H, J = 17.5 Hz), 2.30 (dd, 2H, J = 6.0 Hz and J = 13.0 Hz), 2.19 (dd, 2H, J = 7.5 Hz and J = 14.0 Hz), 1.790-1.031 (m, 11H). ^{13}C NMR (50 MHz, $CDCl_3$), 134.4, 118.8, 76.0, 46.8, 42.5, 28.4, 28.3, 28.1. . IR ($CHCl_3$) 3539 cm^{-1}, 2930 cm^{-1}, 1123cm^{-1} 930 cm^{-1}

General procedure for the allylation of acylpyrazoles in water mediated by indium: See "*General procedure for the allylation of acylimidazoles in water mediated by indium*" Reaction times tended to be longer and the reactions were stopped when thin layer chromatography (tlc) showed full consumption of the starting material; Acylpyrazole:allylic bromide:indium (1:1:3).

2,2-Dimethyl-5-hexen-3-one: 95 mg (75%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.94(m, 1H), 5.14 (d, 1H, J = 10.5 Hz), 5.08 (d, 1H, J = 18.5), 3.28 (d, 2H, J = 5.5 Hz), 1.150 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.9, 131.0, 117.4, 41.7, 26.9, 26.4. IR ($CHCl_3$) 1710 cm^{-1}.

1-Phenyl–2-methyl-3-buten-1-one. 114 mg (88%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.0 (d, 2H, J = 7.0 Hz), 7.49 (m, 3H), 6.00 (m, 1H), 5.20 (d, 1H, J = 12.6 Hz), 5.12 (d, 1H, J = 5.5 Hz), 4.18 (m, 1H), 1.34 (d, 3H, J = 6.8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$), 199.7, 137.4, 135.6, 132.2, 127.9, 116.0, 45.8, 17.7. IR ($CHCl_3$) 1680 cm^{-1}.

1-Phenyl-3-buten-1-one[17b]**:** 88 mg (60%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, 2H, J = 8.5 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.47 (t, 2H, J = 8.0 Hz), 6.09 (m, 1H), 5.24 (m, 2H), 3.77 (dd, 2H, J = 1.5 Hz, J = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) 199.4, 136.9, 136.0, 132.0, 128.1, 115.8, 49.3.

1-(4-Chlorophenyl)-2-methyl-3-buten-1-one.[17b] 83.7 (43%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.92 (d, 2H, J = 8.5 Hz), 7.43 (d, 2H, J = 8.4 Hz), 5.97 (m, 1H), 5.17 (m, 2H), 4.11 (m, 1H), 1.33 (d, 3H, J = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.4, 139.1, 138.6, 137.2, 129.3, 128.3, 116.3, 46.0, 17.7. IR ($CHCl_3$) 1684 cm^{-1}.

1,2-Diphenyl-3-buten-1-one: 211 mg (95%); white solid; mp 59-60 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.00 (d, 2H, J = 8.1 Hz), 7.40 (m, 3H,), 6.40 (m, 1H, 5.32-

5.06 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.0, 137.6, 136.4, 135.7, 132.3, 128.3, 128.2, 127.9, 127.7, 126.6, 116.6, 58.2. MS (EI): m/z 222 (M, 22%), 117 (17%), 115 (15%), 105 (100%), 83 (21%). IR ($CHCl_3$) 1680 cm^{-1}.

1-Cyclohexyl-3-buten-1-one. 126 mg (83%); ^1H NMR (500 MHz, $CDCl_3$) δ 5.95 (m, 1H)), 5.16 (d, 1H, J = 10.5), 5.14 (d, 1H, J = 17.0 Hz), 3.21 (dd, 2H, J = 1.0 Hz and J = 8.0 Hz), 2.40 (m, 1H), 1.85-1.18 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.9, 131.2, 118.8, 51.6, 46.8, 29.9, 27.3, 27.1. IR ($CHCl_3$) 1690 cm^{-1}.

3,6-Dimethyl-1,5-heptadien-4-one. 117 mg (85%); ^1H NMR (500 MHz, $CDCl_3$) δ 5.84 (m, 1H), 5.13 (d, 1H, J = 17.0 Hz), 5.09 (d, 1H, J = 11.5 Hz), 3.17 (m, 1H), 2.13 (s, 3H), 1.88 (s, 3H), 1.17 (d, 1H, J = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.6, 155.3, 137.3, 121.9, 115.7, 52.1, 28.3, 21.5, 16.5. IR ($CHCl_3$) 1682 cm^{-1}, 1618 cm^{-1}.

***cis* and *trans* 3-Methoxycarbonyl-6-methyl-1,5-heptadien-4-one:** 90 mg (50%); mixture of diastereomers (methyl bromocrotonate was used in 3 fold excess); colorless oil;.^1H NMR (500 MHz, $CDCl_3$) δ 7.00 (q, 0.4H, J = 7.5 Hz), 6.87 (q, 1H, 7.5 Hz), 6.23 (s, 1H), 6.13 (s, 0.4H), 3.82 (s, 3H), 3.74 (s, 1.2H), 2.20 (s, 1.2H), 2.13 (s, 3H) 1.96 (d, 1H, J = 7.0 Hz), 1.92 (s, 1.2H), 1.92 (s, 3H), 1.85 (d, 1.2H, J = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 192.5, 187.9, 167.1, 165.2, 157.6, 157.5, 142.7, 139.0, 137.4, 124.6, 120.9, 52.0, 52.0, 28.0, 27.9, 21.2, 21.1, 15.8, 15.1. MS (EI): m/z 182 (M, 5%), 151 (32%), 83 (100%).

6-Methyl-3-phenyl-1,5-heptadien-4-one. 184 mg (92%); ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 5H), 6.23-6.18 (m, 1H), 6.05 (m, 1H), 5.22 (d, 1H, J = 10.3 Hz), 5.07 (d, 1H, J = 17.1 Hz), 4.35 (d, 1H, J = 8.1 Hz), 2.16 (s, 3H), 1.84 (s, 3H); ^{13}C NMR

(50 MHz, $CDCl_3$) δ 196.7, 156.3, 137.7, 135.8, 128.2, 127.8, 126.5, 122.4, 116.9, 63.9, 28.4, 21.6. MS (EI): m/z 200 (M, 4%), 185 (6.8%), 117 (10.2%), 115 (11.3%), 83 (100%) 55 (9.4%). IR ($CHCl_3$) 1680 cm^{-1}, 1615 cm^{-1}.

2-*t*-Butylcarbonyl-3,6-dimethyl-1,5-heptadien-4-one: 179 mg (75%); ^1H NMR (500 MHz, $CDCl_3$) δ 6.27 (s, 1H), 6.10 (s, 1H), 5.55 (s, 1H), 3.61 (q, 1H, J = 7.5 Hz), 2.13 (s, 3H), 1.87 (s, 3H), 1.45 (s, 9H), 1.22 (d, 3H, J = 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.2, 165.7, 150.1, 142.2, 125.1, 122.6, 81.1, 48.4, 27.9, 27.7, 20.8, 15.5. MS CI (NH_3): m/z 239 (M+1, 4.4%), 184 (8%), 183 (69%), 165 (28%), 83 (100%).

Artemisia ketone[22]: 99 mg (65%); ^1H NMR (500 MHz, $CDCl_3$) δ 6.231 (m, 1H), 5.94 (dd, 1H, J = 10.5 Hz, J = 17.0 Hz), 5.91 (d, 1H, J = 11.0 Hz), 5.14 (d, 1H, J = 17.5 Hz), 5.12 (d, 1H, 11.0 Hz), 2.12 (d, 3H, J = 1.0 Hz), 1.88 (d, 3H, J =1.0 Hz), 1.209 (s, 6H), ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.4, 154.8, 142.5, 120.0, 113.2, 50.6, 28.5, 24.3, 21.5. IR ($CHCl_3$) 1690 cm^{-1}.

General procedure for the synthesis of β-ketoesters: The acylpyrazole (1mmol) and α-bromo ester (1.2mmol) were added to 1 ml of THF (undistilled). To the stirring solution was added indium powder (2mmol) and the reaction mixture stirred. The solution gradually developed a bronze appearance and after 12hrs the mixture was quenched with 0.1N HCl. Diethyl ether (3 X 5ml) was then used to extract the product. The organic layer was washed with 10ml of H_2O and dried with anhydrous Na_2SO_4. Evaporation under reduced pressure, gave the crude product which was purified by elution through silica gel with hexanes:ethyl acetate (11:1).

Methyl cyclohexanoylacetate: 157 mg (85%); colorless liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.50 (s, 2H), 2.46 (m, 1H), 1.81-1.29 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.7, 167.8, 52.2, 50.8, 46.9, 28.0, 25.5, 25.3. Some peaks of the enol tautomer were also visible in the ^{1}H and ^{13}C spectra. IR ($CHCl_3$) 1744 cm^{-1}, 1730 cm^{-1}, 1187 cm^{-1}.

3-Benzoyldihydro-2(3H)-furanone: 167 mg (88%); pale yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, 2H, J = 7.5 Hz), 7.63 (t, 1H, J = 7.5 Hz), 7.52 (t, 2H, J = 7.5 Hz), 4.60-4.42 (m, 3H), 2.93 (m, 1H), 2.05 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.6, 171.5, 134.7-127.0 (Ar C's), 67.8, 48.4, 26.7. Some peaks of the enol tautomer were also visible in the ^{1}H and ^{13}C spectra. IR ($CHCl_3$) 1767 cm^{-1}, 1685 cm^{-1}, 1190 cm^{-1}, 1156 cm^{-1}.

Methyl benzoylacetate: 134 mg (75%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.90 (d, 2H, 7.5 Hz), 7.61-7.41 (m, 3H), 4.01 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.0, 166.8, 135.2-125.5 (Ar C's), 52.8, 46.1; Some peaks of the enol tautomer were also visible in the ^{1}H and ^{13}C spectra. IR ($CHCl_3$) 1727 cm^{-1}, 1682 cm^{-1}, 1368 cm^{-1}, 1250 cm^{-1}.

Methyl α-benzoyl-α-methylacetate: 63 mg (33%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, 2H, J = 7.5 Hz), 7.59 (t, 1H, J = 7.5 Hz), 7.48 (t, 2H, J =7.5 Hz), 4.41 (q, 1H, J = 7.0 Hz), 3.69 (s, 3H), 1.50 (d, 3, 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.7, 171.2, 135.5, 133.4, 128.6, 128.4, 52.4, 47.9, 13.7. IR ($CHCl_3$) 1732 cm^{-1}, 1686 cm^{-1},1451 cm^{-1}, 1280 cm^{-1}.

Methyl pivaloylacetate: 111 mg (70%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.61 (s, 3H), 3.55 (s, 2H), 1.15 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 166.5, 51.8, 49.9,

44.3, 29.2. Some peaks of the enol tautomer were also visible in the ^{1}H and ^{13}C spectra. IR ($CHCl_3$) 1740 cm^{-1}, 1720 cm^{-1}, 1180 cm^{-1}.

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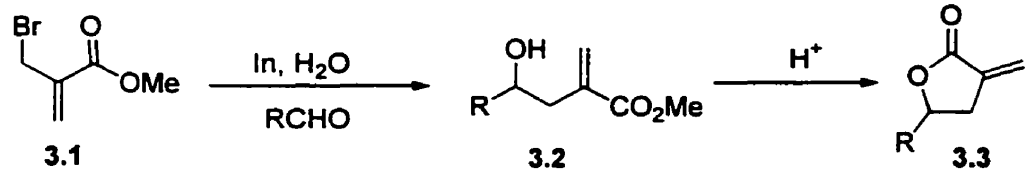
CHAPTER 3

Intramolecular cyclizations mediated by indium in aqueous media. The synthesis of carbocycles and oxygen heterocycles fused to biologically significant α-methylene-γ-butyrolactones.

3.1 Introduction.

It was demonstrated early[1a,1e] that β-carboxyl allyl bromides such as **3.1**, could react to produce α-methylene-γ-hydroxy esters **3.2**, which cyclize readily in an acidic environment to the very valuable α-methylene-lactones **3.3** as shown in Scheme 3.1.

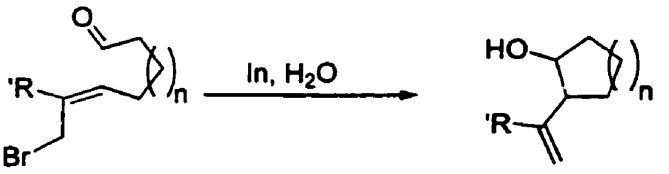


3.1 **3.2** **3.3**

Scheme 3.1

The indium-mediated reaction has been developed rapidly and with some knowledge of its value, we embarked on an expansion of the scope of the reaction and a demonstration of its synthetic utility. One aspect which had not been previously explored was the synthetic utility of performing the reaction in an intramolecular fashion.[3] Functionalized carbocycles are of tremendous abundance in nature and numerous studies into their efficient synthesis are continuously being sought.[4] There are several aspects of the indium-mediated reaction which makes it attractive for investigations in this area of

synthetic chemistry. The reaction had been demonstrated to have high levels of diastereoselectivity in the intermolecular studies. With the increased rigidity of cyclic structures, one could envision high selectivity in intramolecular couplings. Occurring in water, the possibility of hydrophobic forces[5] aiding in the cyclizations would also be present and hence the need to investigate the reaction shown in Scheme 3.2 was evident.



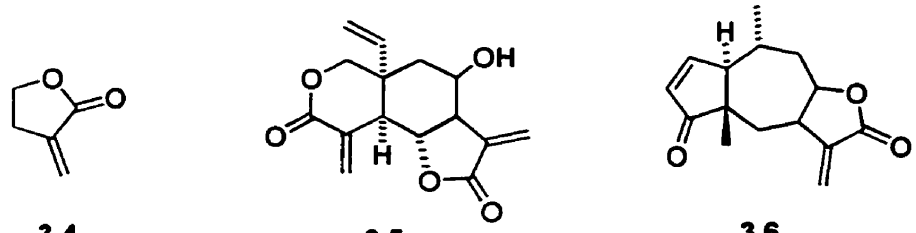
Scheme 3.2

Of interest to us in our investigation were: 1) the type of selectivity associated with any closure obtained; 2) the quantitative extent to which the conversion would occur; 3) the synthetic value of the molecules we would use to illustrate the reaction's utility. For this latter reason, we wanted to focus on the synthesis of cyclic substrates that were essential components of naturally occurring, biologically active molecules. α-Methylene-γ-butyrolactones fused to carbocyles, seemed an appropriate choice in this regard and hence served as the platform for launching our investigation into the intramolecular carbocyclizations mediated by indium in aqueous media.

3.1.1 Fused α-methylene-γ-butyrolactones

As targets for synthetic purposes, fused α-methylene-γ-butyrolactones are of considerable significance, since they are an integral part of many natural products. They are of vast abundance, with many possessing high levels of biological activity as

allergenic agents, cytotoxic and antitumor agents, regulators of plant growth and antimitotic activity and antihistosomal agents.[6] They range from the very simple α-methylene-γ-butyrolactone **3.4** to more complex molecules in which the unit is fused to a cyclic network such as vernolepin **3.5** and aromaticin **3.6**.[7] A wide variety of such molecules exist often fused to 6, 7 and 10-membered carbocyclic rings.[7,8]



3.4 **3.5** **3.6**

Figure 3.1

A number of techniques exist for the synthesis of fused α-methylene-γ-butyrolactones with varying degrees of applicability. Figure 3.2 illustrates the numerous manners in which the unit can be disconnected, each of which is well documented and reviewed.[9]

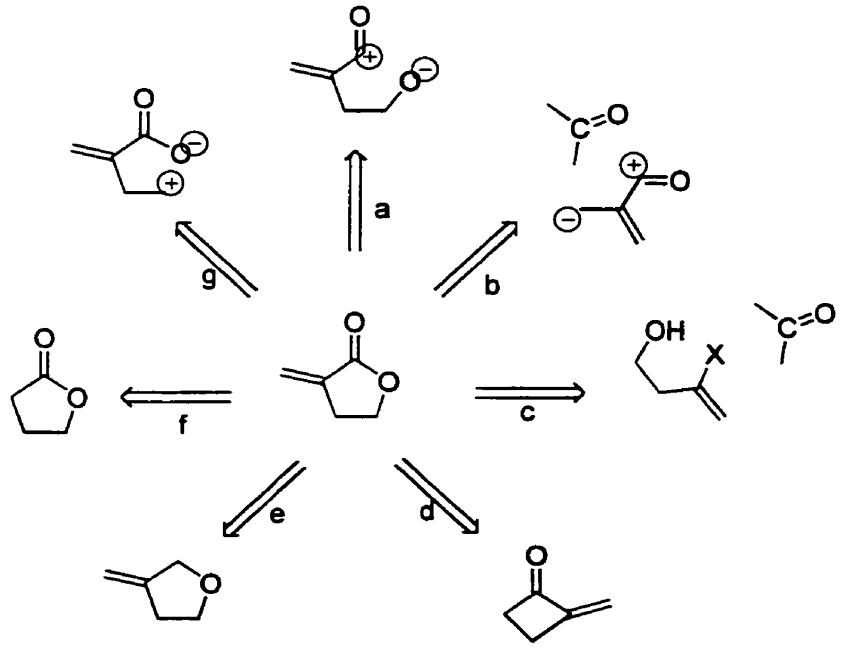
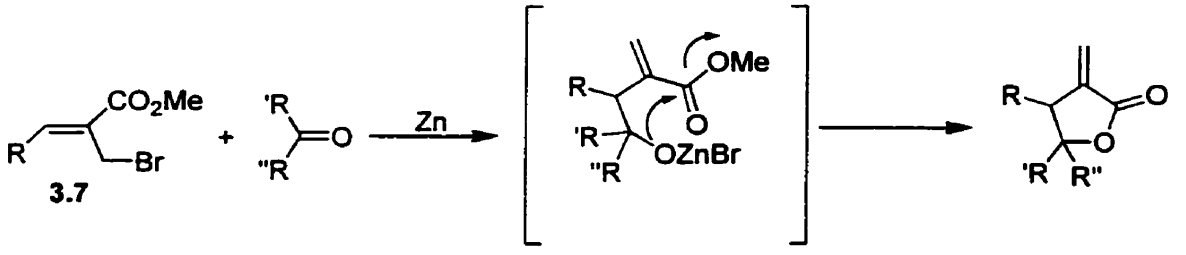


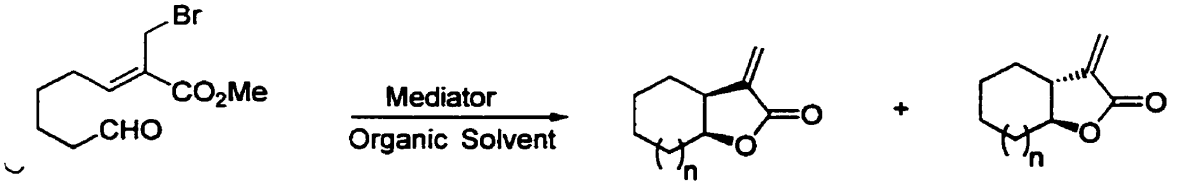
Figure 3.2[9b] : Possible routes of disconnection for the construction of α-methylene-γ-butyrolactones.

Of particular interest to us is the disconnection along path b where the acrylic species can be generated from the corresponding allylic halide which when coupled to the appropriate aldehyde can cyclize spontaneously to the α-methylene-γ-butyrolactone. This method was first demonstrated with zinc mediated coupling of the (Z)-2-bromomethyl-2-alkenoic ester **3.7** with an aldehyde to produce the corresponding monocyclic α-methylene-γ-butyrolactone.[10]



Scheme 3.3

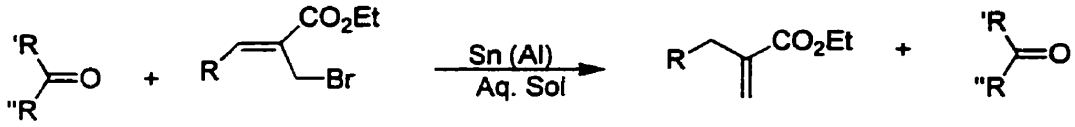
Semmelhack *et al.* extended this protocol to intramolecular reactions for the simultaneous construction of carbocycles fused to α-methylene-γ-butyrolactones as shown in Scheme 3.4.[8a]



Scheme 3.4

They found that Zn-Cu in dilute THF solution, provided a moderate yield of the *cis* fused product. Lower yields of the same product was obtained when $Ni(cod)_2$ was used as the

mediator. Oshima *et al.* reported very similar results with $CrCl_3$- LAH in THF at 0 °C in both the intermolecular and intramolecular reaction.[11] Yamakawa *et al.* used allylsilanes instead of allyl bromides in a similar fashion and was able to get good yields of the desired lactones, though the reactions in general gave cis/trans isomeric mixtures. With the 5-membered carbocycle however the addition of $TiCl_4$ did give exclusively the *cis* fused product.[12]



Aq. Sol = aqueous THF, aqueous DME and aqueous alcohol.

Scheme 3.5

In 1986 Nokami illustrated how the reaction could be performed in aqueous-organic two phase systems with Sn(Al) at 40 °C .[13] Homogeneous aqueous media resulted however in destruction of the starting halides rather than providing the coupled product (Scheme 3.5).

These reactions illustrated a very efficient route to the synthesis of the monocyclic as well as fused α-methylene-γ-butyrolactones but possessed several limitations. Though the selectivity in most cases was very good, none of the yields were greater than 62%, which left lots of room for improvement. In addition attempts at performing the reaction in aqueous media had not been very successful and in this regard the accompanying advantages such as low toxicity levels, low cost, and mildness of conditions were compromised.

The indium-mediated allylation in aqueous media had demonstrated itself to be superior to either Zn or Sn in the intermolecular reaction. It seemed a logical extension to

believe therefore, that the existing intramolecular reaction could be enhanced significantly. We believed that the reaction yields could be increased while at the same time a milder reacting environment would be used. A superior reaction in water for these organic molecules would necessarily mean that one could design substrates which take better advantage of the hydrophobic effect in more elaborate syntheses and open the door to improved means of obtaining synthetically useful carbocycles.

3.2 Contruction of γ-(*n*-oxo-alkyl)-β- methoxycarbonyl allylic bromides.

3.2.1 The mild functionalization of acrylic systems.

Historically the synthesis of acrylic esters functionalized such as **3.7** was performed using masked acrylic systems, since polymerization of the ester under basic conditions was often problematic. To achieve this masking, the conversions seen in Figure 3.3 were commonly used. The carbonyl functionality can be protected along paths a or b as the corresponding ortho ester or acetal respectively. The vinyl group can be protected in either the β or α position as shown in paths c and d by groups which undergo subsequent elimination.

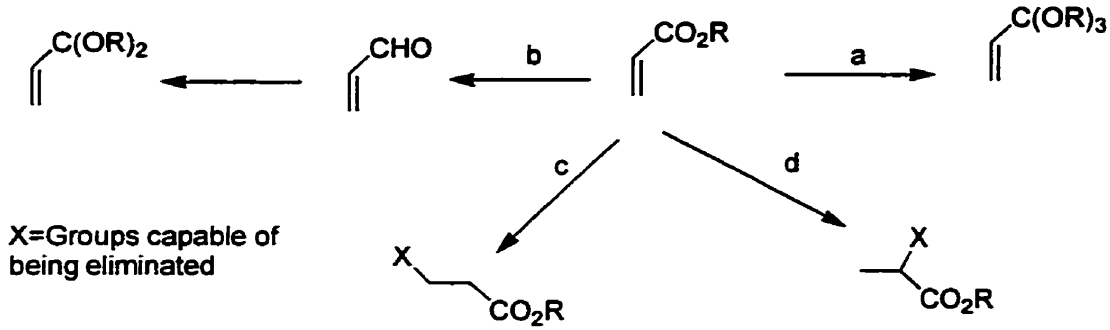
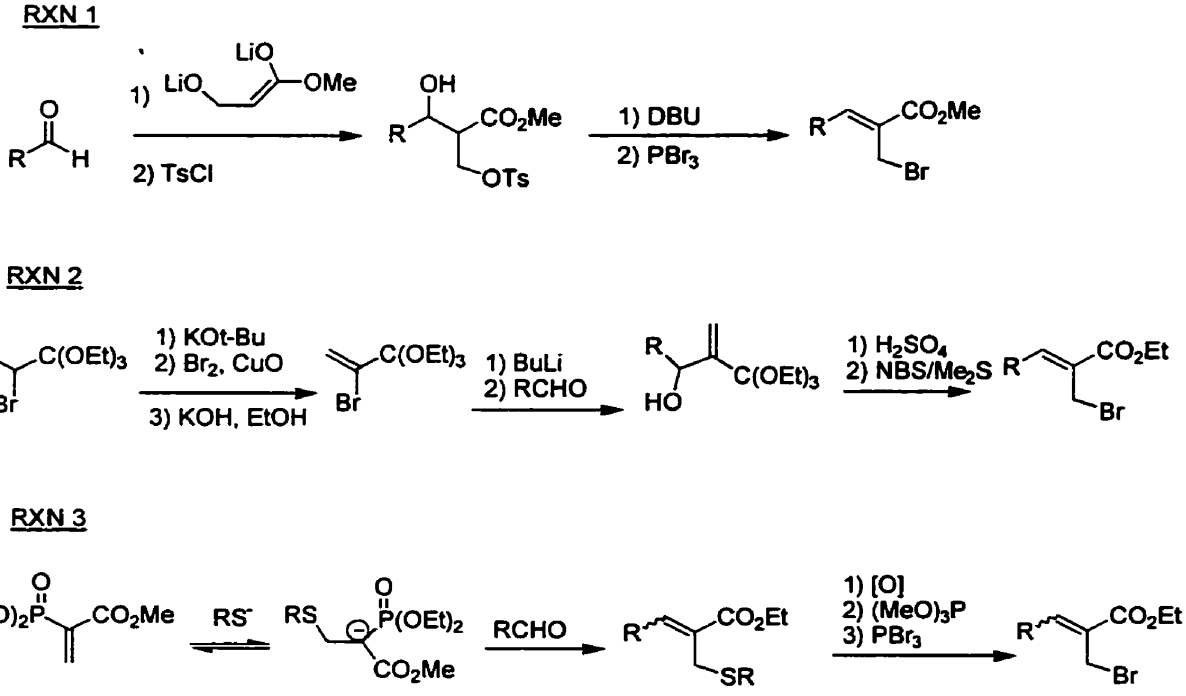


Figure 3.3

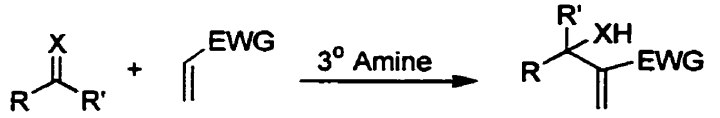
These synthetic procedures though valuable, are of limited scope, as a variety of functional groups cannot remain intact after most of the experimental procedures needed



Scheme 3.6[9b]

in the constructions. Scheme 3.6[9b] illustrates three such procedures, which demonstrate the typically harsh conditions as well as subsequent deprotection steps that often need to be taken. Several other masked acrylic species exist for similar purposes and each can be used with varying levels of difficulty for the synthesis of the desired γ-monosubstituted-β-methoxycarbonyl allylic bromides.

The obvious synthetic limitations of the above techniques led Hoffman *et al.* to investigate a more efficient route to produce the acrylic substrates in the presence of a variety of functional groups.[14] They focused on the elimination of the necessity to mask the acrylic system and sought to fuctionalize the α-position in a direct manner hence removing several laborious steps. Their research revealed that the α-position of acrylic esters could be coupled to aldehydes in a remarkably clean manner in a reaction catalyzed by the reversible addition of 1,4-diazabicyclo[2.2.2]octane (dabco) to the β-position of an α,β-unsaturated ester. This reaction, known as the Baylis-Hillman reaction,[15] (general form represented in Scheme 3.7) provided a direct means for α-functionalization of acrylic esters in a mild, economical (amounts of reagents) and high yielding manner.



X = 0, NR^2 EWG= electron withdrawing group

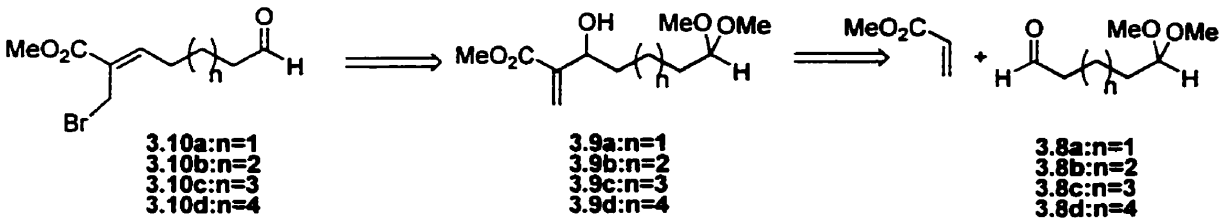
Scheme 3.7

The original reaction as illustrated nicely by Hoffman for the construction of γ-monosubstituted-β-methoxycarbonyl allylic bromides had great synthetic utility with one disadvantage being the slow rate (generally 7 or more days) of the reaction as reported (under neat conditions at room temperature and atmospheric pressure with catalytic amounts of dabco). Several attempts have been made at increasing the rate of the reaction through alteration of the physical and chemical environments.[15,16] They include the incorporation of protic groups or solvents, increase in reaction temperature and pressure,

decrease in reaction temperature, higher proportions of catalyst, sonication and microwave irradiation .[15, 16]

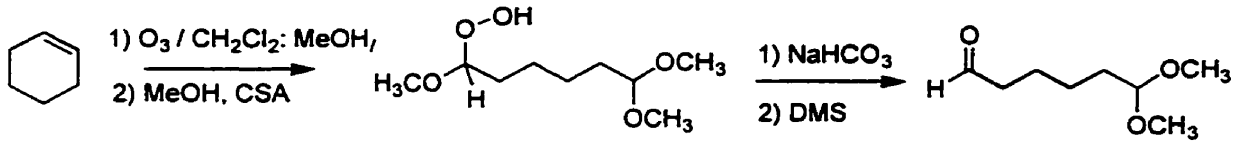
3.2.2 The synthesis of cyclization precursors.

To initiate our study of the indium-mediated intramolecular cyclization it was first of all necessary to synthesize the desired bromo-aldehydes **3.10**. As we have discussed above, several manners of disconnecting acrylic systems of this nature exists, but the pathway employing the Baylis-Hillman reaction (Scheme 3.7) for functionalization of the acrylic system was most attractive (Scheme 3.8).



Scheme 3.8

Hoffman *et al.*[14] had shown how bromides related to **3.10** could be produced from the appropriate aldehyde **3.8** *via* the allylic alcohol **3.9** in high yielding reliable procedures with the Baylis-Hillman reaction as the key initial step. We envisioned synthesizing the necessary aldehyde **3.8** from the corresponding diol or using an ozonolytic procedure which had been developed by Schreiber *et al.*[17] They used a one-pot sequence for production of the monoprotected dialdehyde from the corresponding cycloalkene by careful manipulation the ozonide (Scheme 3.9).

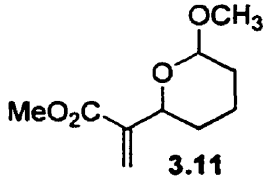


Scheme 3.9

We were able to use this procedure for the cleavage of cyclo-hexene, -heptene and –octene to give moderate yields of the desired starting aldehydes **3.8b, 3.8c and 3.8d**. The procedure obviated the many steps that would be needed with the use of symmetrical diols as starting materials but was not without its shortcomings. The desired material could only be synthesized in a 60-70% yield (determined by ^{1}H NMR), and their physical separation from the accompanying side products was very difficult, as the difference in polarity was very small. It proved more efficient to react the crude mixture in the subsequent Baylis-Hillman coupling after which the product allylic alcohol **3.9** could be more easily purified by flash column chromatography. The selectivity of the dabco-catalyzed reaction was hereby further demonstrated as the aldehyde could be reacted fully in the crude mixture without any complicating side reactions. We were then able to tranform the allylic alcohols **3.9b, 3.9c,and 3.9d** to the corresponding allyic bromides **3.10b**, **3.10c** and **3.10d** by treatment at 0 °C with phosphorus tribromide (PBr_3). This reaction was advantageous as the acidic conditions also resulted in the cleavage of the acetal hence accomplishing two transformations in one single step. In all cases, a single geometric isomer corresponding to the Z-double bond was produced from the S_n2' displacement of the alcohol.

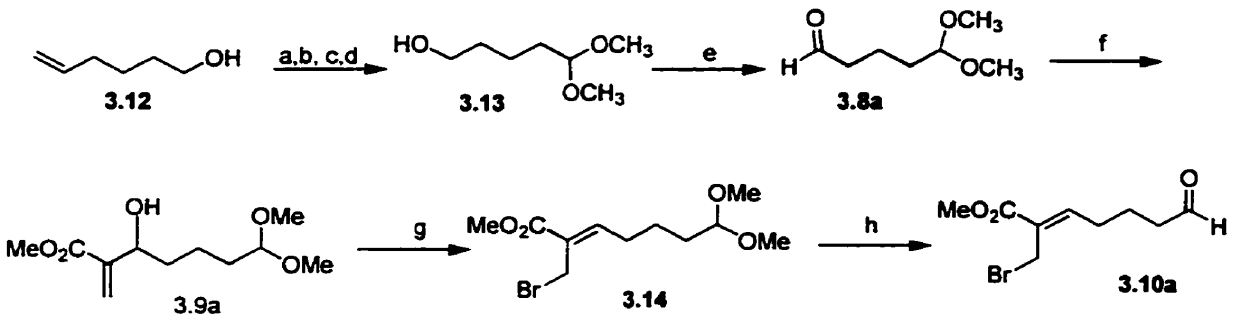
Unlike its larger homologues, cyclopentene did not furnish a sufficient amount of the desired monoprotected-dialdehyde under the ozonolytic procedure. We therefore

decided to use the 5-hexen-1-ol **3.12** in the construction of 5,5-dimethoxypentanal **3.8a**. The alcohol could be fully protected as its benzoyl ester and the alkene cleaved via ozonolysis. After reduction with dimethylsulfide (DMS) the product aldehyde could be protected as its dimethyl acetal and the benzoyl ester removed, furnishing intermediate alcohol **3.13**. To prevent partial cleavage of the dimethyl acetal protecting group, the subsequent PCC oxidation was performed under buffered conditions (AcONa 100mg per 1g of PCC). Oxidation provided a quantitative conversion to the aldehyde, but the isolation of the product had to be performed with multiple extractions of the black product residue. In this manner aldehyde **3.8a** was produced and then coupled to methyl acrylate in the presence of dabco. The reaction with 0.5 equivalents (larger amounts did not significantly enhance the rate of the reaction) of dabco proceeded to near completion within 5-7days. The allylic alcohol product **3.9a** which was unstable after 2h in $CDCl_3$[18] could not be transformed to the cyclization precursor **3.10a** *via* treatment with PBr_3. Rather, we encountered difficulties most likely caused by the ability of the alcohol to form a tetrahydropyran derivative **3.11** under acidic conditions.



3.11

To effect the desired transformation therefore we decided to form the bromide **3.14** under neutral conditions with NBS/ Me_2S[14] prior to the unmasking of the aldehyde.

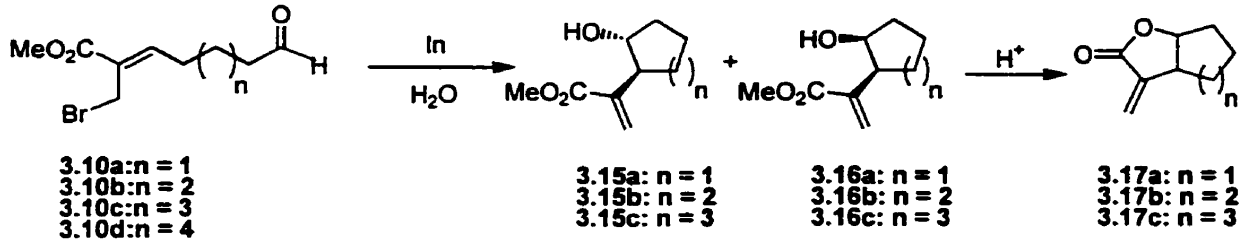


Scheme 3.10 a) Benzoyl chloride, triethylamine, DMAP (cat) / CH_2Cl_2 (6h at rt.); b) O_3, -78^0C / CH_2Cl_2 then dimethyl sulfide -78^0C –rt.; c) MeOH, CSA (cat), reflux, 3 h.; d) NaOH / MeOH (50mg per 7mL); e) PCC / CH_2Cl_2, rt, 2.5 h; f) Methyl acrylate, dabco (0.5equivalents), 5 days; g)[14] N-Bromosuccinimide, dimethyl sulfide / CH_2Cl_2 1h.; h) Acetone/CSA, rt. 12h.

With the starting bromo-aldehydes **3.10 a-d** in hand we were now able to investigate the indium-mediated intramolecular carbocyclization in aqueous media. The feasibility of producing biologically significant fused α-methylene-γ-butyrolactones in water could now be studied with emphasis being focused on the selectivity of the closure (Scheme 3.4), and the yields associated with the production of these important substrates.

3.3 Indium-mediated intramolecular carbocyclization. A facile generation of *cis* fused α–methylene-γ-butyrolactones in water.

Having the desired molecules **3.10 a-d**, we were then able to investigate the reaction shown in Scheme 3.11. The bromo-aldehydes **3.10** (1mmol) were stirred with indium (3mmol) in water (2mL) for 12 h or longer if necessary (disappearance of the starting materials was monitored by thin layer chromatography) before being extracted into diethyl ether and purified by flash column chromatography.



3.10a:n = 1
3.10b:n = 2
3.10c:n = 3
3.10d:n = 4

3.15a: n = 1
3.15b: n = 2
3.15c: n = 3

3.16a: n = 1
3.16b: n = 2
3.16c: n = 3

3.17a: n = 1
3.17b: n = 2
3.17c: n = 3

Scheme 3.11

For n = 1 and 2 the reaction proceeded smoothly to generate the five and six-membered cyclized products in very good yields. The five-membered products were formed as a mixture of the ester **3.16a** and lactone **3.17a** while the ester **3.16b** was formed exclusively with no lactonization observed. The lactonization of this substrate to **3.17b** was performed successfully by treatment with triflouroacetic acid in CH_2Cl_2 (pH ~2) for 24 h. Indium-mediated cyclization of the seven-membered ring proceeded less readily and after 24 h only a 60 % yield of the product **3.17c** was obtained after purification. When the same reaction was attempted for the eight-membered carbocycle the closure was too slow to compete with side reactions in which the starting material was consumed. Attempts at effecting this reaction by increasing the volume of water, adding ytterbium triflate (water stable Lewis acid) or sonication did not result in a successful cyclization of the 8-membered substrate.

Where the cyclizations were successful we were particularly pleased to find that in all cases only a single diasteromeric product was observed. While there exists the potential to form both the *trans* **3.15** and *cis* **3.16** fused products, we found that the stereochemistry across the ring junction was *cis* in all cases. This was confirmed by comparison with data reported in the literature.[19]

Table 3.1: Results of indium-mediated intramolecular carbocyclizations for 5-8 membered rings.

Compounds 3.10 a-d n (ring size)	Reaction time	Compound 3.17 a-d % Yield	Selectivity
1 (5)	12 h	>95	Exclusively cis
2 (6)	12 h	>95	Exclusively cis
3 (7)	12-24 h	~ 60	Only cis isolated
4 (8)	12-48 h	0	NA

The exclusive nature of the cyclization was rationalized based on the energy difference in the transition states shown in Figure 3.4. With the geometry of the halide being fixed the aldehyde approaches in either an up or down fashion leading to species **3.18** (chair-boat) and **3.19** (chair-chair). The increased stability of **3.19** leads to the *cis* fused product as the sole outcome of the cyclization.

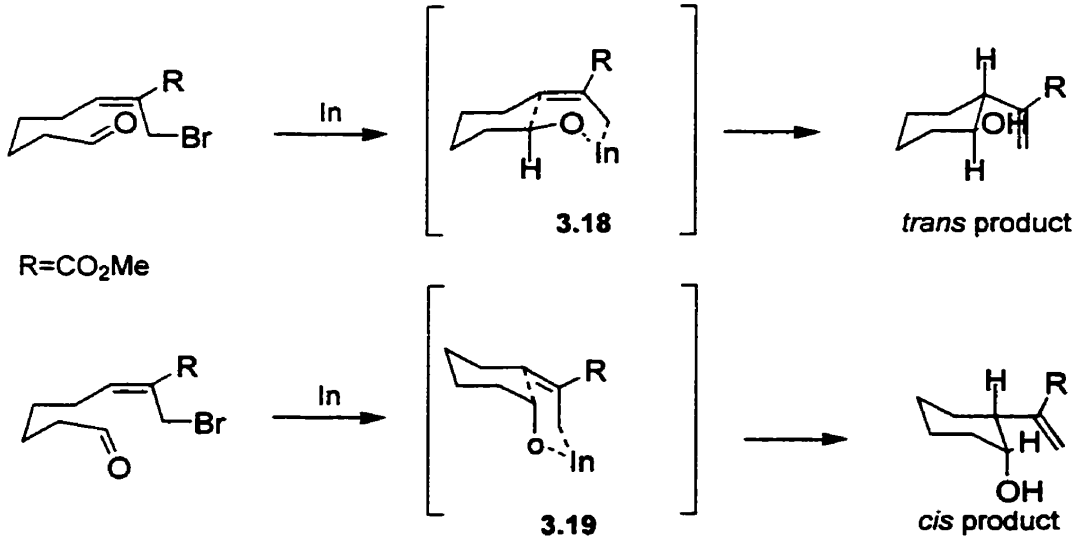


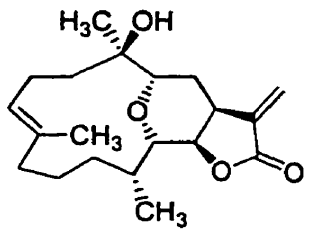
Figure 3.4

The indium-mediated cyclization proved not only to be feasible but also to be high yielding and exclusive in its stereochemical outcome. This expansion of the methodology represented a significant achievement and to further illustrate its applicability we decided to focus on a second series of substrates, in which the α-methylene-γ-butyrolactones were fused to oxygen heterocycles. In addition to the inherent usefulness of such substrates, we were interested in investigating the effect that the inclusion of an oxygen atom would have on the cyclization. In addition to the ability of an ether linkage to inductively affect the electrophilicity of an aldehyde, depending on their proximity to each other, we knew that the solubility of the substrates in water could be affected, as well as the conformations available for reaction purposes.

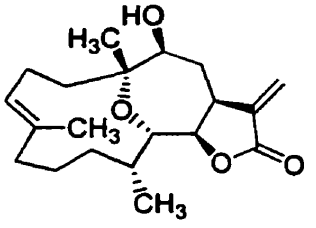
3.4 α-Methylene-γ-butyrolactones fused with oxygen heterocycles.

Recently, biologically active compounds of marine origin[20] have become the focus of much interest. In particular, synthetic chemists have been attracted by the novelty and toxicity associated with many of these species. Oxygen heterocycles of 6-9 membered systems have attracted much attention since their discovery in polyether toxins such as brevetoxin, ciguatoxin, maitotoxin, yessotoxin and the halichondrins.[21] Driven by this, much progress has been made in the synthesis of fused tetrahydropyran rings. The closure of γ–hydroxy epoxides, intramolecular Michael additions of a hydroxy group to an α,β-unsaturated ester, ring closing metathesis reactions and intramolecular allylmetalation reaction of aldehydes are some of the successful routes developed to these species.[20,21]

We were attracted by a different class of oxygen-heterocycles isolated from the sesquiterpenoid and diterpenoid content of Caribbean georgian *eunica succinea* collected in the US Virgin Islands.[22] Rodriguez *et al.*[23] had shown the high biological activity against leukemia cells associated with cembranolides eunicin **3.20** and jeunicin **3.21.**



3.20

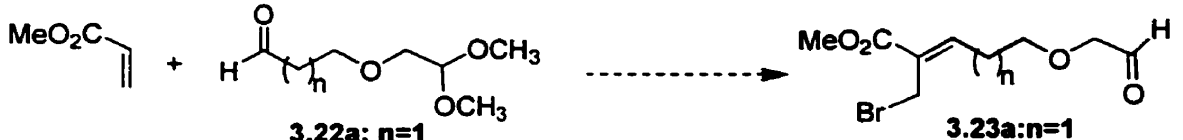


3.21

Figure 3.5: Biologically active cembranolides containing cyclic ethers fused with α-methylene-γ-butyrolactones.

Having established a mild route to the fused lactones with the indium-mediated closure of carbocycles we became interested in extending the protocol to α-methylene-γ-butyrolactones fused with oxygen heterocycles. This system being a constituent of biologically active substrates such as **3.20** and **3.21**, we were also interested in testing the activity associated with our targets.

3.4.1 Synthesis of the cyclization precursors.

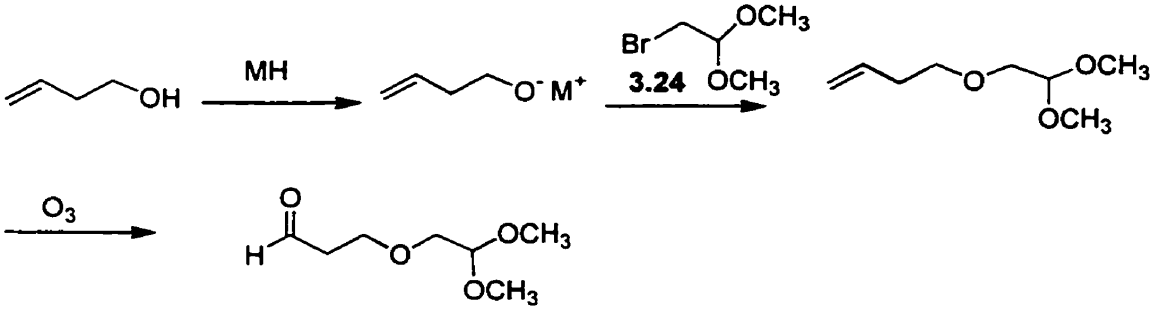


3.22a: n=1
3.22b: n=2
3.22c: n=3

3.23a:n=1
3.23b:n=2
3.23c:n=3

Scheme 3.12

The introduction of our acrylic system was done in the same way as that used previously for the carbocycles (Scheme 3.12). This route illustrated by Hoffman *et. al*[14] served as a very effective and mild manner for the production of the γ-alkyl-β-methoxycarbonyl allylic bromides in good yields. With the choice of the appropriately substituted mono-protected dialdehyde the procedure allows for a wide variety of substrates to be synthesized. We therefore focused on the synthesis of the necessary aldehydes **3.22**. Scheme 3.13 shows the initial path we chose to the desired aldehydes. The alkenols such as 3-buten-1-ol **3.25** (n=1) are readily available and with these we wanted to alkylate bromoacetaldehyde dimethylacetal **3.24.** The resulting product could then be ozonized to provide the desired material. We found however that the alkylation step with either NaH, KH or $Na(Me_3Si)_2N$ as the base did not serve to produce the alkylated product in good yields. In each case we found that the bromide was consumed

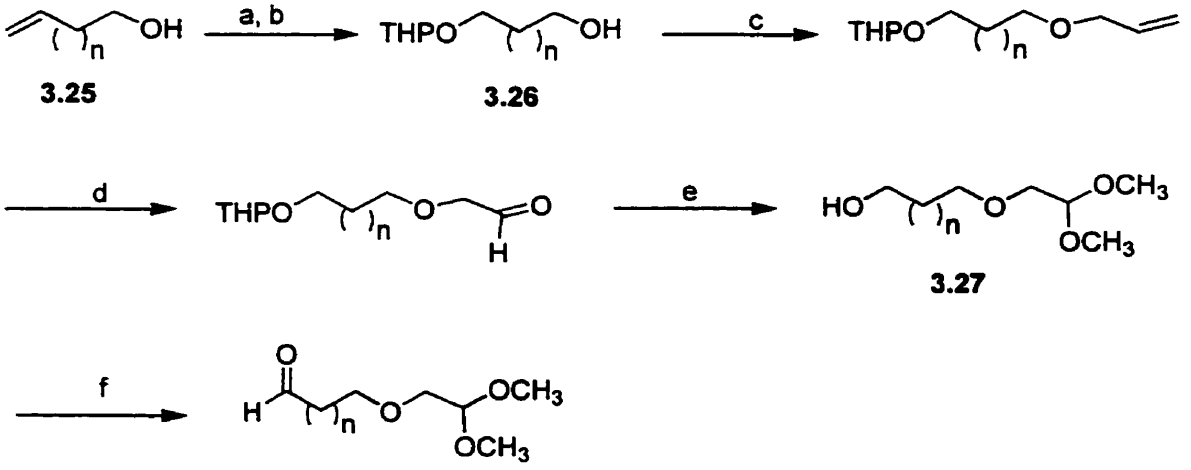


MH = KH, NaH, or Na $((CH_3)_3Si)_2N$

Scheme 3.13

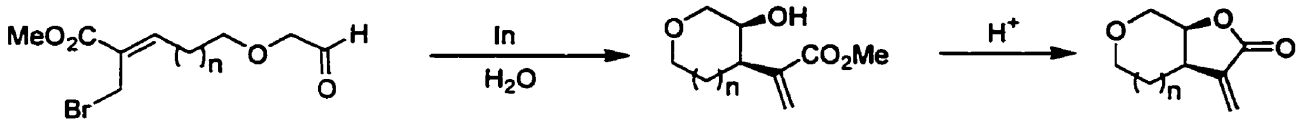
very rapidly upon addition to the basic media. In addition, the ether product and bromide (used in excess) were of similar polarity and that complicated chromatographic

purification. We sought to eliminate these problems by substituting allyl bromide for bromoacetaldehyde dimethylacetal in the alkylation step. This could be done without a problem with the only need being the prior cleavage of the unsaturated bond in the alkylating species. In the redesigned route illustrated above (Scheme 3.14), alcohol **3.25** could be protected as the THP ether and then the double bond ozonized and reduced to the alcohol by treatment with $NaBH_4$. Ozonolysis could be performed free of complications if the temperature was rigorously controlled at –78°C until the double bond was fully consumed. The alkylation of allyl bromide by **3.26** with NaH / DMF was performed, but the alkylation with KH / THF proved much more efficient as the dry THF was more easily available and more easily removed at the end of the reaction. The hydroxyl-protecting group was removed with simultaneous protection of the aldehyde by reflux in MeOH in the presence of CSA. The final oxidation provided the desired alcohol if buffered PCC was used. The necessary precursors were then easily prepared via the Baylis-Hillman reaction with methyl acrylate followed by treatment with phosphorus tribromide.



Scheme 3.14 a) DHP, CSA(cat), CH_2Cl_2 rt.; b) O_3 –78°C then $NaBH_4$;c) KH / THF then allyl bromide; d) O_3, –78°C, dimethyl sulfide. e) MeOH, CSA (cat), reflux; f) PCC / NaOAc (1g/100mg)/CH_2Cl_2.

Having the desired bromides **3.23 a-c**, we were now able to investigate the production of the functionalized oxygen heterocylces using the indium-mediated intramolecular cyclization.



3.23a: n = 1
3.23b: n = 2
3.23c: n = 3

3.28a: n = 1
3.28b: n = 2
3.28c: n = 3

3.29a: n = 1
3.29b: n = 2
3.29c: n = 3

Scheme 3.15

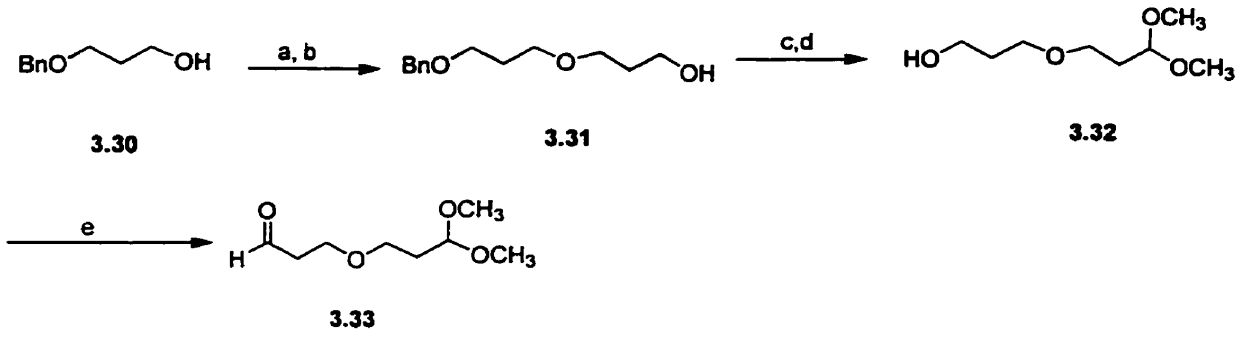
We found that the 6,7 and 8- (n = 1,2 and 3) membered substrates cyclized in a more complete manner (Table 3.2) compared to the corresponding carbocyles (Table 3.1), furnishing the cyclized materials in much improved yields with the eight-membered carbocycle being produced in a 30 % yield. The 6-membered heterocycle was formed as the ester **3.28a** which was induced to cyclize under acidic conditions. The lactone **3.29b** was the only product from cyclization of the 7-membered substrate **3.23b** and the 8-membered product was formed as a mixture of the lactone **3.29c** and ester **3.28c** which cyclized after treatment with TFA to give **3.29c**.

Table 3.2 Results of indium-mediated intramolecular carbocyclizations for 6-8 membered cyclic ethers fused with α-methylene-γ-butyrolactones (Scheme 3.15).

n (ring size)	Reaction time	% Yield	Selectivity
1 (6)	12 h	>95	Exclusively cis
2 (7)	12 h	>95	Exclusively cis
3 (8)	12-24 h	~ 30	Only cis isolated

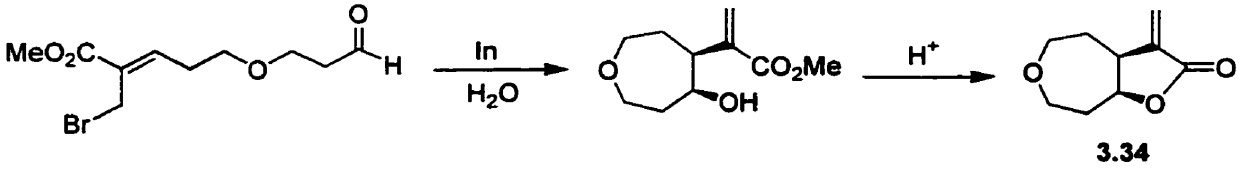
The results indicated that the ether linkage had a significant effect on the cyclization of the 7- and 8-membered substrates (**3.23b** and **3.23c**). If one were to attempt to account for the improved reaction, any of a number of factors could have contributed to the superior results. Firstly, the oxygen being beta to the aldehyde inductively increases the electrophilicity of this center. Secondly, the increased polarity of the ether system compared to the carbocycles, as was evident by thin layer chromatography, could have led to a slight increase in solubility of the organic species in aqueous media. This could be significant, as some solubility in aqueous media is necessary for the hydrophobic effect to provide assistance. It was apparent in the carbocyclization that we had not received much assistance in this regard from the aqueous media but with the improved results in the oxygen systems such effect could not be disclaimed.

Any significant effect of enhanced electrophilicity through an inductive effect caused by having the oxygen in the β- position relative to the aldehyde was investigated. As shown in Scheme 3.16, an additional cyclization precursor which had the oxygen in the γ-position relative to the aldehyde was constructed. In the sequence, the



Scheme 3.16 a) KH / THF, allyl bromide; b) 9-BBN / THF, rt.; c) PCC / CH_2Cl_2 then reflux in MeOH containing CSA (cat); d) H_2/Pd C 24 h.; e) PCC:NaOAc (1g:100mg) / CH_2Cl_2.

monobenzylated diol **3.30** was used to alkylate allyl bromide; hydroboration with BH_3 gave a 75% yield of the primary alcohol **3.31**. The yield of the primary alcohol was increased to 95% with 9-BBN. Following the oxidation of the alcohol, dimethylacetal formation and hydrogenation, alcohol **3.32** was obtained. The final oxidation led to the desired monoprotected dialdehyde **3.33**. Transformation to the cyclization precursor was then done as previously described (Scheme 3.12) and then subjection to the indium-mediated intramolecular cyclization conditions in aqueous media (Scheme 3.17) performed.



Scheme 3.17

We found that moving the ether to the γ-position had no observable effect on the cyclization and the oxygen-heterocycle was produced in quantitative yield. As in the

carbocycles the seven-membered system cyclized almost completely through to the lactone **3.34** in the reaction medium. This result showed that the inductive activation of the aldehyde was not a significant factor in the enhanced yields obtained by inclusion of the ether linkage. This was further supported by the fact that no improved yields in the initial carbocyclizations had been observed even with the addition of ytterbium triflate, a water stable Lewis acid capable of increasing the electrophilicity of the aldehyde. Hence, other factors including possible hydrophobic interactions contributed to a much improved cyclization reaction for the heterocycles compared to the carbocycles.

We were therefore successful in demonstrating the utility of the indium-mediated reaction in aqueous media. Analogs of biologically active cembranolides **3.20** and **3.21,** fused with heterocylic α-methylene-γ-butyrolactones, were synthesized in a high yielding reaction in aqueous media.

3.4.2 Analysis of biological activity.

α-Methylene-γ-butyrolactones fused with oxygen heterocycles are important constituents of biologically active substrates such as eunicin **3.20** and jeunicin **3.21.** Having successfully illustrated their facile production (Table 3.2), we were now interested in submitting these substrates for cytotoxicity studies against cancer cells. The compounds **3.29a** and **3.29b** were tested against breast cancer, renal cancer, and two types of melanoma cell lines. The particulars of the testing can be found in Appendix A and Table 3.3 provides a summary. It was observed that the stated molecules caused significant cell death when the listed cell lines were exposed to them.

Table 3.3: Summary of cytotoxicity study (Appendix A) of cyclic ethers 3.29a and 3.29b against breast **cancer, renal cancer, and two types of melanoma cells lines.**

Cell	Compound 3.29a for 5 days (IC 50 μM)	Compound 3.29a for 7days (IC 50 μM)	Compound 3.29b for 5 days (IC 50 μM)
MCF7wt BREAST CANCER	94	59	77
TK-10 RENAL CANCER	149	28	123
UACC-62 MELANOMA	54	17	32
UACC-257 MELANOMA	68	12	56

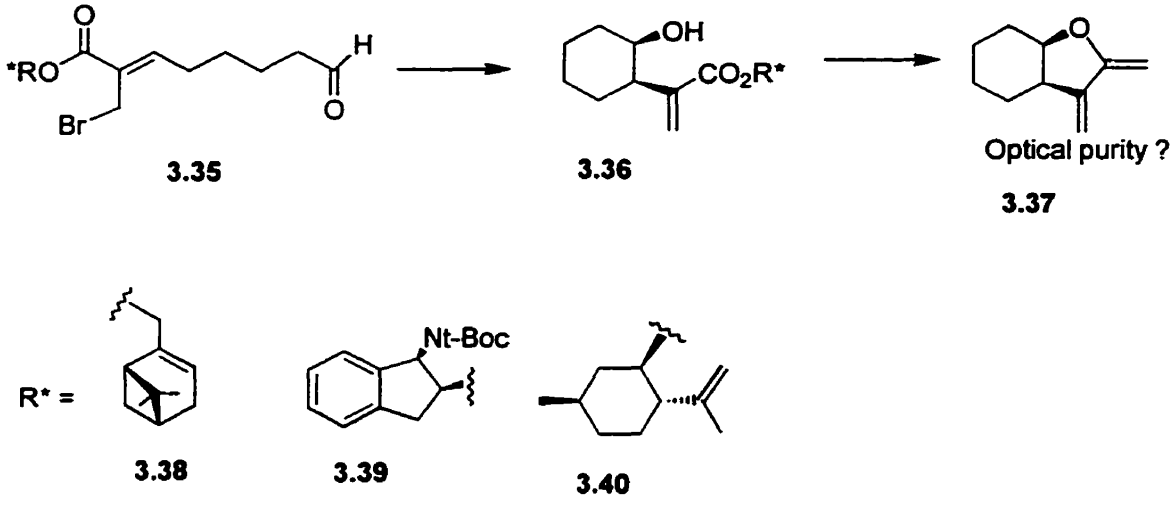
These results served to provide further insight into the utility of indium-mediated allylation methodology. Here we were able demonstrate how biologically active oxygen heterocycles could be easily produced in water in a diastereoselective manner.

3.5 Cyclization of substrates attached to chiral auxiliaries.

Our investigation of the indium-mediated intramolecular cyclization in aqueous media revealed a facile, mild and efficient manner for the production of *cis* fused α-methylene-γ–butyrolactones in good yields. The reaction proved its usefulness in the production of biologically active oxygen heterocycles. Having demonstrated the nature of the high diastereoselectivity associated with the reaction, we wanted to investigate if with chiral auxiliaries we could produce enantiomeric excesses in the products. We had a couple of questions in this regard that required answers: 1) would the large increase in the hydrophobic nature of the molecule create complications in the water-based reaction? 2)

would the compressed conformations in aqueous media allow for simple auxiliaries to have an effect on the selectivity of the cyclizations?

We performed our brief study in this area with (1*R*)-myrtenyl **3.38**, (1*S*, 2*R*)-cis-N-*t*-Boc-aminoindanyl **3.39** and (1*S*, 2*R*, 5*S*)-(+)-menthyl **3.40** esters as shown in Scheme 3.18.



3.35 **3.36** **3.37**

3.38 **3.39** **3.40**

Scheme 3.18

The necessary bromide **3.35** was synthesized in a similar manner as in Scheme 3.10 with methyl acrylate being substituted by the acrylic ester of **3.38**, **3.39** or **3.40**. One point worthy of note is the rapid Baylis-Hillman reaction observed with the ester of **3.39** which was complete in 6 h compared to the other auxiliaries which required several days.

Table 3.4: Results of the cyclization of the 6-membered carbocycle with chiral auxiliaries attached (Scheme 3.18).

Entry	Auxilliary	% Yield	Diasteromeric Excess
1	Myrtenol **3.38**	95%	0[b]
2	Aminoindanol **3.39**	80[a]%	0[c]
3	Menthol **3.40**	78%	12[b]

a)Yield calculation based is on the isolated lactone after cleavage of the auxilliary. b) Determined by ^{1}H NMR (500MHZ) using the methylene protons, which were easily discernable. c) Since the peaks in the ^{1}H NMR were not very discernable the lack of any optical activity in the lactone was used as the determining factor.

We found that in the cases of myrtenol and aminoindanol the cyclizations proceeded well at room temperature. The cyclization produced the esters **3.36** which if possible were analyzed by ^{1}H NMR for diastereoselectivity prior to being cyclized to the corresponding lactones **3.37**. Since the diastereoselectivity of the cyclized product attached to aminoindanol (Entry 2) was not discernable by ^{1}H NMR, the lactone was analyzed for optical activity following cleavage from the auxilliary. The results of these two substrates revealed no excesses were observed either in the ^{1}H NMR or by optical rotation. When menthol was employed (Entry 3), the cyclization at room temperature was not successful. It was only after sonication at rt-40°C for 24 hours that we were able to obtain the cyclized material in 78% yield. Here we observed a small diastereomeric excess of 12% in ^{1}H NMR.

It was evident from the results (Table 3.4) that the reaction was not significantly affected by simple auxiliaries and we were able to see a slight enantiomeric excess in the product mixture only after menthol was introduced. We were pleased to demonstrate however, that the increased hydrophobic nature of the molecule did not inhibit cyclization and that this remains a viable route to enantioselective reactions.

3.6 Conclusion

In conclusion, we have successfully expanded the scope of the indium-mediated allylation in aqueous media beyond intermolecular coupling to the realms of

intramolecular carbocyclizations in aqueous media. In so doing, we were able to demonstrate how carbocycles fused with α-methylene-γ-butyrolactones, structural units which are abundant in nature, could be produced in a *cis*-selective manner, in water at room temperature. In addition to expanding the scope of this mild methodology, we also further demonstrated the synthetic utility with the efficient production of biologically active oxygen heterocycles, analogs of cembranolides such as eunicin **3.20** and jeunicin **3.21**.[23] In this study we revealed that the cyclization of the heterocycles proved superior to the carbocyclization furnishing even the difficult 8-membered cycle, probably with the aid of hydrophobic forces.

In a brief analysis, we also initiated studies into performing the carbocyclizations with the substrates attached to some chiral auxiliaries of a significant size. Although with the auxiliaries used, we were not successful in effectively transferring chirality, we were able to illustrate the feasibility of using the methodology in such a manner and with menthol we did observe a 12% enantiomeric excess in the product (entry 3, Table 3.4).

Our studies have successfully expanded the scope of the indium-mediated allylation and the demonstrations of the synthetic utility has served to illustrate the significant impact the methodology can have on synthetic organic chemistry.

3.7 Experimental procedures

3.7a General. Nuclear Magnetic Resonance spectra were gathered using a VARIAN Gemini 200 (^{1}H 200MHz, ^{13}C 50MHz) or a Unity 500 (^{1}H 500MHz, ^{13}C 125MHz) spectrometer. The Chemical shifts were reported on δ scales in parts per million (ppm) relative to a referenced solvent signal. The designations of singlet (s), doublet (d), triplet (t), quartet (q), multipet (m) were assigned to the appropriate signals with the center of the peaks used as the recorded location. IR were recorded on a Bruker IFS48 spectrometer and Mass Spectra on a Kratos MS25RFA mass spectrometer. Specific rotations were determined with a Jasco DIP-140 digital polarimeter at 20 °C. Reactions were monitored using Thin Layer Chromatography (TLC) with E-Merck silica gel 60 F-254 polyester-backed 250μm plates.

3.7b General procedure for the ozonolysis of terminal alkenes: The olefins were dissolved CH_2Cl_2 (5) / MeOH (1) (1 M) and cooled to –78 °C. The oxygen inlet to the ozone generator was set at 20 lb. /sq. in.; the voltage was set at 75 volts; the pressure on the generator was set at 8 lb. /sq. in.; the sample outlet was set at 0.7 slp. and the open ended outlet was set at 0.3 slp. This resulted in a delivery rate of approximately 0.007 moles of ozone per hour. The ozone was bubbled through the solutions at –78 °C (temperature carefully maintained throughout) until a light blue persistent color representative of excess ozone was seen in the solution. At this point, the power on the ozone generator was switched off, and oxygen gas was bubbled for two minutes beyond the disappearance of the blue color. The oxygen was then disconnected and one of the following reduction procedures employed:

1) **Reduction to the corresponding aldehyde:** Dimethylsulfide (DMS) (2 equivalents) was added at –78 °C and the reaction was allowed to warm to room temperature. After 2 hours at room temperature the flask was heated at 30°C for 1 h and then excess DMS was removed by distillation. The residue was then taken up into diethyl ether (volume equal to that of the solvent used initially), washed with an equal volume of H_2O, and saturated NaCl, before being dried over Na_2SO_4. The solvent was removed under reduced pressure yielding the crude aldehyde.

2) **Reduction to the corresponding alcohol:** An equal volume of MeOH was added followed by $NaBH_4$ (1 equivalent) at –78 °C. The cooling bath was replaced by an ice bath for 1 h and then a water bath at 20 °C. The reaction was stirred and monitored by thin layer chromatography until all of the ozonide had been fully reduced (typically ~12h). The solvent was removed by rotary evaporation, an equal volume replaced and the evaporation repeated (step repeated one more time) yielding the crude alcohols.

3.7c General procedure for PCC oxidations: The starting alcohols in CH_2Cl_2 (1 M) were treated with 1.5 equivalents of PCC (buffered with sodium-acetate [100mg per 1g of PCC], if acid sensitive groups were present) at room temperature. The reaction was followed by thin layer chromatography until completion (usually within 3h). The CH_2Cl_2 was then evaporated under reduced pressure and the residue extracted three times with diethyl ether (20mL per mmol). It was essential at this point to thoroughly scrape the thick black residue from the sides of the flask while washing with diethyl ether as the isolated yields were very dependent on this extraction process and generally varied

between 75% and 85%. The solvent could then be filtered through silica-gel (or basic alumina) and concentrated. The aldehydes were generally of sufficient purity to proceed without purification.

3.7d General procedure for the protection of aldehydes as dimethyl acetals: The aldehydes to be protected were dissolved in MeOH (0.5M) containing CSA (0.2 equivalents) and the mixture was refluxed for 2h. At the end of this period the acid was neutralized with $NaHCO_3$ and the MeOH removed by evaporation. The residue was then taken up into diethyl ether (volume equal to that of the solvent used initially), washed with an equal volume of H_2O, and saturated NaCl before being dried over Na_2SO_4. After evaporation under reduced pressure, the dimethyl acetals were normally present in quantitative yields.

3.7e General procedure for deprotection of dimethyl acetals *via* transacetalization: CSA (0.2 equivalents) was added to a 0.5 M solution of the dimethyl acetal in acetone and the solution stirred at room temperature while being followed by thin layer chromatography. Most aldehydes were deprotected quantitatively within 6-12 h. Upon completion the reactions were stopped by neutralization of the acid with $NaHCO_3$ and diethyl ether was added (3 X volume of acetone). The organic layer was washed with an equal volume of H_2O and NaCl, before drying with Na_2SO_4. Evaporation of the solvents yielded the crude products.

3.7f General procedure for formation of allyl and benzyl ethers: Potassium hydride (1.2 equivalents; 35% in oil) was washed with distilled hexanes (3 X 5mL per g of reagent) under argon, and as much of the hexanes as possible removed. A suspension of the KH in THF (10mL per g of KH, THF distilled over CaH) was then stirred under

argon and the alcohol solution (0.5M in THF) added dropwise. Stirring was continued for 15 minutes and then the solution was cooled to 0 °C. Allyl bromide (or benzyl bromide) (1.2 equivalents) was added very slowly which generally resulted in a change in the appearance of the solution from a light brown to a light cream color. The ice baths were removed following completion of the addition, and after 30 minutes at room temperature, most alcohols were quantitatively converted to the corresponding allyl (or benzyl) ether (reactions were monitored by thin layer chromatography of small aliquots of solution which were removed and transferred into MeOH). The excess KH was destroyed via the slow addition of MeOH and the solvent was removed by evaporation under pressure. The residue was washed with diethyl ether (equal to the solvent removed) and washed with equal volumes of H_2O and saturated NaCl. After drying with Na_2SO_4 the solvent was removed under reduced pressure and any residual oil could be removed by eluting with hexanes through silica gel followed by 1:1 hexanes:ethyl acetate to obtain the product.

3.7g General procedures for the Baylis-Hillman reactions. The crude aldehydes were dissolved in an excess of methyl acrylate (2-3 equivalents) and treated with 0.5 equivalents of 1,4-diazabicyclo[2.2.2]octane (dabco) at room temperature until all of the aldehyde (9.5 -10ppm ^{1}H NMR) had disappeared (usually 5-7days if the aldehydes were not particularly activated). Dissolution in diethyl ether (10mL per 1mmol), followed by washing with an equal volume of H_2O and saturated NaCl, followed by drying with Na_2SO_4, and rotary evaporation produced the crude product allylic alcohol. The purity of the crude product was usually representative of that of the starting aldehyde.

3.7h General procedure for conversion of Baylis-Hillman adducts to the cyclization precursor allylic bromides: One of two methods were employed for the

transformation of allylic alcohols to the corresponding allylic bromides, depending on the ability of the starting material to cyclize to a stable tetrahydropyran derivative under acidic conditions.

1) **Allylic bromide formation under neutral conditions:** The transformations were performed with NBS/DMS *via* a published procedure[14]
2) **Allylic bromide transformation with PBr_3.** If instability under acidic conditions was not a problem then a more advantageous method for the transformation involved the use of PBr_3. In this reaction the substrates were dissolved in dry diethyl ether (0.25 M) and cooled to 0 °C under argon. A quantity of 0.5 equivalents of PBr_3 was delivered dropwise and the reaction stirred at that temperature until the starting material had been consumed (monitored by thin layer chromatography) (~ 1h). Upon completion, the mixture was poured onto ice/brine (equal volume as ether) and poured into a separatory funnel. The aqueous layer was washed two additional times with diethyl ether (equal volume) and then the organic layer was re-washed with saturated $NaHCO_3$, dried with Na_2SO_4 and then evaporated under reduced pressure. This procedure was advantageous as it effected simultaneous hydrolysis of the dimethyl acetals to the desired aldehydes

3.7i General procedure for the indium-mediated cyclizations in aqueous media. The organic substrate (1 mmol) was stirred vigorously in water (2mL) and to this solution was added indium powder (150 mesh, 3mmol) in 3 portions. The reactions were generally stirred overnight (12h) or longer if thin layer chromatography of an aliquot indicated the presence of starting material. The aqueous layer was then saturated with

NaCl, and extracted into ether (3 X 10mL) which was then dried with Na_2SO_4 and concentrated under reduced pressure. The products when necessary were purified by flash column chromatography with hexanes:ethyl acetate 9:1.

3.7j General procedure for the conversion of γ-hydroxy-α-methylene esters to α-methylene-γ-butyrolactones: A solution of the esters in CH_2Cl_2 (0.5M) was treated with TFA (pH 1.5 ~2) under argon until the ester was consumed (monitored by tlc, generally ~ 6h). For the compounds attached to chiral auxilliaries the lactonization was done in toluene (0.5M) at 70°C containing 0.2 equivalents of TFA.

3.7k Experimental procedures and spectroscopic data for specific compounds

5,5-Dimethoxypentanal (3.8a): 5-Hexen-1-ol (1mL, 8.3mmol) was dissolved in CH_2Cl_2 (15mL) containing triethylamine (1.5mL, 10mmol) and a catalytic amount of DMAP and the solution stirred under argon. Benzoyl chloride (1.2mL, 10mmol) was added dropwise and the reaction stirred until completed (6 h; monitored by thin layer chromatography). The terminal double bond was then ozonized (Section **3.7b 1**) and the resulting aldehyde protected as the dimethyl acetal (Section **3.7d**). Stirring of the resulting product in MeOH (15mL) containing NaOH (100mg) for 1 h gave alcohol **3.13** which could be oxidized with buffered PCC (Section **3.7c**) furnishing the desired aldehyde **3.8a**. Purification through silica gel using hexanes:ethyl acetate (9:1) as eluant, gave 1.0g (85% overall) of product. Colorless liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.74 (s, 1H), 4.35 (t, 1H, J = 4.8 Hz), 3.30 (s, 6H), 2.46 (t, 1H, J = 6.0 Hz), 1.65 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.6, 104.7, 54.0, 53.9, 44.7, 33.2, 18.8.

Methyl 7,7-dimethoxy-3-hydroxy-2-methylene-heptanoate (3.9a): A quantity of 1.0g (7.0mmol) of aldehyde **3.8a** was coupled with mehtyl acrylate in the Baylis-Hillman reaction (Section **3.7c**). After 7 days, a quantitative conversion to allylic alcohol **3.9a** was observed. Isolated yield 1.6g (99%), pale yellow liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.23 (s, 1H), 5.81 (s, 1H), 4.37 (m, 2H), 3.79(s, 3H), 3.32(s, 6H), 2.97 (br, OH), 1.75- 1.45 (m, 10H); ^{13}C NMR (50 MHz, $(CD_3)_2CO$) δ 166.7, 142.7, 125.2, 105.1, 72.2, 53.9, 53.0, 37.4, 33.7, 22.5.

Methyl (2Z)-2-(bromomethyl)-7-oxohept-2-enoate (3.10a): 1.0g of **3.9a** (6.8mmol) was transformed to the allylic bromide **3.14** under neutral conditions (Section **3.7b**). The crude product from this reaction was subjected to transacetalization as described above (Section **3.7e**). Yield 1.5g (87 %); pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.80 (s, 1H), 6.93 (t, 1H, J = 7.3 Hz), 4.22 (s, 2H), 3.81 (s, 3H), 2.55 (t, 2H, J = 7.2 Hz), 2.36 (q, 2H, J = 7.4 Hz), 1.87 (m, 2H); ^{13}C (50 MHz, $CDCl_3$) δ 199.8, 164.7, 145.7, 129.5, 52.5, 43.4, 28.5, 24.5, 21.1; MS CI (NH_3) m/z 267 (M + NH_4, 4%), 268 (M + 1 + NH_4, 4%), 250 (M +1, 11 %), 249 (M, 12%), 218 (13%), 217 (13%), 169 (86%), 137 (100%).

Hexahydro-3-methylene-2H-cyclopenta[b]furan-2-one (3.17a): Bromo-aldehyde **3.10a** (250mg, 1 mmol) was subjected to the indium-mediated allylation conditions described above (Section **3.7i**). ^{1}H NMR analysis of the crude product indicated the presence of 1:1.4 ratio of the prelactonized cyclized product **3.16a** and the corresponding lactone **3.17a. Methyl 2-(2-hydroxycyclopentyl)prop-2-enoate (3.16a) :** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (s, 1H), 5.70 (s, 1H), 4.32 (m, 1H), 3.77 (s, 3H), 2.89 (m, 1H), 2.01 (m, 1H), 1.87-1.56 (m, 5H). ^{13}C (125 MHz, $CDCl_3$) δ 168.0, 138.9, 126.3,

73.4, 52.0, 47.5, 34.2, 26.6, 21.7. Lactonization (Section 3.7j) produced a single product which was purified by elution through silica gel with hexanes:ethyl acetate (9:1) giving **3.17a** ; very pale yellow oil (130mg, 95%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19 (d, 1H, J = 2.5 Hz), 5.64 (d, 1H, J = 2.5 Hz), 4.99 (t, 1H, J = 6.1 Hz), 3.41 (m, 1H), 2.070 (m, 1H), 1.93 (m, 1H), 1.72 (m, 4H); ^{13}C (125 MHz, $CDCl_3$) δ 171.2, 140.4, 122.8, 83.2, 42.9, 35.6, 33.8, 23.0.[9a]

Methyl 8,8-dimethoxy-3-hydroxy-2-methylene-octanoate (3.9b): Cyclohexene (1mL, 10mmol) was dissolved in 25 mL of CH_2Cl_2 / MeOH (5 / 1) and cooled to –78 ^{0}C. O_3 was bubbled through at an approximate rate of 0.007 moles per hour until a faint blue persistent color was seen in the flask (~ 1.5 h). At this point, the excess O_3 was removed by bubbling O_2 through the solution for 2 minutes, following which a catalytic amount of CSA (500mg, 2.1mmol) was added. The solution was stirred at room temperature for 6 h after which the acid was neutralized using $NaHCO_3$ and the intermediate peroxide reduced with dimethylsulfide (1.5mL, 20mmol) by stirring for 2h at rt and 1h at 30°C. The solvents were removed by rotary evaporation and the aldehyde was extracted into diethyl ether (50mL) which was subsequently washed with H_2O (50mL) and NaCl (50mL) . After the solvent was dried with Na_2SO_4 and removed by evaporation under reduced pressure, a pale yellow oil was isolated. The crude product was dissolved in methyl acrylate (2mL) and reacted under the conditions for the Baylis-Hillman reaction (Section **3.7g**) until no aldehyde peak (δ 9.8 – 10.0 ppm) was seen in the crude ^{1}H NMR (200 MHz, $CDCl_3$). Following purification through silica gel with gradient elution of hexanes:ethyl acetate (9:1, 6:1), **3.9b** was isolated as a pale yellow liquid.70% overall yield (1.7g) ; (200 MHz, $CDCl_3$) δ 6.20 (s, 1H), 5.80 (s, 1H), 4.39 (m, 2H), 3.76 (s, 3H),

3.30 (s, 6H), 2.61 (br, OH), 1.70- 1.31 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.3, 142.1, 124.8, 104.8, 72.0, 53.4, 52.7, 36.9, 33.1, 25.9, 24.1.

Methyl (2Z)-2-(bromomethyl)-8-oxooct-2-enoate (3.10b): Allylic alcohol **3.9b** (1.7g, 6.9mmol) was transformed to the corresponding allylic bromide by treatment with PBr_3, (Section **3.7h 2)** giving a light brown crude oil. The product was purified by elution through silica gel with hexanes: ethyl actetate (9:1) giving a pale yellow oil (1.6g, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (s, 1H), 6.92 (t, 1H, J = 7.3 Hz), 4.18 (s, 2H), 3.76 (s, 3H), 2.45 (dt, 2H, J =1 Hz and J = 7.1 Hz), 2.29 (q, 2H, J = 7.5 Hz), 1.66 (m, 2H), 1.53 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.1, 164.9, 146.8, 128.8, 52.5, 44.0, 29.1, 28.4, 24.8, 21.7.

Heptahydro-3-methylene-2H-cyclohexa[b]furan-2-one (3.17b): Compound **3.17b** (260mg, 1mmol) was produced from **3.10b** using the methodology employed for the conversion of **3.10a** to **3.17a**. Pale yellow oil; Yield (130mg, 85%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19 (d, 1H, J = 2.4 Hz), 5.51 (d, 1H, J = 2.0 Hz), 4.54 (q, 1H, J = 6.8 Hz), 3.02 (m, 1H), 1.93-1.32 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ171.7, 140.0, 121.7, 82.8, 43.0, 34.4, 32.0, 31.9, 23.9.

Methyl 9,9-dimethoxy-3-hydroxy-2-methylene-nonanoate (3.9c): Compound **3.9c** was produced from cycloheptene (1mL, 8.6mmol) using the same procedure employed for the conversion of cyclohexene to **3.9b**. Yield 1.5g, 67%; yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.22 (s, 1H), 5.80 (s, 1H), 4.36 (m, 2H), 3.80 (s, 3H), 3.31 (s, 6H), 2.64 (br, OH), 1.70- 1.29 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.9, 141.7, 124.3, 104.1, 71.7, 52.8, 52.1, 36.6, 32.9, 29.8, 26.3, 25.1

Methyl (2Z)-2-(bromomethyl)-9-oxononenoate (3.10c): Produced from **3.9c** (1.5g, 6mmol) using the same procedure employed for the conversion of **3.9b** to **3.10b**. Yield 1.4g (88%); pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.75 (s, 1H), 6.94 (t, 1H, J = 7.5 Hz), 4.20 (s, 3H), 3.78 (s, 6H), 2.44 (t, 2H, J = 7.3 Hz), 2.31(q, 2H, J = 7.5 Hz), 1.54(m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.8, 164.9, 147.1, 128.8, 52.4, 44.0, 29.4, 29.2, 28.4, 24.8, 22.4.

Octahydro-3-methylene-2H-cyclohepta[b]furan-2-one (3.17c) : Produced from **3.10c** (277mg, 1mmol) using the same methodology employed for the conversion of **3.10a** to **3.17a**. Yield 60%; Pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.26 (d, 1H, J = 3.0 Hz), 5.53 (d, 1H, J = 2.7 Hz), 4.69 (ddd, 1H, J = 3.9 Hz, J = 8.8 Hz, and J = 10.7 Hz), 3.21 (m, 1H) 2.10-1.22 (m, 10H); ^{13}C NMR 171.7, 139.6, 121.4, 82.2, 43.5, 32.3, 31.8, 31.2, 28.0, 24.9.

Methyl 10,10-dimethoxy-3-hydroxy-2-methylene-decanoate (3.9d): Produced from *cis*-cyclooctene (1mL, 7.7mmol) using the same procedure employed for the conversion of cyclohexene to **3.9b.** Yield 1.3g (62%); Pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.20 (s, 1H), 5.77 (s, 1H), 4.36(t, 1H, J = 5.5 Hz), 4.33 (t, 1H, J = 6.0 Hz), 3.76 (s, 3H), 3.29 (s, 6H), 1.60 (m, 4H), 1.30 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.8, 141.8, 124.1, 104.1, 71.4, 52.6, 52.0, 36.6, 32.9, 29.8, 29.8, 26.2, 25.0.

Methyl (2Z)-2-(bromomethyl)-10-oxodecenoate: Produced from **3.9d** (1.3g, 4.7mmol) using the same procedure employed for the conversion of **3.9b** to **3.10b.** Yield 1.2g (86%); pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 6.94 (t, 1H, J = 7.7 Hz), 4.20 (s, 2H), 3.78 (s, 3H), 2.417 (dt, 2H, J = 1.5 Hz and J = 7.5 Hz), 2.27 (q, 2H,

J = 7.5 Hz), 1.62 (m, 2H), 1.50 (m, 2H), 1.35 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.0, 164.9, 147.3, 128.6, 52.4, 44.1, 29.6, 29.4, 29.3, 28.4, 24.9, 22.5.

3-(2,2-Dimethoxyethoxy)propanal (3.22a): 3-Buten-1-ol (1mL, 12mmol) was protected as its THP ether using an established procedure[24]. The isolated product was ozonized and reduced to alcohol **3.26a** (Section **3.7b**). After being allylated (General Procedure), ether **3.27a** was produced via the ozonolytic procedure outlined above (General Procedure). Oxidation with buffered PCC (General Procedure) yielded **3.22a** as a colorless oil. Yield 1.4g (72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, 1H), 4.46 (t, 1H, J = 5.0 Hz), 3.82 (t, 2H, J = 6.0 Hz), 3.49 (d, 2H, J = 5.0 Hz), 3.36 (s, 6H), 2.67 (t, 2H, J = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.0, 102.6, 70.8, 65.1, 54.0, 43.8.

Methyl 5-(2,2)-dimethoxyethoxy)-3-hydroxy-2-methylene-pentanoate: Produced from **3.22a** (1.4g, 8.6mmol) using the same procedure for the conversion of **3.8a** to **3.9a**. Yield 2.0g (92%, 6 days); pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.29 (s, 1H), 5.96 (s, 1H), 4.69 (dd, 1H, J = 3.0 Hz and J = 8.0 Hz), 4.50 (t, 1H, J = 5.2 Hz), 3.75 (s, 3H), 3.69 (t, 2H, J = 6.2 Hz), 3.50 (d, 2H, J = 5.2 Hz), 3.39 (s, 6H), 1.99 (m, 2H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 165.6, 141.3, 124.5, 102.2, 70.6, 70.1, 69.9, 54.3, 54.2, 52.1, 36.0.

Methyl (2Z)-2-(bromomethyl)-5-(2-oxoethoxy)pent-2-enoate (3.23a): Produced from methyl 5-(2,2)-dimethoxyethyloxy)-3-hydroxy-2-methylene-pentanoate (2.0g, 8.0mmol) using the same procedure employed for the conversion of **3.9b** to **3.10b.** Yield 1.8g (83%); pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.01 (t, 1H, J = 7.5 Hz), 4.22 (s, 2H), 4.10 (s, 2H), 3.79 (s, 3H), 3.69 (t, 2H, J = 6.3 Hz) 2.64 (q, 2H, J = 6.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.7, 165.1, 143.0, 131.0, 76.2,

69.5, 52.3, 29.4, 24.1; MS CI (NH_3) m/z 284 (M+2 + NH_3, 23 %), 282 (M + NH_3, 33 %), 267 (M, 43 %), 265 (M, 46 %), 235 (31 %), 233 (26 %), 187 (40 %), 185 (27 %). 125 (100 %)

7-Methylene-3,9-dioxabicyclo[4.3.0]nonan-8-one (3.29a): Produced from **3.23b** (265mg, 1mmol) using the same procedure employed for the conversion of **3.10a** to **3.17a**. Methyl 2(3-hydroxytetrahydropyran-4-yl)prop-3-enoate (3.28a) was isolated as the only product of the reaction as a pale yellow liquid (180mg, 96%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.39 (s, 1H), 5.68 (s, 1H), 4.05 (dd, 1H, J = 4.0 Hz and J = 11.0 Hz), 3.97 (d, 1H, J = 11.5 Hz), 3.80 (m, 1H), 3.77 (s, 3H), 3.61 (d, 1H, J = 12.5 Hz), 3.50 (t, 1H, J = 12.0 Hz), 2.91 (d, 1H, J = 13.0 Hz), 2.00 (m , 1H), 1.41 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.1, 139.6, 125.7, 72.5, 68.0, 66.4, 52.3, 40.8, 25.2. MS CI (NH_3) m/z 187 (M+1, 100 %), 169 (M – OH, 13%), 155 (M – 31, 63 %), 137 (21 %), 126 (36 %). HRMS(FAB) calcd for $C_9H_{14}O_4$ $(M + H)^+$ 187.20776 found 187.09703. Lactonization using the procedure above required 24 h to proceed to completion yielding 148mg, (96%) of **3.29a** ; Pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (d, 1H, J = 2.4 Hz), 5.59 (d, 1H, J = 2.2 Hz), 4.44 (dt, 1H, J = 4.4 Hz and J = 6.6 Hz), 3.84 (dd, 1H, J = 4.0 Hz and J = 13.0 Hz), 3.74 (dd, 1H, J = 4.5 Hz and J = 13.0 Hz), 3.661 (m, 1H), 3.56 (m, 1H), 3.20 (m, 1H), 1.98 (m, 1H), 1.82 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 138.5, 121.3, 73.0, 67.2, 63.9, 36.3, 26.23; MS EI m/z 154 (M, 40%), 136 (34%), 125 (36%), 81 (100%).

4-(2,2-Dimethoxyethoxy)butanal (3.22b): Synthesized from 4-penten-1-ol (1mL, 10mmol) using the sequence of procedures used for the conversion 3-buten-1-ol to **3.22a**. Yield 1.2g (70%); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (t, 1H, J =

1.5 Hz), 4.47 (t, 1H, J = 5.0 Hz), 3.51 (t, 2H, J = 6.0 Hz), 3.46 (d, 2H, J = 5.0 Hz), 3.38 (s, 6H), 2.53 (dt, 2H, J = 1.5 Hz and J = 7.5 Hz), 1.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 102.6, 70.5, 70.4, 53.9, 40.7, 22.4.

Methyl 6-(2,2-dimethoxyethoxy)-3-hydroxy-2-methylene-hexanoate: Produced from **3.22b** (1.2g, 6.8mmol) using the same procedure for the conversion of **3.8a** to **3.9a**. Yield 1.6g (90%, 6 days); pale yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 (s, 1H), 5.85 (s, 1H), 4.50 (t, 1H, J = 5.3 Hz), 4.45 (br, 1H), 3.76 (s, 3H), 3.52 (t, 2H, J = 5.8 Hz), 3.48 (d, 2H, J = 5.0 Hz), 3.38 (s, 6H), 1.81-1.64 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 142.4, 125.0, 102.5, 71.6, 70.9, 70.4, 53.9, 51.8, 33.4, 25.9.

Methyl (2Z)-2-(bromomethyl)-6-(2-oxoethoxy)hex-2-enoate (3.23b): Produced from methyl 6-(2,2-dimethoxyethyloxy)-3-hydroxy-2-methylene-hexanoate (1.6g, 6.1mmol) using the same procedure employed for the production of **3.9b** to **3.10b**. Yield 1.3g (79%); pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (s, 1H), 6.98 (t, 1H, J = 7.5 Hz), 4.25 (s, 2H), 4.11 (s, 2H), 3.80 (s, 3H), 3.56 (t, 2H, J = 5.8 Hz), 2.44 (q, 2H, J = 7.2 Hz), 1.87 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.4, 165.2, 143.3, 129.9, 76.1, 70.3, 52.2, 29.7, 28.9, 24.3; MS CI (NH_3) m/z 298 (M + 2 + NH_4, 18 %), 296 (M + NH_4, 18 %), 281 (M + 2, 34 %), 279 (M, 35 %), 249 (28 %), 247 (28 %), 199 (38 %), 93 (100 %).

8-Methylene-3,10-dioxabicyclo[5.3.0]decan-9-one (3.29b): Produced from **3.23b** (280mg, 1mmol) using the same methodology employed for the conversion of **3.10a** to **3.17a**. Yield 160mg (95%); pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.36 (d, 1H, J = 3.0 Hz), 5.57 (d, 1H, J = 2.5 Hz), 4.75 (ddd, 1H, J = 3.5 Hz, J = 6.5 Hz and J = 9.5 Hz), 3.89 (dd, 1H, J = 3.5 Hz and J = 13.5 Hz), 3.82 (`dd, 1H, J = 6.5 Hz and J = 13.5

Hz), 3.69 (t, 2H, J = 5.3 Hz), 3.41 (m, 1H), 1.99 (m, 2H), 1.91 (m, 1H), 1.67 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 138.4, 122.5, 79.9, 74.2, 71.5, 41.1, 29.3, 28.5; MS (EI) m/z 168 (M, 40%), 150 (34%), 139 (36%), 124 (78%), 110 (55%), 81 (100%).

5-(2,2-Dimethoxyethoxy)pentanal (3.22c): Produced from 5-hexen-1-ol (0.5mL, 4.1mmol) using the sequence of procedures used for the conversion 3-buten-1-ol to **3.22a**. Yield 560mg (71%); colorless liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.66 (s, 1H), 4.48 (t, 1H, J = 5.1 Hz), 3.50 (t, 2H, J = 6.0 Hz), 3.47 (d, 2H, J = 5.2 Hz), 3.39 (s, 6H), 2.47 (t, 2H, J = 5.8 Hz), 1.67 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.8, 102.4, 71.2, 70.6, 54.2, 44.0, 29.5 19.5.

Methyl 7-(2,2-dimethoxyethoxy)-3-hydroxy-2-methylene-heptanoate: Produced from **3.22c** (560mg, 2.9mmol) using the same procedure for the conversion of **3.8a** to **3.9a**. Yield 730mg (90%, 7days); pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.23 (s, 1H), 5.81 (s, 1H), 4.51 (t, 1H, J = 5.0 Hz), 4.40 (t, 1H, J = 6.2 Hz), 3.78 (s, 3H), 3.52-3.32 (m, 4H), 3.39 (s, 6H), 1.66 (m, 6H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 165.9, 141.8, 124.3, 102.4, 71.6, 70.5, 54.09, 52.1, 36.4, 29.8, 23.0.

Methyl (2Z)-2-(bromomethyl)-7-(2-oxoethoxy)heptenoate (3.23c): Produced from methyl 7-(2,2-dimethoxyethyloxy)-3-hydroxy-2-methylene-heptanoate (730mg, 2.6mmol) using the same procedure employed for the production of **3.9b** to **3.10b**.Yield 620mg (80%); pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.72 (s, 1H), 6.97 (t, 1H, J = 7.7 Hz), 4.23 (s, 2H), 4.08 (s, 2H), 3.79 (s, 3H), 3.56 (t, 1H, J = 5.9 Hz), 2.35 (q, 2H, J = 7.2 Hz), 1.66 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.8, 164.9, 147.0, 128.9, 76.3, 71.5, 52.4, 29.7, 29.1, 25.3, 24.8; MS CI (NH_3) m/z 312 (M + 2 + NH_4, 17 %), 310 (M +

NH_4, 17 %), 295 (M + 2, 36 %), 293 (M, 35 %), 263 (28 %), 261 (28 %), 213 (38 %), 181 (60 %), 93 (100 %).

9-Methylene-3,11-dioxabicyclo[6.3.0]undecan-10-one (3.29c): Produced from **3.23c** (293mg, 1mmol) using the same methodology employed for the conversion of **3.10a** to **3.17a.** Yield 54mg (30%); colorless film; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.26 (d, 1H, J = 3.0 Hz), 5.52 (d, 1H, J = 3.0 Hz), 4.66 (td, 1H, J = 3.2 Hz and J = 7.5 Hz), 3.80 (dd, 1H, J = 3.2 Hz and J = 12.4 Hz), 3.75 (m, 1H), 3.69 (dd, 1H, J = 7.0 Hz and J = 12.5 Hz), 3.60 (m, 1H), 3.24 (m,1H), 2.10 (m, 1H), 1.79(m, 4H), 1.60 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 170.2, 132.1, 120.9, 78.9, 69.5, 65.8, 42.5, 28.5, 28.2, 22.4; MS CI (NH_4) 310 (M + NH_4, 18%), 293 (M, 35%), 263 (28%), 213 (M-Br, 39%), 181 (64%), 93 (100%).

3-(3,3-Dimethoxypropoxy)propanal (3.33): 3-Buten-1-ol (1mL, 12mmol) was protected as its benzyl ether (Section **3.7f**). The isolated product was ozonized and reduced to alcohol **3.30** using the procedure described Section 3.7b. After being allylated (General Procedure), mono-protected symmetrical alcohol **3.31** was produced via hydroboration with 9-BBN[25] yielding the alcohol in 95% yield; pale yellow liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.24 (m, 5H), 4.46 (s, 2H), 3.76 (t, 2H, J = 7.5 Hz), 3.65 (t, 2H, J = 7.2 Hz), 3.54 (t, 4H, J = 7.0 Hz)), 1.91-1.80 (m, 4H). The free alcohol was oxidized using PCC (Section **3.7c**) and protected as the corresponding dimethyl acetal (Section **3.7d**). Debenzylation with H_2/Pd-C[26] gave 93% yield of **3.32**; pale yellow liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.26 (m, 5H), 4.51 (s, 2H), 4.51 (t, 1H, J = 5.8 Hz), 3.60-3.44 (m, 6H), 3.32 (s, 6H), 1.91 (m, 4H). Oxidation with buffered PCC (Section **3.7c**) followed by purification through silica gel with hexanes:ethyl acetate (5:1) gave **3.33** as

a colorless liquid in a 67% (1.3g) overall yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.99 (s, 1H), 4.50 (t, 1H, J = 5.0 Hz), 3.79 (t, 2H, J = 6.5 Hz), 3.51 (t, 2H, J = 6.0 Hz), 3.30 (s, 6H), 2.66 (t, 2H, J = 6.0 Hz), 1.90 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.9, 101.9, 70.7, 70.5, 53.6, 40.7, 29.7.

Methyl 5-(3,3-dimethoxypropyloxy)-3-hydroxy-2-methylene-pentanoate: Produced from **3.33** (1.3g, 8.0mmol) using the same procedure for the conversion of **3.8a** to **3.9a**. Yield 1.8g (92%, 7days); pale yellow liguid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.30 (s, 1H), 5.97 (s, 1H), 4.67 (br, 1H), 4.50 (t, 1H, J = 6.0 Hz), 3.76 (s, 3H), 3.73-3.47 (m, 4H,), 3.33 (s, 6H), 2.02 (m, 1H), 1.88 (q, 2H, J = 6.0 Hz), 1.831 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 142.1, 125.1, 102.3, 70.3, 69.4, 67.2, 53.1, 53.1, 51.8, 35.5, 32.8.

Methyl (2Z)-2-(bromomethyl)-5-(3-oxopropoxy)pent-2-enoate: Produced from methyl 5-(3,3-dimethoxypropyloxy)-3-hydroxy-2-methylene-pentanoate (1.8g, 7.3mmol) using the same procedure employed for the production of **3.9b** to **3.10b**. Yield 1.6g (81%); pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H), 6.98 (t, 1H, J = 7.5 Hz), 4.22 (s, 2H), 3.80 (s, 3H), 3.79 (t, 2H, J = 6.2 Hz), 3.61 (t, 2H, J = 6.5 Hz) 2.68 (t, 2H, J = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.1, 165.0, 144.2, 130.7, 68.6, 64.4, 52.1, 43.6, 29.2, 24.0.

8-Methylene-4,10-dioxabicyclo[5.3.0]decan-9-one (3.34): Produced from **3.23c** (265mg, 1mmol) using the same methodology employed for the conversion of **3.10a** to **3.17a.** Yield 161mg (96%); pale yellow liguid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (d, 1H, J = 3.5 Hz), 5.69 (d, 1H, J = 3.0 Hz), 4.90 (td, 1H, J = 3.7 Hz and J = 9.0 Hz) 3.81 (m, 2H), 3.59 (m, 2H), 3.44 (m, 1H), 2.22-1.96 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

169.8, 139.2, 122.8, 80.0, 68.7, 66.0, 41.3, 35.1, 34.3; MS EI (M, 168, 40 %), 150 (35 %), 139 (36 %), 124 (78 %), 81 (100 %).

(1*R*)-Myrtenyl 8-oxo-2-bromomethyl-2(Z)-octenoate (3.36a): Generated using cyclohexene (1mL, 10mmol) in the same manner as **3.10b** with the only exception being myrtenyl acrylate used in the Baylis-Hillman reaction instead of methyl acrylate. Overall yield 2.3g (61%); yellow liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.76 (s, 1H), 6.91 (t, 1H, J = 7.6 Hz), 5.58 (m, 1H), 4.54 (d, 2H, J = 1.4 Hz), 4.19 (s, 2H), 2.462 (t, 2H, J = 7.0 Hz), 2.43-2.08 (m, 5H), 1.80-1.50 (m, 5H), 1.30(s, 3H), 1.20(d, 1H, J = 8.0 Hz), 0.95 (s, 3H); ^{13}C (50 MHz, $CDCl_3$) δ 201.5, 165.0, 147.0, 142.5, 129.7, 121.6, 67.7, 43.6, 40.8, 38.1, 31.5, 31.4, 28.7, 27.7, 26.2, 24.2, 21.8, 21.3.

(1*R*)-(-) Mrytenyl (*cis*)-2-(2-hydroxycyclohexyl)prop-2-enoate : Produced from bromide **3.36** (383mg, 1mmol) using the same methodology employed for the conversion of **3.10a** to **3.17a;** yield 290mg (95%) equal mixture of diastereomers; colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (d, 1H, J = 1.0 Hz), 6.31 (s, 1H), 5.60 (s, 2H), 5.58 (m, 2H), 4.56 (d, 2H, J = 12.5 Hz), 4.47 (dd, 2H, J = 1.5 Hz and J = 12.5 Hz), 3.98 (s, 2H), 2.72 (m, 2H), 2.41 (t, 1H, J = 5.5 Hz), 2.40 (t, 1H, J = 6.0 Hz), 2.29 (q, 4H, J = 18.0 Hz), 2.12 (m, 1H + OH), 1.91 (m, 2H), 1.82 –1.2 (m, 18H), 1.29 (s, 6H), 0.84 (s, 3H), 0.83 (s, 3H); $^{13}CDCl_3$ (125 MHz, $CDCl_3$) δ 167.8, 167.7, 142.3, 142.2, 125.9, 122.0, 122.0, 67.6, 67.5, 67.0, 67.0, 43.5, 43.2, 40.2, 32.2, 31.6, 31.5, 26.1, 26.0, 24.1, 21.2, 19.8.

(1*S*, 2*R*, 5*S*)-(+)-Menthyl 8-carboxaldehyde-2-bromomethyl-2(Z)-octenoate (3.36b): Same as **3.36a**: Overall yield 2.1g (59%); pale yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.76 (t, 1H, J = 1.5 Hz), 6.90 (t, 1H, J = 7.4 Hz), 4.79 (dt, 1H, J = 4.4 Hz), 4.20

(s, 2H), 2.48 (dt, 2H, J = 1.4 Hz and J = 7.0 Hz), 2.59 (q, 2H, J = 7.4 Hz 2.500- 0.96(m, 13H), 0.91 (d, 3H, J = 2.1 Hz), 0.88 (d, 3H, J = 2.6 Hz), 0.76 (d, 3H, 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.4, 163.9, 145.8, 129.6, 75.1, 47.4, 43.9, 41.2, 34.7, 31.9, 29.1, 28.2, 26.9, 24.9, 24.1, 22.6, 22.4, 21.4, 17.0.

(1*S*, 2*R*, 5*S*)-(+)-Menthyl 2-(2-hydroxycyclohexyl)acrylate: Produced from bromide **3.36b** (387mg, 1mmol) using the same methodology employed for the conversion of **3.10a** to **3.17a**; yield 246mg (80%); colorless liquid; 6.24 (s, 1H), 6.23(s, 0.8H), 5.56 (s, 1.8H), 4.73(m, 1.8H), 3.95 (s, 1.8H), 2.69 (m, 1.8H), 2.00- 1.00 (m, 32.4H), 0.90 – 0.88 (m, 10.8H), 0.75 (m, 5.4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.9, 166.8, 143.2, 143.2, 124.8, 124.8, 74.9, 67.1, 47.1, 47.1, 43.6, 43.5, 40.8, 40.8, 34.2, 32.4, 32.4, 31.4, 26.5, 26.3, 25.9, 25.9, 23.9, 23.8, 23.5, 23.3, 22.0, 21.0, 20.7, 20.7, 19.4, 16.4, 16.2; MS CI (NH_3) m/z 309 (M+1, 29%), 171 (70.4%), 153 (100%) ; Lactonization gave **3.17b** $[a]^{20}_D$ + 10.2° (c, 0.10, $CHCl_3$)

(1S, 2R)-*cis* N-*t*-Boc- O-Acryloyl-aminoindanol: (1S, 2R)-aminoindanol (0.80g, 5.4mmol) was dissolved in 10 mL of CH_2Cl_2 and cooled to 0°C under argon. To the stirring solution was added di-*tert*-butyl dicarbonate (1.3g, 5.9 mmol, dissolved in 10mL CH_2Cl_2) dropwise. The mixture was allowed to warm to room temperature and stirred overnight. Evaporation under reduced pressure furnished the N-t-Boc aminoindanol as the sole product. This product was dissolved in CH_2Cl_2 (15 mL) containing NEt_3 (850ul, 8 mmol). and cooled to 0 °C under a steady flow of argon. To this solution was added acryloyl chloride (500ul, 6mmol) dropwise and the solution warmed to room temperature and stirred overnight. The mixture was diluted with diethyl ether (30 mL), washed with, H_2O (30 mL), saturated NaCl (30 mL), dried with Na_2SO_4 and evaporated to dryness.

Purification via elution through silica gel with hexanes:ethyl acetate (3:1) gave a pale yellow powder (1.3g, 86%): mp 99-100 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27 (m, 4H), 6.39 (dd, 1H, J = 1.5 Hz and J = 17.0 Hz), 6.05 (dd, 1H, J = 10.2 Hz and J = 17.0 Hz), 5.83 (dd, 1H, J = 1.5 Hz and J = 10.4 Hz), 5.70 (t, 1H, J = 4.3 Hz), 5.38 (t, 1H, J = 4.3 Hz), 4.96 (br, 1H), 3.25 (dd, 1H, J = 4.8 Hz and J = 17.0 Hz), 3.03 (d, 1H, J = 17.1 Hz), 1.49 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.4, 154.7, 140.0, 138.5, 130.6, 127.6, 127.5, 126.6, 124.4, 123.3, 79.8, 75.8, 57.4, 37.8, 28.9

N-*t*-Boc-aminoindanyl-8-carboxaldehdye-2-bromomethyl-2(Z)-octenoate ester (3.36c): Produced from N-*t*-Boc- O-Acryloyl-aminoindanol (1.3g, 4.3mmol) in the same manner as **3.36a** with one exception being that the Baylis-Hillman reaction proceeded to completion within 12h. Overall yield 1.4g (65%); light brown oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.27(m, 4H), 6.91 (t, 1H, J = 7.7 Hz), 5.73 (dt, 1H, J = 1.7 Hz and J = 5.1 Hz), 5.40 (br, 1H), 5.24 (br, 1H), 4.10 (m, 2H), 3.28 (dd, 1H, J = 4.8 Hz and J = 17.0 Hz), 3.04 (d, 1H, J = 17.2 Hz), 2.47 (dd, 2H, J = 1.4 Hz and J = 6.9 Hz), 2.30 (m, 2H), 1.68 (m, 4H), 1.48 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 200.3, 163.7, 154.8, 147.1, 140.1, 138.4, 128.9, 127.6, 126.6, 124.4, 123.4, 79.7, 76.4, 57.6, 43.9, 37.8, 28.1, 22.4, 28.9.

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19) Spectra were compared to those reported previously. See. a) Crisp, G. T.; Meyer, A. G.; *Tetrahedron*, **1995**, 51, 5831. b) Grieco, P. A.; Miyashita, M., *J. Org. Chem.* **1974**, 39, 120. c) Marshall, J. A.; Cohen, N., *J. Org. Chem.* **1965**, 30, 3475.

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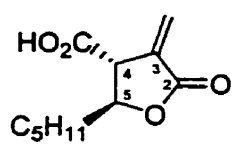
CHAPTER 4

Indium-mediated allylation for the construction of naturally occurring, synthetically useful, densely functionalized five membered systems including a concise synthesis of (±)-methylenolactocin and (±)-protolichesterinic acid.

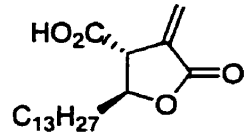
4.1 Introduction.

Polysubstituted α-methylene-γ-butyrolactones represent a class of naturally occurring compounds, which for several reasons haa been the focus of much attention. Very often, molecules of this type exhibit interesting biological activity.[1] Their intrinsic reactivity permits their use in the synthesis of natural products such as alkaloids, macrocyclic antibiotics, lignan lactones, and pheromones.[2] In addition, densely functionalized γ-butyrolactones can serve as a synthetic challenge and can often test the value of methodology for creative construction. One family of densely functionalized γ-butyrolactones is the naturally occurring paraconic fatty acids, of which there are several members usually isolated from moss and lichen[1] as well as culture filtrates of *penicillium sp.*[3] The class is characterized by a C_3 position, which often possesses an α-methylene or methyl group, a carboxyl functionality in the C_4 position and a substituted or unsubstituted alkyl chain at C_5 (Figure 4.1). These groups and their stereochemical relationship to each other govern some of the very interesting biological activity often observed. For instance dihydroprotolichesterinic acid **4.3** is a potent anti-bacterial agent[4]

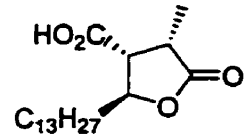
while protolichesterinic acid **4.2** is known for its anti-tumor, anti-fungal, and growth regulating qualities. [5]



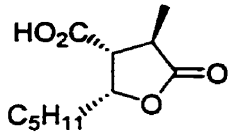
methylenolactocin
4.1



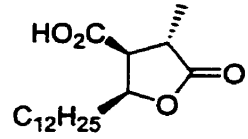
protolichesterinic acid
4.2



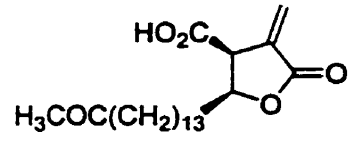
dihydroprotolichesterinic acid
4.3



phaseolinic acid
4.4



neophrosteranic acid
4.5



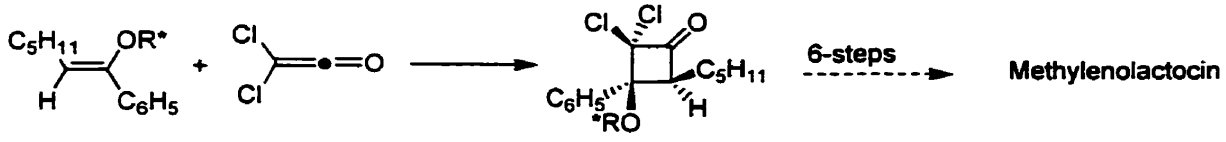
allo-pertusaric acid
4.6

Figure 4.1 Examples of naturally occurring paraconic acids.

Owing to their synthetic utility and biological activity, paraconic acids have been the focus of much attention and several different methods have been used for their synthesis.[6] The paraconic acid (±) methylenolactocin **4.1**, is one such example that was first isolated in 1988 from the culture filtrate of *Penicillium sp.*[3] Physiologically it is a potent antibiotic antitumoral agent; structurally it possesses an alkyl chain of 5 carbons at C_5 and an α-methylene functionality at C_3. Methylenolactocin has been the focus of a few formal syntheses, which have used a wide array of methodologies with varying degrees of success. [7-13]

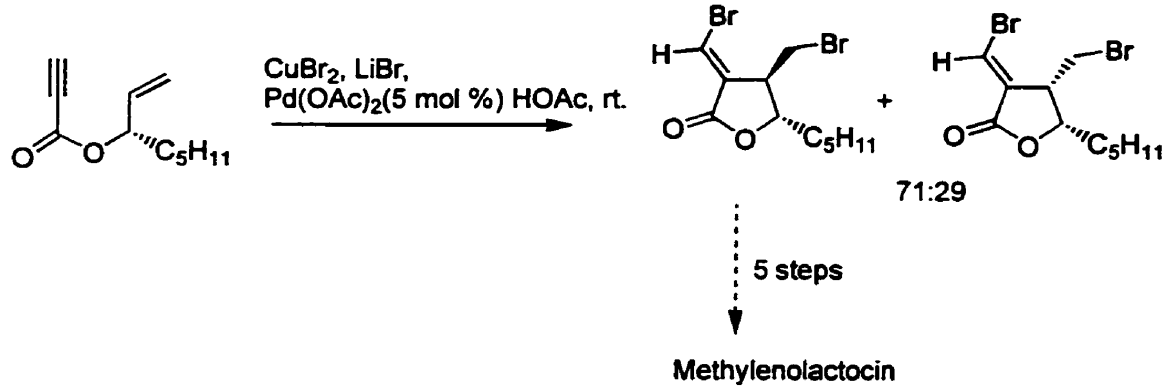
4.1.1 Survey of the methodologies used in previous constructions of the methylenolactocin framework.

The first synthesis of methylenolactocin was performed in 1992 by *Azevedo et al.*[1a] who employed [2 + 2] olefin-ketene cycloaddition as the key step in a novel synthetic procedure. The use of (1R, 2S)-(-)-2-phenylcyclohexanyl as an auxiliary in the enol ether (Scheme 4.1) aallowed the production of (-)-methylenolactocin.



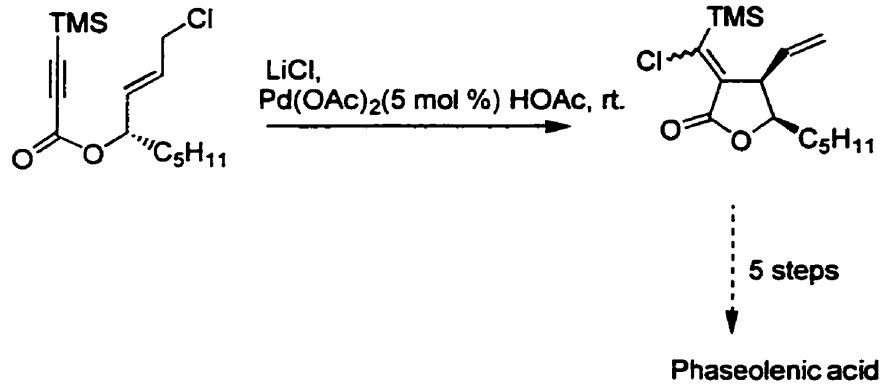
Scheme 4.1

In their synthesis of methylenolactocin, Lu and Zhu used palladium(II)-catalyzed cyclization of allylic 2-alkynoates to obtain the desired framework (Scheme 4.2).[7] This route offered the advantage of providing the paraconic acid in enantiomerically pure forms if the alcohol used in the formation of the allylic 2-alkynoates is enantiomerically pure. It however encountered difficulty as the cyclization step, formed a mixture of diastereomers, that could not be separated prior to hydrolysis of the primary halide. This hydrolysis was not trivial as hydrolysis of the ester did not occur under a wide variety of conditions (e.g. NaOH, LiOH, or $NaHCO_3$ as bases). It was performed successfully in a



Scheme 4.2

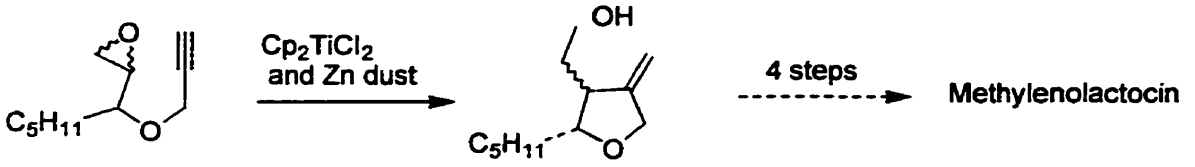
maximum of only 55% yield by employing $CaCO_3$ in DMSO-H_2O at 100°C. With Zhang, Lu later used an improved substrate (Scheme 4.3) which avoided this problem while still employing the palladium(II) catalyzed cyclization of 4-chloro-1-*n*-pentyl-butenyl-3-trimethylsilyl-2-propynoate demonstrated in their synthesis of phaseolenic acid.[8]



Scheme 4.3

In this procedure they also demonstrated that by the incorporation of a trimethylsilyl (TMS) unit in the terminal position of the alkyne they could obtain the *cis* diastereomer opposite to that obtained with H in the position (Scheme 4.2).

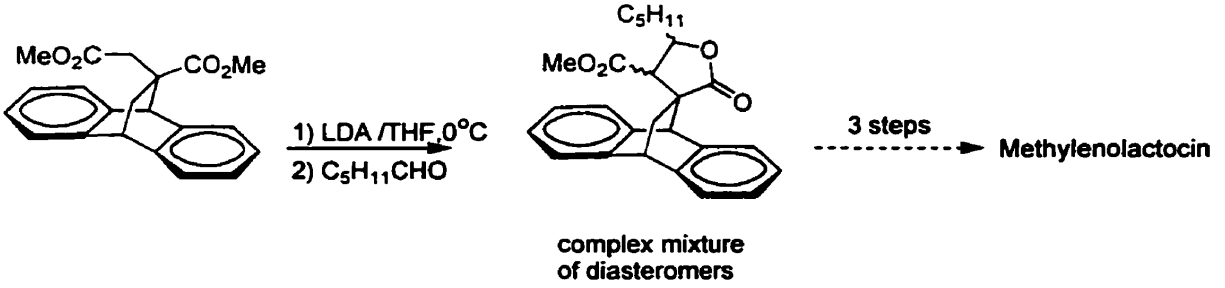
Roy *et al* successfully synthesized methylenolactocin using a route that employed Cp_2TiCl, generated by the reduction of Cp_2TiCl_2 as a radical source for the intramolecular coupling of an olefin to an epoxide as a key step for generation of the functionalized framework (Scheme 4.4).[9]



Scheme 4.4

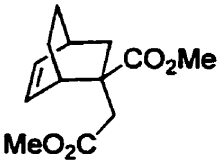
The route is limited in its applicability as the cyclization produced an inseparable mixture of isomers which fortunately isomerized when the final highly acidic oxidation of the primary alcohol to the corresponding acid was performed. In addition, the allylic oxidation to produce the required ester proceeded in only 63% yield.

An interesting route to the production of methylenolactocin was performed by Thebtaranonth *et al*[10] who used itaconate-anthracene adducts as the foundation for the synthesis of functionalized spirolactones. These upon pyrolysis at ~500°C and hydrolysis, provided paraconic acids including methylenolactocin (Scheme 4.5).



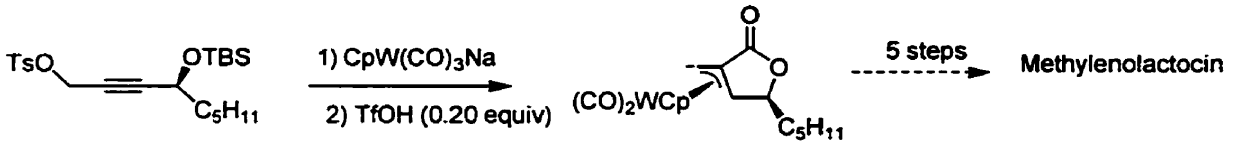
Scheme 4.5

In addition to the harsh condition used in the synthesis, the cyclization produces a complex mixture of diastereomers where the undesired syn diastereomer dominates. This requires a 2-day isomerization in strongly basic media to obtain the desired configuration. Employing a very similar pathway, Ghosh et al[11] used the itaconate derivative **4.7** for the construction of paraconic acids including methylenolactocin.



4.7

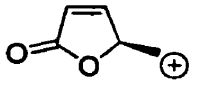
Liu *et al*[12] sought the use of tungsten propargyl compounds which following intramolecular alkoxycarbonylation, yielded a chiral tungsten-π–γ-lactonyl complex ultimately leading to trans-α-methylene-γ-butyrolactones (Scheme 4.6).



Scheme 4.6

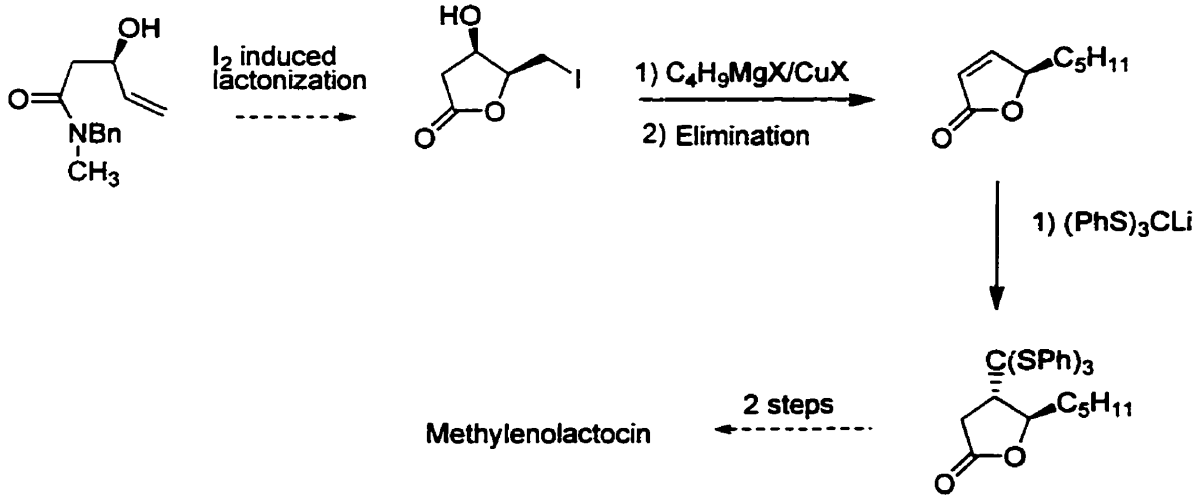
Though employing many synthetic steps the scheme represented a novel route to these valuable compounds.

In their synthetic scheme, Takahata *et al*[13] centered their generation of these densely functionalized butyrolactones around the synthon **4.8**.



4.8

Having previously demonstrated that iodine induced lactonization to species representative of such a synthon, they proceeded to elaborate their procedure to the synthesis of paraconic acids including methylenolactocin (Scheme 4.7).



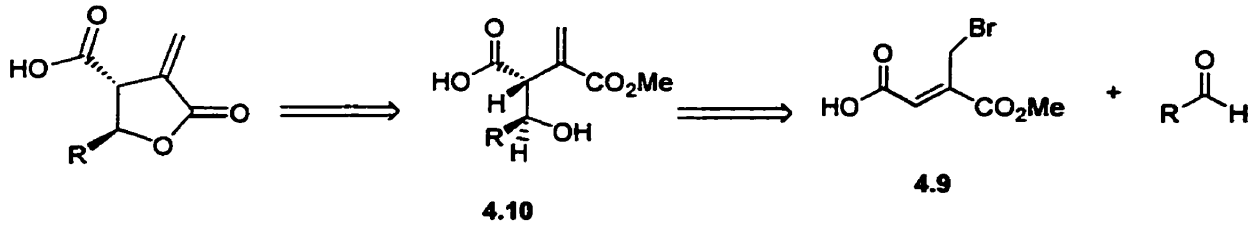
Scheme 4.7

As is evident in Schemes 4.1-4.7, there exists a number of pathways for the synthesis of paraconic acids. If one were to examine many of the existing pathways, it would be recognized that though very interesting methodology has been used in the syntheses, the necessary pathways often require tasks of a tedious nature. Frequently, highly reactive species necessitating many precautions are employed. The retro-Diels Alder procedure, for example (Scheme 4.5), requires temperatures of approximately 500°C to effect a reaction. Many other reactions, which employ Grignard reagents, alkyllithium reagents and/or LDA, necessitate time consuming measures to create a completely anhydrous reacting environment. In addition, some of the milder methods create inseparable isomeric intermediates, which complicate the required routes.

We were interested in further demonstrating how the indium-mediated allylation could be used in the design of a mild efficient pathway to paraconic acids and related derivatives.

4.2 Indium-mediated allylation in water as the key step in the synthesis of naturally occurring, biologically active paraconic acids (±)-methylenolactocin and (±)-protolichesterinic acid.

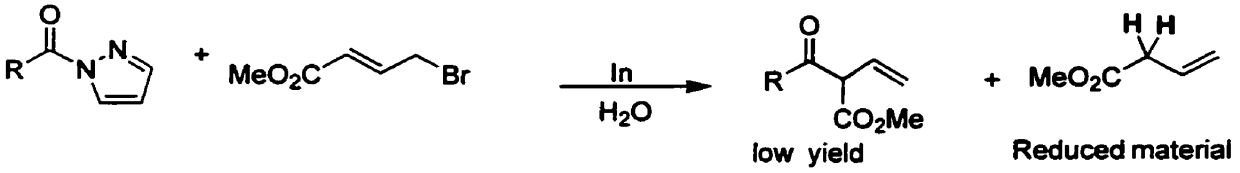
α-Methylene-γ-butyrolactones are present in more than 10 % of natural products which may vary tremendously in their overall constitution. They occur in macrocyclic systems as well as densely functionalized monocyclic systems.[14] We had previously demonstrated the efficient synthesis of α-methylene-γ-butyrolactones fused to carbocyclic and oxygen heterocyclic substrates via the indium-mediated allylation in water. A natural extension of this protocol was an investigation into the utility of this reaction for the construction of densely functionalized naturally occurring paraconic acids. Retrosynthetic analysis of acids **4.1** and **4.2** revealed a rather simple pathway to these important substrates, through the coupling of a γ-carboxylic-β-methoxycarbonyl allylbromide **4.9** to the appropriate aldehyde in water. A subsequent acid catalyzed lactonization of **4.10** would produce the paraconic acid in direct manner (Scheme 4.8). This pathway was very attractive for it simplicity, but was not without its uncertainties which were bothersome to us. Firstly, the geometry of methylenolactocin **4.1** requires an



4.10 **4.9**

Scheme 4.8

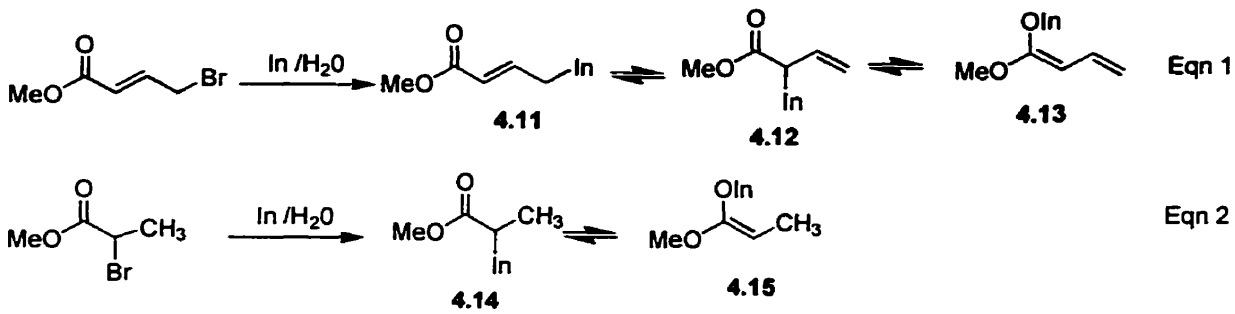
anti-relationship between substituents attached to C_4 and C_5, while we were not sure what level of diastereoselectivity bias in favor of this diastereomer would be obtained. Secondly and perhaps most worrying was the allylic halide **4.9**. It had been well established that indium-mediated allylation of aldehydes proceeded effectively with a variety of substituents including carboxylic acids or esters on the allylic halide. We however had encountered two circumstances in the progress of our research where substrates were found to not couple effectively to suitable electrophiles. Our attempt to couple methyl bromocrotonate to acyloylpyrazoles resulted in a relatively low yield of



low yield Reduced material

Scheme 4.9

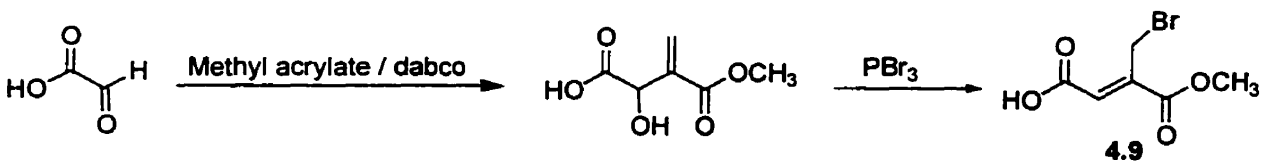
allylation product while a large amount of reduction of the starting bromide was observed. We also encountered a tremendous amount of reduction of α-haloesters, when we attempted to react them with acyloylpyrazoles in water. We believed these two different substrates to encounter complications for similar reasons. As illustrated in Scheme 4.10, both reacted with indium to generate indium-enolates **4.13** and **4.15**.



Scheme 4.10

Unlike a C-In bond, which shows low propensity to react with water in the typical allylation, the O-In species seems to lead to protonation which competes significantly with alkylation of the electrophile.

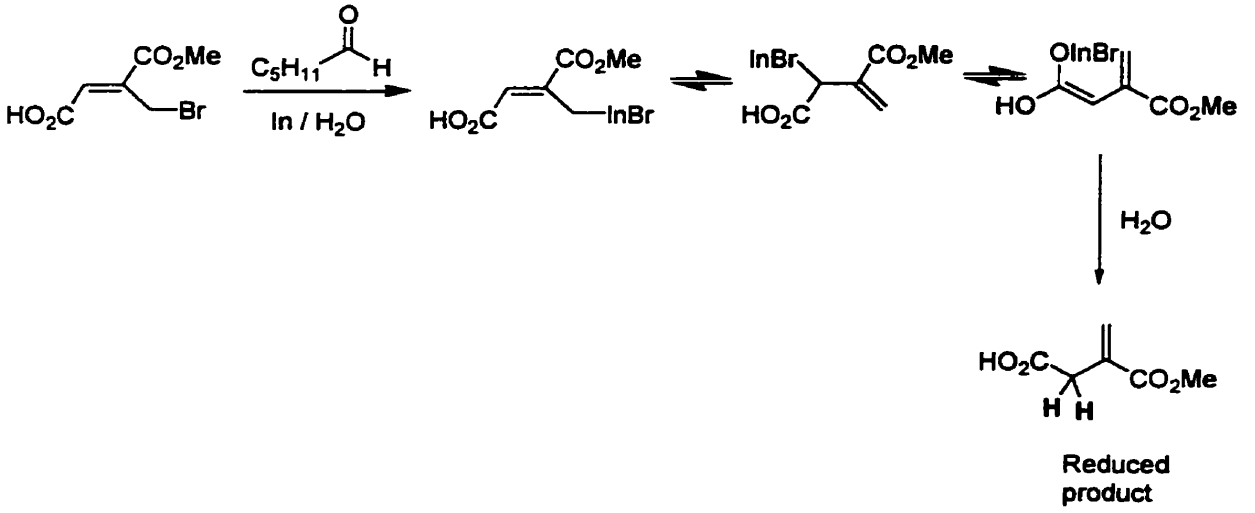
With reservations therefore we proceeded to investigate the allylation illustrated in the retrosynthetic outline (Scheme 4.8). The desired bromide **4.9** could be synthesized from glyoxylic acid and methyl acrylate, which coupled very rapidly in the presence of 1,4-diazabicyclo[2.2.2]octane (dabco) furnishing the corresponding allylic alcohol in a



Scheme 4.11

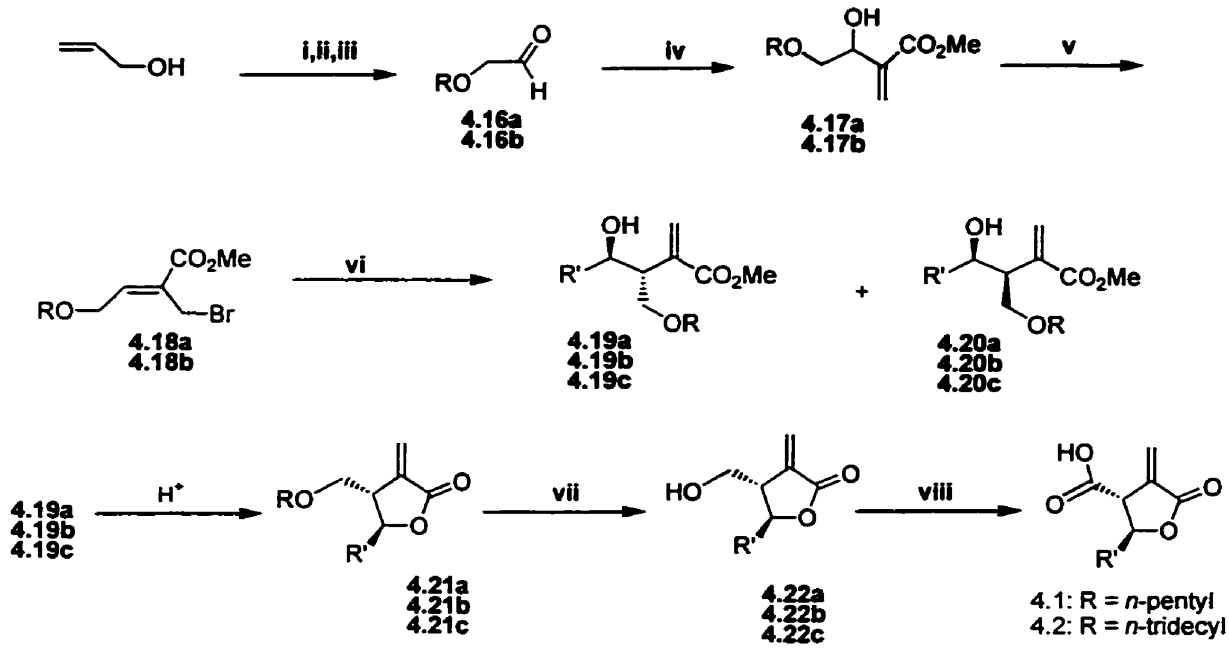
quantitative manner. Bromination of the adduct alcohol then provided the desired starting bromide in 63% yield that could then be tested under the allylation conditions.

We found that the allylic halide was rapidly reduced and indeed no coupling product to hexanal was observed. As shown in Scheme 4.12 we surmised that the γ-activating substituent led to the formation of the indium-enolate which was rapidly protonated.



Scheme 4.12

Suspecting that the inhibiting factor in the reaction was the electron stabilizing carboxylic functionality, we decided to alter the synthesis by employing a protected alcohol on the γ-position of the allylic bromide. The modified procedure was then used for the facile generation of (±)-methylenolactocin as shown below.

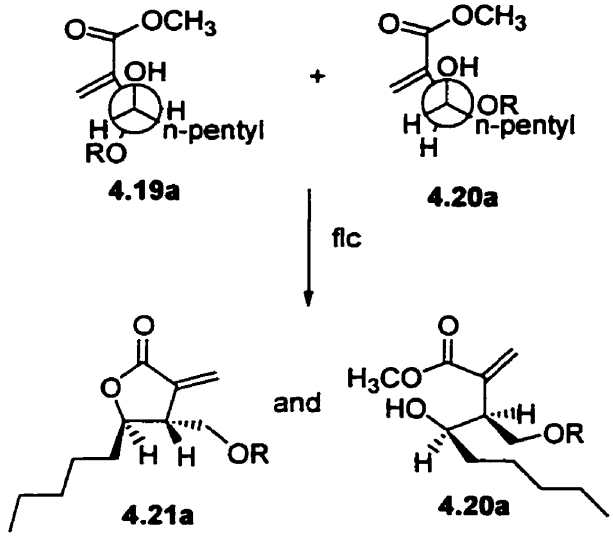


a: R = THP, R' = *n*-pentyl
b: R = TBDMS, R' = *n*-pentyl
c: R = THP, R' = *n*-tridecyl

Scheme 4.13 Reagents and conditions: (i) DHP, CSA, CH_2Cl_2, 0°C to rt. or TBDMS, imidazole, CH_2Cl_2, 12hrs; (ii) O_3, CH_2Cl_2, -78°C; (iii) Dimethyl sulfide -78°C to rt ; (iv) Methyl acrylate, dabco 48hrs; (v) NBS, dimethyl sulfide, 0°C to rt.; (vi) Hexanal, (or tetradecanal), indium/H_2O, 12hr; (vii) TFA, MeOH. pH ~4; (viii) $CrO_3/H_2SO_4/H_20$, acetone 0^0C, 2.5 hrs.

The allylic bromide **4.18a** was synthesized in a very simple manner and coupled to hexanal in water in a quantitative fashion. This resulted in a mixture of the desired anti-coupled **4.19a** product and the undesired *syn*-diastereomer **4.20a** (anti:syn = 1:1). The propensity of the *anti* diastereomer to cyclize under slightly acidic conditions meant that the two could be separated very easily via elution through silica gel with hexane:ethyl acetate 9:1 (Figure 4.1). The pre-cyclization conformations of **4.19a** and **4.20a** shown in

Figure 4.2 illustrates that the steric barrier to lactonization in **4.19a** is less than that in **4.20a** owing to the interaction of the **-OR** and *-n*-pentyl groups



flc = flash column chromatography (through silica gel with hexanes:ethyl acetate 9:1)

Figure 4.2

This facilitated its selective closure under mildly acidic conditions. With **4.21a** in hand, we were able to easily transform it to the paraconic acid, after removal of the alcohol protecting group, using Jones oxidation of alcohol **4.22a.** In a similar manner we synthesized protolichesterinic acid **4.2** by substituting tetradecanal for hexanal (Scheme 4.13, step vi) using the mild indium-mediated allylation in water as the key step for introduction of the desired framework.

We found that the protecting groups employed on the bromide were of significance as they affected the stereochemical outcome of the indium-mediated allylation (ratio of **4.19a : 4.20a**). When we used the tetrahydropyranyl (THP) ether for example, we found that we obtained an equal distribution of the *syn* and *anti* coupled products. This was evident from ^{1}H NMR analysis of the crude product mixture where

the terminal vinylic signals of the 4-diastereomeric products were quite discernable. Though flash chromatography allowed for a separation of the desired anti diastereomer **4.19a** through facile cyclization to the lactone **4.21a** we were not satisfied with the lack of bias in the indium-mediated coupling. Having established the route to the paraconic acids, we sought to improve on the diastereoselectivity in favor of **4.19** versus **4.20**. It was known[15] that the distribution of the anti:syn products is dependent to a large extent on the steric interactions of the substitutents on the aldehyde $\mathbf{R_3}$ and the γ-substituent of the halide $\mathbf{R_1}$ (Fig. 4.3).

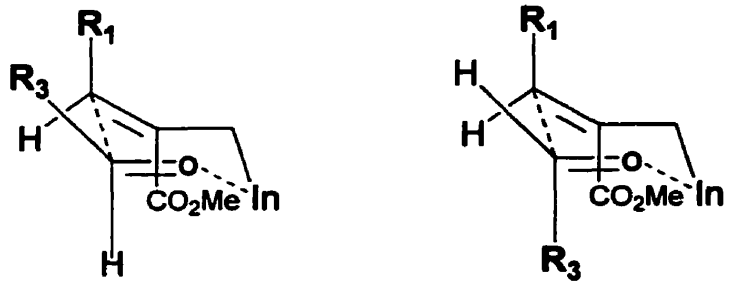
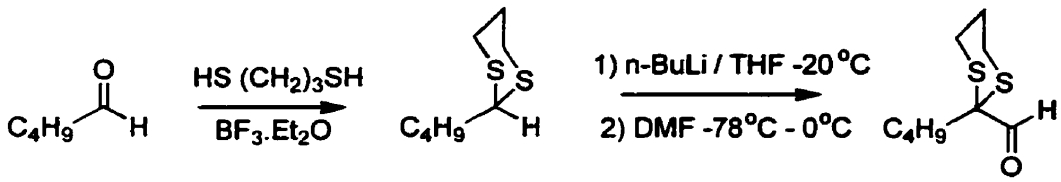


Figure 4.3 Transition states governing the *syn:anti* ratio in the indium-mediated intermolecular allylation in the absence of a chelating functionality in the aldehyde.

In an attempt to increase such interactions we decided therefore, to use a more bulky alcohol protecting group that could still be removed easily. We believed that the *t*-butyldimethylsilyl (TBDMS) functionality would be suitable for such purposes as it offered a significant increase in size while offering no increased difficulty for removal. The change of the $\mathbf{R_1}$ substituent from THP to TBDMS was done and the allylation of hexanal by species **4.18b** investigated. We found the change was sufficient to improve the ratio of **4.19:4.20** from 50:50 to 69:31 respectively. This represented an increase in

the desired diastereomer of approximately 20 %. In an additional effort to enhance the ratio of the anti diastereomer we decided to also increase the bulk of the aldehyde. Again, we needed to incorporate a temporary functionality which would significantly increase the bulk surrounding the aldehyde yet be removed after allylation. The most suitable candidate for our purposes was a thioacetal functionality in the β position of the aldehyde. In this light therefore we synthesized 2-*n*-butyl-1,3-dithiane which could be formylated with *n*-Buli/DMF[15] (Scheme 4.14). Thorough purification of the 2-*n*-butyl-1,3-dithiane was essential to a successful formylation. Even if NMR analysis showed no impurities the presence of a slight yellow color seemed to affect the effectiveness of the reaction.



Scheme 4.14

With the aldehyde in hand, we were able to investigate the allylation with species **4.19** We found that the steric nature of the system was too much to allow reaction with either of the bromides (ie OTHP or OTBDMS) even when sonicated at 40°C.

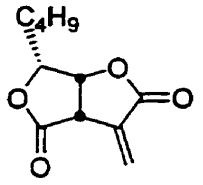
Table 4.1: Results of the allylation of different aldehydes with THP and TBDMS protected bromide 4.19.

Protecting group on bromide **4.19**	Aldehyde	%Yield of Coupled products [a]	%Yield of lactone **4.22** [b]
THP	Hexanal	83	45
THP	2-*n*-butyl-2-formyl-1,3-dithiane	0	0
THP	Tetradecanal	79	46
TBDMS	Hexanal	86	62

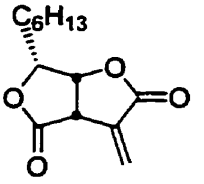
a) Yields determined by ^{1}H NMR of the crude product. b) Yield calculated after isolation and removal of the protecting group.

4.3 Towards the synthesis of canadesolide.

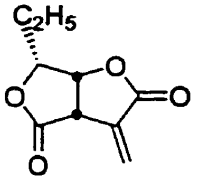
Canadesolide **4.23** is a mold metabolite produced by *Penicillium canadense* which has antigermative activity against fungi.[16] It is a member of the α-methylene-bis-γ-butyrolactone family, which include members such as sporothriolide **4.24**, xylobovide **4.25** and avenaciolide **4.26.** [17,18] Canadensolide has been the focus of a few formal syntheses which have normally been lengthy and low yielding.[19] An improved synthesis using a pathway through carbohydrates, a concept first introduced by Fraser-Reid,[19b] for the synthesis of this molecule, was recently published [20] using L-arabinose as starting material.



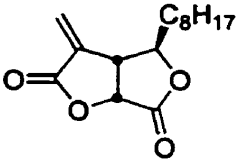
4.23



4.24



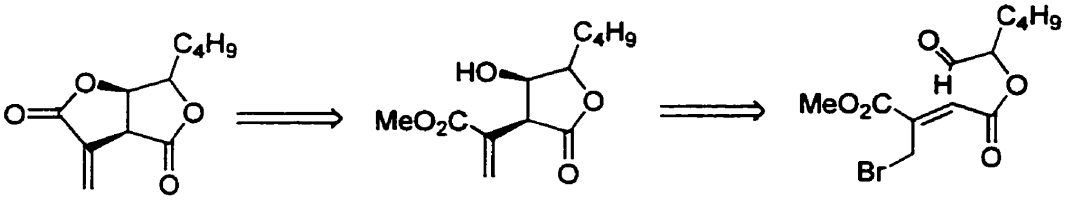
4.25



4.26

Scheme 4.15

As a synthetic target, canadensolide possesses many qualities which make it very attractive. As a naturally occurring substance that exhibits significant biological activity, this molecule is also engaging as it is composed to two densely functionalized lactones in a *bis*-5-membered fused system.



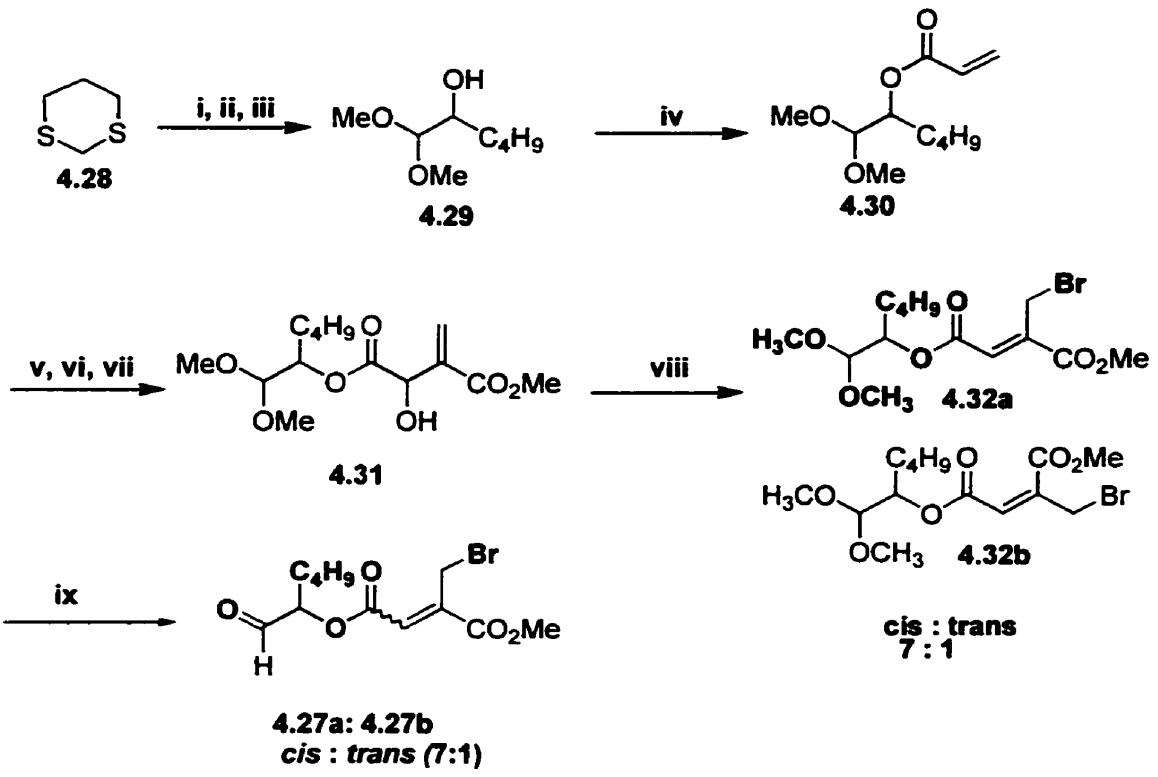
4.27

Scheme 4.16

Having successfully illustrated the synthetic utility of the indium-mediated intermolecular allylation with the efficient synthesis of the paraconic acids, (±)-methylenolactocin and (±)-protolichesterinic acid we wanted to further investigate the utility of intramolecular reaction. We were particularly attracted to canadensolide,

because the retrosynthetic pathway we envisioned (Scheme 4.16) allowed for a further analysis of the limitation we had encountered in our synthesis of (±)-methylenolactocin (Scheme 4.12). Having encountered a serious shortcoming of the indium-mediated allylation in the intermolecular reaction, where enolizable functionalities in the γ-position of the allylic halide inhibited effective coupling, we wanted to investigate the same scenario in an intramolecular cyclization. Would the presence of a carboxylate in the γ-position of the allylic bromide **4.27** inhibit the intramolecular reaction or would cyclization onto the neighboring aldehyde occur before the indium-enolate reacts with water?

We proceeded to synthesize the cyclization precusor **4.27**, as illustrated below. Commercially available 1,3-dithiane **4.28** was lithiated by stirring with a slight excess of butyl lithium at –20°C for 2.5 hrs. The extent of lithiation was monitored by deuteration of a 500ul aliquots at 30 minute intervals. The solution was cooled to –78 °C before the dropwise addition of pentanal to reduce the probability of enolization. The product 1-(1-



Scheme 4.17 i) *n*-Butyllithium, –20 °C / THF; ii) –78°C, pentanal; iii) I_2 / MeOH, reflux; iv) Acryloyl chloride, NEt_3, 0°C / CH_2Cl_2; v) O_3,–78°C / CH_2Cl_2; vi) Methyl sulfide, –78°C – rt.; vii) Methyl acrylate, dabco; viii) Methy sulfide, NBS, 0°C – rt.; ix) Acetone CSA, pH 2.

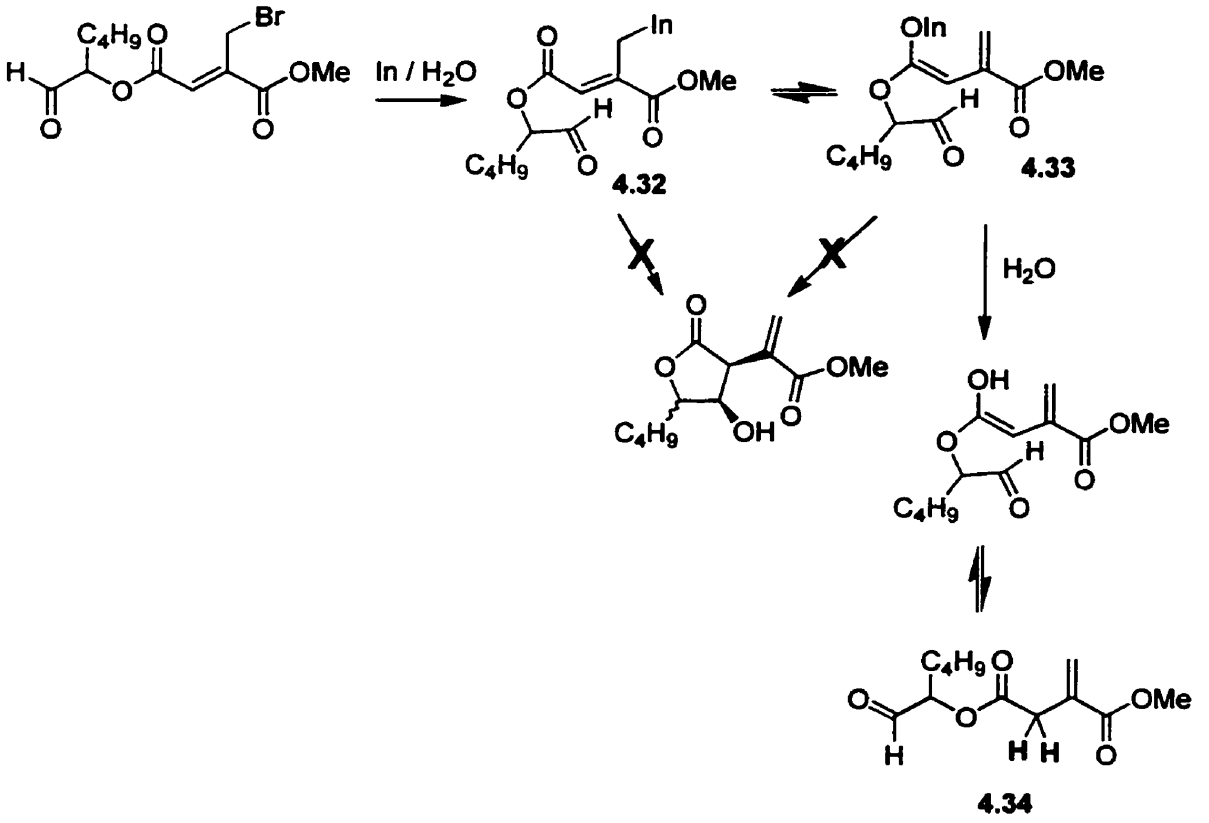
,3-dithian-2-yl)pentan-1-ol was of sufficient purity for subsequent exchange of the thio-acetal protecting group for the dimethyl acetal group without purification. This was achieved by refluxing with I_2 / MeOH, furnishing after purification *via* flash column chromatography 1,1-dimethoxy-2-hexanol **4.29** in 86% overall yield. Esterificaion with acryloyl chloride of alcohol **4.29** gave a 99% yield of (dimethoxymethyl)pentyl prop-2-enoate **4.30.** Ozonolysis of this acrylate provided the corresponding glyoxylate after reduction with dimethyl sulfide (DMS), which could be coupled without isolation to methylacrylate in the presence of dabco providing the allylic alcohol **4.31** (83%). Attempts to transform this substrate to **4.27** in a single step by treatment with PBr_3

yielded a very complex product mixture. We therefore had to convert of **4.31** to **4.32** by reaction with NBS / DMS which resulted in the production of a mixture of *cis* / *trans* diasteromeric bromides. For the first time in our formation of allylic bromides via S_N2' displacement of the β,γ-substituted allylic alcohols, we observed a mixture of geometric isomers in a ratio of 7:1 of the *trans:cis* (**4.32a:4.32b**) compounds respectively in the product. Both bromides were sufficiently different in polarity to allow separation by flash chromatography using hexanes:ethyl acetate 11:1 as the eluting solvent.

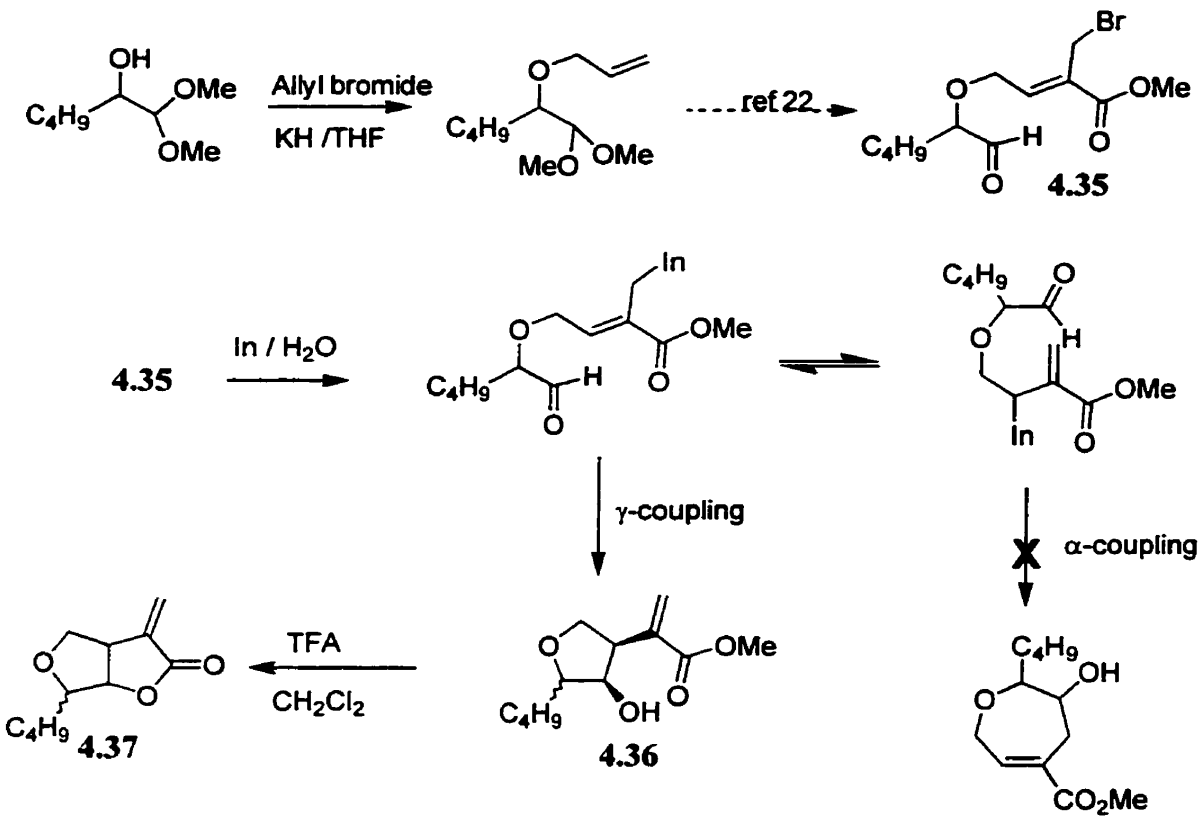
With the bromide **4.27** in hand, we subjected it to the indium-mediated allylation conditions in water and found that it reacted with indium in a relatively rapid manner, furnishing the unwanted reduced product **4.34**. We could observe no coupled material in the crude product. As shown in Scheme 4.18, we believe that most probably the reaction of the bromide with indium led to the formation of the allylindium species **4.32** which normally would couple to the aldehyde, furnishing the desired cyclized product. However, conjugation with the ester functionality allows for transfer of the indium from carbon to oxygen. This indium enolate **4.33** also has the ability to couple to the aldehyde, but as we saw with α-halo esters, the indium enolate also reacts with water. This investigation illustrates that even if the electrophile is in close proximity to the reactive center through an intramolecular network (**4.32** and **4.33**), the reaction of the enolate with water still dominates.

To demonstrate that the intramolecular cyclization of this densely functionalized system would occur absent of the carboxylate in the γ-position, we synthesized the corresponding deoxy analog **4.35**. With γ-ester functionality replaced with an ether linkage, the cyclization could be performed in a near complete manner. Without the

activating species the allylindium shows no affinity for reaction with water, and the cyclization occurs without hindrance furnishing the cis-fused, γ-coupled product **4.36**. Upon treatment with TFA in CH_2Cl_2 this product could be cyclized to the deoxy canadensolide analog **4.37**.



Scheme 4.18



Scheme 4.19

4.4 Conclusion

In conclusion, we were able to demonstrate the synthetic utility of the water based indium-mediated allylation reaction for the construction of densely functionalized, naturally occurring, paraconic acids. In a route that was free from labor intensive tasks, we were able to construct the desired framework with very high yielding sequences. In this manner we were able to produce (±)-methylenolactocin and (±)-protolichesternic acid. We believe this methodology to be easily amenable for the general production of paraconic acids. Through careful manipulation, we demonstrated how the diastereoselectivity of the allylation could be enhanced through controlling the steric

interactions. While illustrating the synthetic utility of the indium-mediated allylation in aqueous media, we also served to demonstrate where the methodology encounters limitations. It was shown that the presence of an electron accepting functionality in the γ-position of the allylic halide could prevent effective allylation. This lends evidence to the existence of a C-In species, which in lieu of reaction with water, couples to appropriate electrophilic species in the typical reaction. When a carboxylate is in the γ-position of the allylic halide, an O-In species is generated through the corresponding enolate that reacts rapidly with water without coupling in an intermolecular fashion to an aldehyde. We were also able to demonstrate that this limitation applies even when the reacting centers are placed in close proximity to each other in an intramolecular network. So while the canadensolide prelactonization precursor could not be formed using indium in water the deoxy analog could be synthesized in a *cis*-fused selective manner.

We have successfully demonstrated the applicability of the methodology for the construction of densely functionalized, naturally occurring, biologically active substrates and related analogs.

4.5 Experimental Procedures.

General procedures: See Chapter 3, section **3.7.**

Preparation of (2Z)-4-bromo-3-(methoxycarbonyl)but-2-enoic acid (4.9) : Glyoxylic acid monohydrate (5g, 54 mmol) was dissolved in 10ml of H_2O and then mixed with methyl acrylate (10 ml, 111mmol). 1,4-Diazabicyclo[2.2.2]octane (dabco) (9g, 81mmol) was then added to the stirring two-phase mixture resulting in an intermediate slightly exothermic reaction and formation of a homogeneous pale yellow solution. Stirring was continued for an additional 6 hrs after which the solution was acidified (pH 2-3) with the dropwise addition of concentrated HCl. The aqueous layer was then saturated with NaCl and extracted with 3 X 25ml of ethyl acetate which were combined and dried with Na_2SO_4. Evaporation under reduced pressure produced a light brown crude oil that was purified on silica gel with EtOAc:CH_2Cl_2:AcOH (5:1:few drops), furnishing a colorless oil (7.7g, 89%) of 1-methoxycarbonyl-3-hydroxy-2-methylene-butanoic acid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.40 (s, 1H), 6.04 (s, 1H), 4.93 (s, 1H) 3.78 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ 175.3, 166.5, 136.9, 130.0, 70.7, 52.5. Treatment of this allylic alcohol (6.5g, 45mmol) with PBr_3 (5ml, 53mmol) as previously described (Chapter 3 section **3.7h**) resulted in the production of a yellow colored oil after isolation. Flash chromatography on silica gel using EtOAc:CH_2Cl_2:AcOH (9:1:few drops) as eluant provided 6.3g (63 % yield) of the desired bromide as a viscous oil . ^{1}H NMR (200 MHz, $CDCl_3$) d 10.74 (br, COOH), 6.85 (s, 1H), 4.70 (s, 2H), 3.90 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), 168.6, 163.8, 143.9, 126.8, 53.5, 22.7.

Preparation of (tert-butyldimethylsilyloxy)acetaldehyde (4.16b): Allylalcohol (680μl, 10mmol) was dissolved in 15ml CH_2Cl_2 containing imidazole (750mg, 11mmol) and cooled to 0 °C under argon. *t*-Butyldimethylsilyl chloride (1g, 6.6mmol) dissolved in CH_2Cl_2 (5 ml) was then slowly added to the stirring mixture which was subsequently allowed to warm to room temperature and left stirring for 12hrs. At this point 50ml of diethyl ether was added and the organic layer washed with H_2O (50ml) and saturated NaCl (50ml). After drying over Na_2SO_4, evaporation under reduced pressure followed by flash chromatography through silica gel with hexanes:ethyl acetate 19:1 gave the desired product (tert-butyldimethylsilyloxy)-propene as a colorless oil in 92% yield (1.6g 9.2mmol). The silyl ether was dissolved in CH_2Cl_2 (20 ml), ozonized and reduced to the corresponding aldehyde (Chapter 3 Section **3.7b**), to give α-tert-butyldimethylsilyloxy)acetaldehyde as a colorless oil (1.6g, 99% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.71 (s, 1H), 4.22 (s, 2H), 0.93 (s, 6H), 0.11 (s, 9H); ^{13}C NMR (50 MHz, CDCl3) δ 200.8, 69.7, 26.3, 18.6 -4.49.

Preparation of methyl 2-hydroxy-3-[tetrahydro-2H-pyran-2yl)oxy-α-methylene butanoate. (4.17a): Allyl alcohol (1ml, 15mmol) was protected as its tetrahydropyranylether,[24] ozonized and reduced as described in Chapter 3 Section **3.7b.** The crude α-(tetrahydro-2-pyranyloxy)acetaldehyde **4.16a** resulting from the procedures was reacted directly under our modified Baylis-Hillman conditions (Chapter 3 Section **3.7g**). After 24hrs no aldehyde was observed by ^{1}H NMR of an aliquot of the solution indicating full conversion. The product was isolated normally and purified by flash column chromatography with an eluant of hexanes:ethyl acetate 4:1 to give **4.17a** as an equal mixture of diastereomers; colorless oil; 73 % yield (2.5g); ^{1}H NMR (500MHz,

$CDCl_3$) δ 6.4 (s, 2H,), 6.0 (s, 1H), 6.0 (s, 1H), 4.7 (t, 2H, J = 8.5 Hz,), 4.6 (m, 2H,), 3.9 (m, 4H,), 3.8 (s, 6H), 3.6-3.5 (m, 4H,), 1.8 (m, 4H,), 1.5 (m, 8H,); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 166.3, 139.4, 138.9, 126.7, 126.5, 100.2, 73.3, 72.0, 69.6, 69.4, 63.3, 63.2, 51.8, 51.8, 30.7, 30.5, 25.1, 25.1, 19.9, 19.8.

Preparation of methyl 3-hydroxy-4-(tert-butyldimethylsilyloxy)-α-methylene butanoate. (4.17b): Methyl acrylate was coupled to aldehyde **4.16b** using the Baylis-Hillman reaction as outlined previously (Chapter 3 Section **3.7g**). 90% (1.5g) yield; ^1H NMR (500 MHz, $CDCl_3$) δ 6.35 (s, 1H), 5.99 (br, 1H), 4.56 (s, 1H), 3.87 (dd, 1H, J = 3.5 Hz and J = 10.0 Hz), 3.77 (s, 3H), 3.47(dd, 1H, J = 6.5 Hz and J = 10.0 Hz), 2.97 (br, 1H, C-OH), 0.89 (s, 9H), 0.06(s, 3H) 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 139.0, 126.5, 70.8, 66.5, 51.8, 25.8, 18.3, -5.4, -5.4

Preparation of methyl 2-bromomethyl-4-tetrahydropyranyloxy-(2Z)-butenoate (4.18a): The allylic alcohol **4.17a** (2g, 8.7mmol) was transformed to the allylic bromide under neutral conditions with NBS and DMS as described in Chapter 3 Section **3.7h**. After flash chromatography through silica gel with hexane:ethyl acetate 9:1 as eluant, an 81 % yield (2.1g) of the bromide **4.18a** was obtained as a light yellow oil. ^1H NMR (200 MHz $CDCl_3$) δ 7.04 (t, 1H, J = 6.1 Hz), 4.68 (t, 1H, J = 3.7 Hz), 4.57-4.25 (m, 2H), 4.25 (s, 2H), 3.82 (s, 2H), 3.28-3.50 (m, 2H), 1.59 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.5, 142.7, 129.4, 98.2, 63.5, 62.6, 52.6, 30.9, 25.9, 24.4, 19.8. MS, CI (NH_3) m/z 293 (2.0), 213 (M-Br, 4.5), 192.9 (M-OTHP, 2.1), 102.06 (6.0), 85 (27.4).

Preparation of methyl (2Z)-2-(bromomethyl)-4-*tert*-butyldimethylsilyloxy-but-2-enoate (4.18b): Transformation of allylic alcohol **4.17b** (1.5g, 5 mmol) to the corresponding rearranged allylic bromide with NBS and DMS was performed as outlined

in Chapter 3 Section **3.7h**; Yield 83% (1.5g); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.95 (t, 1H, J = 5.4 Hz), 4.46 (d, 2H, J = 13.2 Hz), 4.23 (s, 2H), 3.81 (s, 9H), 0.92 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.7, 145.9, 127.9, 60.5, 52.6, 26.4, 18.9, -4.4.

Preparation of methyl 4-hydroxy-3-*syn*-(tert-butyldimethylsilyloxy)methyl-2-methylene-nonanoate (4.20b): The allylic bromide **4.19b** (325mg, 1mmol) and hexanal (240μl, 2mmol) were premixed prior to the addition of 5ml of H_2O. To the stirring mixture at room temperature was added indium powder in (230mg 2mmol) in 3 portions. After stirring vigorously for 12 hrs, the organic products were extracted into diethyl ether and concentrated. After NMR analysis of the crude and purification through silica gel using gradient elution of hexanes:ethyl acetate 1:0, 9:1 and 4:1, compound **4.20b** was one of two compounds isolated. It corresponded to the minor component (31%) observed in the crude ^{1}H NMR. It was isolated as a colorless oil, isolated yield 25 % (25mg) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (s, 1H), 5.70 (s, 1H), 3.69 (m, 3H), 3.76 (s, 3H) 2.82 (q, 1H, J = 6.5 Hz), 1.41-1.24 (m, 8H), 0.89 (m, 12H) 0.07 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 139.5, 127.3, 74.6, 65.7, 52.1, 47.1, 35.5, 31.9, 25.8, 25.3, 22.6, 18.1, 14.0, -5.6, -5.7.

Preparation of *anti*-(4-*tert*-butyldimethylsilyloxy)methyl-3-methylene-5-pentyltetrahydrofura-2-one (4.21b): Experimental procedure was the same as that used for **4.20b;** isolated yield 62% (185mg); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.30 (d, 1H, J = 2.6 Hz), 5.66 (d, 1H, J = 2.1 Hz), 4.36 (m, 1H), 3.68 (m, 2H), 2.85 (m, 1H), 1.72- 1.29 (m, 8H), 0.89 (m, 12H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 170.2, 136.4, 123.1, 81.1, 64.8, 47.0, 36.1, 31.5, 25.8, 24.7, 22.5, 18.1, 14.0, -5.5, -5.6.

Preparation of *anti*–4-hydroxymethyl-3-methylene-5-pentyltetrahydrofuran-2-one (4.22a): The allylic bromide **4.18a** (300mg, 1mmol) was reacted with hexanal (240μl, 1mmol) under the same conditions described for the corresponding TBDMS ether (see preparation of **4.20b**). The products of the reaction were examined and purified in a similar manner. ^{1}H NMR analysis of the crude showed the presence of 4 products in equal amounts; flash chromatography through silica gel with hexanes:ethyl acetate 9:1 as eluant , led to the isolation of diastereomeric mixtures of the syn coupled products **4.20a** and the diasteromeric mixtures of the known[9] lactone **4.21a**. Both pairs of diastereomeric products were dissolved in 5ml of MeOH containing CSA (pH 3) and stirred for 6hrs at room temperature. The mixture was then taken into 15ml of diethyl ether, washed with sat'd $NaHCO_3$ and dried over Na_2SO_4 before removal of the solvents under reduced pressure. From **4.20a** a mixture of inseparable compounds was formed; from **4.21a**, compound **4.22a** was formed in a smooth conversion of 45% overall yield from bromide **4.18a** . ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (d, 1H, J = 2.5 Hz), 5.72 (d, 1H, J = 2.0 Hz), 4.41 (dt, 1H J = 4.5 Hz, J = 6.0 Hz), 3.76 (d, 2H, J = 6.4 Hz), 2.88 (m, 1H), 2.53 (br, OH) 1.70- 1.28 (m, 8H) 0.89 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, CDCl3) δ 170.2, 136.2, 123.6, 80.8, 63.9, 46.8, 36.0, 31.4, 24.6, 22.5, 13.9.[9b] Compound **4.21b** was likewise treated with CSA/ MeOH to remove the TBDMS protecting group, furnishing **4.22b** which proved to be identical to **4.22a.**

Preparation of *anti*–4-hydroxymethyl-3-methylene-5-tridecyltetrahydrofuran-2-one (4.22c): Compound **4.22c** was synthesized in a similar manner from **4.19c** as was **4.22a from 4.19a** in 46% yield (140mg). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.34 (d, 1H, J = 2.5 Hz), 5.73 (d, 1H, J = 2.2 Hz), 4.42 (m, 1H), 3.75 (m, 2H),

2.89 (m, 1H), 2.77 (br, OH), 1.70-1.20 (m, 24H), 0.88 (t, 3H, J = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.0, 136.4, 123.9, 81.7, 65.0, 48.1, 37.5, 33.4, 31.1-30.8 (overlapping C's), 26.5, 24.2, 15.8.

Preparation of (±)-methylenolactocin (4.1): Alcohol **4.22a** (30mg, 0.15mmol) was dissolved in acetone (1ml) and was treated dropwise with Jones reagent (freshly prepared) at 0°C until a persistent orange color was observed and stirred for 2hrs at that temperature. After quenching with methanol, the product was extracted CH_2Cl_2 (3 X 5ml). The organic layer was washed with sat'd NaCl (5ml) and dried over Na_2SO_4. Flash column chromatography using EtOAc: CH_2Cl_2:AcOH (9:1:few drops) yielded 26 mg (82 %) of a colorless oily film. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.44 (d, 1H, J = 3.0 Hz), 5.99 (d, 1H, J = 2.5 Hz), 4.79 (dt, 1H, J = 6.0 Hz, J = 6.2 Hz), 3.61 (m, 2H), 1.72 (m, 2H), 1.51-1.23 (m, 6H) 0.88 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 168.4, 132.5, 125.7, 79.2, 49.3, 35.7, 31.3, 24.4, 22.4, 13.9.[9b]

Preparation of (±) protolichesterinic acid (4.2): Compound **4.2** was produced in a similar procedure from **4.22c** (30mg 1 mmol) as that used for **4.1** from **4.22a**. . Yield 25mg (79%), white solid; mp 102-106 °C ; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.50 (d, 1H, J = 3.0 Hz), 6.02 (d, 1H, J = 2.8 Hz), 4.81 (q, 1H, J = 6.2 Hz), 3.63 (m, 1H), 1.80- 1.70 (m, 2H), 1.20-1.55 (m, 22H), 0.91 (t, 3H, J = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 173.0, 167.9, 132.4, 125.5, 78.7, 49.3, 35.6, 32.0, 29.5 (overlapping C's), 29.4, 29.3, 29.2, 29.1, 24.6, 22.5, 13.9.[9b]

Preparation of 2-butyl-1,3-dithiane: Pentanal (1 ml, 9.4mmol) was reacted with 1,3-propanedithiol in the presence of $BF_3.Et_2O$ using a published reaction.[24] Purification to produce a colorless oil was very important for the subsequent reaction and this was

accomplished via elution through silica gel using hexanes:ethyl acetate 99:1; yield 1.5 g (89%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.04 (t, 1H, J = 6.8 Hz), 2.90-2.79 (m, 4H), 2.10 (m, 1H), 1.87 (m, 1H), 1.75 (q, 2H, J = 7.0 Hz), 1.48 (m, 2H), 1.32 (m, 2H), 0.90 (t, 3H, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.7, 35.2, 30.5, 28.8, 26.1, 22.3, 13.8.

Preparation of 2-butyl-2-formyl-1,3-dithane: 2-Butyl-1,3-dithiane (1.5 g) was formylated using butyllithium (2.5 M in hexanes) and DMF (dry) according to an established experimental protocol.[15] Purification by elution through silica gel with hexanes:ethyl acetate (99:1) gave a colorless oil; yield 1.2g (73%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.01 (s, 1H), 3.01 (dd, 2H, J = 2.6 Hz), 2.62 (t, 1H, J = 3.7 Hz), 2.55 (t, 1H, J = 3.7 Hz) 2.06-1.25 (m, 8H), 0.89 (t, 3H, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 188.3, 58.3, 36.2, 36.2, 27.3, 26.5, 25.1, 23.5, 14.4.

Preparation of 1,1-dimethoxy-2-hexanol. (4.29) : All glassware was oven dried for 24 hrs and kept in a dessicator which was flushed with argon and contained $CaCO_3$ as a drying agent. Commercially available 1,3-dithiane (2.5g, 21mmol) was dissolved in 25ml of THF (distilled over CaH) in a 50ml, two-necked, oven dried (24hrs) flask and cooled to –20 °C under argon. BuLi (2.5M in hexanes), (9.2ml, 23mmol) was added and the solution left stirring. At 30-minute intervals 500ul was transferred into D_2O and the extent of lithiation determined by ^{1}H NMR. A maximum of ~90% was observed after 3hrs beyond which point no significant change was seen. The temperature was then lowered to –78°C and pentanal (2.5ml, 24mmol) was slowly added and stirring continued for 10 minutes after the addition was completed. The reaction was quenched with saturated NH_4Cl and warmed to room temperature. The organic substrate was extracted with diethyl ether (3 X 50 ml), which were subsequently combined and dried over

Na_2SO_4. The solvents were removed under reduced pressure and the crude product dissolved in 25 ml of MeOH. Iodine crystals (8 g, 32mmol) were added and reaction refluxed for 3hrs. Excess iodine was destroyed with sodium thiosulfate 15g / 50 ml H_2O. Extraction with diethyl ether (3 X 25 ml), subsequent drying and removal of the solvent gave a yellow oil. purification via flash chromatography through silica gel using hexanes:ethyl acetate (9:1) gave the desired alcohol **4.29** in 86% overall yield (2.9g). ^1H NMR (500 MHz, $CDCl_3$) δ 4.11 (d, 1H, J = 6.0 Hz), 3.57 (m, 1H), 3.44 (s, 3H), 3.41 (s, 3H), 2.14 (br, OH), 1.60-1.45 (m, 6H), 0.90 (t, 3H, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 106.9, 71.1, 55.0, 55.0, 31.4, 27.6, 22.7, 14.0.

Preparation of (dimethoxymethyl)pentyl methyl 3-hydroxy-2-methylenebutane-1,4-dioate (4.31) : Compound **4.29** (1g, 6mmol) was dissolved in 15ml of CH_2Cl_2 containing 1ml of TEA and cooled to 0 °C under argon. Acryloyl chloride (584ul, 7 mmol) was then added dropwise and the solution warmed to room temperature. Monitoring by thin layer chromatography served to indicate when all of the starting alcohol had been consumed (12 hr). The mixture was then taken up into diethyl ether (50 ml), washed with 0.1 N HCl (25 ml) and saturated NaCl (25 ml), dried with Na_2SO_4 and evaporated under reduced pressure to give the acrylic ester **4.30**. Dissolution of this substrate in 15ml of CH_2Cl_2 followed by cooling to –78 °C preceded ozonolysis under normal conditions (Chapter 3 Section **3.7**) with the only exception being that after reduction the glyoxylate was concentrated by removal of 10 ml of CH_2Cl_2 instead of being isolated. Methyl acrylate (2ml, excess 20mmol) was added followed by dabco (336mg, 3mmol) and stirred for 12hrs. The mixture was then taken up into diethyl ether (50 ml), washed with 0.1N HCl (15 ml), NaCl (15 ml), and dried over Na_2SO_4.

Evaporation followed by flash column chromatography with hexane:ethyl acetate 5:1, furnished the desired allylic alcohol **4.31** as an equal mixture of diastereomers in 77 % (1.4g) overall yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (s, 1H), 6.37 (s, 1H), 5.96 (s, 1H), 5.95 (s, 1H), 5.00 (m, 2H), 4.91 (s, 1H), 4.88 (s, 1H), 4.27 (d, 1H, J = 6.0 Hz), 4.20 (d, 1H, J = 6.5 Hz), 3.77 (s, 3H), 3.76 (s, 3H), 3.39 (s, 3H), 3.36 (s, 3H), 3.34(s, 3H), 3.30 (s, 3H), 1.66-1.51 (m, 4H), 1.32-1.16 (m, 8H), 0.88 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 171.7, 165.4, 165.4, 137.7, 137.7, 129.1, 128.8, 103.8, 103.8, 74.4, 74.4, 71.1, 70.9, 55.1, 54.9, 54.1, 54.1, 51.9, 28.5, 28.5, 27.0, 26.7, 22.3, 22.2, 13.7, 13.7.

Preparation of (dimethoxymethyl)pentyl methyl (2Z)-2-(bromomethyl)but-2-ene-1,4-dioate (4.32a) and of (dimethoxymethyl)pentyl methyl (2E)-2-(bromomethyl)but-2-ene-1,4-dioate (4.32b): The allylic alcohol **4.31** (1.4g, 4.6mmol) was treated with the NBS/DMS procedure as described previously (Chapter 3 Section **3.7**) . The transformation proceeded sluggishly and after 24 hr only **88%** of **4.31** was consumed (^{1}H NMR, $CDCl_3$). Flash column chromatography through silica gel with hexanes:ethyl acetate 12:1, furnished the allylic bromides **4.32a** and **4.32b** in 73% yield (1.2g), and 9% (150mg) yield respectively. **Compound 4.32a:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (s,1H), 5.10 (m,1H), 4.70 (s, 2H), 4.32 (d, 1H, J = 5.5 Hz), 3.87 (s, 3H), 3.41 (s, 3H), 3.39 (s, 3H) 1.72-1.59 (m, 2H), 1.31 (m, 4H), 0.89 (t, 3H, J = 6.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 164.1, 142.2, 129.8, 104.2, 73.5, 55.2, 54.6, 53.0, 28.9, 27.254, 22.6, 22.5, 13.9. MS CI (NH_3) m/z 339 (M – [2*CH_3], + 2 (Br^{81}), 9 %), 337 (M – [2*CH_3], 9 %), 257 (32 %), 75 (31 %). **Compound 4.32b:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.25 (s,1H), 5.01 (m,1H), 4.29 (d, 1H, J = 5.0 Hz), 4.13 (s, H), 3.84 (s, 3H), 3.40 (s, 3H), 3.38 (s, 3H) 1.75-1.59 (m, 2H), 1.30 (m, 4H), 0.88 (t, 3H, J = 6.0 Hz); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 165.8, 163.7, 141.8, 125.3, 104.1, 73.5, 55.3, 54.5, 52.6, 29.5, 28.4, 27.0 22.4, 13.7. MS CI (NH_3) m/z 339 (M – [2*CH_3], + 2 (Br^{81}), 9 %), 337 (M – [2*CH_3], 9 %), 257 (32 %), 75 (31 %).

Preparation of 1-butyl-2-oxoethyl methyl (2Z)-2-(bromomethyl)but-2-ene-1,4-dioate (4.27a) and of 1-butyl-2-oxoethyl methyl (2E)-2-(bromomethyl)but-2-ene-1,4-dioate (4.27b): The transacetalization of **4.32a** (1.2g, 3mmol} to obtained the desired aldehyde was performed (85% conversion, ^1H NMR) as described in Chapter 3 Section **3.6**. Flash column chromatography through silica gel with 12:1 hexanes:ethyl acetate yielded 850mg (81%) of **4.27a**. ^1H NMR (200 MHz, $CDCl_3$) δ 9.53 (s, 1H), 6.92 (s, 1H), 5.13 (dd, 1H, J = 5.1 Hz and J = 7.9 Hz), 4.72 (d, 1H, J = 9.7 Hz), 4.64 (d, 1H, J = 9.3 Hz), 3.88 (s, 3H), 1.80-1.52 (m, 2H), 1.39 (m, 4H), 0.90 (t, 3H, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.1, 164.2, 164.0, 143.7, 127.5, 79.1, 53.2, 28.2, 27.0, 22.3, 13.8; Compound **4.27b** : Formed in a similar manner from **4.32b** (150mg, .4mmol) as was compound **4.27a** from **4.32b**. (83% conversion) isolated yield 75% (100mg); ^1H NMR (200 MHz, $CDCl_3$) δ 9.52 (s, 1H), 6.33 (s, 1H), 5.04, (dd, 1H, J = 5.2 Hz and J = 7.3 Hz), 4.13 (d, 2H, J = 6.0 Hz), 3.82 (s, 3H),.1.89-1.50 (m, 2H), 1.34 (m, 4H), 0.92 (t, 3H, J = 6.8 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.7, 163.8, 163.5, 143.0, 126.9, 78.9, 52.9, 28.2, 27.3, 26.5, 22.1, 13.6.

Preparation of 1-butyl-2-oxoethyl methyl 2-methylenebutane-1,4-dioate (4.34): The attempted indium-mediated cyclization of **4.27a** (367mg 1mmol) was performed as described in Chapter 3 Section **3.6.** ^1H NMR (500 MHz, $CDCl_3$) δ 9.51 (s, 1H), 6.37 (s, 1H), 5.79 (s, 1H), 5.00 (dd, 1H, J = 3.0 Hz and J = 5.0 Hz), 3.78 (s, 3H), 3.46 (s, 2H), 1.58 (m, 2H) 1.25 (m, 4H), 0.89 (t, 3H, J = 7.5 Hz); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 198.3, 170.4, 166.5, 133.0, 129.1, 78.7, 52.2, 37.5, 28.3, 26.9, 22.6, 13.8. MS CI (NH_3), 260 (M + NH4, 2 %), 243 (M + 1, 15 %), (127, 100%).

Preparation of methyl (2Z)-2-bromomethyl-4-(1-butyl-2-oxoethyl)-but-2-enoate (4.35): See the transformation of **4.29** to **4.27**, with one exception being that the allylether of **4.29** was used instead of the acryloyl ester. The allylation was performed as described in Chapter 3 Section **3.7** on **4.29** (1g, 10mmol) yielding 100 % conversion (^{1}H NMR) to the desired 1,1-dimethoxy-2-(allyloxy)hexane. ^{1}H NMR (500MHz, $CDCl_3$) δ 5.92 (m, 1H), 5.26 (d, 1H, J = 16.6 Hz), 5.14 (d, 1H, J = 10.5 Hz), 4.19 (m, 2H), 4.03 (dd, 1H, J = 6.0 Hz and J =12.0 Hz), 3.46 (s, 3H), 3.41 (s, 3H), 3.30 (m, 1H), 1.6-0.96 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.2, 116.6, 107.0, 79.3, 72.0, 55.6, 55.1, 29.9, 27.4, 22.7, 14.0. The subsequent transformations were similar to those stated above, leading to bromide **4.35** as a single product in 57% overall yield (1.7g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.00 (t, 1H, J = 6.5 Hz), 4.43 (dd, 1H, J = 5.8 Hz and J = 14.8 Hz), 4.28 (dd, 1H, J = 6.0 Hz, J = 15.0 Hz), 4.22 (d, 1H, J = 10.0 Hz), 4.18 (d, 1H, J = 10.0 Hz), 3.82 (s, 3H), 3.80 (m, 1H), 1.71 (m, 2H), 1.43-1.33 (m, 4H), 0.91 (t, 1H, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 165.3, 142.3, 130.6, 84.5, 66.5, 52.5, 29.4, 26.8, 23.5, 22.5, 13.8.

Preparation of methyl 2-(5-butyl-(*syn*-4)-hydroxyoxolan-3-yl)prop-2-enoate (4.36). Bromide **4.35** (310mg, 1mmol) was reacted in an identical manner to bromide **4.27a**. Isolation was performed as described for indium-mediated carbocyclizations in Chapter 3, Section **3.7**. ^{1}H NMR analysis of the crude indicated 100 % conversion after 12hrs; isolated yield was 210mg (92%) of a mixture of two diastereomers in a ratio of 1:1.7. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.42 (s, 1H), 6.40 (s, 1.7H), 4.26 (m, 1H), 4.15 (m,

1H), 4.05-3.22 (m, 8.1H), 3.80 (s, 8.1H), 2.01-1.24 (m, 16.2 H), 0.91 (m, 8.1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 167.5, 135.7, 135.6, 127.6, 127.3, 86.7, 84.0, 76.4, 72.8, 68.8, 68.0, 52.3, 52.2, 46.7, 45.8, 33.7, 28.9, 28.4, 28.0, 22.8, 22.7, 14.0. MS CI (NH_3) m/z 326 (M + NH_4 + 2 (Br^{81}), 12 %), 324 (M + NH_4, 12 %), 309 (M + 2, 4 %), 307 (M, 4 %),192 (100 %), 190 (100 %).

4-Butyl-1-methylene-3,4,5,6,3a,6a-hexahydro-3,5—dioxapentalen-2-one (4.37). Compound **4.37** was synthesized from **4.36** using the procedure outlined in Chapter 3 Section **3.7j** Mixture of diastereomers (1:1.5): colorless liquid; IR ($CHCl_3$) 2930 cm^{-1}, 1752 cm^{-1}, 1200 cm^{-1}, ^1H NMR (500 MHz, $CDCl_3$) δ 6.33 (s, 2.5), 5.74 (s, 1.5), 5.71 (s, 1.5), 4.91 (m, 1H), 4.7 (m, 1.5), 4.23-3.55 (m, 10H), 1.74-1.25 (m, 15H), 0.914 (m, 7.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 169.6, 138.3, 137.0, 124.0, 123.6, 84.6, 64.1, 83.0, 81.2, 74.6, 72.5, 43.8, 43.4, 30.5, 28.1, 27.9, 27.4, 22.5, 22.3, 13.8. MS, CI (NH_3) m/z 214 (M + NH_4, 22%), 197 (M+1, 100%), 179 (6%), 166 (49%), 139 (M – Bu^n, 9%) . HRMS (FAB) calcd for $C_{11}H_{16}O_3$ $(M + H)^+$ 197.25410 found 197.11769.

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CHAPTER 5

Conclusion and a consideration of future perspectives.

5.1 Introduction

With some knowledge of the indium-mediated allylation, we embarked on our endeavors of expanding the scope of the reaction and in so doing further demonstrate its synthetic utility. In the preceding chapters we described how we increased the range of the intermolecular reaction (Chapter 2, Sections 2.2.1 and 2.3.1; Chapter 4, Section 4.2) as well as moved the reaction into the realms of intramolecular carbocyclizations. (Chapter 3, Sections 3.3 – 3.5; Chapter 4, Section 4.3) The following sections concentrates on the major conclusions and offers avenues for future developments in this area of chemistry.

5.2 The synthesis of β,γ-unsaturated ketones and β-ketoesters via indium-mediated allylations.

The synthesis of ketones *via* the addition of organometallic species to carboxylic acid derivatives is often complicated by over addition problems.[1,2] This coupled with the high level of chemoselectivity of the allylindium species previously reported[3] rendered our task of expanding this reaction to include the controlled production of β,γ-unsaturated ketones much more than a trivial one. Indeed, we were able to successfully allylate acylimidazoles in water at 0°C (Table 2.2). The control exhibited by the reaction for the synthesis of the desired ketone however, was less than satisfactory, as the tertiary alcohol dominated in the absence of bulk. This led to the discovery of a novel role for

acylpyrazoles, substrates not used previously in such a manner for establishment of the necessary control over the allylation reaction. Possibly serving in a Wienreb-amide type manner (Scheme 2.11) this unique role for pyrazoles represented a significant advancement of the methodology. Using it, a variety of homoallylic ketones including the naturally occurring artemisia ketone were synthesized in high yielding reactions (Chapter2, Section 2.2.1, Table 2.3).

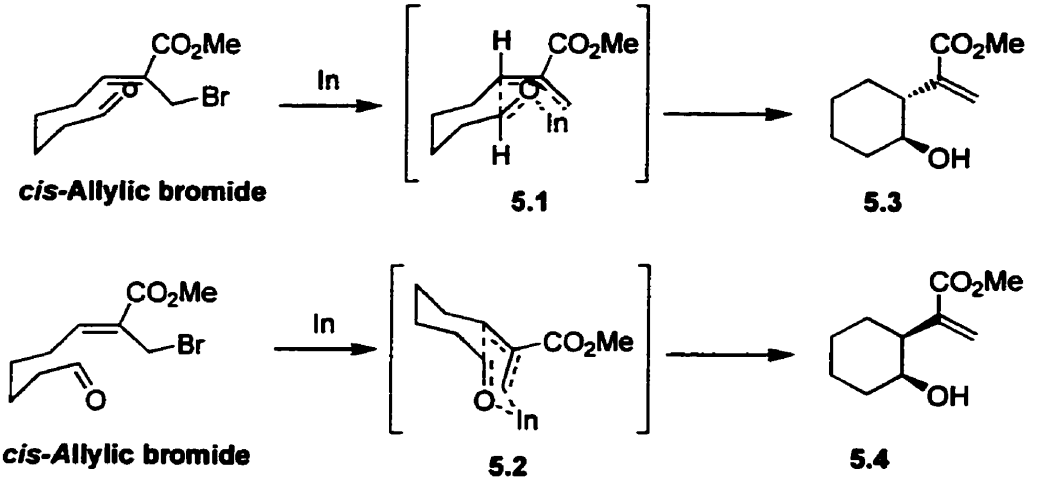
The N-acylpyrazoles also proved suitable for the production of important β-ketoesters (Table 2.3), though we were never able to successfully perform this reaction in aqueous media. This limitation of the reaction is most likely caused by the rapid rate of reaction of O-In species (formed from enolization of the C-In species) with water (Scheme 4.10). This is a serious limitation and the solution most probably best lies in a change of the mediating metal to one such as zinc, tin or mercury which forms more stable enolates. The ease of preparation of the acylpyrazoles, the exclusive nature of the regioselectivity, the high yields, and mild nature of the reaction conditions, each contribute to the usefulness of the expansion created in this work.

5.3 Intramolecular carbocyclizations in aqueous media.

α-Methylene-γ-butyrolactones fused with carbocycles are abundant in nature and methods for their synthesis are continuously being sought.[4] They represent a class of compounds which possess interesting biological activity. In Chapter 3, we revealed a mild, and facile production of 5-,6-, and 7-membered fused carbocycles in aqueous media (Scheme 3.11,Table 3.1). The methodology allowed for a high yielding reaction and

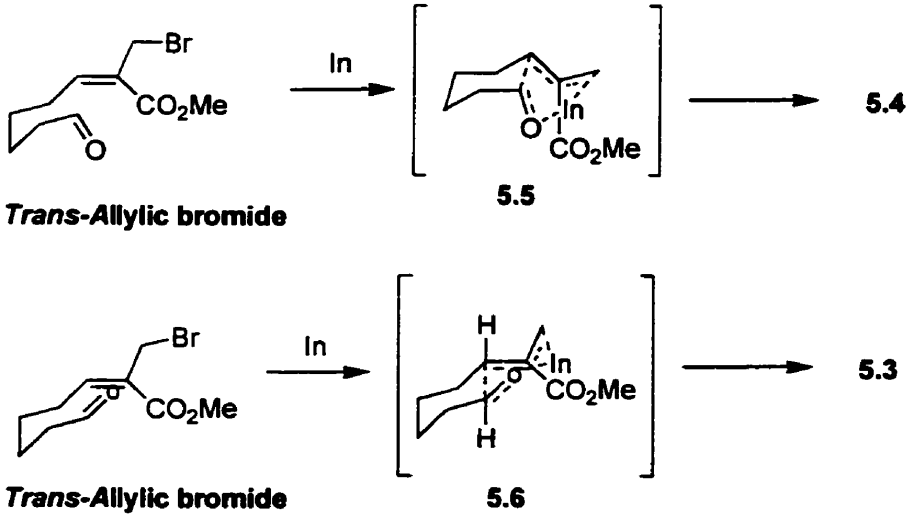
furnished exclusive γ-regioselectivity as well as *cis*-diastereoselectivity. The extension to oxygen heterocycles (Section 3.4) served to illustrate how biologically active cembranolide analogs (Appendix) could be easily produced via indium-mediated allylations in aqueous media. Here we demonstrated that increased polarity led to increased ease of cyclization (Table 3.2 compared to Table 3.1), probably due to assistance from the hydrophobic forces bringing the reacting ends in closer proximity to each other. While the reaction possessed inherent diastereoselectivity we also illustrated a possible route to synthesizing these important substrates in an enantioselective manner.

With the expansion to intramolecular cyclizations we made a significant contribution to the range of substrates accessible *via* the mild indium-mediated methodology. The door has been opened, but the room for expansion remains. For example there are several other target molecules including heterocyclic substrates which can be efficiently produced via this method. In addition, a consideration of the diastereoselectivity would reveal that it was in part determined by the geometry of the allylic unit. The β-methyl ester fixes this geometry such that the pathways shown in Scheme 5.1, govern the reaction outcome. Transition state **5.2**, possessing the chair-chair *cis* decalin type geometry is favored over the chair-boat transition state **5.1**. As a result the *cis* cyclized compound **5.4** is the sole product obtained.



Scheme 5.1

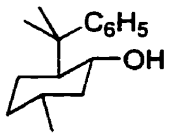
We believe based on this proposal, that the *trans* cyclized product **5.3** can be produced likewise if the geometry of the double bond was altered. Such that if the *trans* allylic bromide is used (Scheme 5.2) then the favored transition state would be **5.6** (chair-chair *trans* decalin type geometry) over **5.5**. We propose therefore that the trans cyclized product **5.3** would then become the major product of the reaction.



Scheme 5.2

Our studies using oxygen heterocycles illustrated that a possible slight increase in the hydrophilic nature of the cyclization precursor could lead to much improved results for the carbocycles. In this regard one can envision that the use of a carboxylic acid group instead of the methyl ester in the β-position of the allylic bromide, can probably lead to enhanced carbocyclization reactions including possibly the 8-membered product with the aid of hydrophobic forces. Indeed similar groups can be incorporated into reaction substrates and the unique characteristics of the aqueous solvent taken full advantage of, possibly leading to an even wider variety of substrates that would be attainable via the indium-mediated methodology.

Though we have initiated studies into the incorporation of auxiliaries into the cyclization substrates, we were not successful in obtaining greater than 12% ee (with menthol as an auxiliary). The illustration that the reaction is not inhibited by the presence of the large hydrophobic auxiliary should however serve to encourage a search for improved chiral auxilliaries which can provide enhanced results. One example is phenylmenthol **5.7** which has the potential to provide much improved results over those observed with menthol.

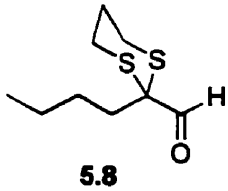


5.7

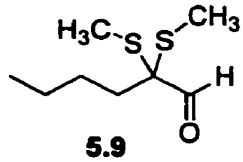
5.4 Paraconic acids and *bis* fused 5-membered lactones.

Paraconic acids is a class of densely functionalized γ-butyrolactone fatty acids usually isolated from moss and lichen as well as culture filtrates of pencillium *sp.*[5] The group is attractive as slightly different substituents or stereochemical relationship amongst the members usually result in interesting biological activity such as anti-tumor, anti-fungal, and growth regulating properties.[6] In Chapter 4 we unveiled a facile manner in which the indium-mediated allylation could be used for the construction of the necessary frameworks. In this manner we were able to synthesize racemic methylenolactocin and protolichesterinic acid.

During this work we were successful in obtaining a 20% increase in the desired anti diastereomer of the allylation just by substituting TBDMS protecting group for THP. We believe that even larger enhancements can be achieved my carefully manipulating the bulk of the aldehydes involved in the coupling. We attempted this with 2-butyl-2-carbonyl-1,3-dithane **5.8** but the thio acetal used proved too bulky for coupling purposes. In this regard, the use of less hindered acetals such as **5.9** could serve as a means of providing an even more efficient route to the paraconic acids.



5.8



5.9

Figure 5.1

In addition, the utility of the methodology can be further enhanced if the coupling could be performed in an enantioselective manner. There is therefore a need to further

explore the effect of chiral auxiliaries or the design of appropriate chiral ligands that may be able to effect the desired results.

In regards to our attempted synthesis of canadensolide, we discovered that there exists a serious limitation when the need to have a γ-carboxylate is present (Scheme 4.18). The route however is very attractive and as demonstrated with our deoxy analog of canadensolide (Scheme 4.19), it can be used for the construction of *bis* fused substrates not needing such a γ-substituent. The solution to the limitation in the synthesis of substrates such as canadensolide may lie in the use of metals which produce more stable enolates in aqueous media.

5.5 References and notes:

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APPENDIX

Details of biological testing of cembranolide analogs (Chapter 3, Section 3.4.2)

APPENDIX 1

The screening of oxygen heterocycles 3.29a and 3.29b.

Appendix 1.0 Cell culture

The four cell lines used in this screening (a breast cancer cell line: MCf7wt; a renal cancer cell line; TK-10; two melanoma cell lines: UACC-62 and UACC-257) were obtained from the National Cancer Institute (Maryland, USA). They were maintained as monolayer cultures at 37°C in a humidified atmosphere of 5% CO_2-95% air in RPMI-1640 cell culture media, supplemented with 10% fetal bovine serum, 2mM L-glutamine, 50U/mL penicillin and 50 mg/mL streptomycin. Cells were maintained in logarithmic growth by harvesting with a trypsin-EDTA solution and reseeding before the cells reached confluency. In all assays, the cells were plated in 96-well plates of 24 h prior to drug administration.

Appendix 1.1 Drug treatment

After allowing them to attach for 24 h, the cells were incubated with the drug (**3.29a** or **3.29b**) for 5 days or 7 days under continuous exposure. Drug stocks of 1.0 M dissolved in DMSO were routinely used. The highest concentration of drug used, 1000 μM, was made up and serially diluted using cell culture media.

Appendix 1.2 Cytotoxicity assay

Cytotoxicity was evaluated by the sulforhordamine B assay. Briefly, at the appropriate times, the cells were fixed by the addition of 50 μL of a 50% stock solution of cold trichloroacetic acid and the plates were incubated at 4°C for 1 h. They were subsequently washed with water and stained with 0.4% sulforhodamine B dissolved in 1 % acetic acid. After a 30 min incubation at room temperature, the plates were washed using a 1 % acetic acid solution. The resulting colored residue was dissolved in 200μL of 10 mM Tris base. The optical density was measured at 540nm with a BioRad Microplate Reader (model 3550). The results represent the average of at least two independent experiments run in triplicate.

Appendix 1.3 Results

When the panel of cell lines was exposed for 5 days to the **3.29b** compound significant cell killing was observed using the SRB cytoxicity assay. We observed an IC_{50} of 59μM in MCF77wt cells, 28μM in TK-10 cells, 17μM in UACC-62 cells and 12 μM in UACC-257 cells.

When the same panel of cells were exposed for 5 days to the **3.29a** compound significant cell killing was observed using the same assay. We observed an IC_{50} of 94μM in MCF77wt cells, 149μM in TK-10 cells, 54μM in UACC-62 cells and 68μM in UACC-257 cells.

We also treated the same panel of cell lines for 7 days continuous exposure to the **3.29a** compound. By using the SRB assay, we observed an IC_{50} of 77μM in MCF77wt cells, 123μM in TK-10 cells, 32μM in UACC-62 cells and 56μM in UACC-257 cells.

Appendix Table 1.0: Summary of results

Cell line	**3.29a** for 5 days (IC_{50} μM)	**3.29a** for 7 days (IC_{50} μM)	**3.29b** for 5 days (IC_{50} μM)
MCF7wt - breast cancer	94	77	59
TK-10 - renal cancer	149	123	28
UACC-62 – melanoma	54	32	17
UACC-257 – melanoma	68	56	12