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Total Synthesis of (–)-Dihydroprotolichesterinic Acid via a Diastereoselective Conjugate Addition, Development of Enantioselective Halocyclization Reactions, and Progress Towards the Total Synthesis of Jiadifenolide

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by

John Caleb Hethcox, B.A.

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Dedication

To my father, my first chemistry teacher.

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Total Synthesis of (–)-Dihydroprotolichesterinic Acid via a Diastereoselective Conjugate Addition, Development of Enantioselective Halocyclization Reactions, and Progress Towards the Total Synthesis of Jiadifenolide

John Caleb Hethcox, Ph.D.

The University of Texas at Austin, 2015

Supervisor: Stephen F. Martin

In an effort to develop a unified route to functionalized succinic acid derivatives, a new diastereoselective conjugate addition of monoorganocuprates, Li[RCuI], to a chiral fumarate was developed. The conjugate addition proceeded with good yields and a high degree of diastereoselectivity for a variety of alkyl and aryl nucleophiles. Application of this new methodology culminated in the shortest total synthesis of (–)-dihydroprotolichisterenic acid to date.

The novel organocatalyst developed by the Martin group was applied to enantioselective iodolactonization reactions. Reaction conditions were optimized and the resulting halolactones were obtained in high yields and enantioselectivities for a number of olefinic acids. Of particular note is the disclosure of the first iodolactonization reactions forming a C–I bond at a stereogenic center. The utility of this catalyst was further extended to kinetic resolution reactions. Additionally, this catalyst was found to promote the first enantioselective halolactamization reaction with moderate enantioselectivity. Finally, the catalyst was modified in an effort to enhance the enantioselectivity and verify the proposed bifunctional nature of the catalyst.

Lastly, an enantiospecific total synthesis of the neurotrophic sesquiterpenoid natural product (–)-jiadifenolide was progressed. The stereochemistry was introduced by the use of commercially available (+)-pulegone as the starting material. The first diastereoselective decarboxylative allylation on a cyclopentanone was developed A samarium diiodide mediated radical annulation was planned to forge two of the rings, and late stage oxidation manipulation could then lead to the completion of the synthesis.

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TOTAL SYNTHESIS OF (–)-DIHYDROPROTOLICHESTERINIC ACID VIA A DIASTEREOSELECTIVE CONJUGATE ADDITION

Chapter 1: Strategies for the Synthesis of Enantioenriched Succinic Acid Derivatives and Select Total Syntheses of Succinate Based Natural Products

1.1 Biologically Active Succinic Acid Derivatives

Core structures based upon succinic acid (**1.1**) are prevalent motifs in a number of biologically active molecules of both natural and unnatural origin (Figure 1.1). The simplest members include disubstituted succinic acids, sphaeric acid (**1.2**) and rocellic acid (**1.3**).[1,2] The paraconic acid family of natural products, including protolichesterinic acid (**1.4**), dihydroprotolichesterinic acid (**1.5**), and nephromopsinic acid (**1.6**) among others, show broad spectrum anti-fungal and anti-bacterial properties and serve as a common testing ground for developing methods to access chiral succinates.[3] Additionally, glaucoma treatment pilocarpine (**1.7**),[4] matrix metalloproteinase inhibitor BB-1101 (**1.8**),[5] and anti-viral agent antrodin D[6] (**1.9**) are based on a chiral succinic acid core. In addition to serving as the core structure of these small molecules, functionalized succinic acid derivatives can serve as functionalized four-carbon building blocks for the synthesis of more complex molecules.

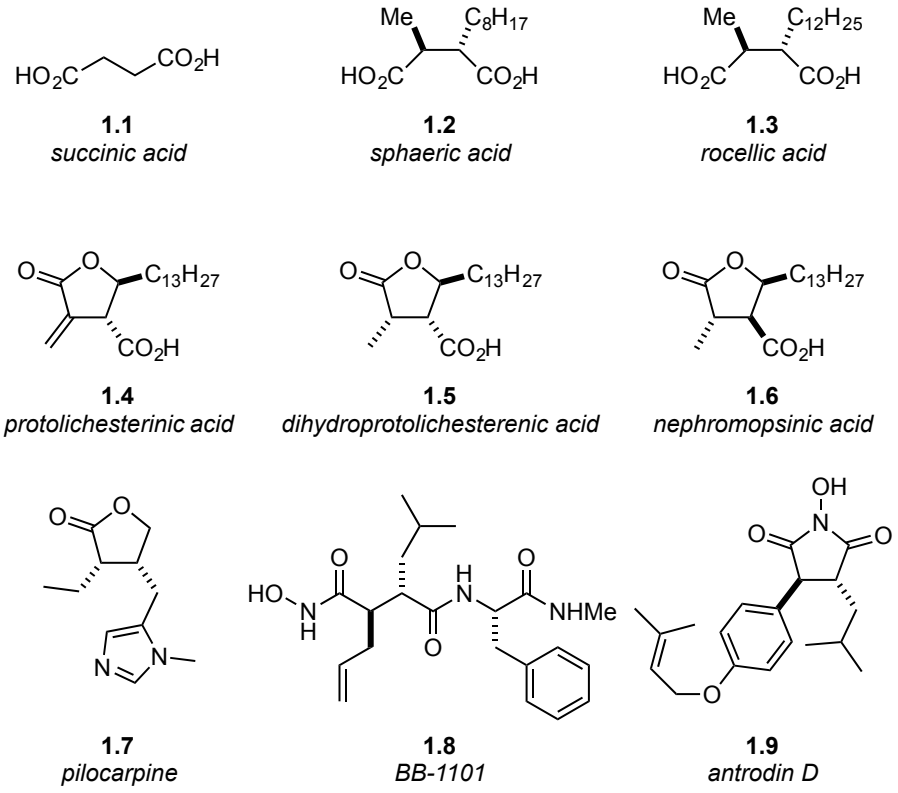


Figure 1.1 Natural products based on a succinic acid core.

Due to the near ubiquity of the succinate moiety, there has been a significant amount of work directed toward their synthesis.[7] While numerous methods have been established to synthesize succinates as racemic mixtures, a number of recent advances have been made towards the synthesis of enantioenriched succinic acids. This review serves to cover the advances in asymmetric syntheses of succinates, and due to the numerous methods that have been developed over the years some have no doubt been overlooked. Previously, this topic was discussed in a 2002 review by Arason and Bergmeier wherein the synthesis of succinate derivatives was discussed in general with some highlights of enantioselective syntheses,[7] here we will specifically address the

advances in the field of synthesis of enantioenriched succinic acid derivatives divided into sections based on the method of chiral induction (e.g. auxiliary or ligand) and subdivided by reaction type (e.g. aldol, alkylation, and conjugate addition).

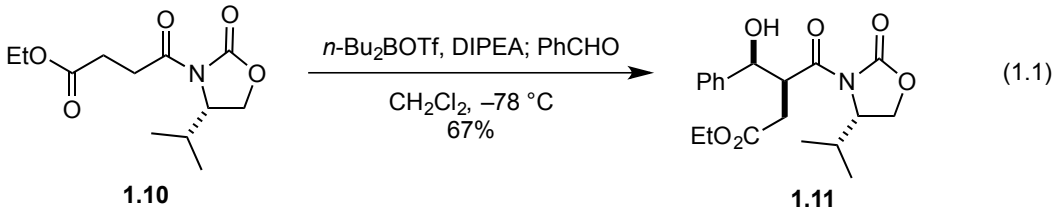
1.2 General Strategies for the Synthesis of Enantioenriched Succinates

1.2.1 Chiral Auxiliary

Chiral auxiliaries have been broadly utilized as cheap, efficient, reliable, and recyclable sources of chirality for the synthesis of enantioenriched molecules. Thus, it should come as no surprise that they have been extensively explored for the synthesis of chiral succinates. Aldol reactions, alkylations, conjugate additions, hydrogenations, and oxidative enolate coupling reactions of substrates with removable chiral appendages have been developed to deliver enantioenriched chiral succinic acid derivatives.

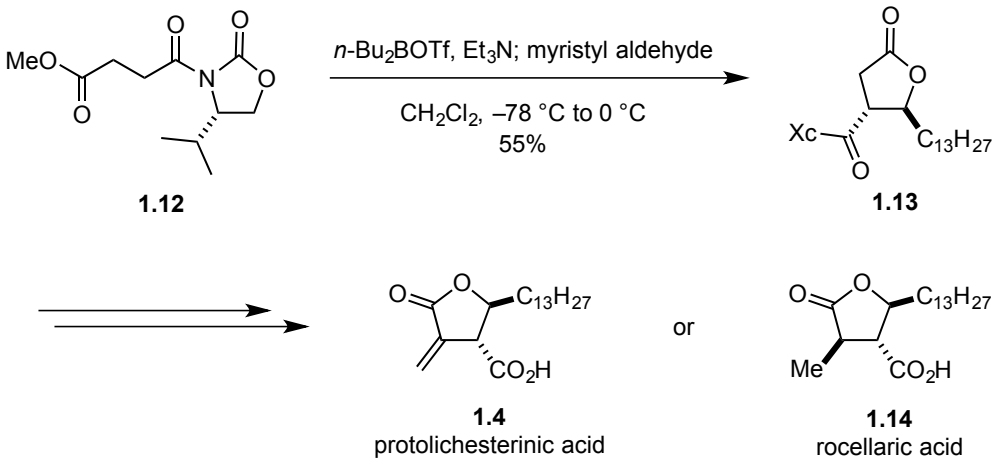
1.2.1.1 Aldol Reactions

The first reported synthesis of a chiral succinic acid derivative via an asymmetric aldol reaction came in Evans's seminal report on chiral oxazolidinones as a chiral auxiliaries for aldol reactions.[8] In order to demonstrate that the method could tolerate a more complex substrate, chiral succinate **1.10** was subjected to his newly developed conditions (Equation 1.1). In the event, the boron enolate of **1.10** was exposed to benzaldehyde providing substituted succinate **1.11** in 67% as a single diastereomer. This pioneering work opened the door to a number of possibilities that would not be explored for another fifteen years.



1.10 **1.11** (1.1)

Sibi and co-workers picked up the development of this reaction, effectively demonstrating that the reaction tolerated the *n*-alkyl aldehyde myristaldehyde (tetradecanal). This reaction provided access to the paraconic acids protolichesterinic acid (**1.4)** and rocellaric acid (**1.14)** (Scheme 1.1).[9] He also demonstrated the utility of this strategy using alkyl aldehydes for the synthesis of 3-amino sugars.[10]



1.12 **1.13**

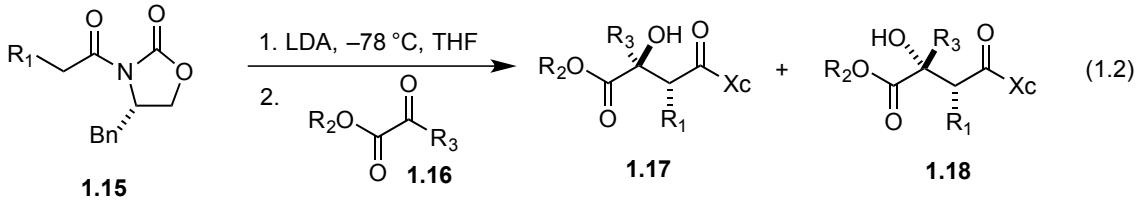
1.4
protolichesterinic acid

1.14
rocellaric acid

Scheme 1.1 Sibi's diastereoselective aldol reaction in the synthesis of **1.4** and **1.14**

The next extension of Evans's oxazolidinones in the enantioselective synthesis of succinates was disclosed by Jacobson in 1996, wherein the use of chiral imide **1.15** provided access to tri-substituted hydroxy succinic acid derivatives **1.17** and **1.18** when reacted with α-keto esters **1.16** (Equation 1.2).[11] The auxiliary controlled the

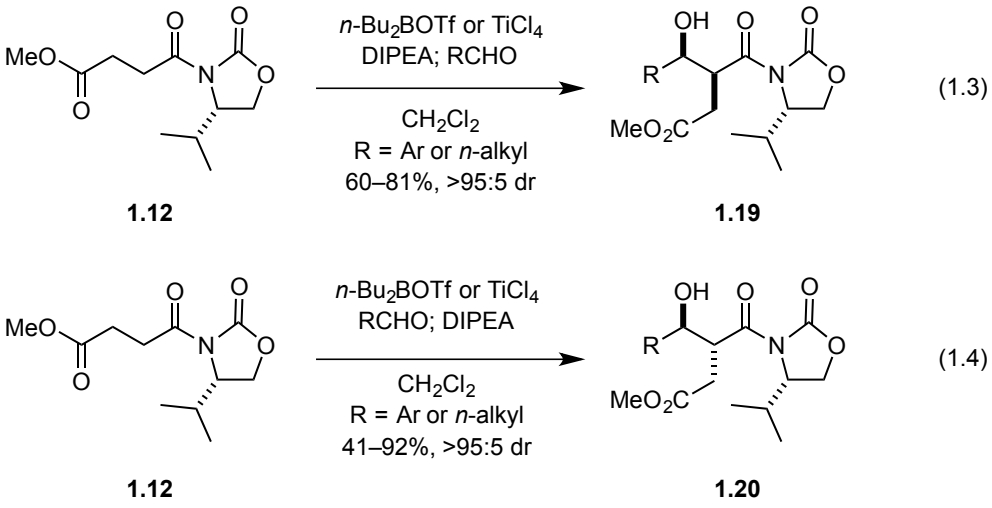
stereochemical outcome at the position α to the imide as expected; however, the facial selectivity of the addition to the ketone was less selective (dr = 63:37–83:17). The diastereomeric ratio could not be improved with the use of *n*-Bu_2BOTf, $TiCl_4$, $SnCl_4$, or Et_2AlCl.



R_1 = CH_3, CH_2Ph, $(CH_2)_2Ph$, $(CH_2)_3Ph$
R_2 = CH_3, CH_2CH_3, CH_2Ph
R_3 = CH_3, $(CH_2)_2Ph$
70–91%, 63:37–83:17 dr

Perhaps the greatest contribution to this field was the discovery of a tactic to modify the diastereoselectivity of the aldol reaction without using the enantiomeric auxiliary. Hajra demonstrated that simply changing the order of addition of base and aldehyde, led to diastereomeric products of the aldol reaction with succinate **1.12**.[12] As shown in Equation 1.3, standard conditions using *n*-Bu_2BOTf or $TiCl_4$ followed by base and then aldehyde provided the Evans syn-aldol product **1.19** in moderate yields with excellent stereoselectivity. Conversely, adding base to a mixture of succinate **1.12**, Lewis acid, and aldehyde provided the Evans anti-aldol product **1.20** in similar yields with excellent stereoselectivity (Equation 1.4). It should be noted that this technique only worked with chiral succinates like **1.12**, thus the authors propose a tetra-coordinate transition state to explain the anti diastereoselectivity (Figure 1.2). Finally, the authors demonstrated the utility of this methodology by using the same starting material to access

two pseudo-diastereomeric natural products, phaeseolinic acid (**1.22**) and protolichesterinic acid (**1.4**), from a single starting material **1.12** (Scheme 1.2). This divergent strategy has been used for the synthesis of a number of other natural products.[13,14]



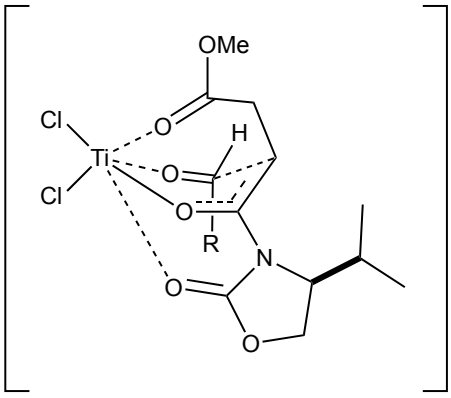
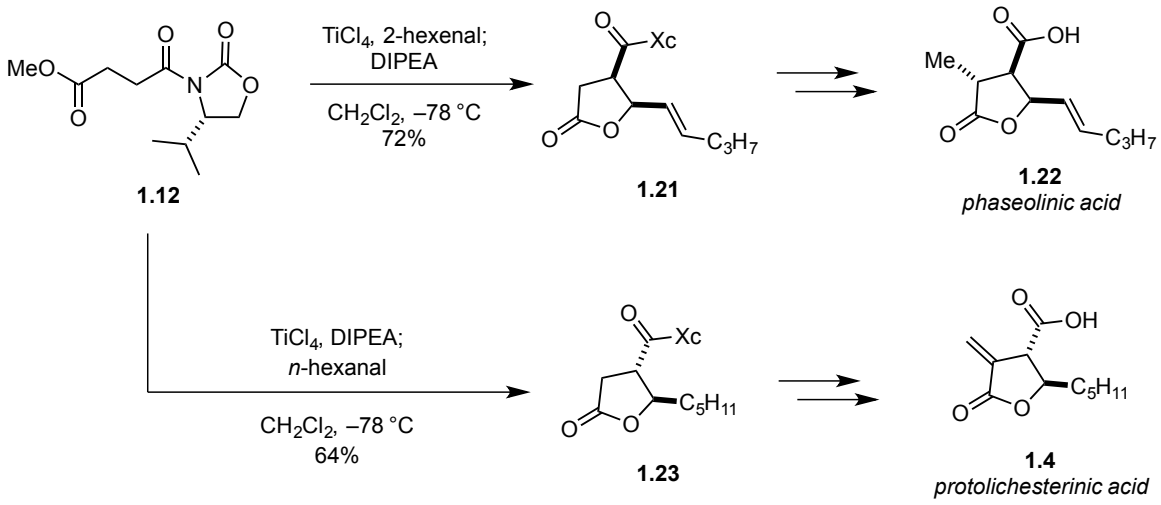
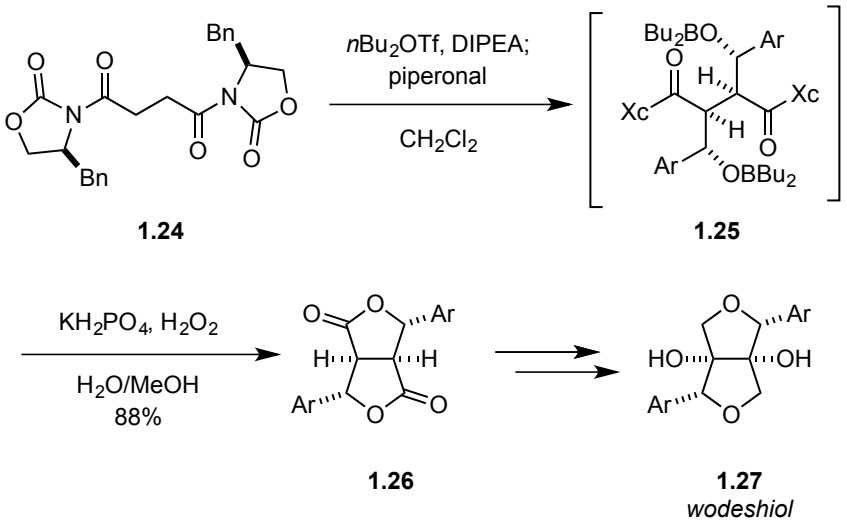


Figure 1.2 Proposed transition state for Hajra's switchable aldol reaction



Scheme 1.2 Hajra's synthesis of phaseolinic acid (**1.22**) and protolichesterinic acid (**1.4**)

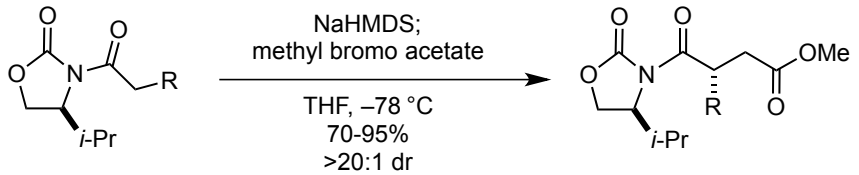
As a final example of auxiliary directed aldol reactions, Park and co-workers showed that succinate **1.24** could direct two aldol reactions via the bis-boron enolate (Scheme 1.3).[15] Intermediate **1.25** underwent lactonization upon oxidation of the borate to provide bicycle **1.26** in 88% as a single isomer. Piperonal was the only aldehyde shown to be effective in this transformation. Nevertheless the method provided a high yielding and selective strategy to access C2-symmetric bicyclic lactones and resulted in the total synthesis of wodeshiol (**27**).



Scheme 1.3 Bis-aldol reaction and synthesis of wodeshiol (**1.27**) by Kim.

1.2.1.2 Alkylations

Fadel reported that various chiral imides **1.28** underwent alkylation with methyl bromoacetate in good yields and excellent diastereoselectivities (Equation 1.5).[16] Indeed, Evans had previously reported one example of this transformation in his seminal publication on auxiliary controlled alkylation reactions with **1.28** (R = Me),[17] but the systematic exploration of the steric and functional group tolerance by Fadel proved this reaction to be general for the synthesis of chiral mono-substituted succinic acid derivatives. The reaction even worked well on *tert*-butyl substituted imides **1.28** (R = *t*-Bu). This methodology using chiral oxizolidinones was further explored and demonstrated to be useful for the synthesis of β-amino acids and lactone natural products by Evans,[18] Sibi,[19,20] Seebach,[21,22] and Sewald.[23]



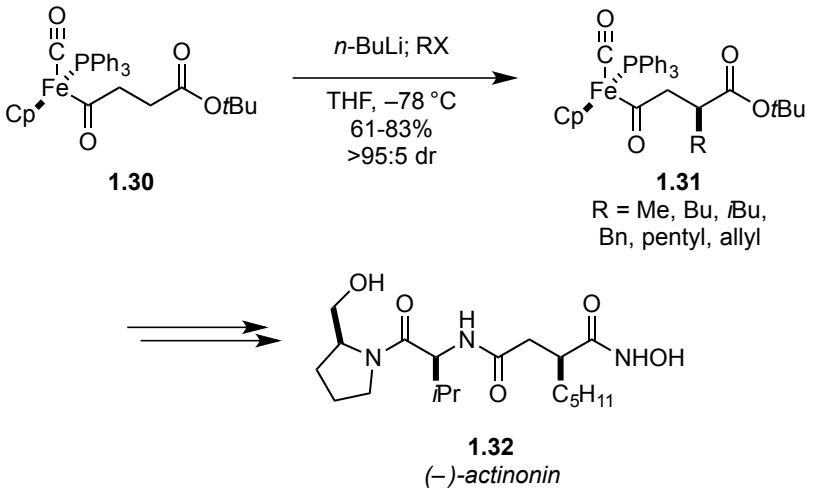
(1.5)

1.28

R = Me, *i*-Pr, *t*-Bu, CH_2CH_2OPMB, CH_2CH_2OTBS, $CHCHCH_3$

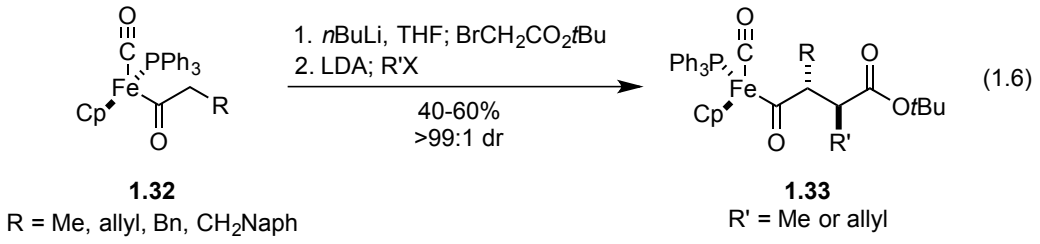
1.29

The Davies group reported a competing auxiliary in 1989, demonstrating that chiral succinoyl complex **1.30** could be alkylated with a variety of electrophiles with moderate yields and excellent diastereoselectivities (Scheme 1.4).[24] The auxiliary could be cleaved with NBS in wet THF to reveal the chiral succinate. Unfortunately, the auxiliary is destroyed in this transformation and therefore not recyclable like Evans's oxazolidinone. The procedure provided the products in lower yields than the reaction using Evans's auxiliary, but it does represent an alternate strategy for the synthesis of chiral succinates. Surprisingly, this method worked well with *iso*-butyl iodide, whereas the Evans protocol required more reactive electrophiles. In fact, the yields and selectivities for less reaction electrophiles were generally higher than with more reactive electrophiles, though the authors provided no comment on the reason for this. The group demonstrated the utility of this methodology in the synthesis of the natural product (–)-actinonin (**1.32**).[25]



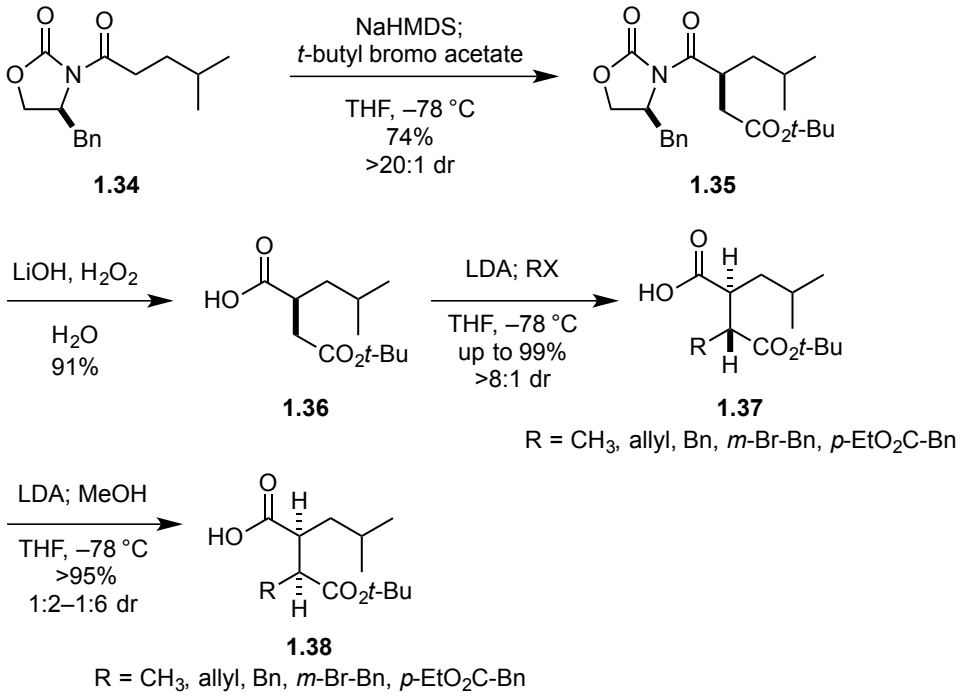
Scheme 1.4 Davies's asymmetric alkylation and application to (–)-actinonin (**1.32**)

Davies later expanded upon this methodology in a two step procedure that allowed for the synthesis of disubstituted succinic acid derivatives.[26] Using various chiral iron complexes **1.32**, stereoselective alkylation with *tert*-butyl bromoacetate followed by stereoselective alkylation with methyl or allyl iodide provided disubstituted succinates **1.33** in moderate yield with excellent diastereoselectivity for the two steps (Equation 1.6). However, unlike their previous work, it is unclear whether or not this two-step method tolerated less reactive electrophiles.



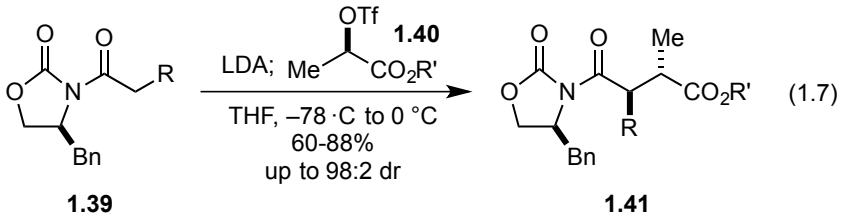
(1.6)

Crimmins reported an alternate strategy for the synthesis of disubstituted succinates wherein mono-substituted succinates **1.35**, available with excellent stereoselectivity from **1.34** (*vide supra*), underwent further transformation to di-substituted succinates **1.37** (Scheme 1.5). In the event, **1.35** was hydrolyzed using standard conditions to provide acid **1.36** in 91% yield. The key discovery was that the dianion of **1.37** could be alkylated with good diastereoselectivity (>8:1) to provide trans-disubstituted succinates **1.37**. In order to increase the utility of this method, epimerization to the cis-disubstituted succinates **1.38** was explored; however, the diastereoselectivity was low and highly variable based on substitution.



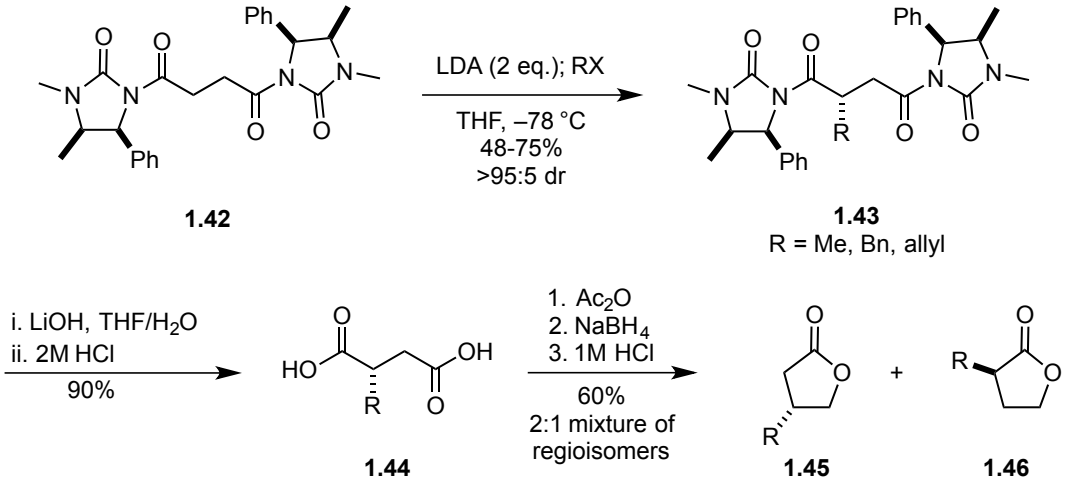
Scheme 1.5 Method to access di-substituted succinates by Crimmins

The Decicco group disclosed an alternate strategy for the production of chiral disubstituted succinates, wherein a chiral imide **1.39** was alkylated with a chiral ester **1.40** to provide disubstituted succinates **1.41** in moderate to good yields with excellent diastereoselectivity (Equation 1.7).[27] The enantiomer of **1.40** could be successfully used to provide cis-disubstituted succinates *epi*-**1.41** with similar yields and stereoselectivities. Although the reaction was tolerant of a wide variety of substitution on the imide, the yield was reported to decrease significantly for anything other than a methyl group on the α position of the ester. The major drawback of this transformation was that it required the synthesis of two chiral starting materials, whereas other strategies utilized the chiral auxiliary to control all of the stereoselectivity.



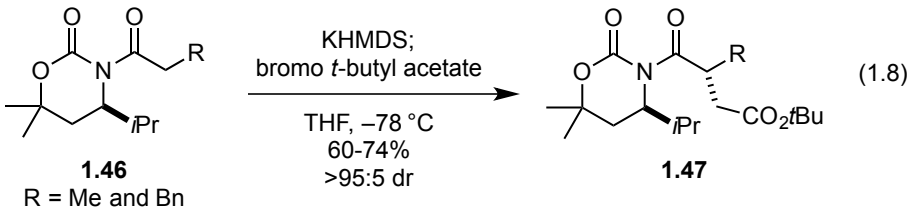
Pohmakotr and co-workers disclosed a procedure for the enantioselective alkylation of vicinal dianions in 2004.[28] Their technique relied on succinate **1.42**, which was deprotonated with two equivalents of LDA prior to introduction of the electrophile. The substituted succinic acid derivative was isolated in moderate yield with excellent diastereoselectivity, and could be hydrolyzed to a chiral succinic acid **1.44** in 90% yield. Unfortunately, as one might predict, further manipulation of diacid **1.44** was problematic. Conversion to butyrolactones **1.45** and **1.46** via a three-step procedure delivered a mixture (2:1) of diastereomers. This is likely due to the low level of steric differentiation

that a single R group next to one carbonyl group provided. Although the protocal delivered chiral acids **1.44** in moderate yield, reactions involving symmetrical starting materials like **1.42**, would most likely have the most success in methods that make symmetric products like the aldol reaction by Kim (Scheme 1.3).



Scheme 1.6 Synthesis of chiral succinates and application to butyrolactones by Pohmakotr

The most recent development in the field was reported by Davies using chiral oxazinanones.[29] This new auxiliary from Davies was prepared as part of their ongoing efforts to improve upon the chiral oxizolidinone auxiliary. In this report, they found that this auxiliary performed as well as the standard Evans's chiral oxizolidinone in a number of alkylation reactions, including alkylation reactions that provided chiral succinates (Equation 1.8). One drawback to this method was that rather than starting from a commercially available amino acid, the enantioenriched β-amino acid derivative must first be synthesized.



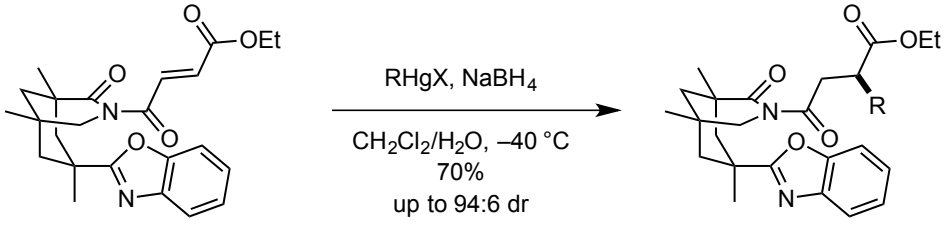
1.46
R = Me and Bn

1.47

(1.8)

1.2.1.3 Conjugate Additions

In 1991, Curran and Rebek disclosed a radical mediated conjugate addition reaction to chiral fumarimide **1.48** (Equation 1.9).[30] This unique auxiliary, which was available in six steps from Kemp's triacid, was acylated with a fumarate derivative and treated with an alkyl mercuric halide and sodium borohydride to effect conjugate addition providing **1.49** in an average of 70% yield and up to 94:6 dr. Unfortunately, only branched nucleophiles (*tert*-butyl mercuric chloride and cyclohexyl mercuric chloride) worked well, whereas the linear *n*-hexyl mercuric chloride delivered **1.49** (R = *n*-hexyl) in 42% yield and 82:18 dr. It was interesting to note that competition experiments between the fumarimide and diethyl fumarate suggested that the origin of the regioselectivity was not due to increased activation of the β carbon atom of the conjugated imide, thus steric effects most likely accounted for the high degree of regioselectivity.

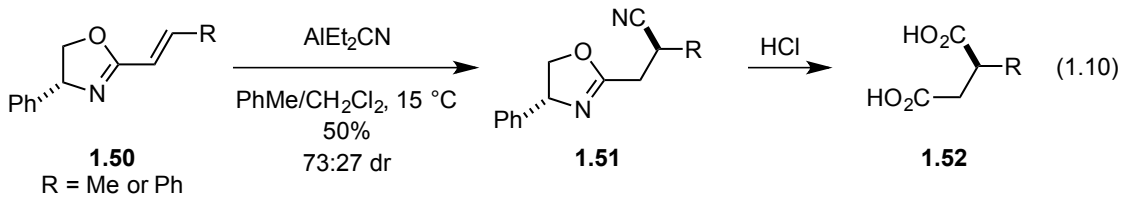


1.48

1.49
R = hexyl, cyclohexyl, *t*Bu

(1.9)

Langlois has shown that simple succinic acid derivatives can be accessed via the conjugate addition of cyanide ion to conjugated oxazoles like **1.50** (Equation 1.10).[31] However, the reaction provided oxazoles **1.51** in only 50% yield with a disappointing 73:27 dr. The substrate scope was not explored any further than **1.50** (R = Me or Ph), and even with a thorough screen of conditions, neither the yield nor diastereoselectivity could be improved. The conjugate addition adduct **1.51** could be hydrolyzed to succinic acid derivative **1.52** with no erosion of stereoselectivity.



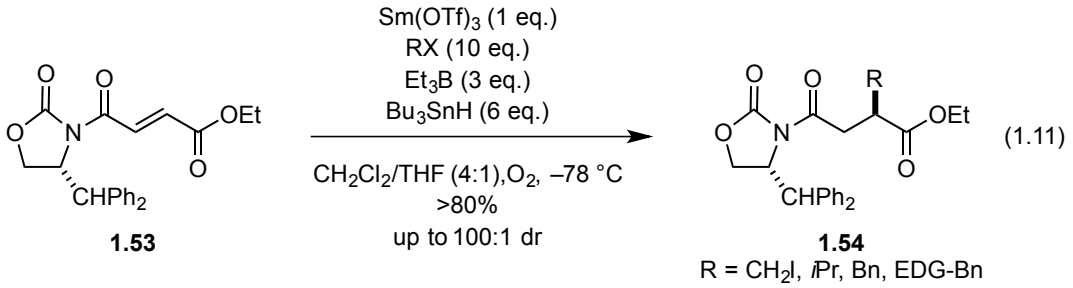
1.50
R = Me or Ph

1.51

1.52

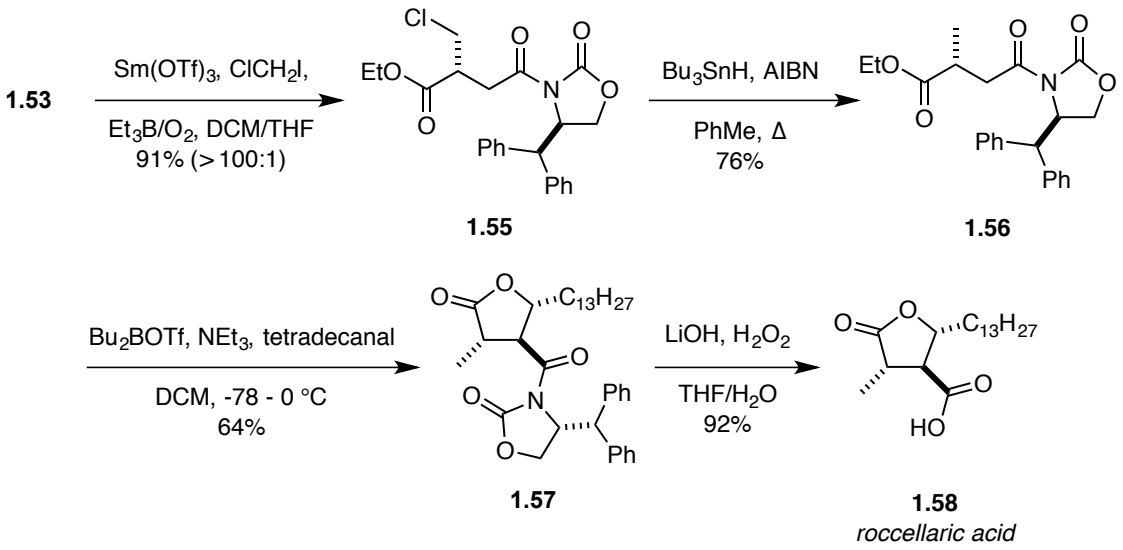
(1.10)

Sibi and co-workers developed a highly selective, radical-mediated conjugate addition to chiral fumarate **1.53** (Equation 1.11).[20,32-38] In the presence of $Sm(OTf)_3$, an alkyl halide (RX), tri-*n*-butyltin hydride, and triethylborane/oxygen, **1.53** underwent conjugate addition to provide **1.54** in greater than 80% yield and up to 100:1 dr. A major drawback to this method was the use of a full equivalent of Lewis acid and super stoichiometric amounts of alkyl halide, triethylborane, and tin. Unfortunately, this was required as without the excess alkyl halide, the ethyl radicals compete in the conjugate addition, and without the excess tinhydride to quickly quench the resulting radical, byproducts would arise. Despite the need to use excess reagents, Sibi has developed a nice strategy to access a number of succinate based natural products.[37,39]



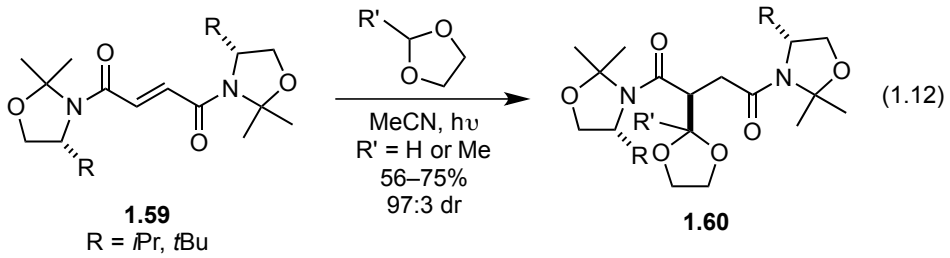
(1.11)

Unlike other radical conjugate addition reactions, which generally only proceed well with branched nucleophiles, Sibi's conditions allowed for the use of *n*-alkyl halides. They could even install a methyl group using iodo chloromethane to provide a stabilized radical, followed by radical dehalogenation, a tactic they exploited in their synthesis of rocellaric acid (**1.58**) (Scheme 1.7).[37] In the event, conjugate addition of the radical generated from iodo chloromethane provided **1.55** in 91% yield and greater than 100:1 dr. Radical dehalogenation proceeded in 76% yield to give **1.56**, treatment of which with tetradecanal under modified Evans's conditions delivered lactone **1.57** in 64% yield; hydrolysis under standard conditions provided rocellaric acid (**1.58**) in 92% yield. Thus, Sibi successfully demonstrated the utility of their conjugate addition reaction, completing the synthesis of **1.58** in four steps from **1.53** and 40% overall yield.



Scheme 1.7 Synthesis of rocellaric acid (**1.58**) via radical conjugate addition by Sibi

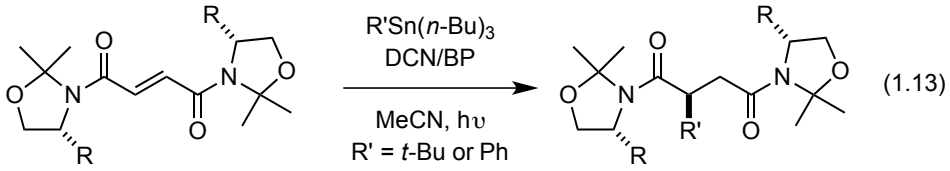
An alternate approach to generate radicals for these types of conjugate additions was reported by Fagnoni and Albini, who used light to generate the radicals (Equations 1.12 and 1.13).[40] They showed that dioxalanes could add to the chiral fumarimide **1.59** in moderate yields with excellent diastereoselectivity (Equation 1.12). They also demonstrated that photosensitizers (1,4-dicyanonaphthalene (DCN)/biphenyl (BP)) could be used in conjunction with alkyl and aryl stanananes to provide **1.61** in similar yields and selectivities (Equation 1.13). The reaction, though highly stereoselective, provided only moderate yields of the desired products. Additionally, as demonstrated with previous C_2-symmetrical substrates, like **1.59**, chemoselective elaboration of the two amides in products **1.60** and **1.61** might be a challenge.



1.59
R = *i*Pr, *t*Bu

1.60

(1.12)

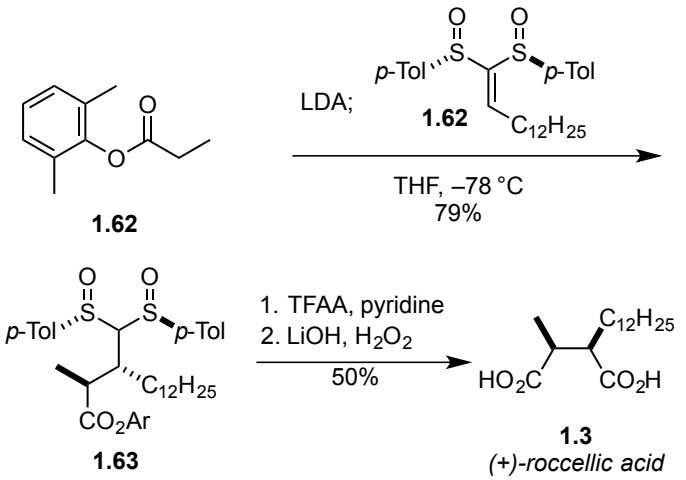


1.59
R = *i*Pr, *t*Bu

1.61

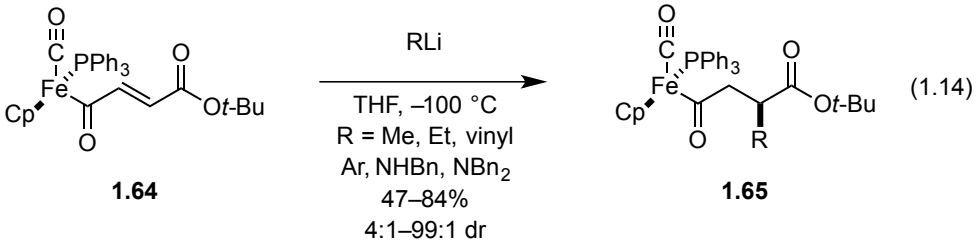
(1.13)

Another protocol to access chiral disubstituted succinates is the Michael addition of enolates to chiral alkylidene bis(sulfoxides) (Scheme 1.9).[41] Through the use of this methodology, Fensterbank and Malacria realized a three-step synthesis of (+)-roccellic acid. The sequence began with the aforementioned conjugate addition reaction, which proceeded in 79% yield and complete stereocontrol to provide **1.63**. Sequential Pummerer reaction and hydrolysis delivered roccellic acid (**1.3**) in 50% yield over two steps. Conjugate additions into conjugated sulfoxides like **1.62** were also high yielding and equally as diastereoselective for a number of other nucleophiles (e.g. amines, alcohols, cuprates, and malonates).



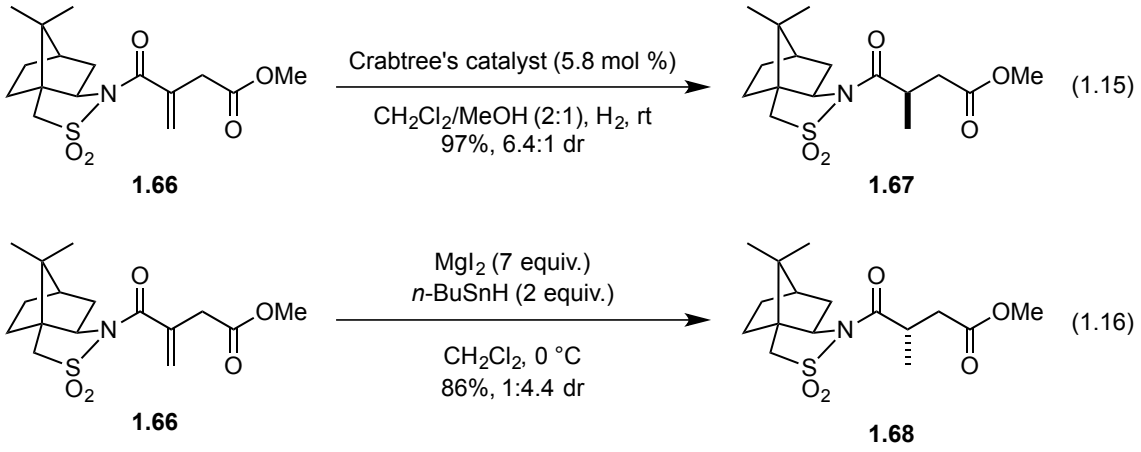
Scheme 1.9 Synthesis of roccellic acid via diastereoselective conjugate addition by Fensterbank

A final example of preparing enantioenriched succinates via auxiliary directed conjugate addition reactions is the work of Davies, who has shown that his chiral iron based auxiliary could direct conjugate addition reactions (Equation 1.14).[26] Chiral iron fumarate derivative **1.64** underwent conjugate addition when treated with a variety of alkyllithiums, vinyllithium, aryllithiums, or lithiated amines to provide chiral iron succinimide derivates **1.65** (Equation 1.14). The reaction provided low to moderate yields of the desired products with a range of stereoselectivities (4:1–99:1 dr). The reaction was developed as part of a broader effort to expand the utility of their iron-based auxiliary, which has been in development since 1989.



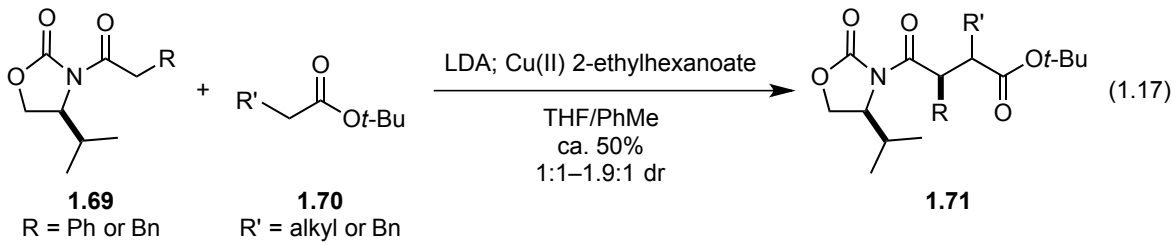
1.2.1.4 Hydrogenation

Nagano has shown that hydrogenation of chiral itaconates provided divergent access to both diastereomers of methyl succinate derivatives **1.67** and **1.68** (Equation 1.15 and 1.16).[42] After screening a number of chiral auxiliaries, they discovered that the chiral sulfonimide **1.166** provided the highest diastereoselectivity. Under hydrogenation conditions catalyzed by Crabtree's catalyst, **1.66** was converted to **1.67** in 97% yield and 6.4:1 dr (Equation 1.15). Conversely, under conjugate reduction conditions, using magnesium iodide and tri-*n*-butyltin hydride, the epimer **1.68** was recovered with 86% yield and 1:4.4 dr (Equation 1.16) The authors did not explore the scope of the reaction any further than itaconate derivatives, but they did lay the ground work for future improvements on this divergent route to chiral succinates.



1.2.1.5 Oxidative Enolate Coupling

In 2006, Baran reported an intermolecular oxidative enolate heterocoupling that provided access to chiral succinate derivatives (Equation 1.17).[43,44] Baran and co-workers discovered that the lithium enolates of a chiral imide **1.69** and an ester **1.70** in the presence of a copper oxidant underwent heterocoupling to provide chiral succinates **1.71**. Unfortunately, the reaction averaged only 50% yield across all of the substrates and there was little to no diastereoselectivity attained. Nevertheless they did manage to overcome a statistical mixture of products, but homocoupling was still a probablem, which led to the modest yield.



(1.17)

1.2.1.6 Summary

The use of a chiral auxiliary is a classic strategy to access enantioenriched products, so it is no surprise that many methods have been developed around their use to access enantioenriched succinic acid derivatives. One downside to the auxiliary strategy is that classically, one would need to have both enantiomers of the chiral moiety on hand to access various enantio- and diastereomeric succinates. However, Hajra's switchable aldol,[45] Crimmin's epimerization strategy,[46] and Nagano's hydrogenation[42] provide hope for the development of a divergent strategy to access a multitude of chiral succinates from a single starting material, although the Crimmin's protocol is the only divergent

route to disubstituted succinic acid derivatives. As the auxiliary approach has already proved its efficiency in many cases with respect to yield and diastereoselectivity, further development of divergent methods to a multitude of products is likely the best way to add utility to this method.

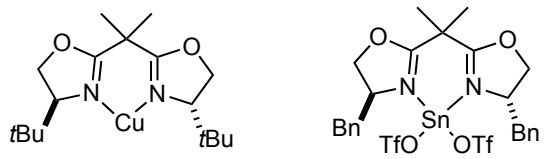
1.2.2 Chiral Lewis Acid Catalysts

In an effort to move away from auxiliary controlled reactions, a number of chiral Lewis acid-mediated methods including aldol reactions, conjugate additions, and homologations have been explored to provide access to chiral succinic acid derivatives. While this area remains less developed than the chiral auxiliary strategies discussed above, these reactions lay the foundation for future work in the field. Despite the sparse examples, the reported methods provide access to enantioenriched succinic acid derivatives with good yields and stereoselectivities, obviating the need for a stoichiometric source of chirality in the process.

1.2.2.1 Aldol

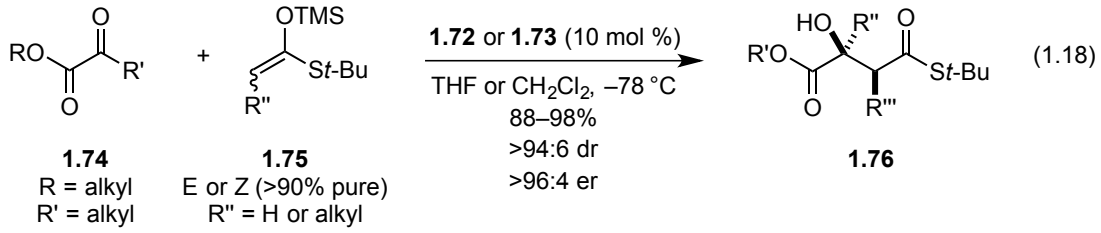
Evans disclosed the first report of chiral Lewis acid catalyzed aldol reactions to form succinate derivatives in 1997. During the course of this study, Evans and co-workers found that the copper complex **1.72**[47,48] and the tin complex **1.73**[49] both promoted the aldol addition of enol silanes to pyruvate esters to provide succinate derivatives with good yields and a high degree of both enantio- and diastereoselectivity (Equation 1.18). The reaction was limited to the use of thioester silylketene acetals **1.75**, as silylketene acetals were shown to result in poor enantioselectivity (ca. 39% ee). Although this seemingly limits the scope of the reaction, it comes with the added bonus of

differentiating the two ester moieties in the product, which could improve selectivity in further transformations.



1.72 **1.73**

Figure 1.2 Chiral lewis acid catalysts developed by Evans



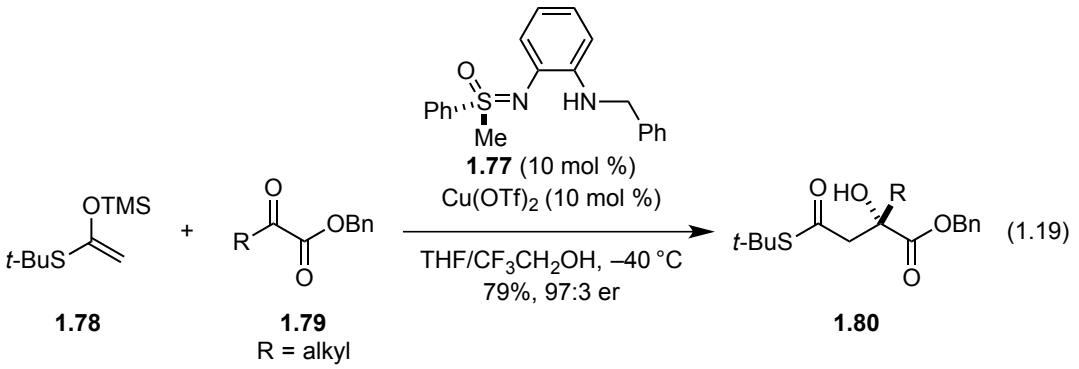
1.74
R = alkyl
R' = alkyl

1.75
E or Z (>90% pure)
R'' = H or alkyl

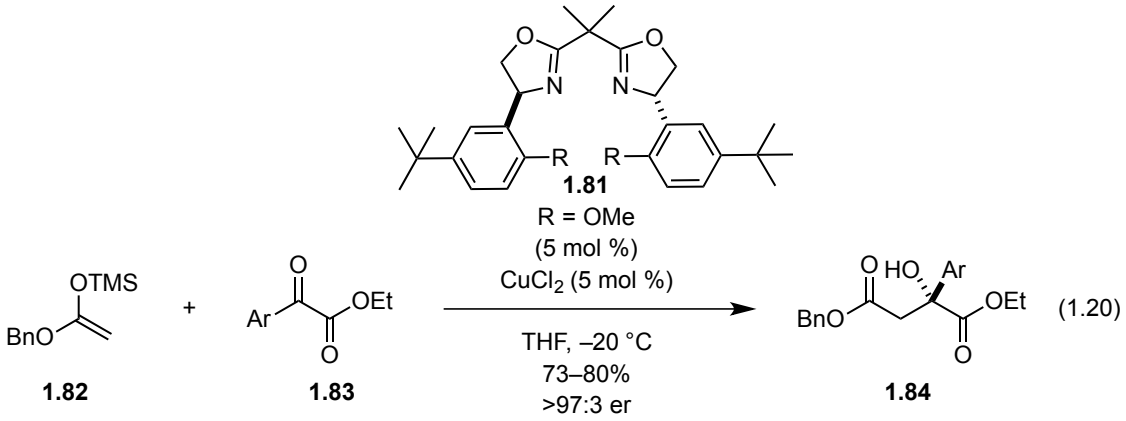
1.76

In an effort to extend the utility of aminosulfoximines beyond their use as ligands in palladium catalyzed reactions,[50] Bolm and co-workers found that aminosulfoximine **1.77** was a suitable ligand for copper (II) triflate in aldol reactions (Equation 1.18).[51] They found that the reaction proceeded with good yields and high enantioselectivities for a variety of aldol reactions using thioester silylketene acetals like **1.78**. Using a variety of pyruvate esters **1.79** (R = alkyl), alkyl substituted hydroxy succinate derivatives were synthesized in good yields with excellent stereoselectivity. The scope of the transformation was not explored with respect to substitution on the silyl ketene acetal.

Therefore, unlike the conditions developed by Evans (Equation 1.18), this reaction appears limited to the synthesis of mono-substituted hydroxy succinates.



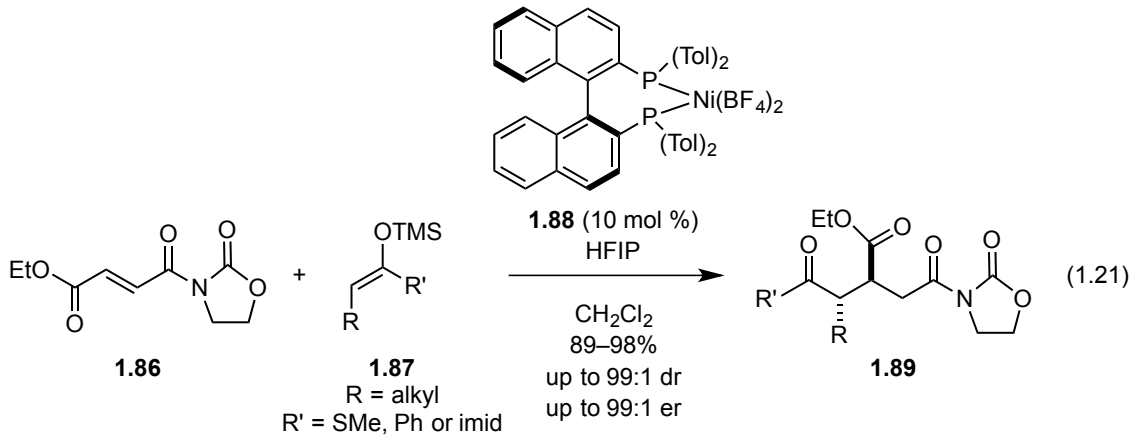
In 2009, Pagenkopf disclosed a modified pybox ligand **1.81** for a copper catalyzed aldol reaction of pyruvate esters (Equation 1.20).[52] The pybox ligand **1.81** effectively catalyzed the addition of silyl ketene acetal **1.82** to the aryl pyruvate esters **1.83**. This reaction was noteworthy for extending the substrate scope of the reaction to aryl pyruvate esters, whereas the Evans protocol was only shown to work on alkyl pyruvates. Unfortunately, the authors found that **1.81** did not provide the same excellent stereoselectivity with alkyl pyruvates, instead providing a range of moderate enantioselectivities from 70–80% ee. Additionally, in contrast to the competing methodology, which only worked well thioester silyl ketene acetals, this reaction worked with a benzyl silyl ketene acetal, which also provides differentiation from the ethyl ester for further transformations.



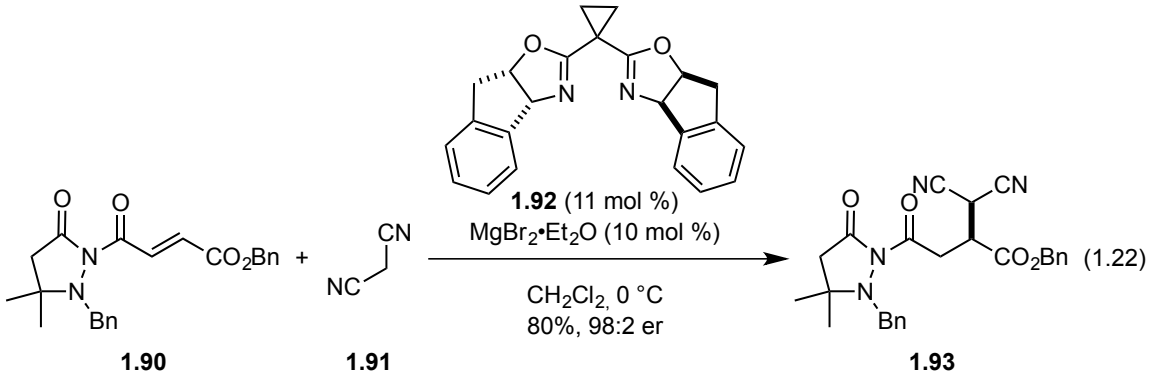
(1.20)

1.2.2.2 Conjugate Addition

Lewis acid-mediated conjugate additions to provide chiral succinates have also been disclosed. Evans discovered that the cationic nickel complex **1.88** promoted Mukaiyama-Michael additions to fumarate derivatives **1.86**.[53,54] A variety of silyl enol eithers **1.87** added with excellent yields and enantio- and diastereoselectivites to fumarate **1.86** to provide chiral succinates **1.89** (Equation 1.21). While the reaction was amazingly selective, one draw back was the need to activate the system for Michael addition with an oxazolidinone. Ultimately, the oxazolidinone must be put on and removed, which leaves room to question why one would not just employ a chiral oxazolidinone instead. Nevertheless, Evans laid the foundation for future work in this area, and perhaps a chiral Lewis acid mediated conjugate addition to a simple fumarate derivative (e.g. diethyl fumarate) will be reported eventually.

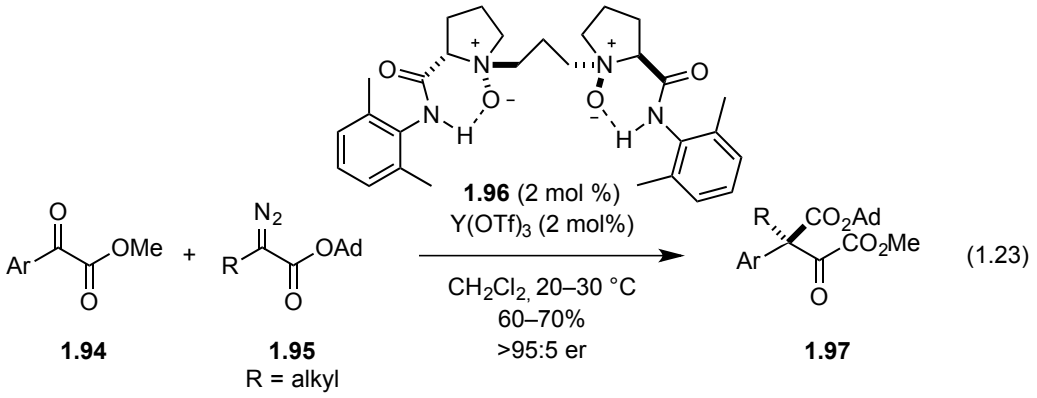


Sibi and co-workers have used a similar strategy for the conjugate addition of malononitrile (**1.91**) to fumarate derivative **1.90** (Equation 1.22).[55] The resulting chiral succinic acid derivative was formed in 80% yield and excellent enantioselectivity (98:2). While this method was only reported to work with unsubstituted malanonitrile, it was only a preliminary investigation into what could be accomplished using ligand **1.92** to complex Lewis acids. With many more avenues to explore, it will be exciting to see what will be unveiled in the future. Like the Evans procedure, this method also required the use of an imide to activate the system for addition, rather than Michael addition on a simple fumarate.



1.2.2.3 Homologation

Finally, to conclude the survey of methodologies that employ chiral Lewis acids, Feng reported an interesting homologation reaction to form chiral quaternary succinic acid derivatives **1.97** using the chiral ligand **1.96**. (Equation 1.23).[56] In the event, a wide range of aryl substituted pyruvate esters **1.94** and alkyl diazoesters **1.95** underwent reaction in the presence of **1.96** complexed with yttrium triflate to provide succinates **1.97** in greater than 95:5 er. It should be noted that the method required the use of adamantyl-substituted diazoesters to achieve high enantioselectivity. Nevertheless, this remains a valuable and versatile method, and one of the few methods available for the synthesis of succinates containing a stereogenic quaternary center.



(1.23)

1.2.2.4 Summary

While relatively little work has been reported in the field of enantioselective synthesis of succinic acid derivatives using chiral Lewis acids, the reactions that have been disclosed thus far laid the foundation for the development future methods. These methods provided access to succinates with a high degree of enantioenrichment and good

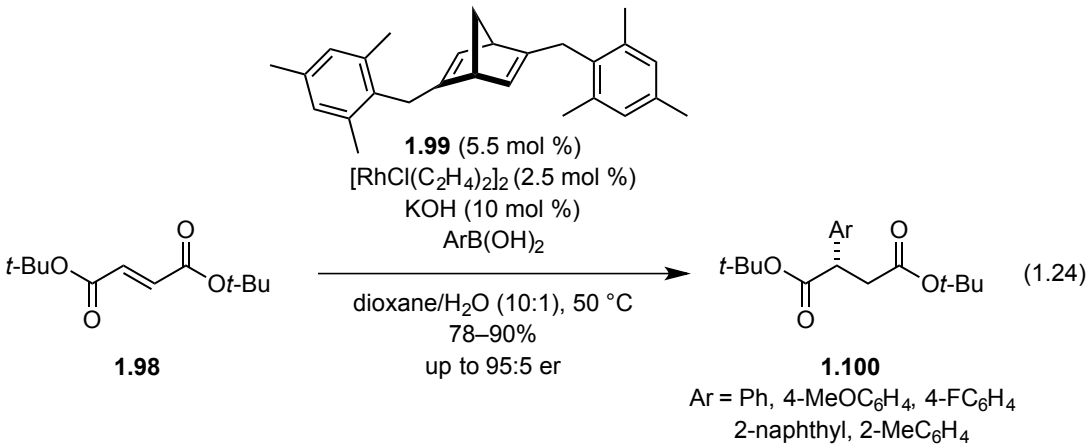
to excellent yields. All three of the types of reactions discussed are not without drawbacks, mainly in that they require an activating group of some kind, (i.e. oxazolidinone, adamantyl ester, thioester, etc.) to effect the desired transformation. Ideally, all starting materials would bear only the functionality wanted in the desired product, and the chiral catalyst would provide that product directly, without the need for the addition of functionality before and removal of the functionality after the reaction.

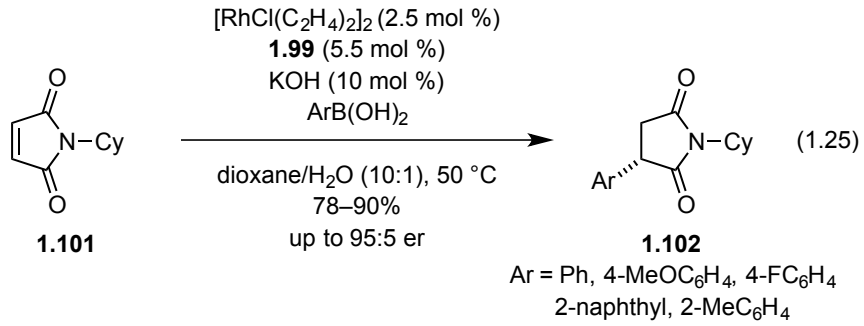
1.2.3 Transition Metal Catalysis

Given the ubiquity of transition metal catalysis in organic synthesis, it comes as no surprise that a number of transformations have been developed using chiral transition metal complexes to synthesize succinic acid derivatives. Both conjugate addition reaction and reduction reactions have been developed to provide high enantioenriched succinates.

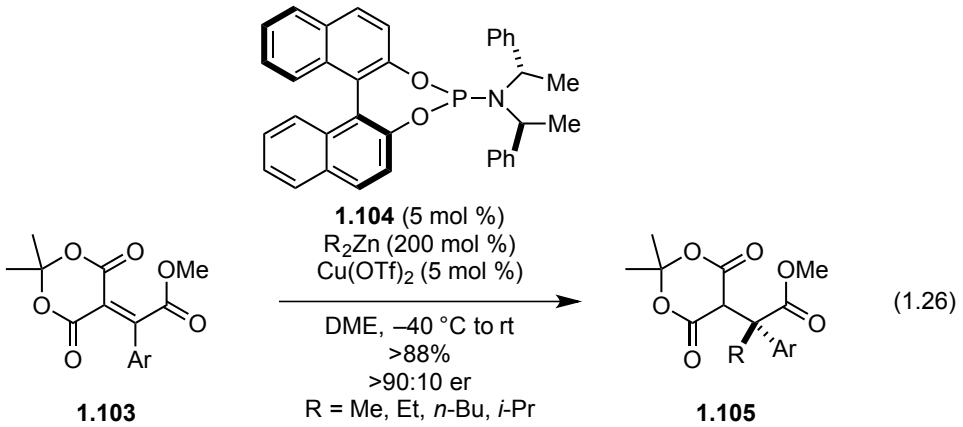
1.2.3.1 Conjugate Addition

The first transition metal-catalyzed, conjugate addition to provide chiral succinic acid derivatives was reported in 2004 using chiral norbornadiene **1.99**.[57] Hayshi and co-workers demonstrated that di-*tert*-butyl fumarate underwent conjugate addition in the presence of **1.99**, rhodium, and aryl boronic acids to provide aryl succinates **1.100** in good yields and up to 95:5 er (Equation 1.24). Furthermore, they established that this method was also applicable to maleimide **1.101**, delivering the aryl succinimides **1.102** in similar yields and selectivities as the fumarate derivatives. However, the method was limited to aryl boronic acids; additionally, being that two carbonyls of the succinate **1.100** and succinimide **1.102** are very similar, selective transformations of the material will most likely prove difficult, as discussed previously (Scheme 1.6).

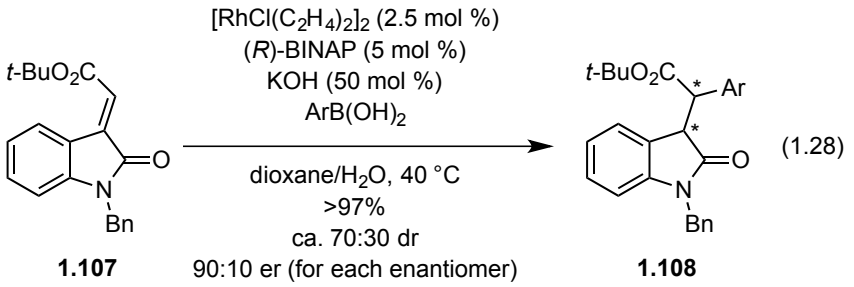




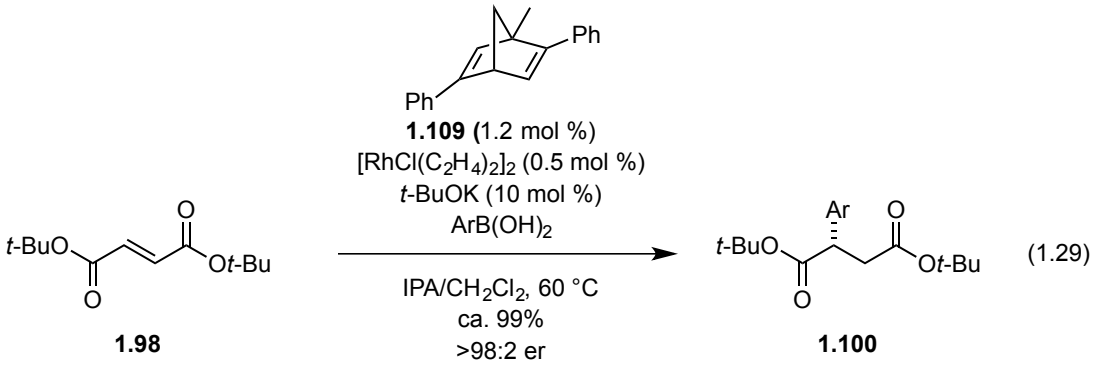
Fillion successfully used phosphoramidite **1.104** in conjunction with copper triflate to perform conjugate additions of dialkyl zinc reagents to **1.103** (Equation 1.26).[58] The resulting adducts **1.105** were obtained in good yields and up to 90:10 er. The products **1.105** readily underwent reaction with primary amines to deliver chiral succinimides **1.106** in good yields (Equation 1.27). This method remains one of the few reactions to form succinic acid derivatives with a chiral quaternary center, but required the substrate **1.103** to be aryl substituted.

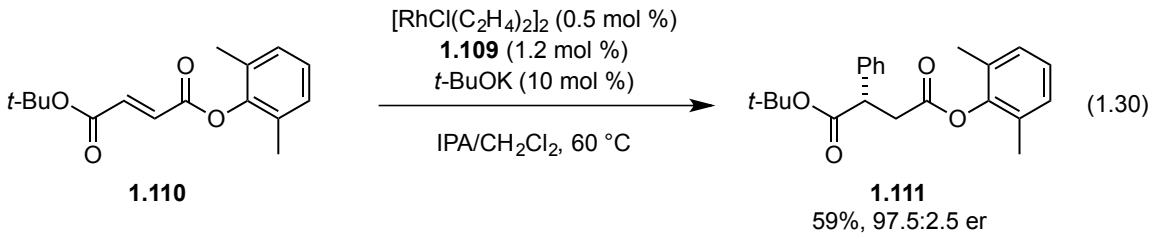


Utilizing a strikingly different substrate **1.107**, Liao and co-workers reported a conjugate addition of aryl boronic acids to conjugated oxindoles **1.107** (Equation 1.28).[59] The reaction produced unique succinic acid derivatives **1.108** with excellent yields and good enantioselectivities for a range of aryl boronic acids. However, the diastereoselectivity was modest (70:30 dr).

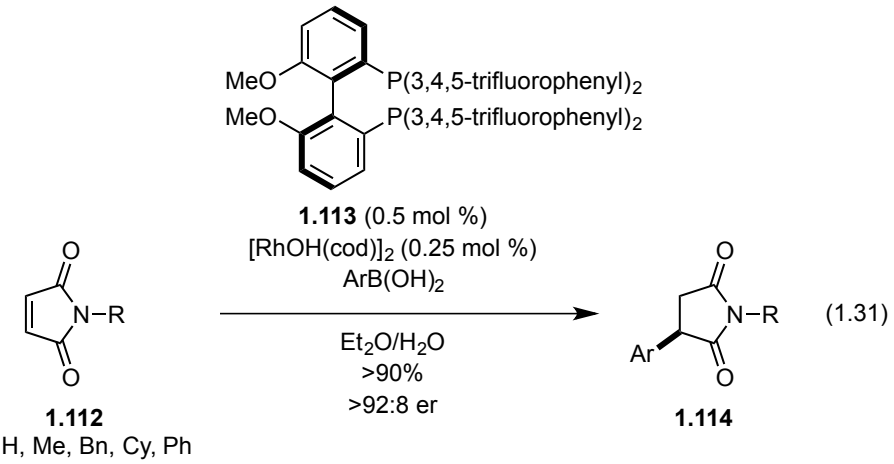


The Wu group disclosed a conjugate addition similar to that of Hayashi using **1.109** as a ligand for the rhodium catalyzed conjugate addition of aryl boronic acids to fumarate **1.98** (Equation 1.29).[60] The yields and enantioselectivities of the resulting succinate **1.100** were only slightly better than Hiyashi's approach, which used ligand **1.99** (Equation 1.24). Wu attempted to solve the problem of ester differentiation with the use of **1.110** (Equation 1.30), but they found that while they did receive succinate **1.111** in 59% yield with excellent enantioselectivity, 41% of the product was the regioisomer. Thus, while **1.111** could conceivably be transformed via chemoselective reactions, there was not enough bias in the starting material to achieve good regioselectivity in the conjugate addition step.





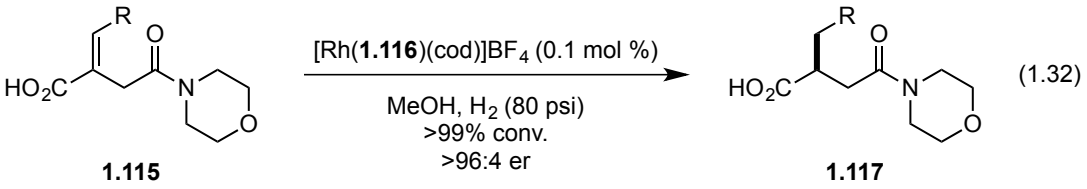
The latest transition metal catalyzed conjugate addition reaction reported thus far came from the Korenage group, who found that BIPHEP ligand **1.113** could provide succinimide derivatives **1.114** with great enantioselectivities (Equation 1.31).[61] This reaction had previously been reported by Hiyashi using a different ligand, and while Korenga's yields and selectivities are slightly better, there is no improvement in substrate scope.



(1.31)

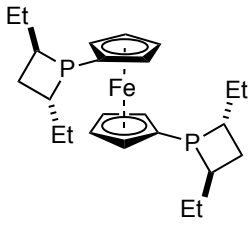
1.2.3.2 Reduction

Reductions of itaconates, malaeates, and succinates have also been explored as useful methods for the synthesis of enantioenriched succinic acid derivatives. Burk reported that the hydrogenation of itaconic acid derivatives **1.115** with a chiral rhodium complex delivered succinic acid derivatives **1.117** in greater than 96:4 er (Equation 1.32).[62] The reaction proceeded well for a range of substitution on the olefin; however, no substrate tolerance of the acid or amide was explored.



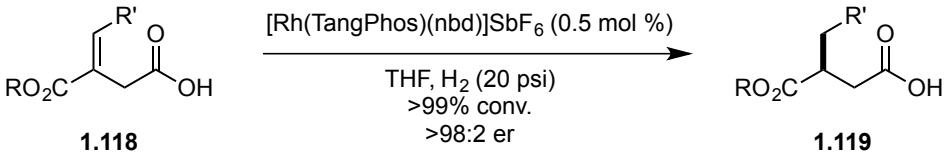
1.115 **1.117** (1.32)

R = Ph, *p*-FC_6H_4, *p*-BrC_6H_4, *p*-$MeSC_6H_4$, thienyl, *n*-Bu, *i*-Pr, *t*-Bu



1.116
Et-FerroTANE

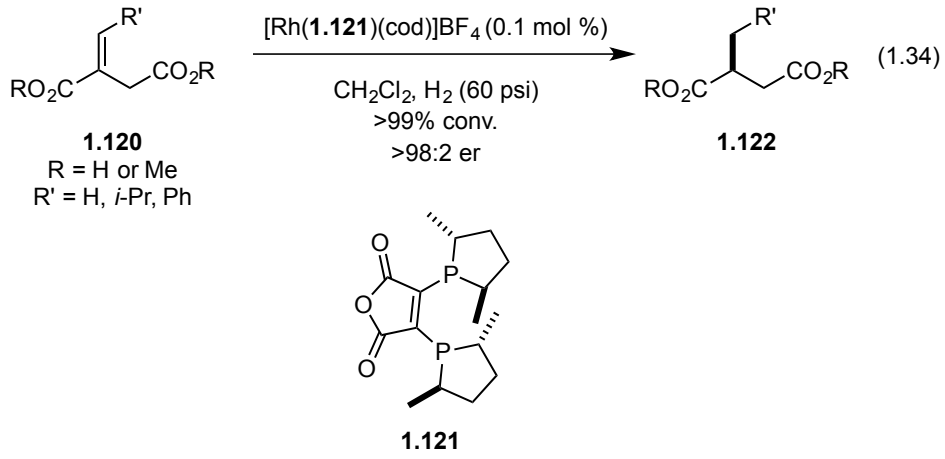
Zhang reported a similar hydrogenation of itaconic acid derivatives in 2003, wherein itaconates **1.118** were hydrogenated in the presence of a chiral rhodium catalyst to give **1.119** with excellent conversion and enantioselectivity (Equation 1.33).[63] The reaction tolerated substitution at one of the acids (R = Me or H), which allowed for selective functionalization of the resulting succinates **1.119**. The reaction proceeded with similar enantioselectivities for a range of unsubstituted, alkyl, and aryl substituted olefins. This reduction was utilized in the synthesis of the platensimycin core by Ito in 2011.[64]

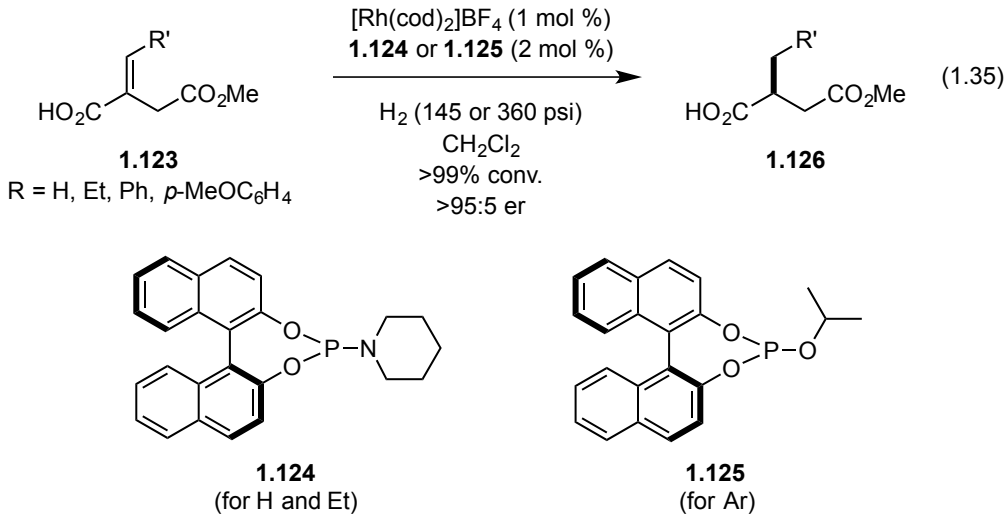


1.118 **1.119** (1.33)

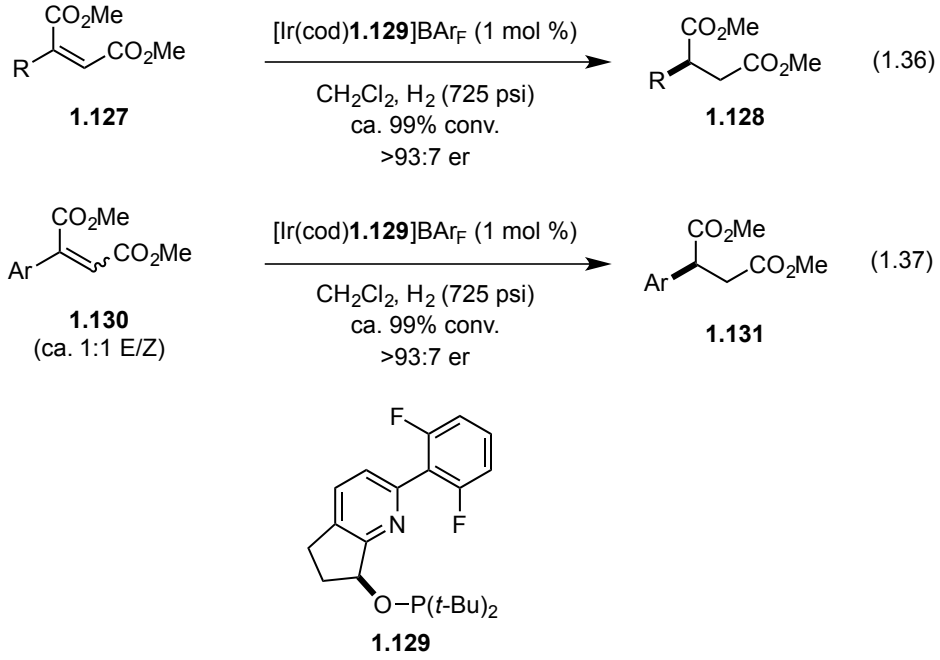
R = H or Me
R' = H, *i*-Pr, *p*-MeO-C_6H_4, *p*-Me-C_6H_4,
p-Cl-C_6H_4, 1- naphthyl, 2-naphthyl

One year later, Almena and Börner reported a similar hydrogenation of **1.120** to provide **1.122** with good conversation and excellent stereo control (Equation 1.34).[65] A similar reduction was also developed by Rutjes, using phosphoramidite ligands **1.124** and **1.125** (Equation 1.35)**.** [66] Both of these reactions provided the succinic acid derivatives in excellent enantioselectivities, demonstrating that a variety of ligands were effective in these transformations. However, the substrate scope among all of these transformations was similar with respect to substitution on the olefin and carboxylate moieties and expansion of this scope should be addressed in future development of the hydrogenation of itaconates.





Pfaltz demonstrated that maleates **1.127** underwent smooth hydrogenation to provide succinates **1.128** with excellent conversion and a high level enantioselectivity using a chiral iridium complex (Equation 1.36).[67] The reaction worked well for a wide range of both akyl and aryl substituted maleates, but due to the similar reactivity of the two resulting esters, further transformations would most likely be difficult. An interesting observation was the conversion of a mixture of maleate and fumarate **1.130** converging to a single enantiomer **1.131** (Equation 1.37), thus allowing for the resolution of a mixture of olefin isomers to a single chiral succinic acid derivative.



1.2.3.3 Summary

Although transition metal catalysis has proved to be a reliable method in organic synthesis, the utility of these transformations for the synthesis of succinic acid derivatives remains underdeveloped. While a number of ligand and metal combinations have been reported, ultimately all of the substrates and products are similar. Further developments of these technologies are needed to widen the substrate tolerance of these reactions in order to solidify the usefulness of these transformations in this specific field.

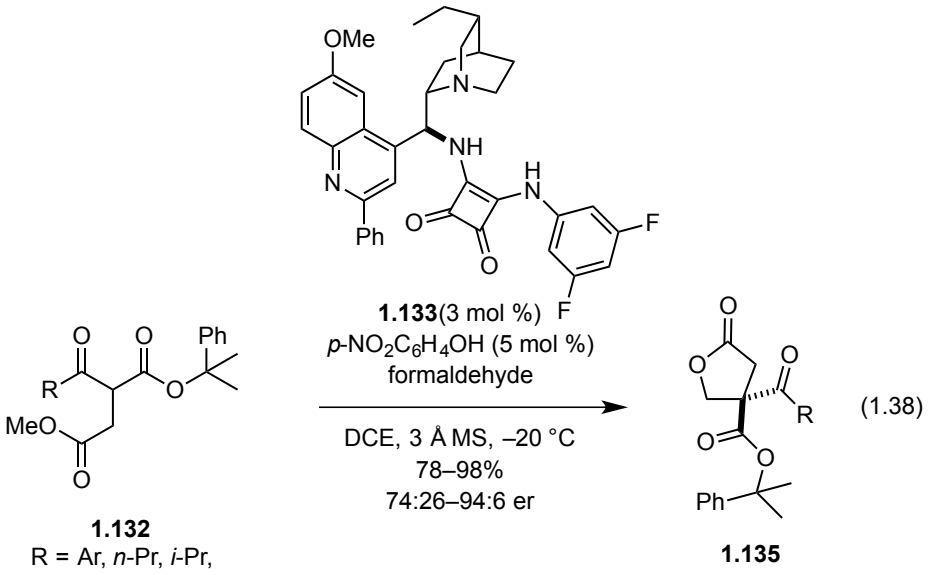
1.2.4 Organocatalysis

Enantioselective methods to access succinic acid derivatives have also been developed using organocatalysis as a method to move away from stoichiometric sources of chirality. These methods include aldol and conjugate addition reactions. While still in

the early stages of development, these methods demonstrate the feasibility of chiral succinate syntheses with organocatalysts.

1.2.4.1 Aldol

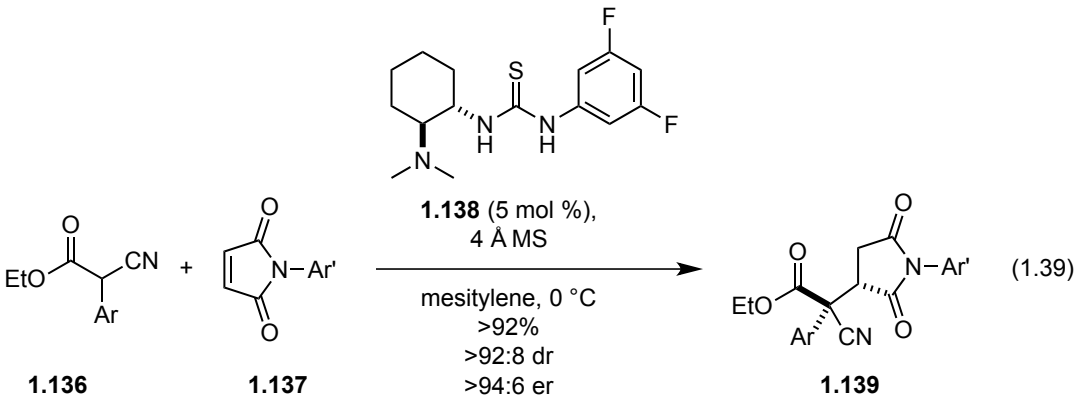
Lattanzi and co-workers developed an enantioselective aldol reaction with β-keto esters **1.132** to provide lactones **1.135** in good to excellent yields and enantioselectivities (Equation 1.38).[68] The reaction using chincona derivative **1.133** in only 3 mol % generated a stereogenic quaternary center for a wide range of aryl substituted ketones as well as for *n*- and *iso*-propyl-substituted ketones. Besides the highly variable enantioselectivities, the reaction required the use of the dimethylphenyl ester moiety or the enantioselectivity suffered tremendously. Nevertheless, the reaction provided a chiral quaternary center and provided a number of differentiated functional groups intact for further transformations.



(1.38)

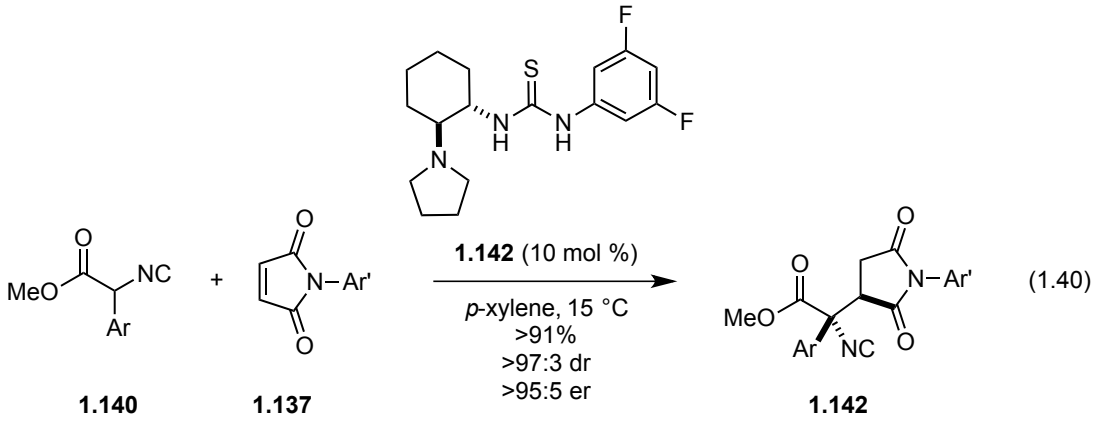
1.2.4.2 Conjugate Addition

Conjugate addition reactions promoted by chiral organocatalysts have received more attention than aldol reactions; however, while a range of possible catalysts has been explored, the substrate scope remains fairly limited. Yuan disclosed the first organocatalyzed conjugate addition of this kind in 2011.[69] Using chiral thiourea **1.138**, they found that cyanoester **1.136** added to maleimide **1.137** to deliver chiral succinates **1.139** in excellent yields, diastereoselectivities, and enantioselectivities (Equation 1.39). The reaction provided similar selectivities with a range of substitution on the aryl moieties, including both electron withdrawing and donating groups.

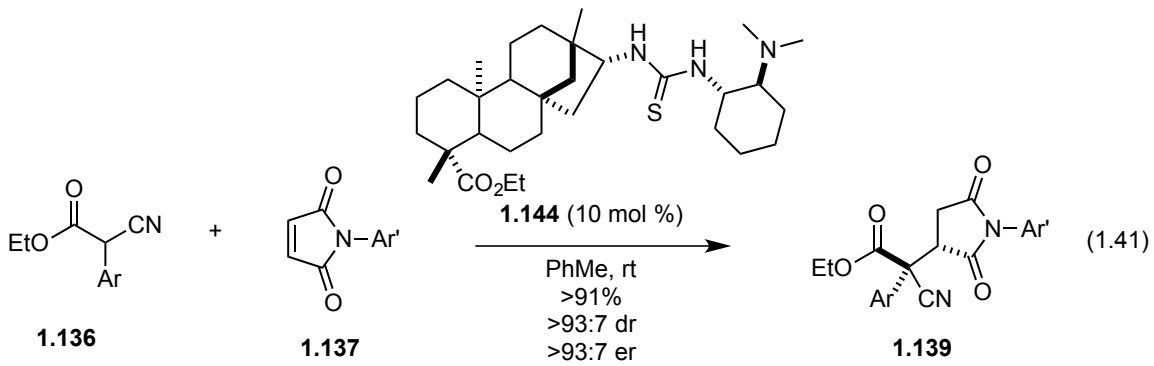


(1.39)

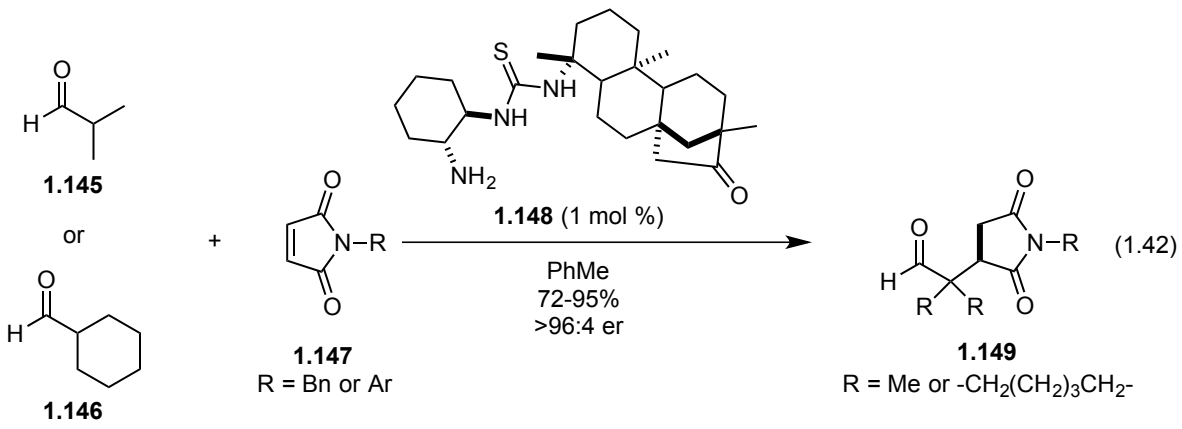
This reaction was also shown to work with catalyst **1.142** by Xu and Wang (Equation 1.40).[70] Tao demonstrated that catalyst **1.144** could perform this same reaction with similar yields and selectivities (Equation 1.41).[71] Tao also found that the related catalyst **1.148** could perform the reaction using aldehydes (Equation 1.42).[72] Finally, Shi demonstrated the utility of chincona derived catalyst **1.149** in a similar transformation (Equation 1.43).[73]



1.140 **1.137** **1.142**

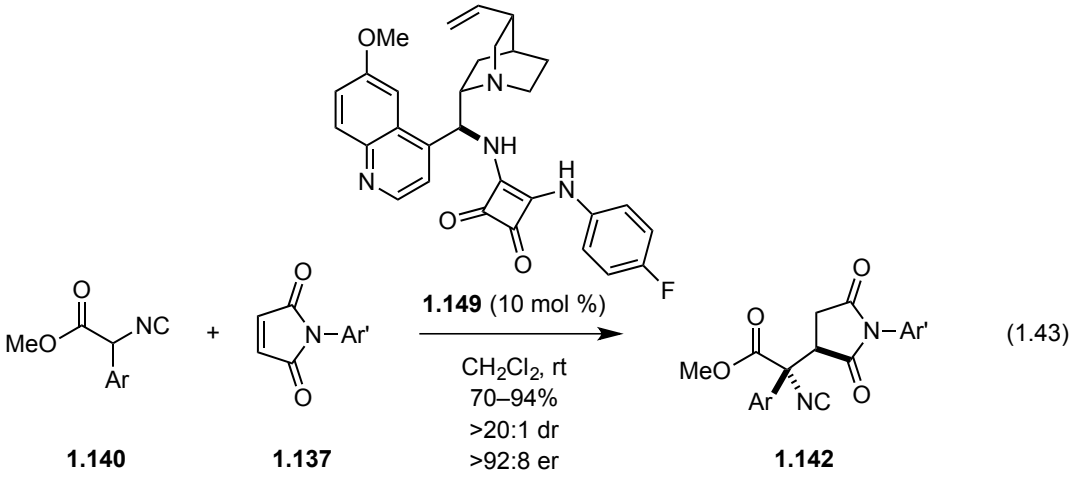


1.136 **1.137** **1.139**



1.147
R = Bn or Ar

1.149
R = Me or -$CH_2(CH_2)_3CH_2$-

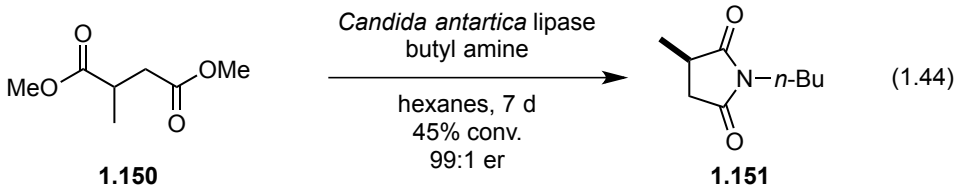


1.2.4.3 Summary

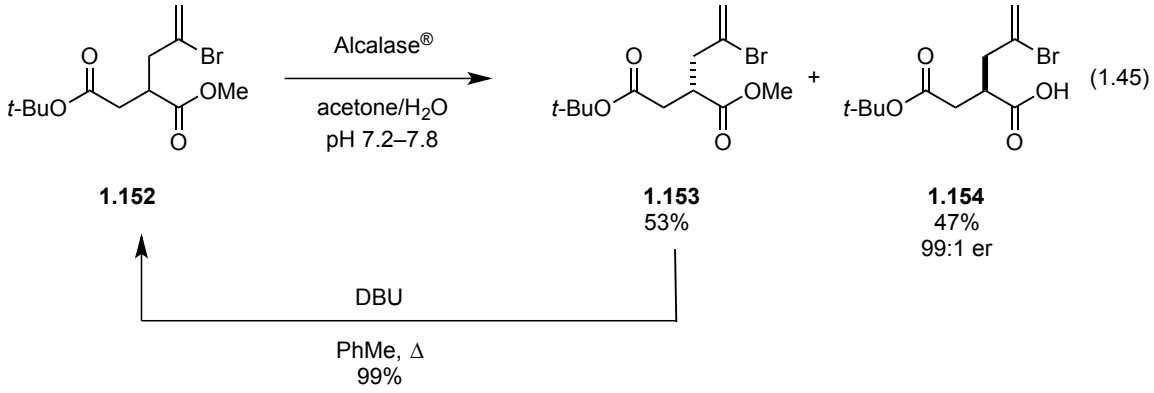
Like transition metal catalysis, the field of organocatalyzed reactions remains underdeveloped in the context of the synthesis of chiral succinates. The substrate scope for the variety of catalysts remains narrow. Significant development is needed in this field to fully realize the potential for organocatalyzed synthesis of succinic acid derivatives.

1.2.5 Resolution

Resolution of racemic succinic acid derivatives remains a valuable tool for the preparation of enantioenriched succinates. Toward this end, Gotor found that *Candida antarctica* lipase could resolve a simple succinate derivative **1.150** to succinimide **1.151** in good yield and excellent enantioselectivity (Equation 1.44).[74] While this transformation was not applied to more complicated substrates, this report did provide the foundation for further work in this area.

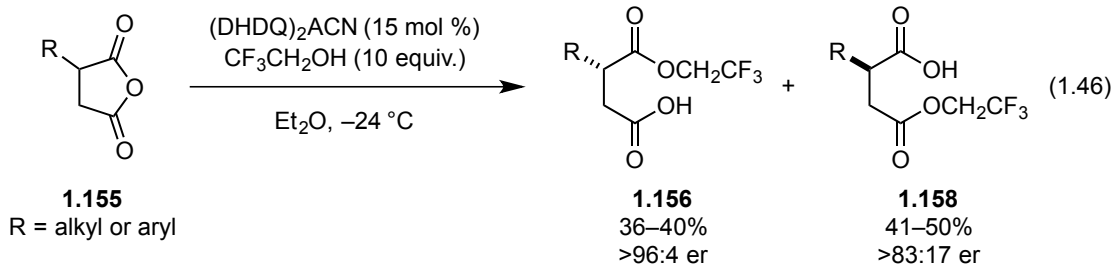


Perhaps the most versatile resolution reaction came from Bailey in 1999.[75] Using Alcalase®, *rac*-**1.152** was selectively hydrolyzed to provide **1.154** in 47% yield and 99:1 er (Equation 1.45). The unreacted **1.153** was epimerized and resubjected to the resolution to further increase the yield of **1.154** over multiple cycles. This method was reported to work for a wide range of substituted succinic acids derivations and was showcased in the synthesis of the orally active renin inhibitor BILA 2157 BS.[76]



In 2001, Deng and co-workers found that a modified Sharpless ligand ($(DHDQ)_2$-ACN) performed the selective alkanolysis of *rac*-**1.155** to provide mono-esters **1.156** and **1.158** in good enantioselectivities (Equation 1.46).[77] The reaction worked for a number of alkyl and aryl substituted succinic anhydride derivatives with similarly high yields and selectivities. This was the first report of a parallel kinetic resolution of any kind, wherein

two simultaneous enantioselective and divergently regioselective reactions occurred using a single catalyst.



1.155
R = alkyl or aryl

1.156
36–40%
>96:4 er

1.158
41–50%
>83:17 er

Ultimately, while the resolution reported by Bailey allowed for the recycling of the unwanted enantiomer, a dynamic kinetic resolution would prove most useful in this field. Perhaps a future report will disclose an even more efficient resolution of racemic succinic acid derivatives, or even a dynamic kinetic resolution. Additionally, a number of other methods have found the synthesis of enantioenriched succinic acids via resolution to be difficult.[78,79]

1.2.6 Summary

As discussed, it is obvious that the most versatile strategies to reliably provide enantioenriched succinic acid derivatives rely on the use of a chiral auxiliary for stereocontrol. However, while most of the auxiliaries can be recycled and for the most part provide good yields and enantioselectivities, the synthetic community is moving away from stoichiometric sources of chirality. Nevertheless, there is still chemistry to explore in this area, namely the further development of methods to allow for the divergent access to multiple products from a single diastereomer, which would add value to this stoichiometric approach to chiral succinic acids.

In the context of future directions, most research groups will likely focus on catalytic transformations. This could be accomplished with chiral Lewis acid catalysts, organocatalysts, transition metal catalysts, or enzymes. Unfortunately, for Lewis acid catalysts, one current drawback is the necessity for a functional group to activate the system. While this does allow the transformation to take place and removes the need for a stoichiometric source of chirality, it still suffers a similar drawback in that a functional group must be appended prior to the reaction and then removed afterward.

Transition metal catalysts, though they have proven extremely effective for a number of other transformations, still fall short in the synthesis of succinates. Future studies should most likely explore substrate tolerance rather than rehash the same substrates with new ligands. In summary, many avenues for improving the enantioselective synthesis of functionalized succinates exist. With the continuing development of catalysis technologies, it is only a matter of time until efficient methods are developed for the synthesis of succinates. Until then, auxiliary based approaches remain the most reliable tactic for the synthesis of enantioenriched substituted succinic acid derivatives.

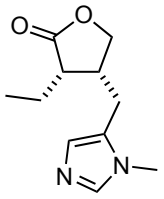
1.3 Total Syntheses of Select Succinate Derived Natural Products

1.3.1 Select Syntheses of Pilocarpine (1.7)

1.3.1.1 Isolation and Overview of Syntheses

Pilocarpine (**1.7**) (Figure 1.4) was first isolated in 1875 by Hardy and Gerrard from a South American tree, *Pilocarpus jaborandi*.[4,80] Pilocarpine has been shown to be useful as a parasympathetic system stimulant as well as a diaphoretic and miotic agent. Currently, due to its lack of selectivity, it is only used in an eye drop solution to treat

glaucoma. There are currently ten total syntheses[81-88] and three formal syntheses of pilocarpine.[89-91] In order to provide a concise survey and provide comparison for our own work in the field (*vide supra*), this section will only highlight the shortest total synthesis of pilocarpine (**1.7**) reported to date by Büchi as well as a formal synthesis by Zhang which would result in the lowest total step count to the natural product to date.



1.7
pilocarpine

Figure 1.4 Pilocarpine

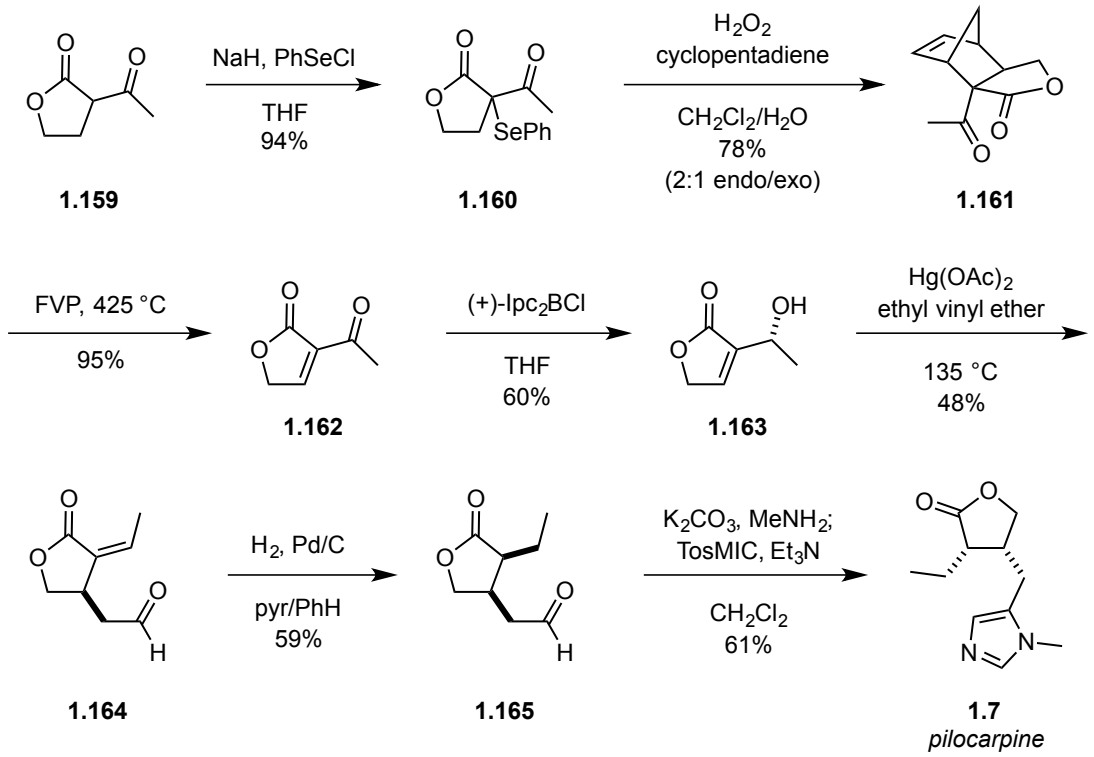
1.3.1.2 Büchi's Total Synthesis of (+)-Pilocarpine (1.7)

The total synthesis of **1.7** by Büchi began with the oxidation of commercially available **1.159** to butenolide **1.162**.[85] This sequence proceeded through selenide **1.160**, which was prepared in 94% yield. Unfortunately, they found that direct oxidative elimination of **1.160** to **1.162** could not be achieved, because the product was not stable to the reaction conditions. In a clever work around, performing the oxidative elimination in the presence of cyclopentadiene provided Diels-Alder adduct **1.161** in 78% yield. Flash vacuum pyrolysis of bicycle **1.161** afforded butenolide **1.162** in 95% yield.

To set the absolute stereochemistry, enantioselective reduction of **1.162** using (+)-diisopinocamphyl chloroborane ((+)-$(Ipc)_2BCl$) provided enantioenriched alcohol **1.163** in 60% yield. A Claisen rearrangement completed the installation of both side chains

providing aldehyde **1.164** with no erosion of enantioselectivity. Hydrogenation of the enone provided the penultimate intermediate **1.165** in 59% yield, which upon imidazole formation using the van Leusen protocol delivered pilocarpine (**1.7**) in 61% yield.

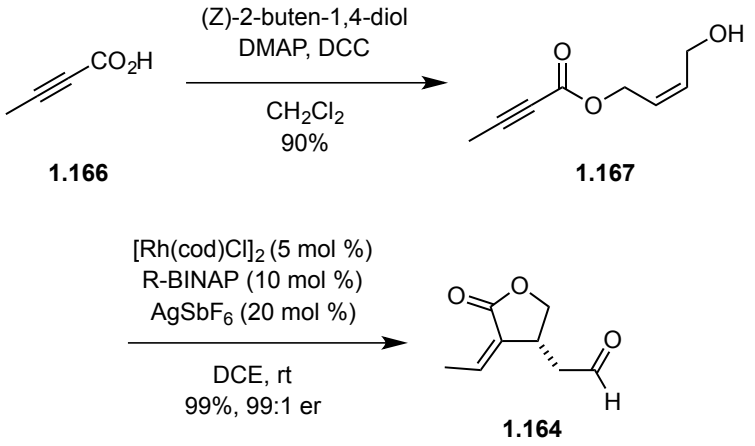
The synthesis required a series of seven steps to deliver pilocarpine (**1.7**) in a 7% overall yield. The synthesis resulted in a solution to the long-standing problem of the oxidation of **1.59** to **1.162**, but due to the moderate yields across the last four steps, the overall yield suffered.



Scheme 1.10 Synthesis of pilocarpine (**1.7**) by Büchi

1.3.1.3 Zhang's Formal Synthesis of (+)-Pilocarpine

Nine years later, Zhang improved upon the synthesis by Büchi using a rhodium catalyzed Alder-ene reaction of allyl ynoates they had developed.[91] The requisite substrate for this transformation was synthesized in one step from 2-butynoic acid (**1.166)** to provide **1.167** in 90% yield (Scheme 1.11). Treatment of the ynoate with a chiral cationic rhodium complex delivered lactone **1.164** in 99% yield and 98% ee. Thus, by extrapolation, Zhang could complete pilocarpine (**1.7**) in a total of four steps and a 32% overall yield. This route is currently the shortest route to **1.7** reported to date.

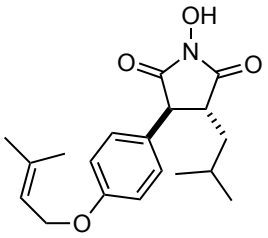


Scheme 1.11 Formal synthesis of pilocarpin (**1.7**) by Zhang

1.3.2 Lee's Total Synthesis of Antrodin D (1.9)

Antrodin D (**1.9)** (Figure 1.5), also known as camphorataimide E, is a succinimide based natural product first isolated from *Antrodia cinnamomea* and *Antrodia camphorata*, fungi that grow solely in the heartwood of the tree *Cinnamomum kanehirai*.[6] The fungus has historically been used as an anti-cancer, anti-itching, anti-fatigue, and liver protecting folk medicine in Taiwan. Antrodin E has been shown to have activity

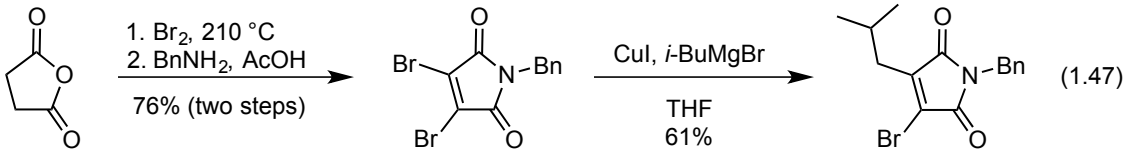
against MRSA,[92] HBV, and HCV.[93] To date, only one total synthesis of the product has been completed by the Lee group.[94]



1.9
antrodin D

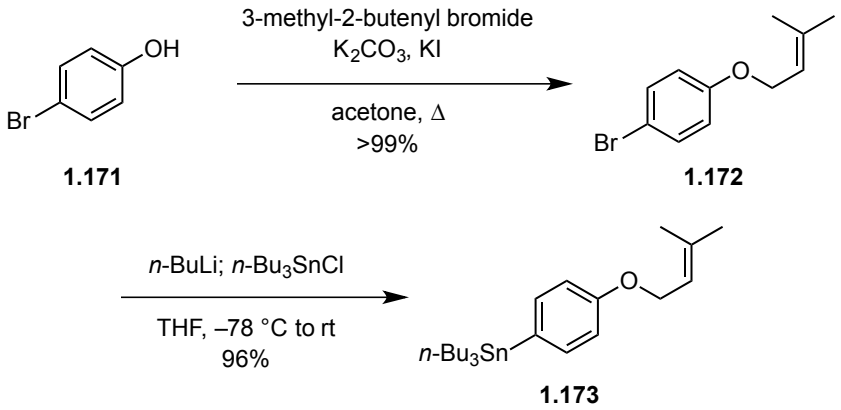
Figure 1.5 Antrodin D

The synthesis began with the preparation of cross coupling partner **1.170** from succinic anhydride (**1.168**) (Equation 1.47), whereupon treatment with bromine followed by benzylamine delivered bis-bromo maleimide **1.169** in 76% yield over two steps. Finally, copper mediated coupling of isobutylmagnesium bromide gave the desired product **1.170** in 61% yield.



1.168 **1.169** **1.170**

Next, the complementary cross coupling partner **1.173** was synthesized (Scheme 1.12). Prenylation of *p*-bromophenol (**1.171**) proceeded smoothly to give **1.172** in quantitative yield. Stannylation of **1.172** via the lithiated arene delivered stannane **1.173** in 96% yield. The stage was then set for the next cross coupling reaction.

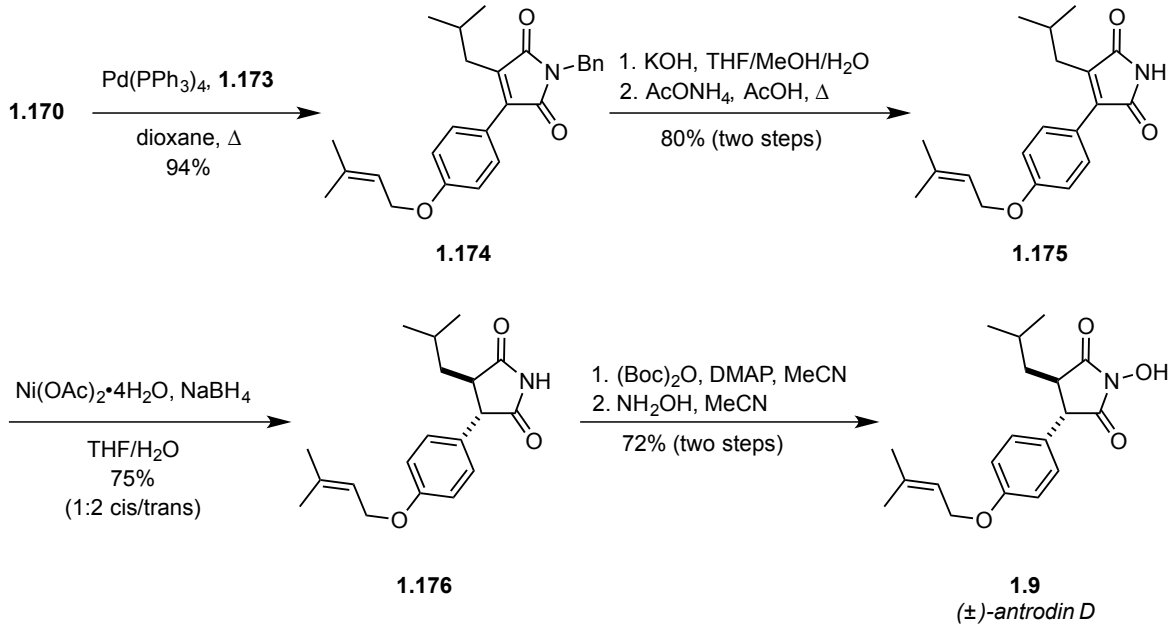


Scheme 1.12 Synthesis of coupling partner **1.173**

In the event, **1.170** and **1.173** were coupled in the presence of palladium tetrakis(triphenylphosphine) to give disubstituted maleimide in 94% yield (Scheme 1.13). Next, the imide was hydrolyzed to the anhydride and treated with ammonium acetate to provide unprotected maleimide **1.175**. Reduction of the olefin with nickel boride delivered succinimide **1.176** in 75% yield as a mixture (2:1) of diastereomers. Finally, protection of the nitrogen atom with Boc anhydride followed by reaction with hydroxylamine furnished the target compound **1.9** in 72% yield over two steps.

Lee thus completed the first and only synthesis of antrodin D (**1.9**) in eleven steps with a 12% overall yield. The synthesis hinged on the sequential cross coupling reactions of bis-bromo maleimide **1.169** to provide bis-substituted maleimide **1.174**. Unfortunately,

manipulation of the benzyl protected imide to the hydroxylimide required a total of four steps. Additionally, the reduction to succinimide **1.176** was poorly selective providing the product as a mixture (2:1) of diastereomers. While the synthesis managed to complete the product, this route leaves room for improvement in both yield and overall step count.



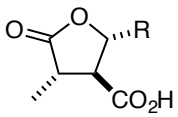
Scheme 1.13 Synthesis of antrodin D (**1.9**) by Lee

1.3.3 Total Syntheses of Dihydroprotolichesterinic Acid (DHPLA)

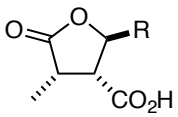
1.3.3.1 The Paraconic Acid Family of Natural Products

The paraconic acid family of natural products comprises roccellaric acid (**1.14**), nephrosteranic acid (**1.6**), dihydroprotolichesterinic acid (**1.5**), phaseolinic acid (**1.177**), nephromopsinic acid (**1.178**), protolichesterinic acid (**1.4**), and methylenolactocin (**1.179**) among others (Figure 1.6).[95] These natural products have been shown to exhibit anti-bacterial and anti-fungal properties. Although the paraconic acids are structurally simple,

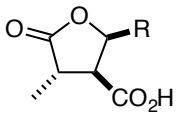
they have received a lot of attention from the synthetic community as a platform to demonstrate stereocontrol in a number of methodologies.[3] Dihydroprotolichesterinic acid (**1.5**) had been synthesized five times prior to our work in the field.[96-100]



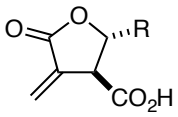
1.14 R = *n*-$C_{13}H_{27}$: roccellaric acid
1.6 R = *n*-$C_{11}H_{23}$: nephrosteranic acid



1.5 R = *n*-$C_{13}H_{27}$: dihydroprotolichesterinic acid



1.177 R = *n*-C_5H_{11} : phaseolinic acid
1.178 R = *n*-$C_{13}H_{27}$: nephromopsinic acid



1.4 R = *n*-$C_{13}H_{27}$: protolichesterinic acid
1.179 R = *n*-C_5H_{11} : methylenolactocin

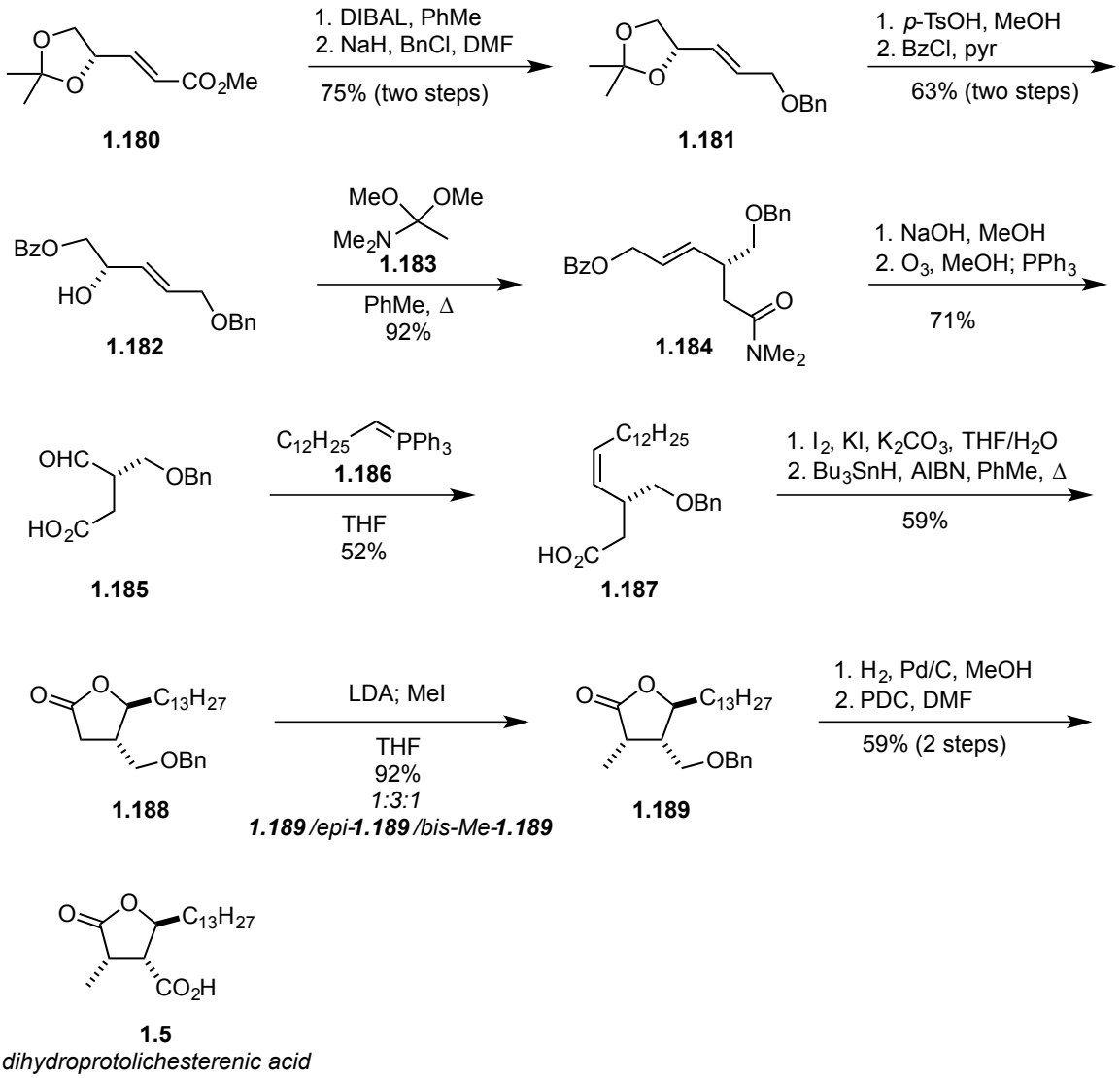
Figure 1.6 Representative members of the paraconic acid family of natural products.

1.3.3.2 Mulzer's Synthesis of (–)-Dihydroprotolichesterinic Acid

The first total syntheses of both DHPLA (**1.5**) and roccellaric acid (**1.14**) were completed by Mulzer in 1993 (Scheme 1.14).[96] The synthesis commenced from enoate **1.180**, which was available in two steps from (*R*)-glyceraldehyde. Enoate **1.180** was reduced and protected as a benzyl ether to provide olefin **1.181** in 75% yield over two steps. Removal of the acetonide moiety followed by reprotection of the primary alcohol delivered allylic alcohol **1.182** and set the stage for the key Eschenmoser-Claisen rearrangement. In the event, **1.182** was heated with *N*,*N*-dimethylacetamide dimethyl acetal (**1.183**) giving rise to amide **1.184** with no erosion of enantioenrichment. Hydrolysis and ozonolysis of **1.184** provided aldehyde **1.185**, setting the stage for the next key sequence.

The alkyl side chain was installed via Wittig olefination with ylide **1.186** to provide 52% of the pure Z-isomer of **1.187**. Iodolactonization followed by radical dehalogenation generated lactone **1.188** in 59% yield as a single diastereomer. It should be noted that the authors found the Z-olefin to be crucial to the diastereoselectivity of the iodolactonization, even though the stereogenic C-I bond was subsequently destroyed. Methylation of lactone **1.188** delivered tri-substituted lactone **1.189** as the minor diastereomer in a mix (1:3:1) of **1.189**, *epi*-**1.189**, and bis-methyl **1.189**. Finally, hydrogenolysis and oxidation delivered DHPLA (**1.15**) in 59% yield over two steps.

Mulzer thus completed the first total synthesis of DHPLA (**1.5**) in 15 steps and a 1% overall yield from enoate **1.180**. During the course of this study, the utility of the Eschenmoser-Claisen reaction was demonstrated in a highly diastereoselective rearrangement, effectively transferring the chirality from (R)-glyceraldehyde to intermediate **1.184**. Additionally, the authors exploit a diastereoselective iodolactonization reaction to set the stereocenter at the γ carbon atom. Unfortunately, this sequence suffered during the alkylation of **1.188**, wherein the desired product **1.189** was received as the minor product. Fortunately, *epi*-**1.189** could be taken forward to roccelaric acid (**1.14**) providing access to two members of the paraconic acid family.

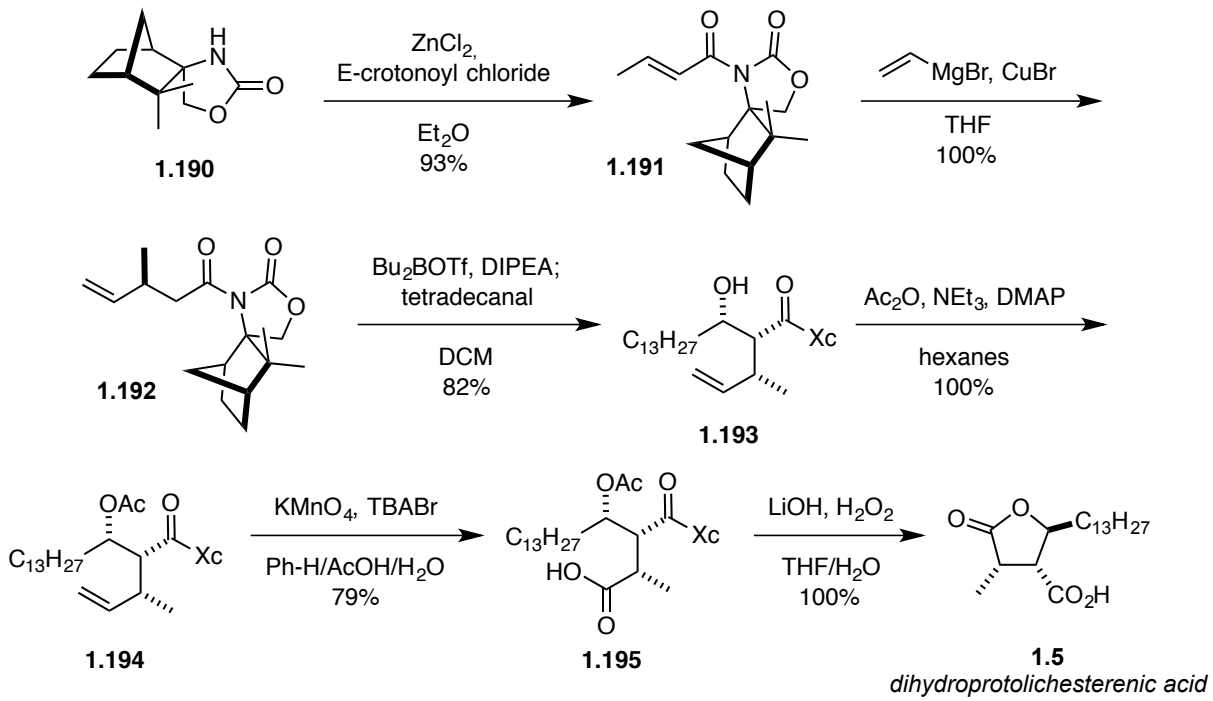


Scheme 1.14 Synthesis of DHPLA (**1.5**) by Mulzer.

1.3.3.3 Banks's Synthesis of (–)-Dihydroprotolichesterinic Acid

Banks and co-workers reported a much shorter synthesis of **1.9** in 1995 using their chiral auxiliary (–)-chiracamphox (**1.190**) to set the stereochemistry (Scheme 1.15).[97] Auxilliary **1.190** was coupled to E-crotonoyl chloride in the presence of zinc chloride to deliver **1.191** in 93% yield. Copper mediated conjugate addition of vinylmagnesium

bromide provided **1.192** in 100% yield. Under Evans's conditions, imide **1.192** underwent an aldol reaction with tetradecanal to give **1.193** in 82% yield. Protection of the alcohol delivered **1.194** in 100% yield, which was oxidized to provide acid **1.195** in 79% yield. Finally, hydrolysis of both the acetate and the auxiliary provided DHPLA (**1.5**) in 100% yield. Thus, Banks completed the total synthesis of (–)-DHPLA (**1.5**) in six steps with an overall 60% yield. The key to their synthesis hinged on the effectiveness of their recently developed auxiliary (–)-chiracamphox (**1.190**), which set all of the stereocenters through a remarkably high yielding two-step Michael addition and aldol reaction sequence. With a 60% overall yield, this synthesis remains the highest yielding route to DHPLA (**1.5**) to date.



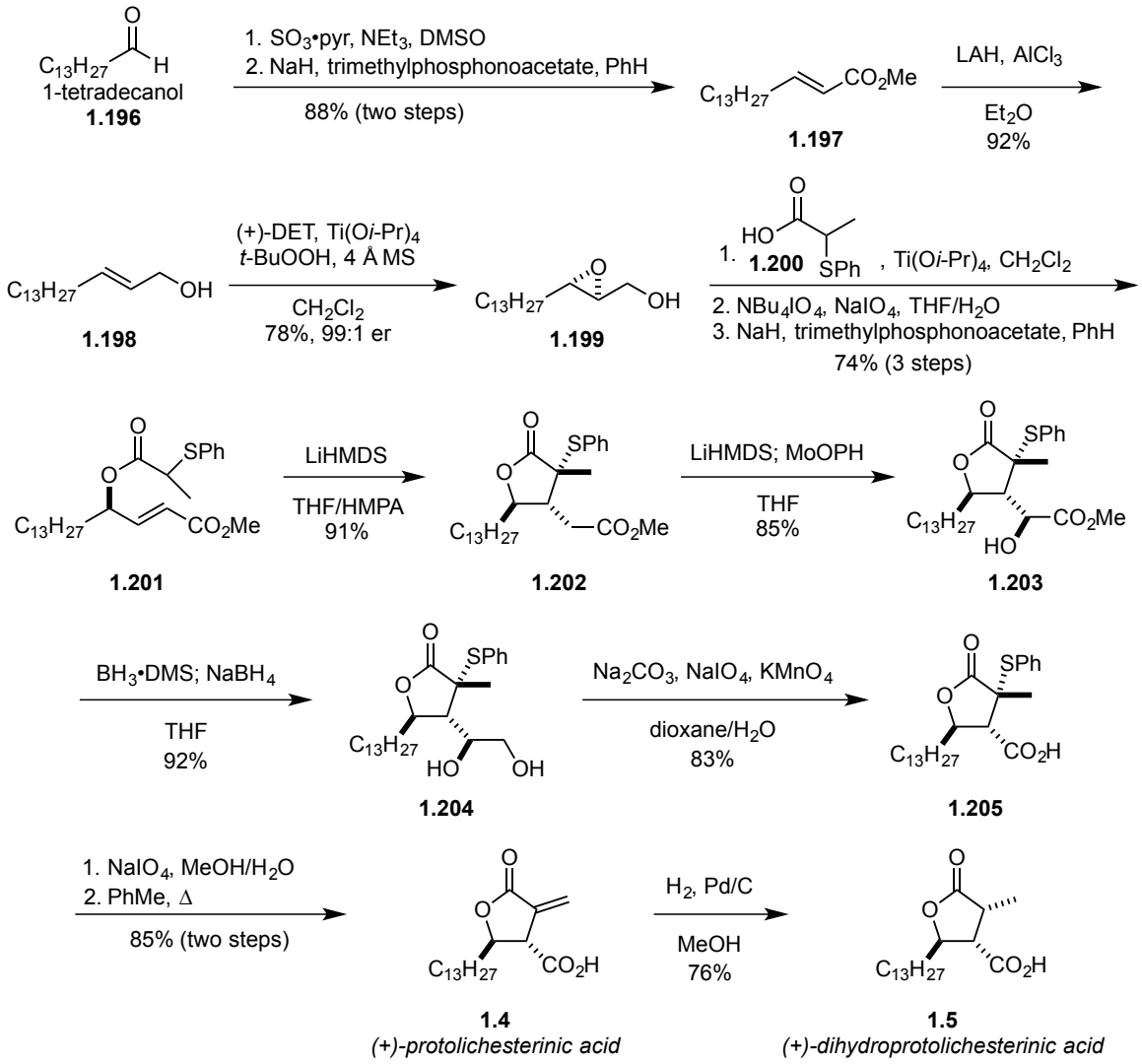
Scheme 1.15 Total synthesis of (–)-DHPLA (**1.5**) by Banks.

1.3.3.4 Martín's Synthesis of (+)-Dihydroprotolichesterinic Acid

In 1996, Martín reported a 14 step route to (+)-DHPLA (**1.5**) utilizing a four step strategy they developed for the synthesis of α-phenylthio γ-butyrolactones from enantioenriched epoxides (Scheme 1.16).[98,101,102] The set up for their key step required the enantioselective synthesis of epoxide **1.199**. The route began with 1-tetradecanol (**1.196**), which was oxidized and subjected to Wittig olefination to provide enoate **1.197** in 88% yield over two steps. Reduction of the ester followed by asymmetric epoxidation under the Sharpless protocol delivered epoxide **1.199** in 98% ee. Opening epoxide **1.199** with acid **1.200**, followed by oxidative cleavage and Wittig olefination provided key ester **1.201** in 74% yield over three steps. Finally, diastereoselective, intramolecular Michael addition yielded lactone **1.202.**

Next, the synthesis required a three-step degradation of the ester. Towards this goal, α-oxidation of the ester moiety of **1.202** with MoOPH under Vedejs's conditions provided **1.203** in 85% yield. Reduction of the ester followed by oxidative cleavage completed the degradation furnishing acid **1.205**. Finally, oxidative elimination of the sulfide followed by hydrogenation delivered (+)-DHPLA (**1.5**).

Unfortunately, at 14 steps with an 18% overall yield, Martín fails to improve the yield or step count. The synthesis nicely showcased their strategy for the synthesis of γ-butyrolactones, but the route falls short in the four-step synthesis of the enantioenriched epoxide as well as the three-step degradation of the ester functionality. In short, showcasing the method required a forced route, which led to no improvement over the previous synthesis by Banks.



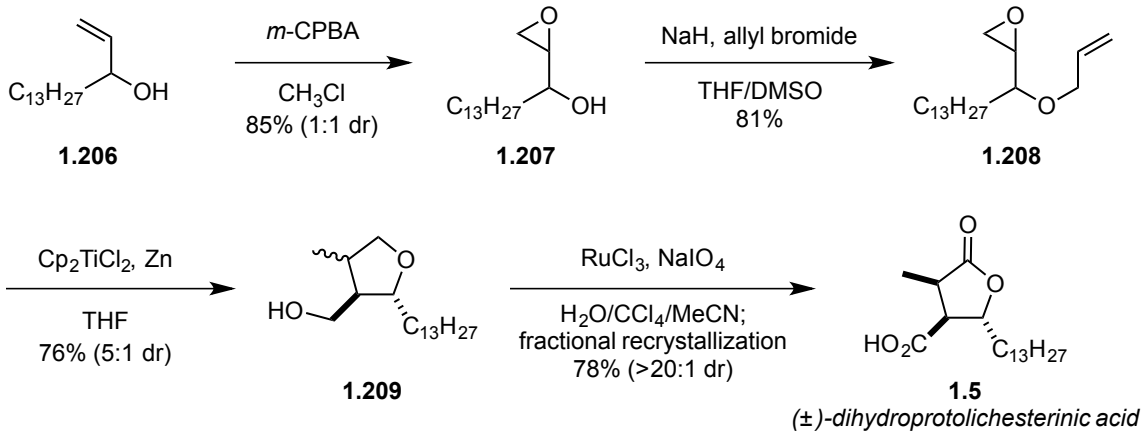
Scheme 1.16 Total synthesis of (+)-DHPLA (**1.5**) by Martín.

1.3.3.5 Roy's Synthesis of (±)-Dihydroprotolichesterinic Acid

Roy chose DHPLA (**1.5**) as well as rocellaric acid (**1.14**) to showcase an epoxide triggered radical annulation reaction (Scheme 1.17).[99,103] The synthesis began with allylic alcohol **1.206**, which is available in one step from tetradecanal. Epoxidation of the olefin led to **1.207** in 85% yield as a mixture (1:1) of diastereomers. The mixture of

diastereomers was allylated in 81% yield, and the product was subjected to radical annulation mediated by titanocene dichloride to deliver tetrahydrofuran **1.209** as a mixture (5:1) of diastereomers. Oxidation of **1.209** delivered a mixture of diastereomers, which after fractional recrystallization provided (±)-DHPLA (**1.5**) in 78% yield as a single diastereomer.

(±)-Dihydroprotolichesterinic acid (**1.5**) was synthesized in five steps and 41% overall yield from allylic alcohol **1.206**. The synthesis is concise and exploits a diastereoablative radical annulation of **1.207** (1:1 dr) to deliver **1.209** as a mixture (5:1) of diastereomers. While lacking in yield in comparison to Banks, this inventive route swiftly provided access to the target molecule with a unique strategy.



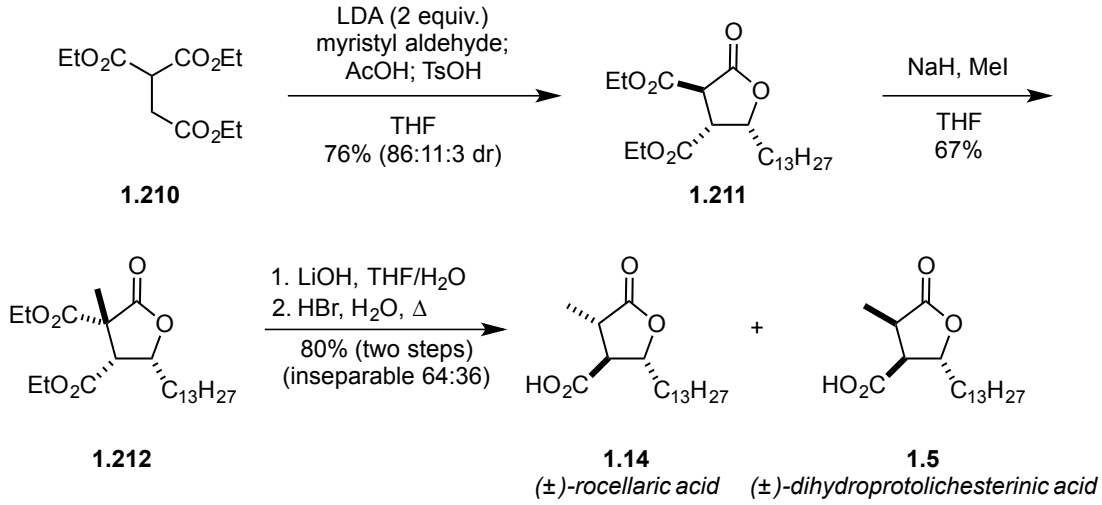
Scheme 1.17 Total synthesis of (±)-DHPLA by Roy.

1.3.3.6 Pohmakotr's Synthesis of (±)-Dihydroprotolichesterinic Acid

Pohmakotr realized a unique route to both DHPLA (**1.5**) and rocellaric acid (**1.14**). While the sequence required only four steps, the natural products were prepared as an inseparable mixture. The synthesis commenced with the key reaction, wherein the

vincinal dianion derived from **1.210** underwent aldol reaction with concomitant lactonization to provide lactone **1.211** in 76% yield a an mixture (86:11:3) of diastereomers. During the course of optimizing this reaction, the authors found that quenching with PTSA led to a loss in yield, whereas quenching with acetic acid followed by PTSA to promote lactonization gave them a moderate yield of the lactone.

Alkylation of the lactone with methyl iodide delivered **1.212** in 67% yield. Finally, saponification followed by decarboxylation delivered both rocellaric acid (**1.14**) and DHPLA (**1.5**) in 80% yield as an inseparable mixture (64:36). Pohmakotr thus completed the synthesis of DHPLA (**1.5**) in four steps with an overall 13% yield, but the product could not be separated from rocellaric acid (**1.14**).



Scheme 1.18 Total synthesis of (±)-DHPLA by Pohmakotr.

1.3.3.7 Summary

Since the first synthesis of dihydroprotolichesterinic acid (**1.5**), the molecule has come to serve as a testing ground for the development stereoselective methodology. The

five syntheses have explored a number of strategies that can access the relatively simple molecule (Table 1.1). Unfortunately, barring cleavages of chiral auxiliaries, almost every synthesis thus far requires refunctionalization either through redox transformation or the removal of extra atoms. Thus, the syntheses of DHPLA (**1.5**) still have room for improvement before an ideal synthesis can be attained.

Table 1.1 Syntheses of DHPLA (**1.5**)

Group	Year	(+)/(–)/(±)	Steps	Yield
Mulzer	1993	(–)	14	0.4%
Banks	1995	(–)	6	60%
Martín	1996	(+)	14	13%
Roy	1999	(±)	6	29%
Pohmakotr	2002	(±)	4	13%

1.4 SUMMARY

A number a natural products have been used to showcase the utility of methods that can access functionalized succinic acid cores. For such small molecules, 14 steps is unreasonable. Additionally, a number of the syntheses suffer from lack of diastereoselectivity leading to mixtures of products. Since these molecules can be used as drugs, an attractive strategy to access the natural products and derivatives thereof would be an expedient, divergent route wherein a single molecule can rapidly be manipulated into a variety of products, be they different natural products or derivatives of the biologically active molecules.

Chapter 2: Development of a Diastereoselective Conjugate Addition to a Chiral Fumarate and Application to the Total Synthesis of (–)-Dihydroprotolichesterinic Acid

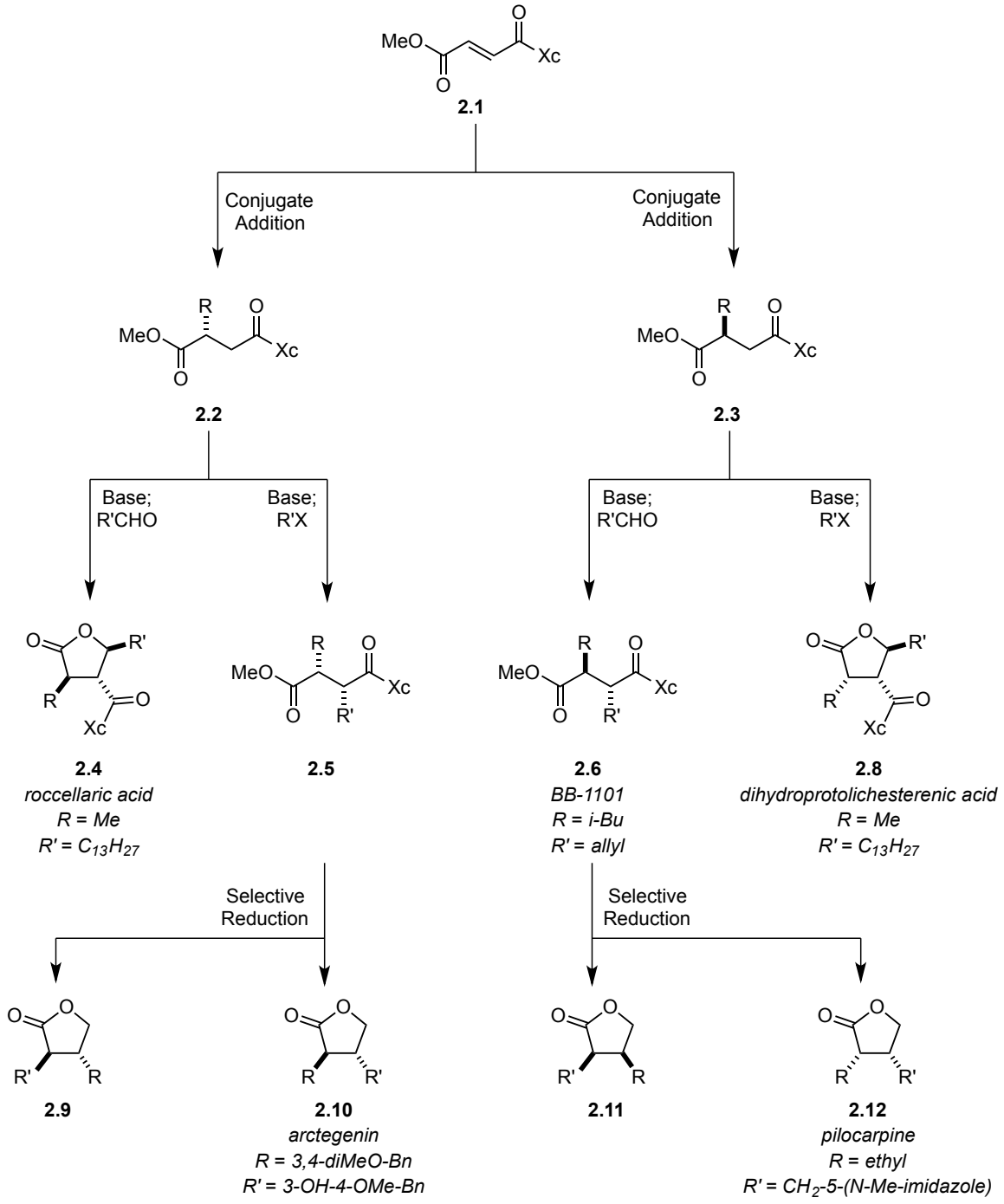
2.1 Strategy and Inspiration

2.1.1 Martin Group Strategy for the Synthesis of Functionalized Succinic Acid Derivatives

Due to the numerous examples of biologically active molecules containing a succinate moiety (Section 1.1), a unified route to disubstituted succinic acid derivatives available from a single, simple chiral starting material would be of considerable value. Indeed, there is a single report of where a chiral auxiliary provides selective access to more than one possible diastereomer of enantioenriched disubstituted succinates (Section 1.2.1.2),[46] but this method is limited in scope. We thus realized there was significant opportunity to develop a strategy for the enantioselective and diastereoselective synthesis of 2,3-disubstituted succinic acid derivatives.

We reasoned that if the diastereoselectivity of a conjugate addition reaction to chiral fumarate **2.1** could be modulated, we would be able to selectively access both monosubstituted succinic acid derivatives **2.2** and **2.3** (Scheme 2.1). An aldol reaction of the resultant adducts **2.2** and **2.3** would provide trisubstituted lactones **2.4** and **2.8**, which could be elaborated to natural products such as rocellaric acid and dihydroprotolichesterinic acid. Additionally, **2.2** and **2.3** could undergo diastereoselective alkylation reactions to provide both the syn- and anti-substituted succinates **2.5** and **2.6**, which could be used in syntheses of matrix metalloproteinase inhibitors, like BB-1101. Finally, selective reduction of succinates **2.5** and **2.6** could provide access to four different disubstituted lactones, which with appropriate choice of substituents (R and R')

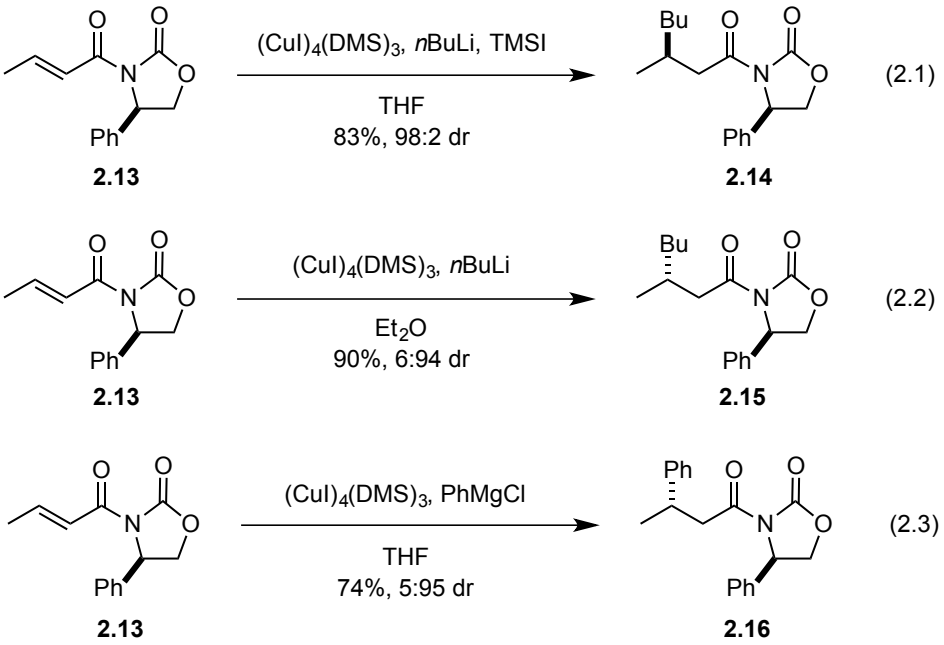
represent the natural products arctegenin and pilocarpine. With the methodology for auxiliary controlled alkylation and aldol reactions already known, we had only to develop a "switchable" diastereoselective conjugate addition reaction to fumarate **2.1** to realize this goal.



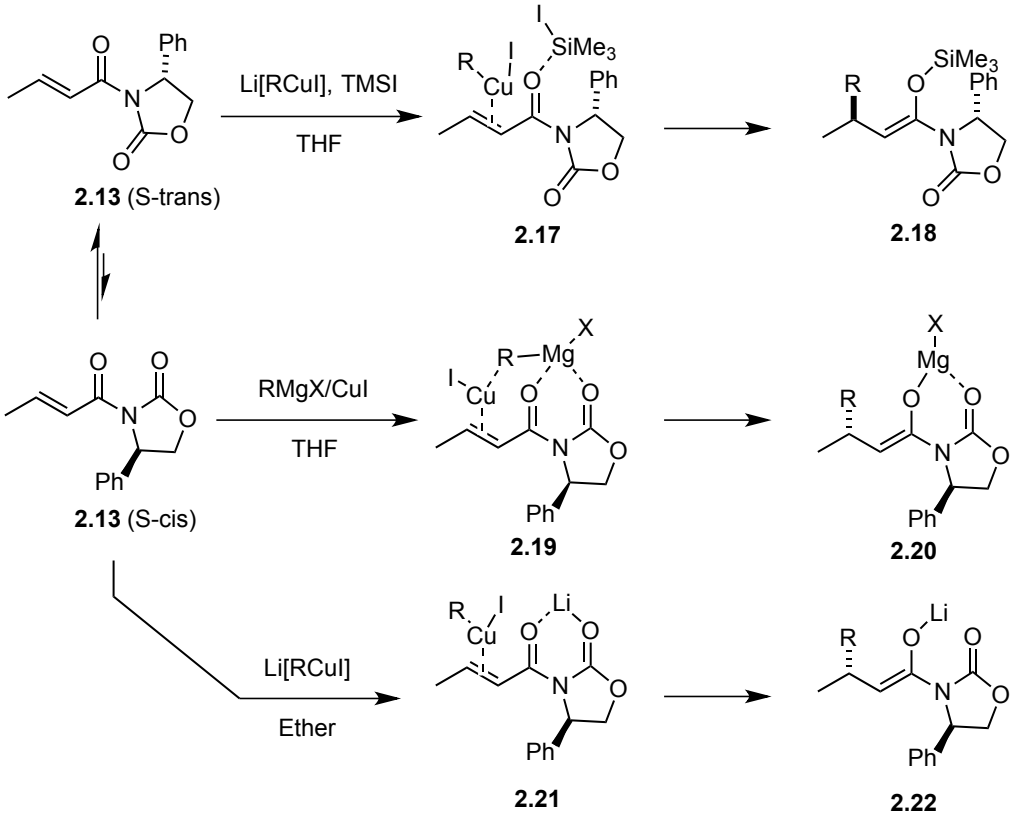
Scheme 2.1 Potential strategy for the divergent synthesis of chiral succinates.

2.1.2 Divergent Conjugate Addition to Chiral Crotonates by Bergdahl

While there were no reports of conditions to switch the diastereoselectivity of conjugate addition reactions to chiral fumarates, Bergdahl reported a tactic to modulate the diastereofacial addition of monoorganocuprates, [RCuI]Li, to chiral crotonates in 2004.[104] This discovery allows for chiral crotonate **2.13** to be differentiated into either diastereomer **2.14** or **2.15**, simply by changing the reaction conditions. Inclusion of iodotrimethylsilane (TMSI), delivers product **2.14** in 98:2 dr (Equation 2.1), whereas removal of TMSI (Equation 2.2) or use of a Grignard reagent (Equation 2.3) provides the opposite diastereomer. This significant advancement provides divergent access to either diastereomer **2.14** or **2.15** for the first time since the initial report of oxizolidinone directed conjugate additions in 1993.[105] Prior to this discovery, switching the selectivity required the use of the enantiomeric starting material (*epi*-**2.13**).



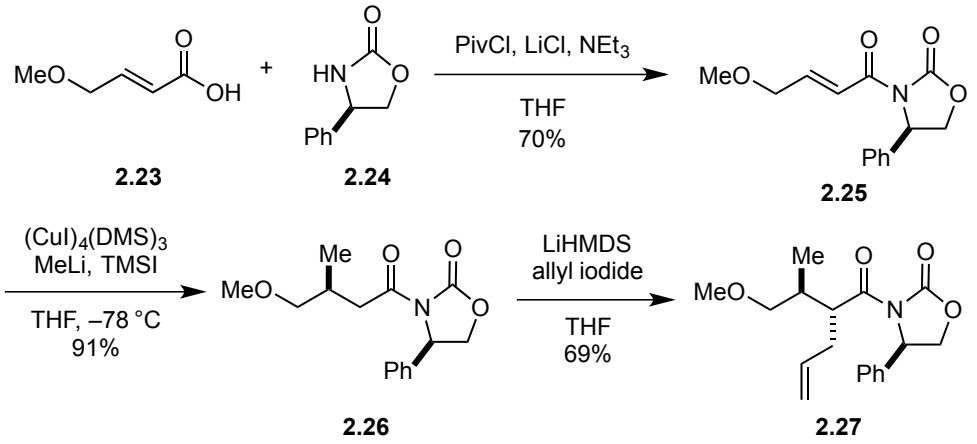
The origin of the stereoselectivity can be explained via the differing modes of action of the Lewis acid in the reaction (Scheme 2.2). In the Bergdahl protocol, TMSI is presumed to coordinate to only one of the carbonyl moieties of **2.13** to give **2.17**. The auxiliary adopts an S-trans conformation to minimize the dipole, with the phenyl group blocking the back face of the molecule and delivering **2.18** as the major product. When TMSI is no included, **2.13** is chelated by either magnesium **2.19** or lithium **2.21**, which locks the auxiliary with the phenyl group blocking the front face of the olefin providing the intermediates **2.20** or **2.22**.



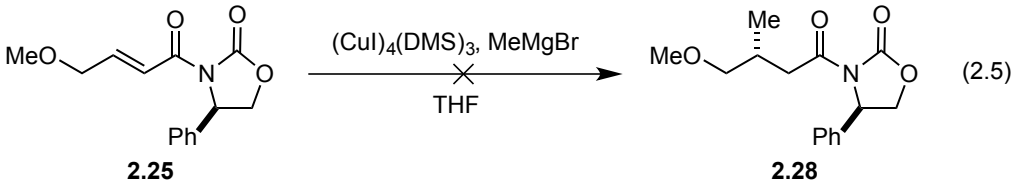
Scheme 2.2 Rationale for the observed stereoselectivity in Bergdahl's conjugate addition.

2.1.3 Martin Group Conjugate Addition to γ-Alkoxy Crotonates

The Martin group previously explored the extension of the Bergdahl protocol in work directed toward alkaloids of stemofoline family,[106,107] wherein we sought to utilize the Bergdahl protocol in a conjugate addition reaction to a γ-alkoxy crotonate **2.25**. Chiral crotonate **2.25** was prepared in 70% yield from **2.23** and **2.24** and subjected to the reaction conditions developed by Bergdahl, providing **2.26** in 91% as a single diastereomer. Imide **2.26** was subjected to standard allylation conditions to deliver **2.27** in 69% yield. Intermediate **2.27** was then advanced in a set of model studies that ultimately led to the syntheses of didehydrosemofoline and isodidehydrosemofoline.[108,109] During the course of this work, we found that conditions to provide the diastereomeric adduct **2.28** were unsuccessful (Equation 2.5); however, we did not experiment with conditions extensively.



Scheme 2.3 Martin group conjugate addition to γ-Alkoxy Crotonates



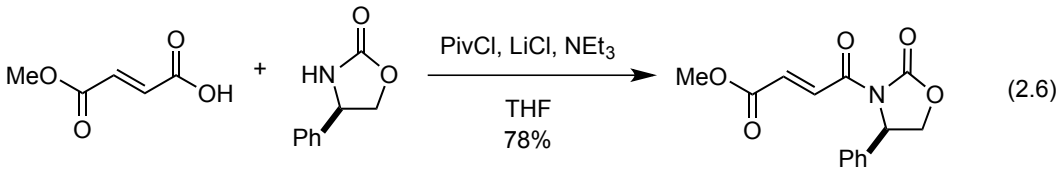
2.25 **2.28**

2.2 DEVELOPMENT OF THE COPPER MEDIATED CONJUGATE ADDITION REACTION

Inspired by the success of the Bergdahl protocol with γ-alkoxy crotonates, we believed that the conditions could be extended further to chiral fumarate **2.31** to realize our goal of a divergent route to succinic acid derivatives. While standard conditions failed to switch the diastereoselectivity in preliminary experiments with γ-alkoxy crotonate **2.25** (Equation 2.5), we believed that extensive experimentation would reveal optimal conditions for reactions with **2.31**. If the regio- and stereochemical outcome of this conjugate addition reaction could be controlled, it would represent the first switchable diastereoselective conjugate addition reaction of its type and only the second divergent route to disubstituted succinic acid derivitives using substrate control. However, while radical conjugate additions[32,37,39,110] and Mukaiyama-Michael reactions[111,112] occur β to the imide moiety of fumarates like **2.31**, there was no guiding precedent for the reactions of organocuprate-derived reagents with such substrates.

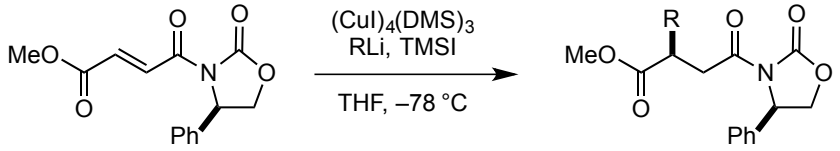
In order to probe the feasibility of the designed method, fumarate **2.31** was prepared from commercially available monomethyl fumarate (**2.29**) and chiral oxizolidinone **2.30** in 78% yield (Equation 2.6).[113] The stage was then set for the unprecedented conjugate addition reaction. When fumarate **2.31** was treated with lithium monomethyl cuprate (Li[MeCuI]) in the presence of TMSI under the conditions reported by Bergdahl,[104] we were pleased to find that the expected succinate **2.32** (R = Me) was isolated in 89% yield with excellent stereoselectivity (Table 2.1, entry A). The scope of

the method was evaluated for monoalkylcuprates derived from ethyl- and *n*-butyllithium, which proceeded equally well to deliver **2.33** and **2.34** with excellent stereoselectivity (Table 2.1, entries B and C). We also found that the process could be extended to monophenyl cuprate with good yield and excellent stereoselectivity (Table 2.1, entry D). Unfortunately, we found that the method could not be extended to monoorganocuprates derived from *tert*-butyllithium, vinyllithium, and acetylides.



2.29 **2.30** **2.31** (2.6)

Table 2.1 Substrate scope for the conjugate addition reaction

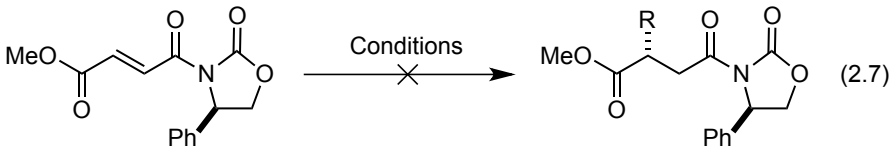


2.31 **2.32–2.38**

Entry	Product	RLi	Yield (%)	dr
A	**2.32**	MeLi	89	19:1
B	**2.33**	EtLi	72	19:1
C	**2.34**	*n*-BuLi	83	19:1
D	**2.35**	PhLi	82	19:1
E	**2.36**	*t*-BuLi	NR	—
F	**2.37**	vinyl lithium	NR	—
G	**2.38**	lithium pheylacetylide	NR	—

Next, we turned our attention to switching the diastereofacial delivery of the nucleophile in order to access succinates derived from the other diastereomer, but these efforts were unsuccessful (Equation 2.7). Simply removing the TMSI from the reaction with either Grignard reagents or alkyllithium species in a number of solvents provided no desired product. Chelating Lewis acids, $ZnCl_2$, and $MgBr_2$ were also ineffective. Even the more reactive Gillman reagent (Me_2CuLi) failed to deliver the desired product. Finally, it was suggested that monobutylcuprate might aggregate less than the corresponding monomethylcuprate, thus leading to increased reactivity; however, no improvement was observed using these conditions. Most of these attempts returned starting material;

decomposition, including some 1,2-addition, was seen upon warming or with the more reactive reagents.



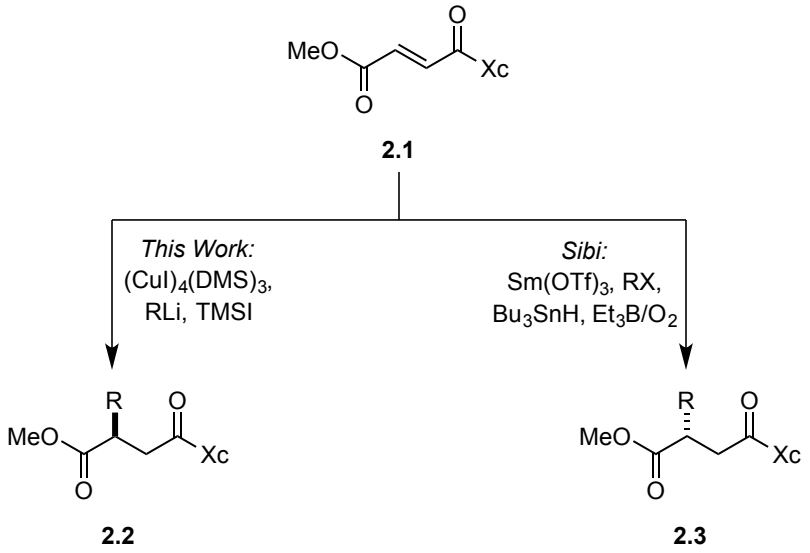
(2.7)

2.31

2.39 (R = Me)
2.40 (R = Bu)

Conditions
$(CuI)_4(DMS)_3$, MeMgBr, Et_2O
$(CuI)_4(DMS)_3$, MeMgBr, THF
$(CuI)_4(DMS)_3$, , MeLi, THF
$(CuI)_4(DMS)_3$, MeLi, CH_2Cl_2
$(CuI)_4(DMS)_3$, MeLi, $MgBr_2$, THF
$(CuI)_4(DMS)_3$, MeLi, $ZnCl_2$
Me_2CuLi, THF
$(CuI)_4(DMS)_3$, *n*-BuLi, THF
$(CuI)_4(DMS)_3$, *n*-BuLi, Et_2O
$(CuI)_4(DMS)_3$, *n*-BuLi, TMSCl, THF

Although we were unable to reverse the diastereoselectivity of the conjugate additions to **2.31** by changing the reaction conditions, these experiments did, for the first time, establish the feasibility of effecting highly regio- and stereoselective additions of monoorganocuprates to a chiral fumarate. Because this method thus complements the radical conjugate addition reactions developed by Sibi,[39] it is now possible to enable selective access to the substituted succinates **2.2** and **2.3** from a single fumarate **2.1** (X_c = Evans's oxazolidinone) (Scheme 2.3). Despite the failure to realize our original goal, a number of biologically active targets are potentially accessible using this new methodology, so we turned to the task of proof-of-principle studies.

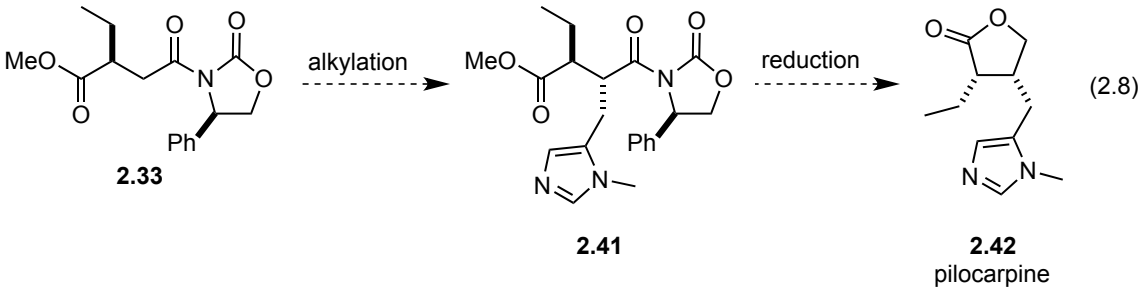


Scheme 2.3 Divergent access to diastereomeric succinates from a single chiral fumarate

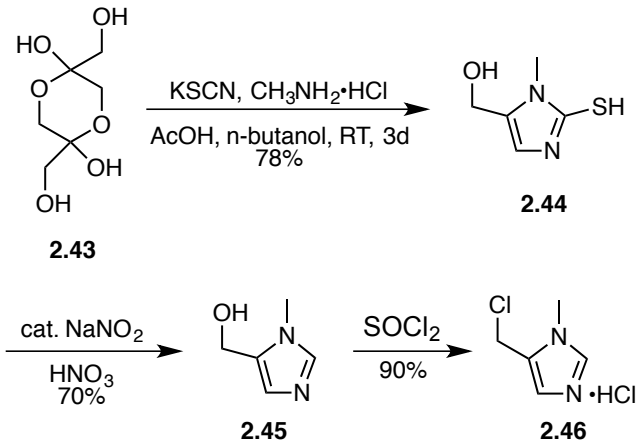
2.3 ATTEMPTED SYNTHESIS OF (+)-PILOCARPINE

2.3.1 Initial Strategy for the Synthesis of (+)-Pilocarpine

Having identified conditions for enantioselective conjugate addition developed, only two steps from **2.33** would be required prepare the glaucoma drug pilocarpine (**2.42**). We imagined that alkylation of succinate **2.23** with the **2.46** would provide **2.41** (Equation 2.8). Finally, selective reduction of the imide moiety followed by lactonization could provide pilocarpine (**2.42**) in four steps from commercially available material; this would represent the shortest synthesis of **2.42** to date.

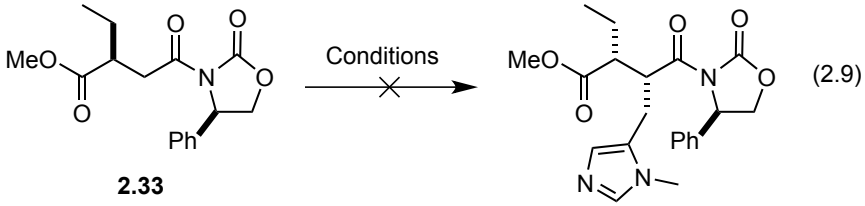


Although imidazole **2.46** is commercially available, it is fairly expensive, but it is readily available in three steps (Scheme 2.4).[114] Namely, reaction of dihydroxyacetone dimer (**2.43**) with potassium thiocyanate and methylamine provides **2.44** in 78% yield. Cleavage of the thiol with catalytic sodium nitrite in nitric acid produces **2.45** in 70% yield, and reaction of the resulting product in neat thionyl chloride provides the desired compound **2.46** as the hydrochloride salt. With chloride **2.46** in hand, the alkylation of **2.33** could be explored.



Scheme 2.4 Synthesis of electrophile **2.46**

Halide **2.46** is known to undergo alkylation with softer nucleophiles such as anilines and malonates,[86,87,115] but nothing has been reported about its reactivity with harder enolates. Unfortunately, despite extensive experiments involving freebasing **2.46**, enolization of **2.33**, solvents, additives, and temperatures, we were unable to find conditions that provided any more than a trace amount of **2.41**. The recalcitrant nature of enolates related to those derived from **2.33** was previous noted by Evans, who found that only more reactive alkylating agents such as methyl iodide, allyl bromide, and benzyl bromide provided alkylated products in good yields.[17,116] Thus, we turned our attention to an alternate route to pilocarpine (**2.42**).

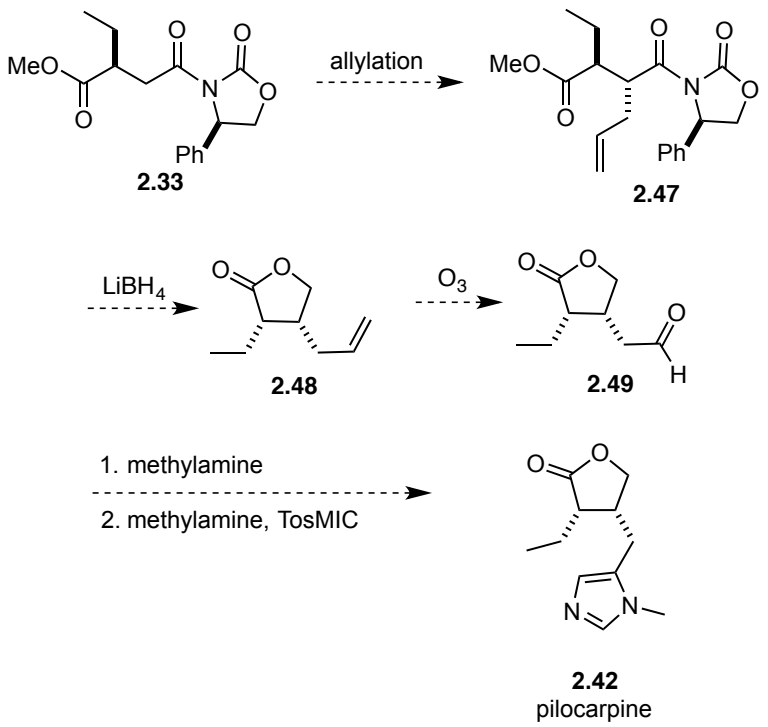


2.33 **2.41** (2.9)

Conditions
Freebase **2.46**: K_2CO_3, NaH, LDA
Enolize **2.33**: LDA, NaHMDS, LiHMDS, NaH, Hünig's/$TiCl_4$
Solvent: THF, CH_2Cl_2
Additives: HMPA, TBAI
Temperature: –78 °C, 0 °C, rt

2.3.2 Revised Strategy for the Synthesis of (+)-Pilocarpine

The revised strategy to access pilocarpine relied on utilizing a more reactive allyl electrophile to provide **2.47** from **2.33** (Scheme 2.42). Selective reduction of the imide moiety would provide lactone **2.48**, which might be converted by oxidative cleavage to lactone **2.49**, an intermediate in Büchi's synthesis of pilocarpine.[85] Finally, van Leusen imidazole synthesis, as demonstrated by Büchi, would complete the synthesis.

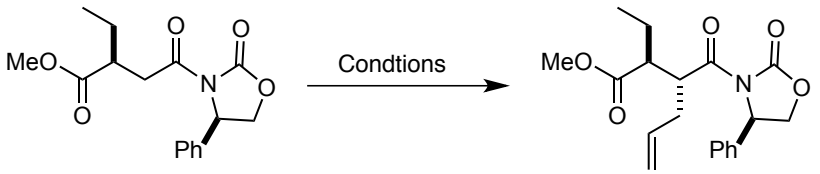


Scheme 2.5 Revised strategy for the synthesis of pilocarpine (**2.42**)

Unfortunately, our initial attempts involving deprotonation of **2.33** with either lithium hexamethyl disilazide (LiHMDS) or sodium hexamethyl disilazide (NaHMDS) were unsuccessful, giving only trace amounts of **2.47**. Imagining that aggregation of the enolate might be plaguing the reactivity, we added hexamethylphosphoramide (HMPA) after the deprotonation, but achieved the same results. Because deuterium quenching studies using similar conditions suggested we were not forming the enolate, thus we added HMPA prior to the deprotonation. Fortunately, this resulted in a 36% yield of the desired product. However, we were unable to optimize this yield by raising the temperature, increasing equivalents of allyl iodide, or increasing the concentration.

Finally, we imagined that the use of a Lewis acid ($MnCl_2$•2LiCl) in the enolization step could lead to increased product formation; however, we received **2.47** in only 20% yield. With **2.47** in hand, we moved forward to the selective reduction of the imide moiety.

Table 2.2 Allylation of **2.33**

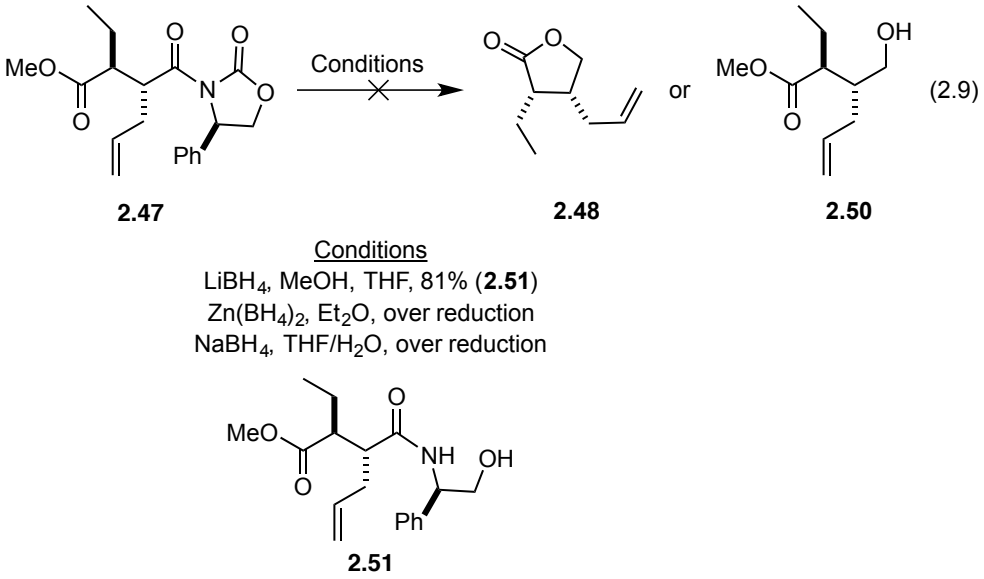


2.33 **2.47**

Entry[a]	Base	Additive	Yield (%)
A	NaHMDS	—	trace
B	LiHMDS	—	trace
C	LiHMDS	HMPA[b]	trace
D	LiHMDS	HMPA[c]	36%
E	LiHMDS	$MnCl_2$•2LiCl	20%

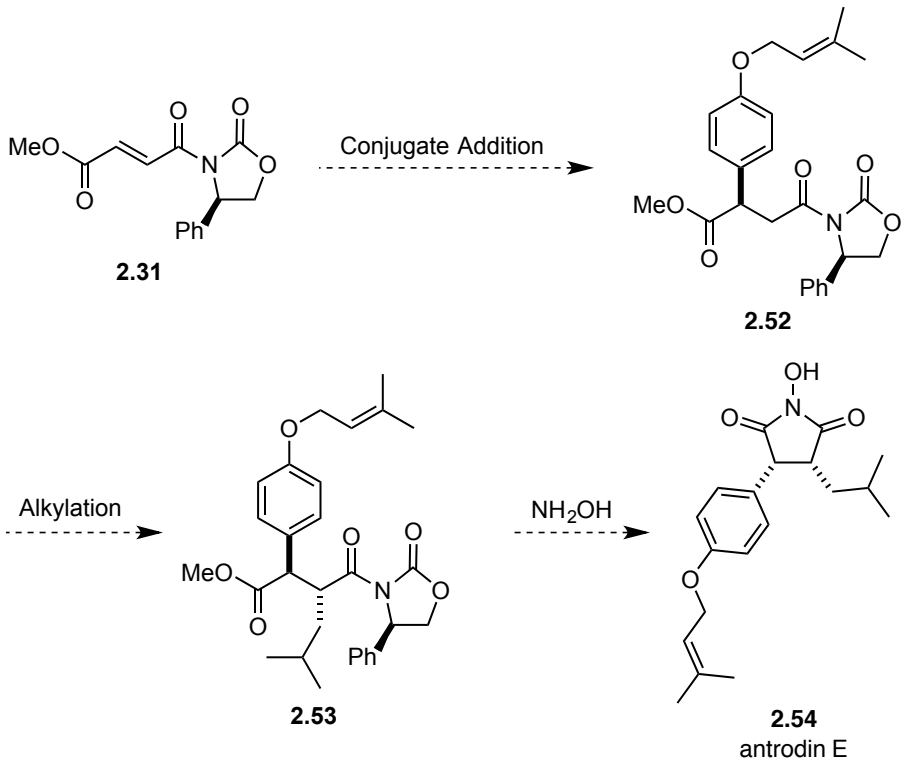
a) Reactions performed in THF using allyl iodide b) HMPA added after deprotonation c) HMPA added prior to deprotonation

Despite our best efforts and in contrast to literature precedent,[117,118] reduction of **2.47** with $LiBH_4$ in THF/MeOH gave the ring-opened product **2.51** instead of the expected lactone **2.48** or alcohol **2.50**. Although a number of other condition have been reported to selectively reduce succinates related to **2.47**,[89,119,120] standard condition involving $Zn(BH_4)_2$ in THF and $NaBH_4$ in MeOH/H_2O either led to no reduction or over-reduction. Unfortunately, our inability to selectively reduce **2.47** to give **2.48** or **2.50** precluded our efforts to develop a short synthesis of pilocarpine (**2.42**). Thus, we turned our focus to alternate succinate-derived natural products.



2.4 Attempted Synthesis of Antrodin E

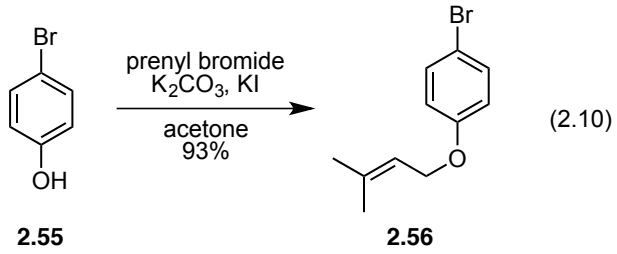
We envisioned that chiral succinimides, such as antrodin E (**2.54**), could also be accessed via our methodology. The symmetrical nature of the imide moiety would thereby obviate the need for selectivity, which had beset us previously in the attempted synthesis of pilocarpine (**2.42**). The synthesis would commence from chiral fumarate **2.31**, which we imagined would undergo a conjugate addition reaction to provide succinate **2.52** (Scheme 2.6). Alkylation of **2.52** would lead to disubstituted succinic acid derivative **2.53**, which upon cyclization with hydroxylamine would deliver antrodin E (**2.54**) in four steps.



Scheme 2.6 Strategy for the synthesis of antrodin E (**2.54**)

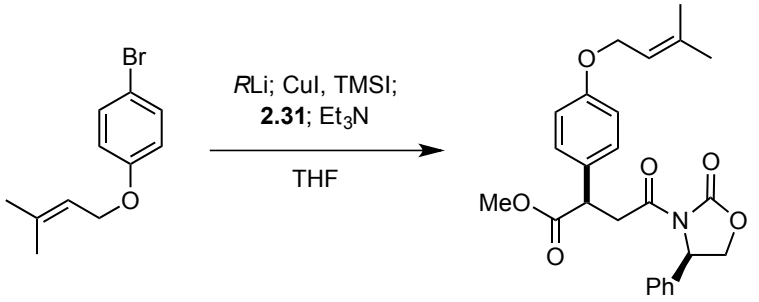
This route required a yet untested conjugate addition using a substituted aryl nucleophile derived from **2.56**. Known aryl bromide **2.56** was available in one step from 4-bromophenol (**2.55**) in 93% yield (Equation 2.10). After subjecting the aryl bromide **2.56** to lithium halogen exchange with *n*-butyllithium, we found that the monoarylcuprate added to fumarate **2.31** in 48% yield (Table 2.3, entry A). Imagining that the low yield might be do to alkylation or elimination between the aryllithium and *n*-butyl bromide, we tried *t*-butyllithium for the exchange, but those conditions led entirely to decomposition (Table 2.3, entry B). We also used two equivalents of *n*-butyllithium to solve this potential problem, but this led to recovery of the product of 1,4-addition of the butyl group to **2.31** (Table 2.3, entry C). Finally, use of TMEDA to facilitate lithium-halogen

exchange led to a mixture of aryl and butyl addition (Table 2.3, entry D). Ultimately, through deuterium and methyl iodide quenching of the resultant aryllithium species we found that lithium halogen exchange was complete. The reaction could not be improved by changing the equivalents or temperature, and it is still unclear what the cause of the surprising lack of reactivity could be.



2.55 **2.56** (2.10)

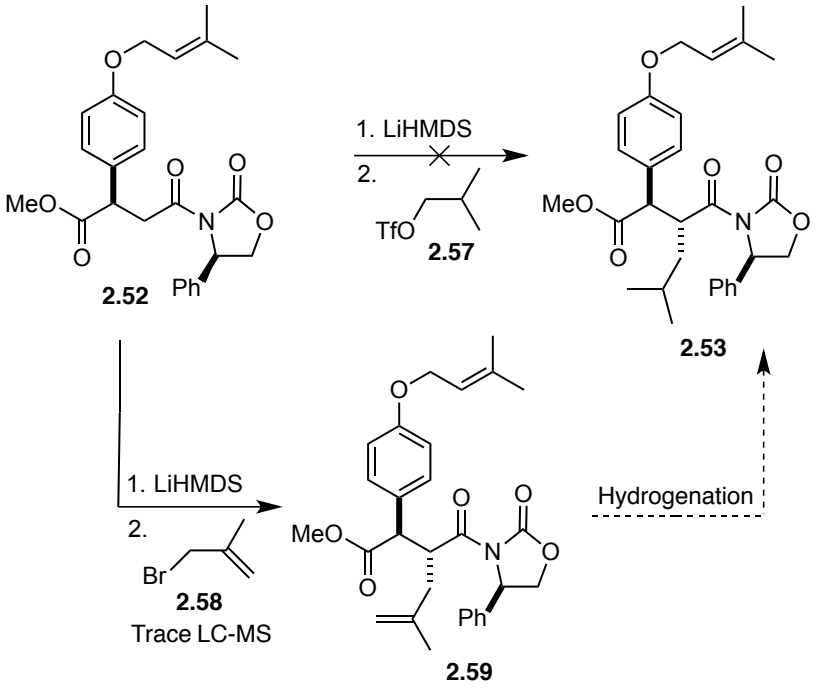
Table 2.3 Optimization of conjugate addition.



2.56 **2.52**

Entry	RLi	Additive	Results
A	*n*-BuLi (1.1 eq.)	—	48%
B	*t*-BuLi (2.1 eq.)	—	decomp.
C	*n*-BuLi (2.1 eq.)	—	Bu addition
D	*n*-BuLi (1.1 eq.)	TMEDA	Ar and Bu addition

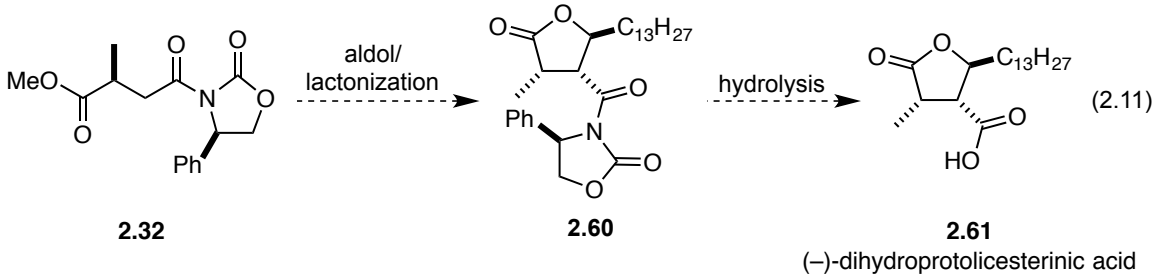
Next, we turned our attention to the alkylation of **2.52**. Although not unexpected, based upon the observed reactivity of the enolate of **2.33**, it was nevertheless disappointing that treating the enolate of **2.52** with isobutyl triflate (**2.57**) and 2-methallylbromide (**2.58**) under a variety of conditions failed to deliver **2.53**. Because alkylation of enolates of substituted succinates are challenging, it occurred to us to examine aldol reactions of such enolates as the products of these reactions also map onto a number of interesting natural products.



Scheme 2.7. Attempted alkylation of **2.52** towards antrodin E (**2.54**)

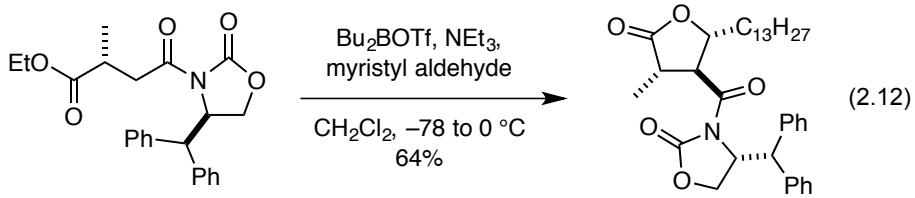
2.5 TOTAL SYNTHESIS OF (–)-DIHYDROPROTOLICHESTERINIC ACID

In order to explore the effectiveness of aldol reactions on substituted succinates, we pursued (–)-dihydroprotolichesterinic acid (**2.61**). With **2.32** in hand, an aldol reaction, which we imagined might proceed with concomitant lactonization, would provide **2.60** (Equation 2.11). Finally, hydrolysis of the auxiliary would provide the target molecule **2.61**. Unlike our previous attempts at natural product synthesis, which further exemplified the stubbornness of succinates like **2.32** in alkylation reactions, there was precedent for successful aldol reactions on these types of systems. Specifically, Sibi had used the related intermediate **2.62** in the synthesis of a rocellaric acid (Section 1.2.1.3), although it only provided a modest 64% yield of lactone **2.63** (Equation 2.12).[37]



2.32 **2.60** **2.61**
(–)-dihydroprotolicesterinic acid

(2.11)

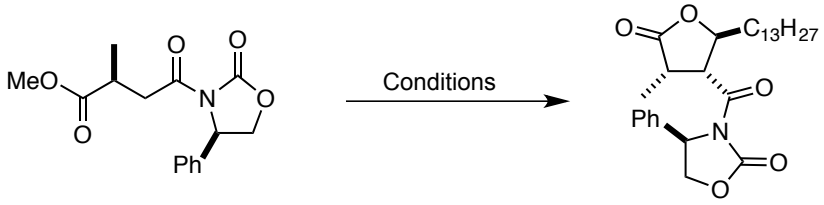


2.62 **2.63**

(2.12)

We were disappointed to find that when **2.32** was subjected to the reaction conditions we recovered only 24% of the desired product **2.60** along with returned starting material (Table 2.4, entry A). We began our optimization attempts by concentrating the reaction and switching to Hünig's base,[8] which provided the desired lactone in 36% yield (Table 2.4, entry B). Increasing the equivalents of aldehyde, changing the Lewis acid, and changing the base did not improve the reaction (Table 2.4, entries C, D, E, and F). We then began incrementally increasing the concentration (Table 2.4, entries F, G, H, and I), finding 0.9 M to be the optimum concentration, delivering lactone **2.60** in 54% yield (95% based on recovered starting material. Finally, we tested to see if order of addition had any effect on the yield, but the yield was left unchanged (Table 2.4, entry J).

Table 2.4 Optimization of aldol/lactonization reaction of **2.60**



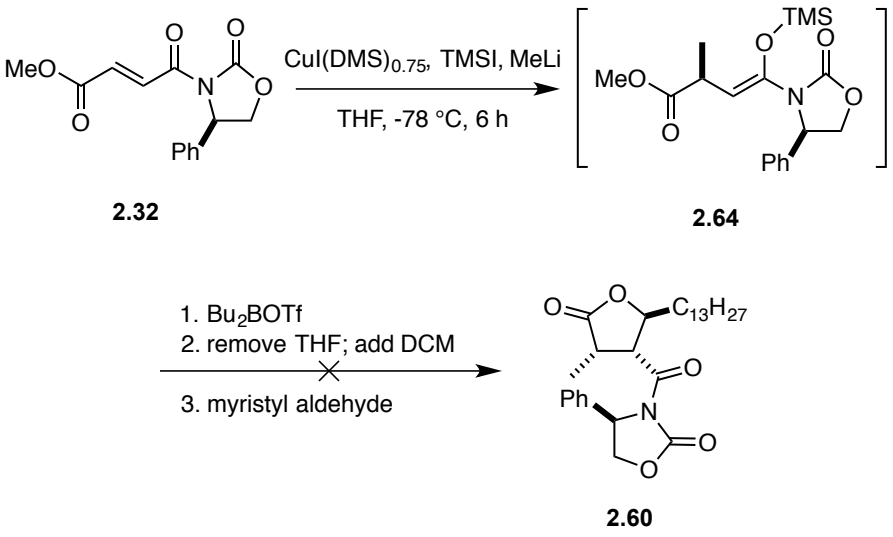
2.32 **2.60**

Entry[a]	Aldehyde	L.A. (eq.)	Base (eq.)	Conc. (M)	Result[b]
A	1.2	Bu_2BOTf (1.2)	TEA (1.4)	< 0.1	24%
B	1.2	Bu_2BOTf (1.2)	DIPEA (1.4)	0.3	36%
C	3	Bu_2BOTf (1.2)	DIPEA (1.4)	0.3	38%
D	3	$TiCl_4$ (1.2)	DIPEA (1.4)	0.3	26%
E	3	Bu_2BOTf (1.2)	*t*-Bu_2Pyr (1.2)	0.3	Trace
F	3	Bu_2BOTf (1.2)	DBU (1.2)	0.3	NR
G	1.2	Bu_2BOTf (1.2)	DIPEA (1.4)	0.45	38%
H	1.2	Bu_2BOTf (2)	DIPEA (2.1)	0.45	44%
I	1.2	Bu_2BOTf (1.2)	DIPEA (1.4)	0.9	54%
J[c]	1.2	Bu_2BOTf (1.2)	DIPEA (1.4)	0.9	52%

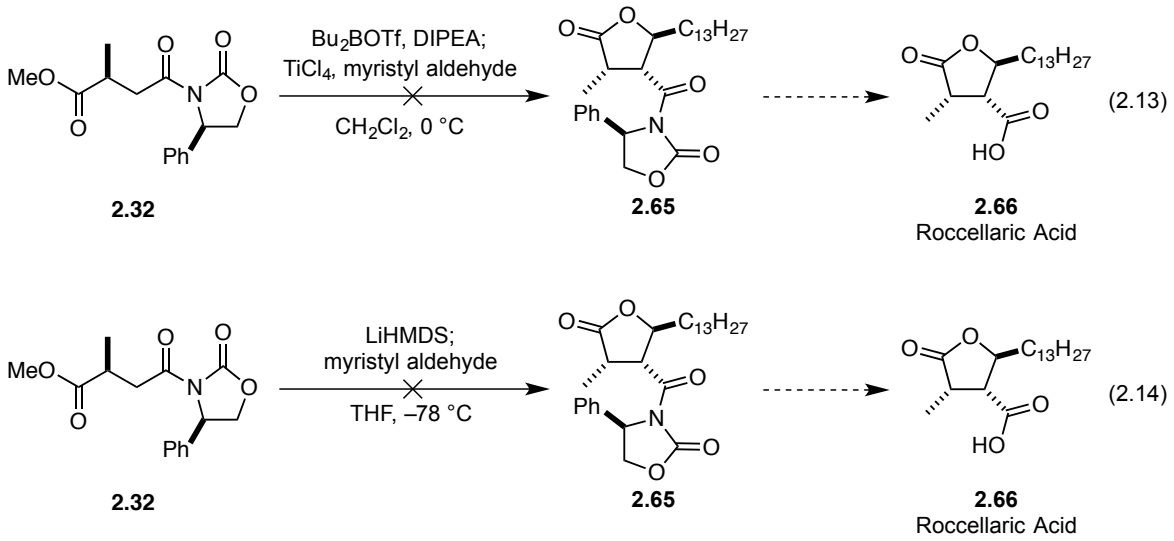
a) Reactions performed in CH_2Cl_2 at 0 °C for 15 h. b) Yield based on isolated material after column chromatography. c) Inverse addition (enolate into solution of aldehyde)

In an effort to reduce the step count, we attempted to perform a one-pot conjugate addition/aldol/lactonization reaction. Indeed, Kuwajima,[121] Wada,[122] and Evans[123] have reported the transmetallation of silyl enol ethers with di-*n*-butylboron triflate, wherein treatment of adduct **2.64** with di-*n*-butyl boron triflate prior to introduction myristyl aldehyde should lead to **2.60** (Scheme 2.8). Unfortunately, these conditions were unsuccessful in our hands. Additional effort was placed into further diverging our route to

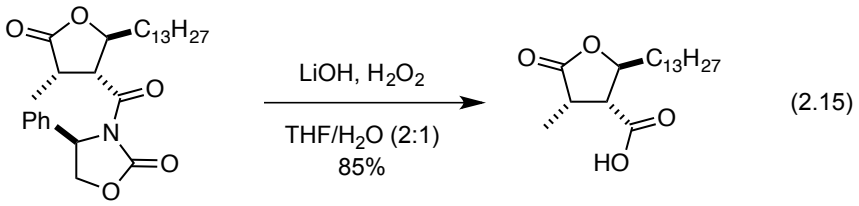
multiple diastereomers of the lactones. Heathcock has reported that pre-complexation of the aldehydes with titanium tetrachloride results in non-Evans syn aldol products,[124] but these results did not produce any desired product (Equation 2.13). Alternatively, the lithium enolates of substituted succinates like **2.32** have also been shown to give rise to non-Evans syn aldol products,[10] however we once again met failure in our attempts (Equation 2.14).



Scheme 2.8 Attempted one-pot conjugate addition/aldol/lactonization of **2.32**



Cleavage of the auxiliary from **2.60** under standard conditions[39] proceeded unremarkably to provide (–)-dihydroprotolichesterinic acid (**2.61**) in 85% yield. The rotation and melting point of **2.61** matched that reported in the literature,[96] but while similar, the ^{1}H and ^{13}C spectra exhibited discrepancies (between both our spectra and literature as well as between the reports in the literature). We presume that this is due to concentration differences between the samples, which leads to slight shifts due to hydrogen bonding between the compounds. While performing the experiment in MeOD could solve this problem, there was no published spectrum with which to compare. Thus, the structure of compound **2.61** was unambiguously determined via X-ray crystallography.[125] We thus completed the total synthesis of (–)-DHPLA (**2.61**) in four steps with a 31% overall yield (56% based on recovered starting material).



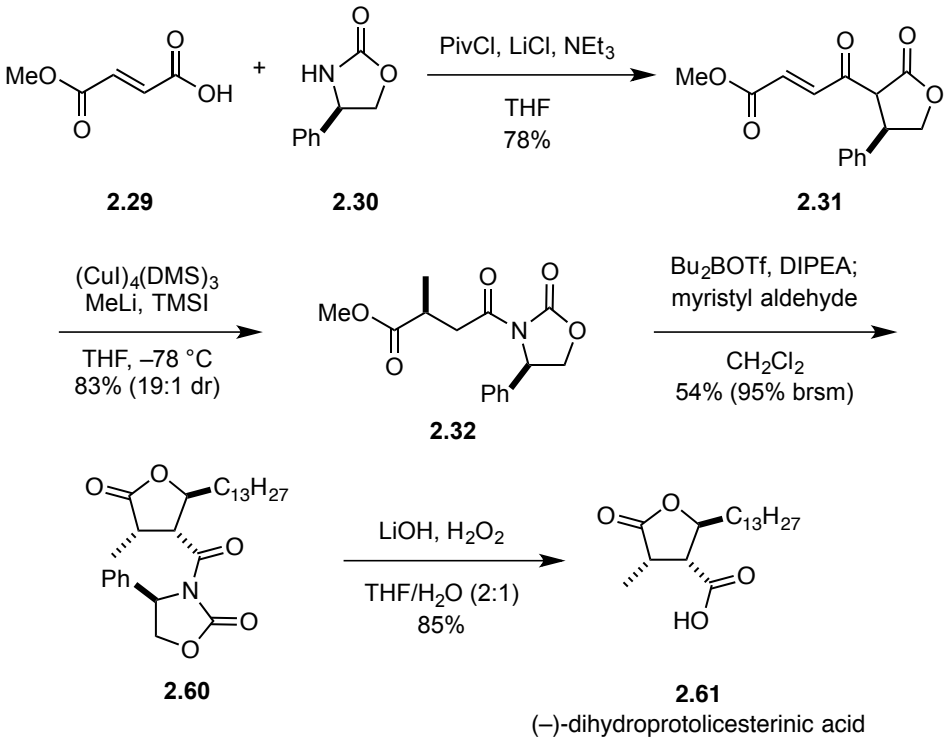
2.60

2.61
(–)-dihydroprotolicesterinic acid

(2.15)

5.6 SUMMARY

Through the extension of the Bergdahl protocol to chiral fumarates, we realized the first conjugate addition of a monoorganocuprate to a chiral fumarate.[126,127] Unfortunately, we were unable to achieve the goal of switching the diastereoselectivity of this transformation. However, in conjunction with the radical conjugate developed by Sibi,[39] it is now possible to diverge a single chiral fumarate to both possible diastereomers. Our applications of this protocal towards the synthesis of pilocarpine and antrodin E ultimately ended in failure, due to the difficulty in both alkylating these substituted succinates as well as in selectively reducing the imide moiety. However, synthesis of (–)-dihydroprotolichesterinic acid via an aldol reaction resulted in the shortest total synthesis of the molecule to date at four steps and a 31% overall yield (56% based on recovered starting material).



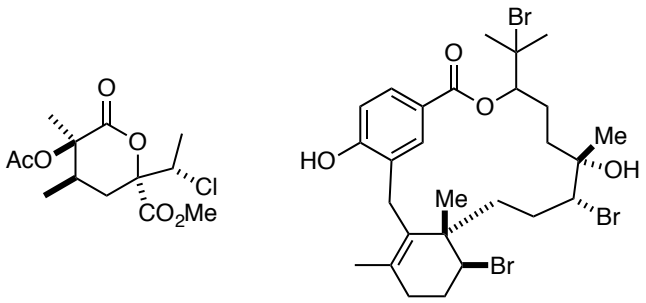
Scheme 2.9 The total synthesis of (–)-dihydroprotolichesterinic acid (**2.61**)

DEVELOPMENT OF ENANTIOSELECTIVE HALOCYCLIZATION REACTIONS

Chapter 3: Catalytic Enantioselective Halocyclization Reactions

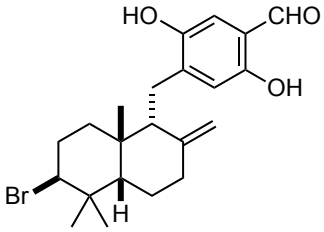
3.1 INTRODUCTION

Halogenated natural products like liguhodgcin A (**3.1**),[128] bromophycolide A (**3.2**),[129] peyssonal A (**3.3**),[130] and pannosallene (**3.4**)[131] have inspired the burgeoning field focusing on the development of enantioselective halocyclization reactions (Figure 3.1).[132-137] To date, halolactonizations (Y = O, Z = OH),[138-174] haloetherifications (Y = O, Z = H-$_2$),[175-184] and haloaminocyclizations (Y = NHR, Z = H_2)[185-192] have been extensively explored (Equation 3.1). Less explored areas include oxazolidinone formation,[193,194] oxazoline formation,[195-198] and cyclization of oximes.[199] Additionally, catalytic enantioselective halo-polyene cyclization reactions (Equation 3.2), arguably the holy grail of the field, have yet to be realized. However, towards this end, Ishihara has reported an enantioselective halo-polyene cyclization using a stoichiometric reagent, and Denmark has demonstrated a catalytic enantioselective sulfonium-induced carbocyclization reaction on simple systems.[200-203]

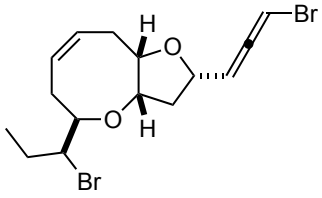


3.1
liguhodgcin A

3.2
bromophycolide A

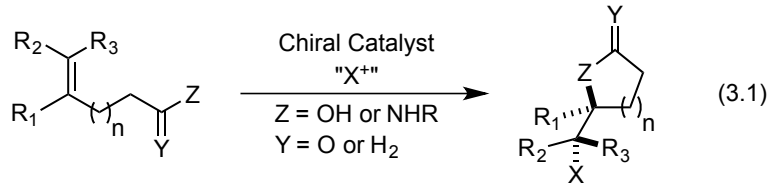


3.3
peyssonol A

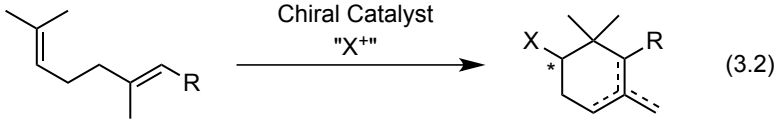


3.4
pannosallene

Figure 3.1 Select examples of halogenated natural products



3.5 **3.6** (3.1)



3.7 **3.8** (3.2)

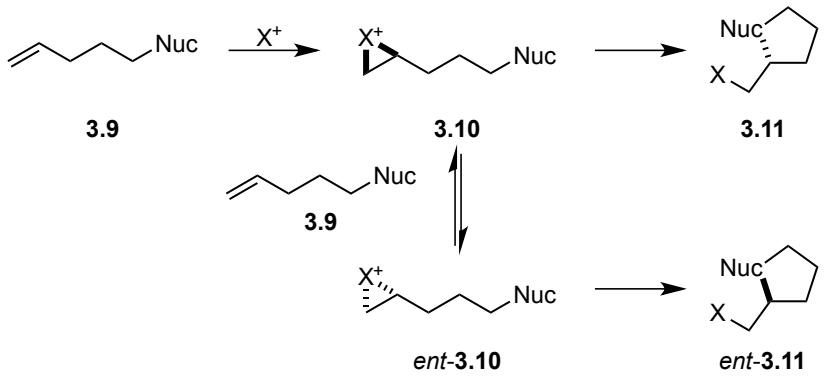
While a number of catalysts have been disclosed, a general halocyclization catalyst (i.e. one that can promote every halonium-induced cyclization) has yet to be reported. In fact, no catalyst reported thus far has been able to effect the cyclization of every substrate within a class of halocyclization (e.g. halolactonization). For example, most catalysts have a very limited substrate scope with respect to substitution on the olefins, which leads to the need for a different catalyst for each type of substrate within the class of reaction (e.g. lactonization and etherification). Furthermore, these reactions are typically specific to a given halogen, which necessitates a different catalyst for each halogen subtype (iodo-, bromo-, chloro-, or fluoro-) of the reactions. All of these reactions are mechanistically similar, involving the capture of a halonium by a nucleophile, so in principle a single catalyst should be able to promote all of these reactions; nevertheless, this ideal has yet to be achieved. In order to provide focused context and comparison for our work in this field, only the general challenges in developing halocyclization reactions and an evolutionary account of halolactonization reaction development will be discussed.

3.2 Challenges in Developing Enantioselective Halocyclizations

3.2.1 Olefin-Olefin Transfer of Halonium Ions

One potential problem inherent in the development of enantioselective halocyclization reactions involves the transfer of halonium ions between olefins (Scheme 3.1). Brown discovered that bromonium and iodonium ions transfer between olefins at cryogenic temperatures.[204-206] In the context of halocyclization reactions, if olefin **3.9** is treated with a halogenating reagent to selectively provide intermediate **3.10**, an additional

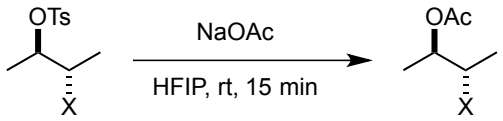
equivalent of **3.9** can react with **3.10** to form the enantiomeric intermediate *ent*-**3.10**. This will result in an erosion of enantioselectivity.



Scheme 3.1 Transfer of halonium ions between olefins

In order to probe the configurational stability of halonium ions, Denmark and co-workers measured the enantiospecifity of the reaction of **3.12** with sodium acetate to give **3.13**.[132,207] As seen in Table 3.1 entry A, displacement of the tosylate in **3.12** with sodium acetate was completely enantiospecific. However, in the presence of dodecene, the enantiospecifity was only 28% (Table 3.1, entry B). On the other hand, the chloronium examples were completely stereospecific even in the presence of dodecene (Table 3.1, entries C and D). It was postulated that this was most likely due to the electronegativity of chlorine versus bromine. Specifically, the chlorine atom is less able to stabilize the building positive charge in the transition state (**3.18** to *ent*-**3.18**) thereby attenuating the propensity of the chloronium to transfer between olefins. Moreover, the complete stereospecificity of this reaction was perplexing as carbocationic, rather than chloronium-like intermediates, are thought to exist in these processes, which in theory should lead to decreased enantiospecificity in cases with and without dodecene (*vide infra*).

Table 3.1 Configurational stability of halonium ions

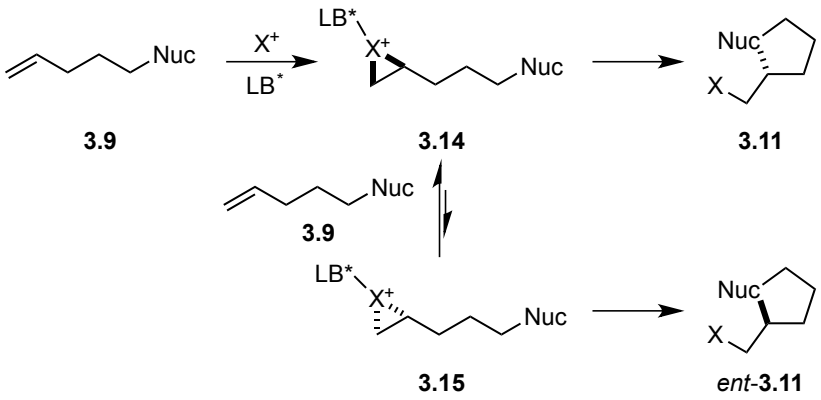


3.12 **3.13**

Entry	X	Additive (1 equiv.)	es[a]
A	Br	—	100%
B	Br	E-6-dodecene	28%
C	Cl	—	100%
D	Cl	E-6-dodecene	100%

a) $es = (ee_{product}/ee_{s.m.})\bullet 100$

In order to mediate this detrimental side reaction, Denmark hypothesized that the epimerization via olefin-olefin transfer of halonium ions would be reduced if the two halonium ions were diastereomeric rather than enantiomeric.[208] If a chiral Lewis base was included in the reaction, upon coordination to the halonium ions two diastereomeric intermediates **3.14** and **3.15** would be produced (Scheme 3.2). This should skew the equilibrium and funnel the two diastereomeric intermediates through the lower energy pathway, leading to enantioenrichment.

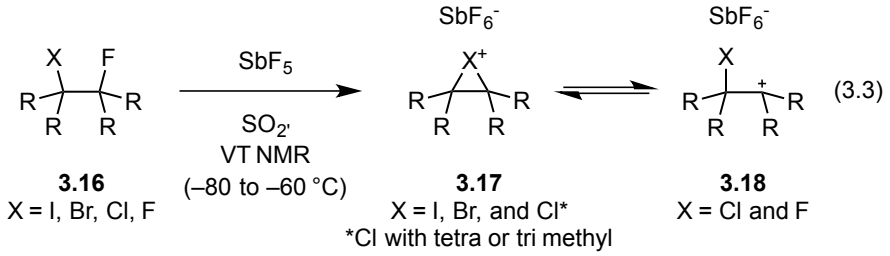


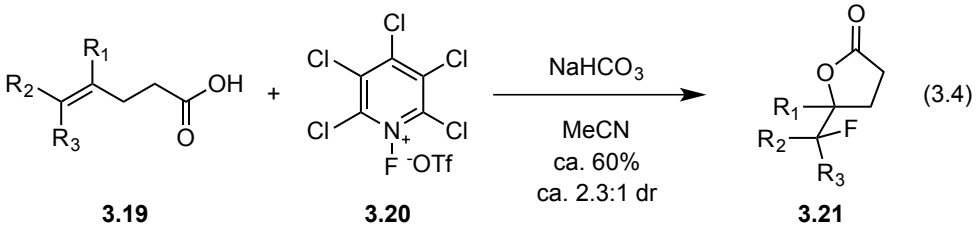
Scheme 3.2 Mediation of olefin-olefin epimerization

3.2.2 Stereoselectivity via Stereoselective Halonium Formation

Another problem that might arise during chloro- and fluorolactonization reactions is poor stereoselectivity due to carbocation rather than halonium character in the transition state.[132] When studying the stability of halonium ions using **3.16** and SbF_5 at low temperature, Olah found that all bromo- and iodo-substituted substrates **3.16** (X = Br or I) existed as the halonium ion **3.17** (Equation 3.3).[209-211] On the other hand, chloro- (with the exception of tri- and tetra-substituted substrates) and fluoro-substituted substrates **3.16** (X = Cl or F) existed as the cationic species **3.18**. This is potentially detrimental to the stereoselectivity of the halocyclizations, as demonstrated in fluorolactonization reactions. When various olefinic acids **3.19** were treated with **3.20**, the product lactones **3.21** were formed in 2.3:1 dr (Equation 3.4).[212,213] This was most likely due to the cationic intermediate providing little steric differentiation between either face of the cation, whereas the nucleophile would attack from the opposite face of a fully formed halonium ions leading to excellent diastereoselectivity. This cationic character also has interesting effects in chlorolactonization reactions as demonstrated by Borhan (*vide infra*).[144] Despite these potential hurdles that could inhibit effective enantioselective

halocyclization reactions, the field has flourished with a number of reagents and catalysts capable of delivering enantioenriched halocyclization products.

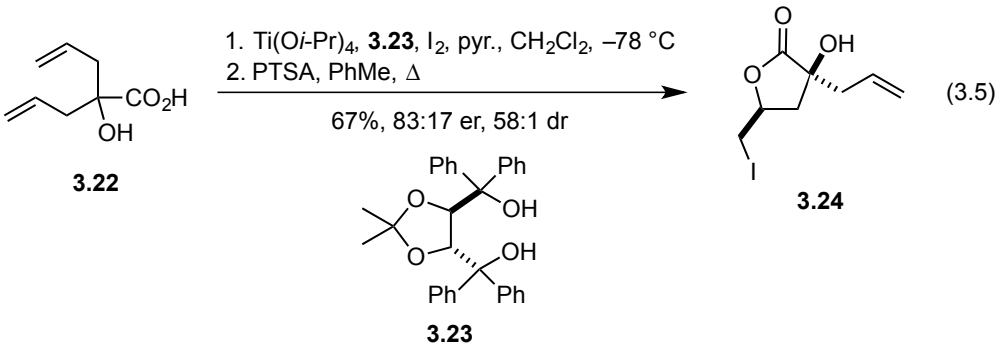




3.3 REAGENT CONTROLLED HALOLACTONIZATION (1992-2009)

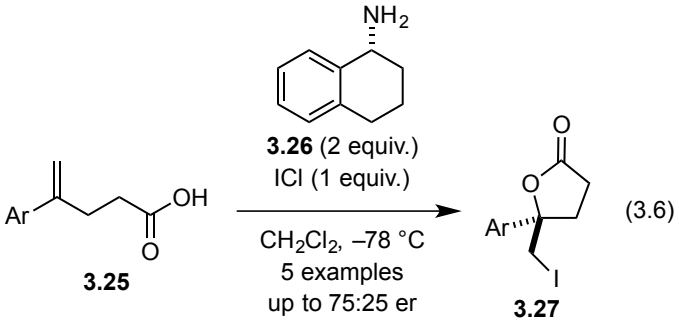
3.3.1 Stoichiometric Enantioselective Halolactonization Reactions

Taguchi reported the first enantioselective halolactonization reaction in 1992.[214] In the event, prochiral diene **3.22** underwent lactonization to provide **3.24** in 67% yield with an 83:17 er in the presence of iodine, titanium isopropoxide, and ligand **3.23** (Equation 3.5). Some of the lactone **3.24** suffered ring opening during the course of the reaction by isopropoxide, thus an acid catalyzed lactonization was necessary to increase the yield. Although this report went unnoticed for almost 10 years, this reaction represented the first time a reagent was used to induce chirality in a halolactonization reaction and laid the initial foundation for future work in the field.



(3.5)

In 2000, Brown attempted to use a chiral amine to induce enantioselectivity in a bromolactonization reaction but was unsuccessful.[215] However, two years later Wirth found success with amine **3.26** as a stoichiometric source of chirality.[139,140] In particular, he showed that aryl substituted olefinic acids **3.25** underwent iodolactonization in the presence of **3.26** and ICl to provide lactones **3.27** with moderate enantioselectivity (Equation 3.6). In 2007, Rousseau found a similar chiral amine could be used for the same transformation.[216]

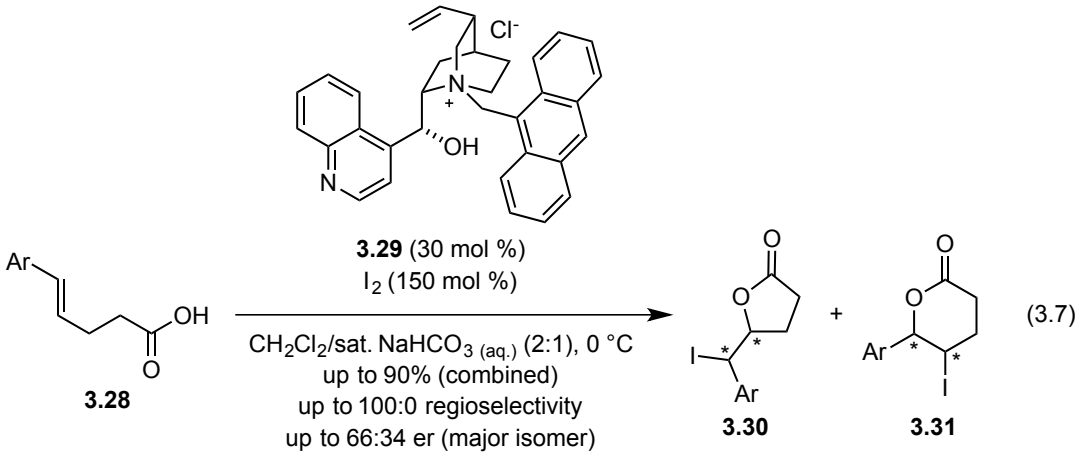


(3.6)

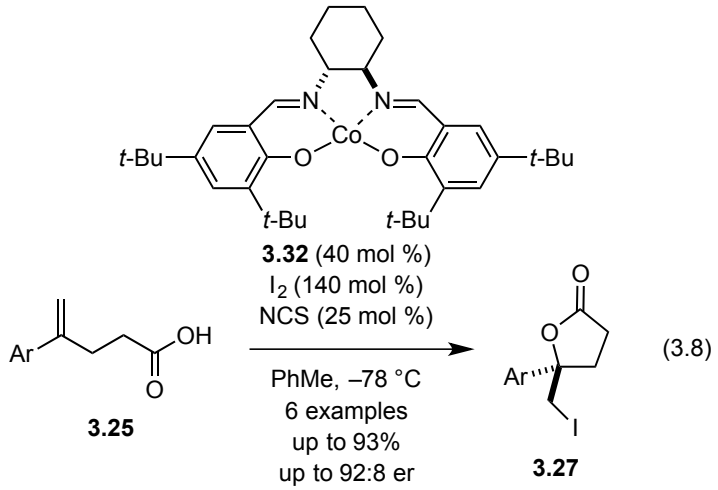
3.3.2 Seminal Catalytic Enantioselective Halolactonization Reactions

It did not take long after the first stoichiometric amine-based reagent was disclosed for the first catalytic, enantioselective reaction to surface. While Gao initially disclosed **3.29** as a stoichiometric reagent for iodolactonization reactions,[142] he quickly

learned that it could be used in substoichiometric quantitites.[217] 1,2-*Trans*-aryl olefinic acids **3.28** were cyclized with iodine under phase transfer conditions using **3.29** to provide a mixture of endo- and exo-cyclized lactones **3.30** and **3.31** (Equation 3.7). While Guo was able to achieve excellent regioselectivity favoring the endo adduct **3.31** for a number of substrates, the enantioselectivity was poor (up to 66:34 er). Nevertheless, this transformation represented the first time a catalyst provided enantioenriched products via a halolactonization reaction.



In 2009, Gao demonstrated that chiral salen complex **3.32** effected the iodolactonization of the aryl olefinic acids **3.25** to provide iodolactones **3.27** with good yields and enantioselectivities (Equation 3.8). With this report, the use of a catalyst to provide synthetically useful enantioselectivities in a halolactonization reaction was finally demonstrated, and the race was on in the search for the ideal catalyst.



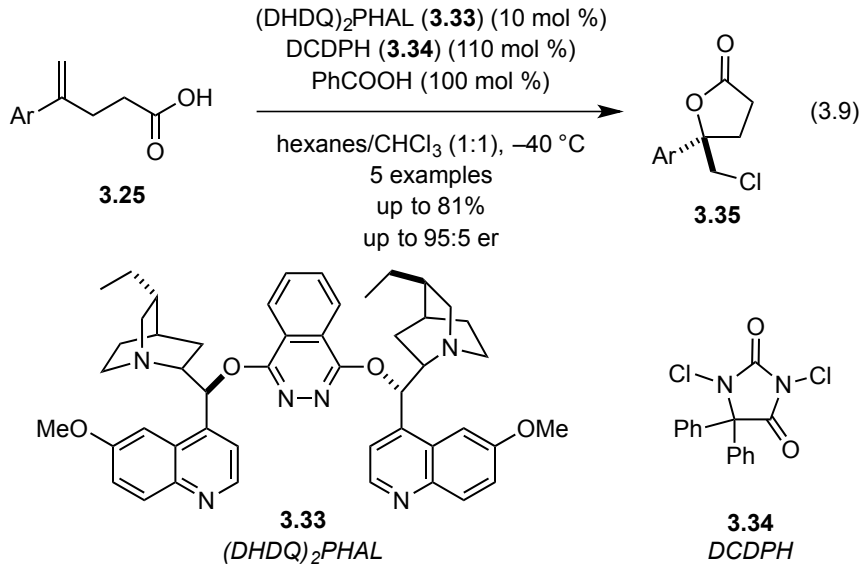
3.4 CATALYTIC HALOLACTONIZATION GOLD-RUSH (2010–PRESENT)

Once Gao had broken ground in the area, other groups quickly joined the effort. In 2010, a few additional reports appeared, but over the past five years, there has been an average of one publication a month in the field of catalytic enantioselective halolactonization reactions. This section will summarize these efforts and is organized by group in order of their entrance into the field.

3.4.1 Borhan

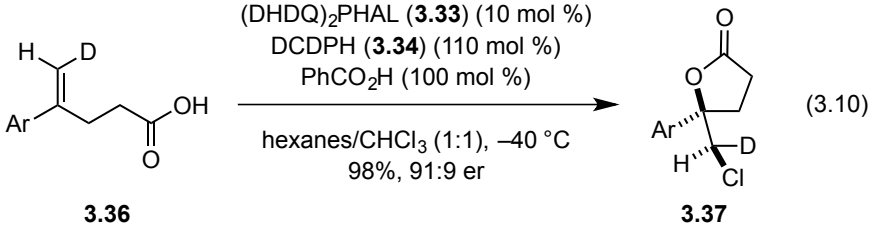
Borhan reported the first enantioselective chlorolactonization in 2010, wherein the benzoic acid salt of $(DHDQ)_2PHAL$ (**3.33**) effected the lactonization of 5-aryl-5-hexenoic acids **3.25** with good yields and enantioselectivities (Equation 3.9).[143] Yeung later reported that similar conditions could be used to perform selenolactonizations,[159] and Armstrong demonstrated that this catalyst can be used for a variety of bromolactonization reactions.[170] Unfortunately, like most catalysts, the scope of these reactions was limited. For example, the enantioselectivity decreased with increasing electron-donating groups on the aromatic ring. In separate reports, Borhan detailed the optimization of various

hydantoin chlorinating reagents and the development of a halonium affinity scale for the prediction of olefin reactivity with halonium ions.[218,219] Additional studies on bromolactonization reactions were performed using peptide based catalysts, but these were largely unsuccessful.[145]



Because experiments by Olah had demonstrated that carbocationic intermediates rather than chloronium ions exist in these types of transformations, Borhan investigated the diastereoselectivity of this reaction.[144] As their method did not generate a C-Cl bond at a stereogenic center, substrate **3.36** was prepared. Surprisingly, when deuterated substrate **3.36** was subjected to the reaction conditions, the syn-addition product was received (Equation 3.10). When the reaction was run without catalyst, *rac*-**3.37** was isolated as a mixture (1:0 of diastereomers. When run in the presence of quinuclidine, the product lactone was produced as a mixture (1:5, syn/anti) of diastereomers. Thus,

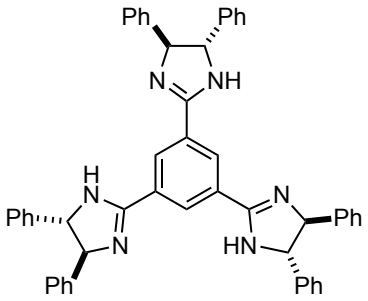
$(DHDQ)_2PHAL$ (**3.33**) must have controlled both the facial selectivity of the chloronium delivery as well as the facial selectivity of the carboxylate addition, rather than relying of the facial delivery of the chlorine to the alkene to determine the stereoselectivity.



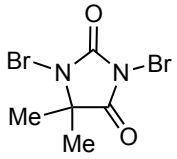
3.36 **3.37** (3.10)

3.4.2 Fujioka

Fujioka entered the field in 2010, with his C_3-symmetric tri-amidine catalyst **3.38**. Catalyst **3.38** in conjunction with DBDMH (**3.39**) induced 6-exo bromolactonizations on a number of geminally substituted 5-hexenoic acids **3.40** (Equation 3.11).[146] The reactions were generally high yielding with good enantioselectivities; however, the enantioselectivity decreased for alkyl (R = Cy) or electron-rich aromatic-substituted olefinic acids.

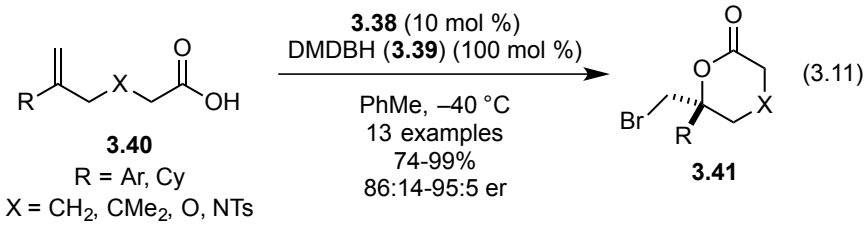


3.38

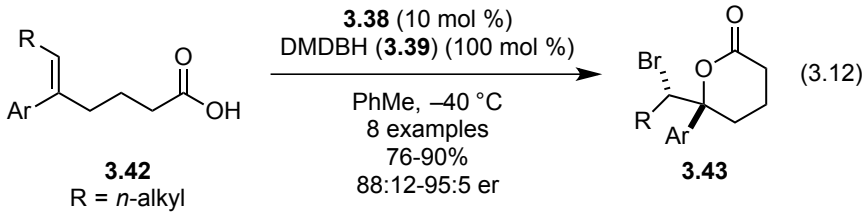


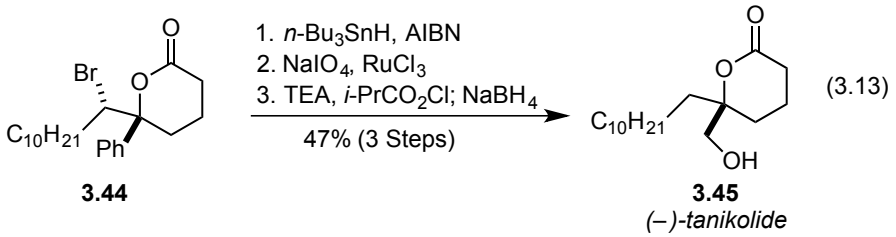
3.39
DBDMH

Figure 3.2 Fujioka's catalyst **3.38** and DBDMH



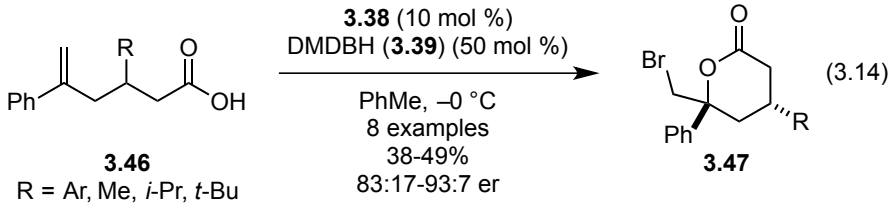
They later demonstrated that this catalyst **3.38** could promote similar 6-exo bromolactonizations on tri-substituted substrates **3.42** with good to excellent yields and enantioselectivities (Equation 3.12).[148] The utility of this method was demonstrated in a short total synthesis of the natural product (–)-tanikolide (**3.45**) from bromolactone **3.44** in 47% yield over three steps (Equation 3.13).





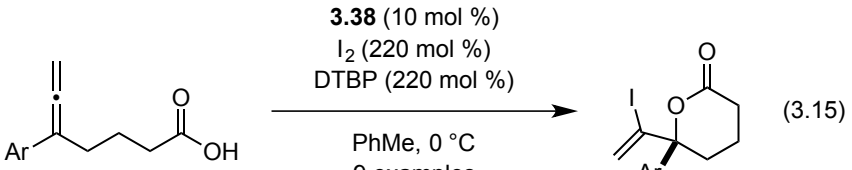
3.44 **3.45** *(–)-tanikolide* (3.13)

Additional experimentation revealed this catalyst to be suitable for the kinetic resolution of *rac*-3-substituted olefinic acids **3.46** with generally high enantioselectivities (Equation 3.14).[149] Furthermore, catalyst **3.38** could induce iodolactonizations of allenes **3.48** to provide chiral vinyl iodides **3.49** with moderate enantioselectivity (Equation 3.15).[147] Fujioka accomplished a variety of transformations using catalyst **3.38**, but all of these were limited to 6-exo lactonization pathways on aryl-substituted olefinic acids. The tri-substituted olefinic acids did, however, represent a very challenging substrate class that their catalyst managed to handle with ease.



3.46
R = Ar, Me, *i*-Pr, *t*-Bu

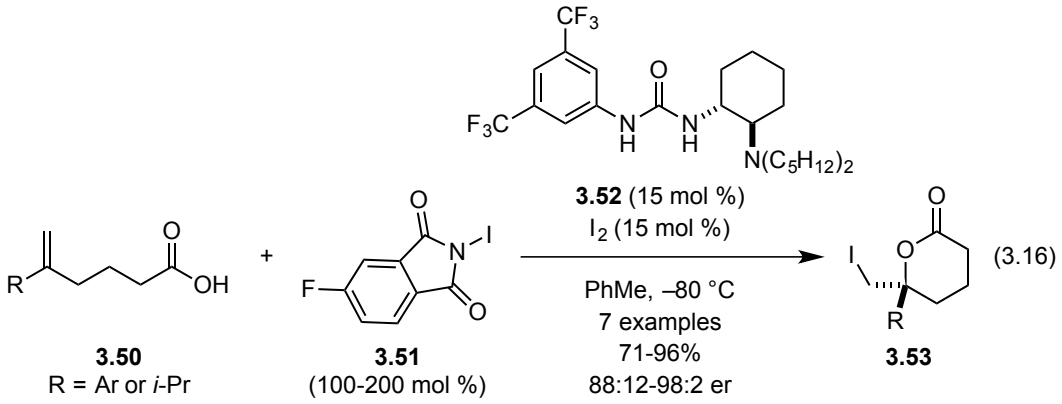
3.47 (3.14)



3.48 **3.49** (3.15)

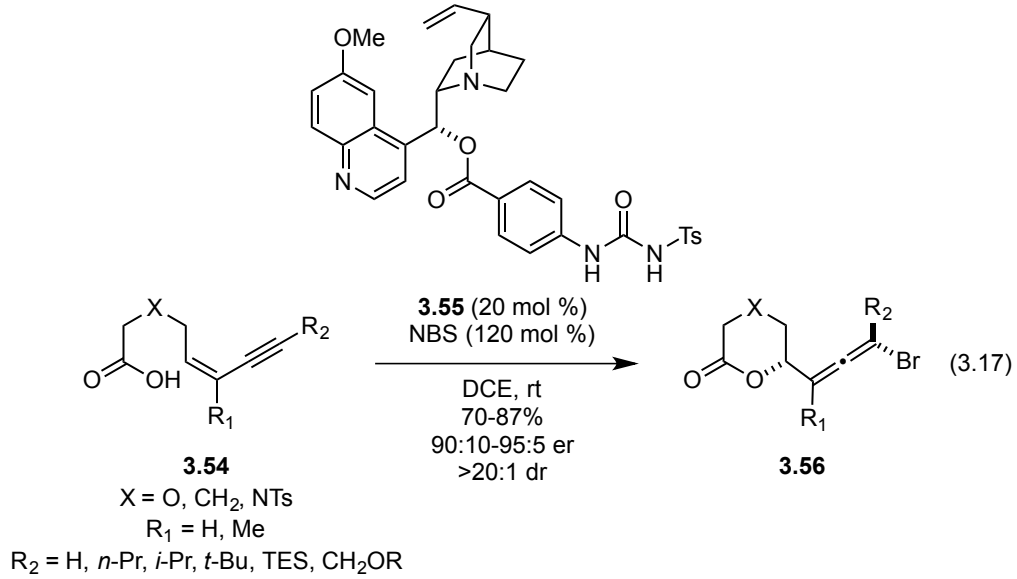
3.4.3 Jacobsen

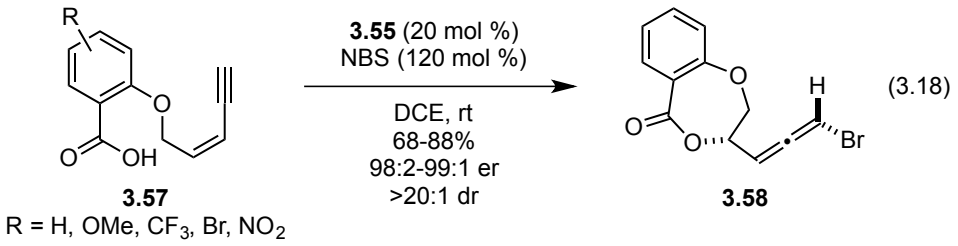
Jacobsen and co-workers showed that the amine/urea catalyst **3.52** effected highly enantioselective iodolactonization reactions on 5-aryl-5-hexenoic acids **3.50** to provide iodolactones **3.53** (Equation 3.16).[150] The substrate scope was the same as Fujioka's bromolactonization, and both saw decreased selectivities for electron-rich aryl- and alkyl-substituted olefinic acids. The most interesting observation from this report was that the inclusion of a catalytic amount of iodine slightly enhanced the enantioselectivity. This discovery has been used in a number of other iodolactonization reactions, including our own. While the exact reason for the enhancement has yet to be revealed, it is believed that the combination of *N*-iodo compounds, I_2, and protic acid produce I_3^+ *in situ*.[220] Jacobsen noted that I_2 does not effect the rate of the background reaction, so perhaps the triiodonium is more effective at transferring the iodonium to the catalyst thereby enhancing the rate of the catalyst-promoted reaction versus the background reaction, leading to enhanced enantioenrichment.

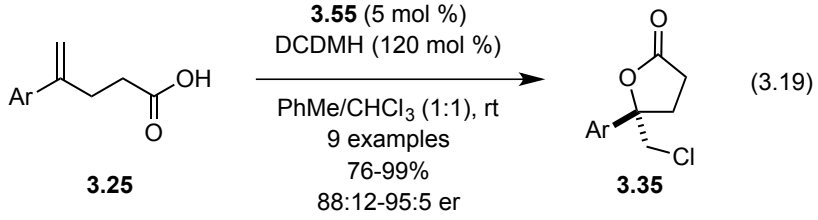


3.4.4 Tang

Tang developed a modified cinchona catalyst **3.55** for the bromolactonization of enynes **3.54**.[151] In the event, enyne derivative **3.54** underwent bromolactonization to provide chiral halo-allene **3.56** in moderate to good yields with excellent enantio- and diastereoselectivity (Equation 3.17). The same conditions could be used to lactonize aryl-tethered substrates **3.57** to provide **3.58** with similarly high selectivities (Equation 3.18). These substrates have been otherwise unexplored in the halolactonization field. Tang also demonstrated that catalyst **3.55** promoted enantioselective, chlorolactonization reactions of 4-aryl-4-pentenoic acids.[152] However, as these acids had previously been explored and the enantioselectivity was not improved upon, the chlorolactonization provided little advancement to the field.





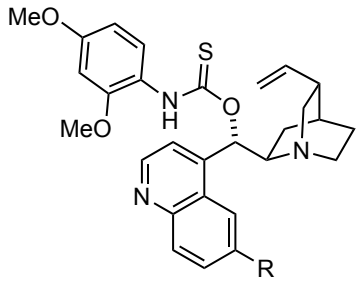


3.4.5 Yeung

Yeung, the most prolific contributor to the field, has showcased a number of catalysts capable of performing a wide variety of halolactonization reactions. While his group has managed to discover highly selective catalysts for these transformations, each substrate required a slightly different catalyst. Unfortunately, while they have solved problems associated with each substrate, an ideal catalyst applicable to a variety of substrates was not found.

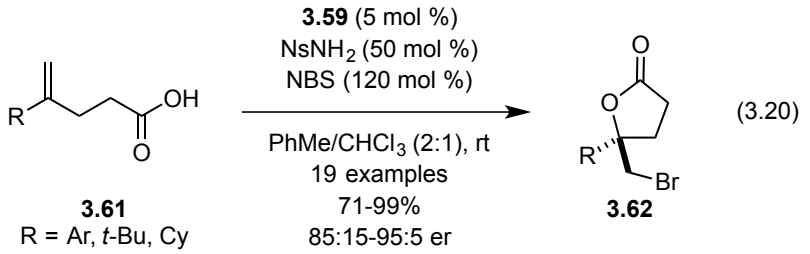
Yeung's first generation catalysts **3.59** and **3.60,** based on the cinchona alkaloids, promoted bromolactonizations of 5-aryl-5-hexenoic acids **3.61** and *E*-6-aryl-5-hexenoic acids **3.28**, the two most common substrates in the field. In his first report, catalyst **3.69** was demonstrated to effect in the bromolactonization of **3.61** to provide bromolactones **3.62** with a high degree of enantioselectivity (Equation 3.20).[153] The use of nosyl amide as a co-catalyst was found to be important, though it is unclear whether or not it enhanced halogen transfer or slowed the background reaction; recent studies by Borhan suggest the former. [221] The reactions suffered the same drawbacks as the other methodologies in that

the presence of electron-rich aryl groups decreased the enantioselectivity; however, unlike previous reports, *tert*-butyl-substituted **3.61** cyclized with high enantioselectivities, the first alkyl substituted substrate to do so. They later found that catalyst **3.60** induced a 6-endo cyclization to give lactones **3.63** with good selectivity (Equation 3.21).[154] The 6-endo cyclization pathway, rather than the 5-exo, is preferred on the *trans*-5-aryl-5-pentenoic acid derivatives due to the electronic bias that the aromatic ring provides, which stabilizes the building positive charge most at the benzylic carbon atom making the benzylic position more electrophilic. During these initial investigations, studies were undertaken to demonstrate that these reactions could tolerate trace amounts water, thereby obviating the need to rigorously dry the solvents;[155] however, based the prior art, there was no reason to believe that these reactions required completely anhydrous conditions.

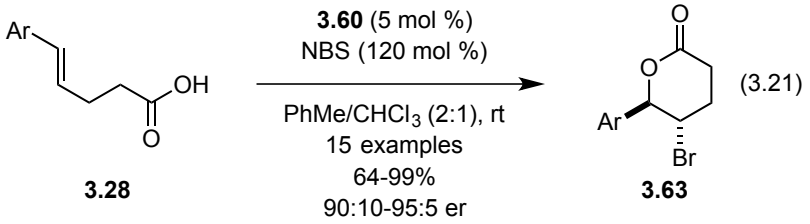


3.59, R = H
3.60, R = OMe

Figure 3.3 Yeung's first generation catalysts **3.59** and **3.60**

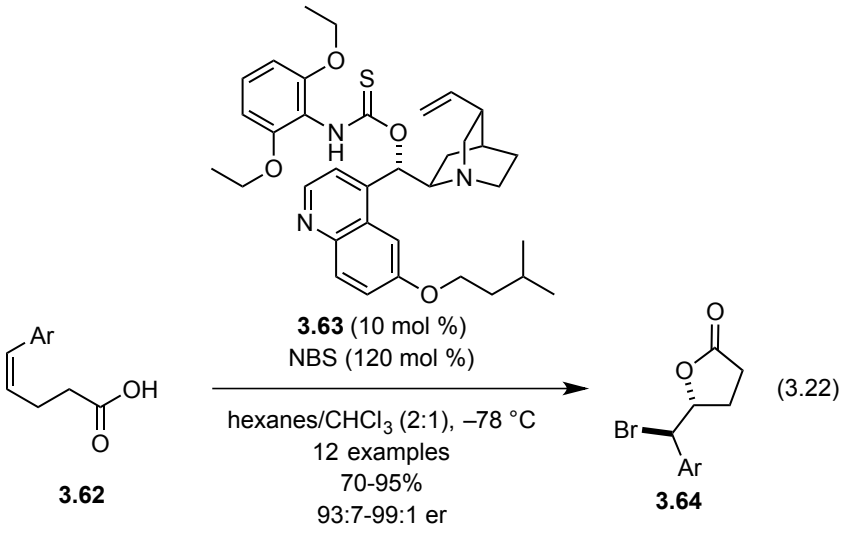


(3.20)



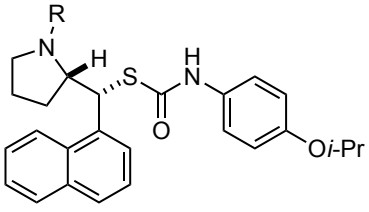
(3.21)

By further modification of the cinchona scaffold to yield catalyst **3.63**, Yeung was able to lactonize *Z*-aryl olefinic acids with a high degree of enantioselectivity to afford bromolactones **3.64**, wherein the newly installed C-Br bond formed an exocyclic stereogenic center (Equation 3.22).[156] While this reaction represents a new substrate in the context of this review, our group was in fact the first to explore these substrates.[166]



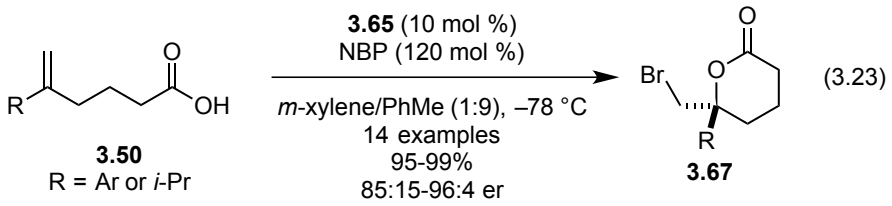
(3.22)

Yeung then developed a new class of catalysts based on proline derivatives; however, he again was unable to find a general catalyst for these transformations.[157] Catalyst **3.65** promoted 6-exo cyclizations of acids **3.50** with good to excellent enantioselectivities (Equation 3.23), and catalyst **3.66** lactonized **3.61** with similarly high yields and selectivities (Equation 3.24). Despite the development of the new catalysts, neither **3.50** nor **3.61** represented new substrates, and the yields and selectivities were similar to those previously reported, hence there was minimal advancement in the field.

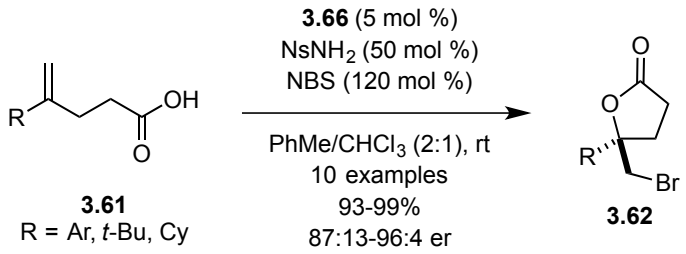


3.65, R = Me
3.66, R = allyl

Figure 3.4 Yeung's second generation catalyst **3.65** and **3.66**

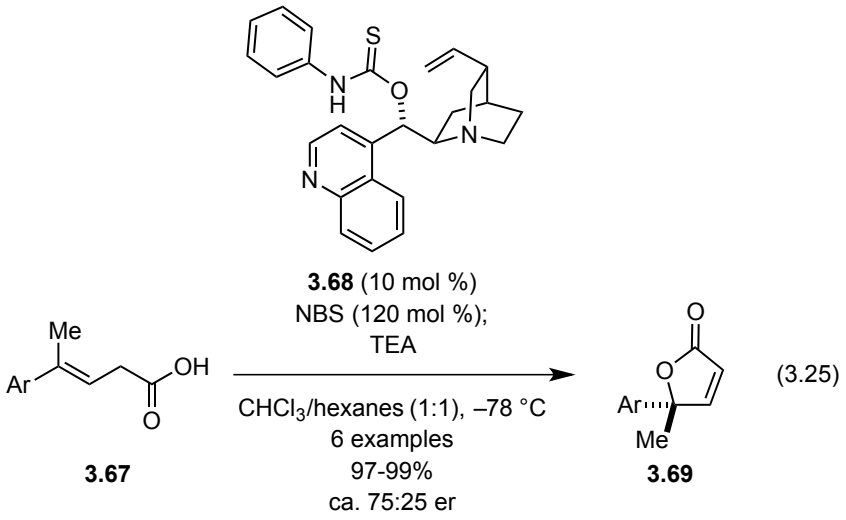


(3.23)



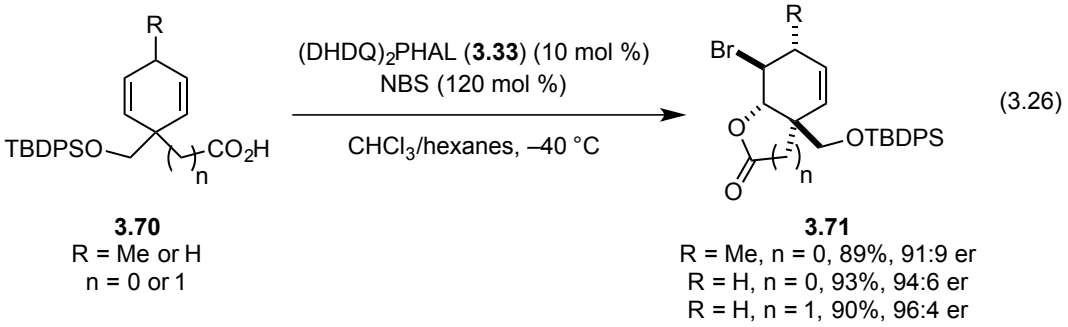
(3.24)

Lastly, Yeung developed a 5-endo cyclization/elimination sequence using catalyst **3.68** to form chiral butenolides **3.69** (Equation 3.25).[158] Again, a new catalyst was required for this substrate. While Yeung contributed significantly to this field, the goal of realizing a common catalyst for halofunctionalization reactions was not obtained. Because a different catalyst required for each type of substrate, the methodology involving chincona-based catalysts is not yet ready for mainstream adoption. Who wants to buy or make a new catalyst for every substrate they want to lactonize?

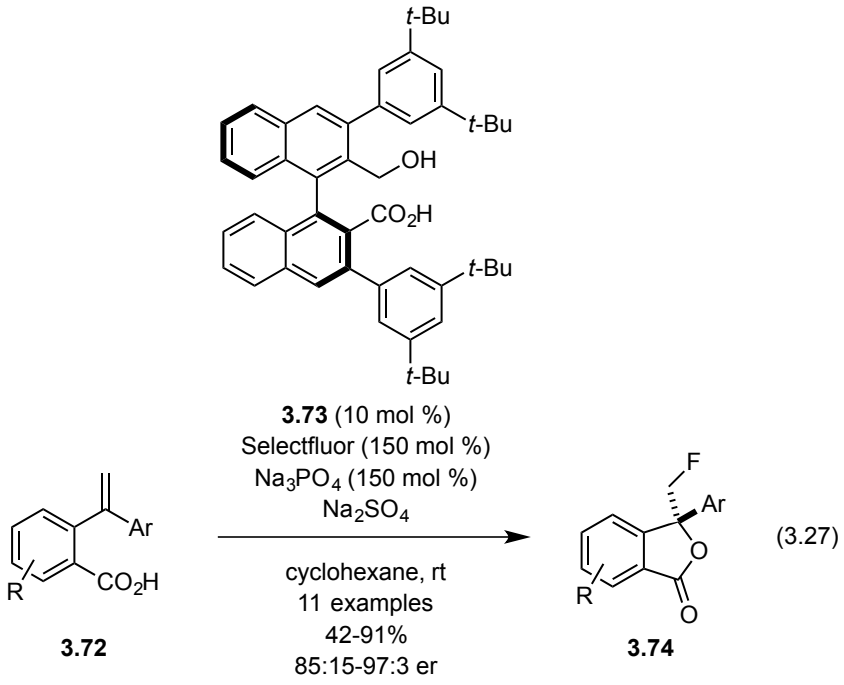


3.4.6 Hamashima

Hamashima entered the field in 2012 with a focus on desymmetrization reactions.[222] They reported that $DHDQ_2PHAL$ (**3.33**) and NBS could desymmetrize prochiral dienes **3.70** to provide either β- or γ-bromolactones **3.71** with good enantioselectivities (Equation 3.26). While this represents a new substrate within this review, we reported the first desymmetrization of prochiral dienes via a bromolactonization reaction earlier the same year.[166] Hamashima demonstrated the utility of this methodology by synthesizing enantioenriched material for their total synthesis of (–)-myriocin.[223]



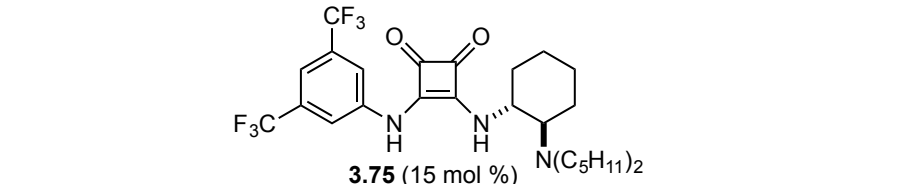
Their next contribution came as the first enantioselective fluorolactonization reaction.[161] Using bifunctional catalyst **3.73**, Hamashima demonstrated the successful lactonization of acids **3.72** to give fluorolactones **3.74** with great enantioselectivities (Equation 3.27). The Rueping group had previously attempted this same transformation with $(DHDQ)_2PHAL$, but only achieved a 27% ee at best.[173] It would be interesting to see how a 1,2-disubstituted olefinic acid or a deuterated substrate (Section 3.4.1) behaved in this reaction, so that the relative stereochemistry between the C-F and C-O bonds could be ascertained. As previously discussed in Section 3.2.2, the carbocationic character of the intermediate after fluorine delivery can lead to poor diastereoselectivity of these reactions. Hopefully, Hamashima will report whether or not his catalyst can overcome this challenge in the near future.



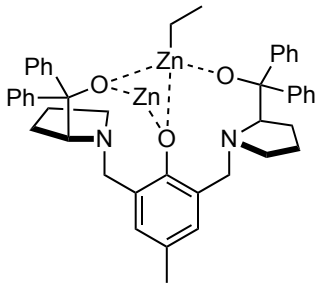
(3.27)

3.4.7 Hansen

Hansen reported a squarimide based catalyst **3.75** that could effect enantioselective 6-exo lactonization reactions (Equation 3.28).[162] The catalyst was extremely similar to Jacobsen's catalyst **3.53**, as was the substrate scope they explored, which was limited to 6-exo lactonization reactions of 5-aryl-5-hexenoic acids **3.50**. Hansen did report that he tried to perform 5-exo lactonizations with **3.75**, but these reactions delivered lactones with 14% ee at best. He later explored catalyst **3.76** for the same iodolactonization substrates as Equation 3.28, but the enantioselectivities were even lower.[163]



3.50 **3.53**

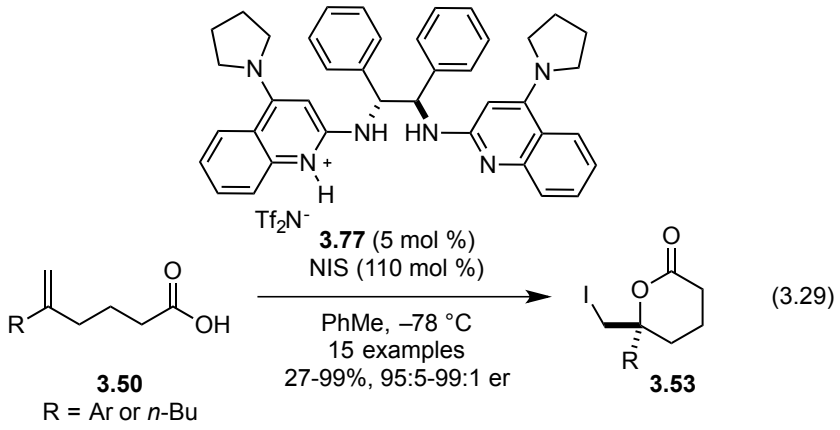


3.76

Figure 3.5 Hansen's zinc based iodolactonization catalyst

3.4.8 Johnston

The Johnston group developed the catalyst **3.77**, which promoted the iodolactonization of substrates **3.50** (Equation 3.29).[164] While the substrate scope was generally the same as all of the other 6-exo iodolactonizations, they did demonstrate the highest enantioselectivity (95:5 er) for the lactonization of an *n*-alkyl substituted olefinic acid **3.50** (R = *n*-Bu) to date. The observation that the achiral counter anion played a major role in the enantioselectivity of the transformation was interesting. However, there was no speculation as to what its role might be. Nevertheless, besides ruling out yet another catalyst scaffold as a generally applicable catalyst, there was once again little advancement to the field from this report.

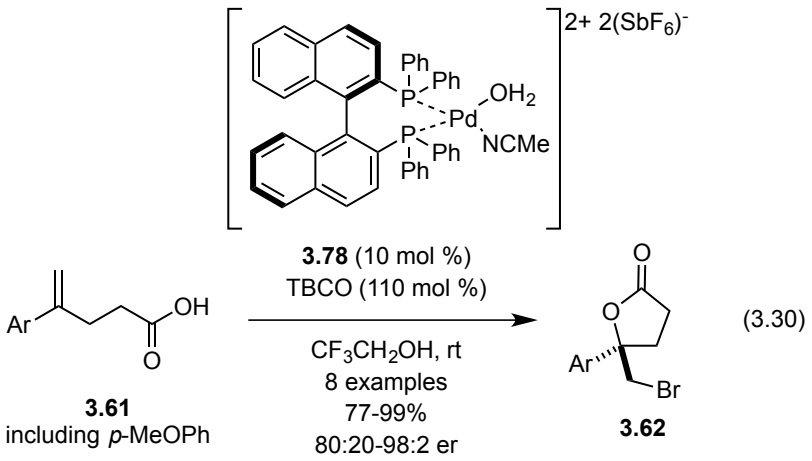


(3.29)

3.4.9 Kim

Kim and co-workers disclosed a di-cationic palladium catalyst that induced bromolactonizations of aryl olefinic acids **3.61** with good enantioselectivities and yields (Equation 3.30).[165] Since the substrate class had been explored extensively in previous studies, the catalyst seemed less than remarkable. However, unlike previously reported

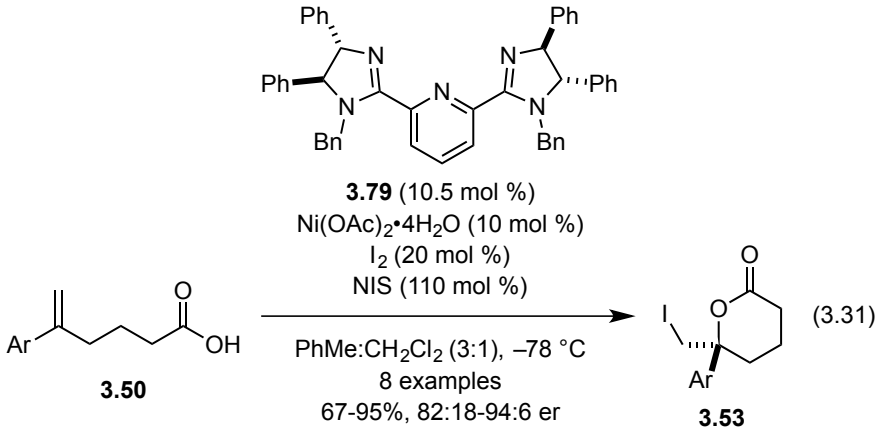
methodologies, which suffered from poor enantioselectivity with electron-rich aromatic-substituted olefins, catalyst **3.78** worked best with electron-rich substrates.

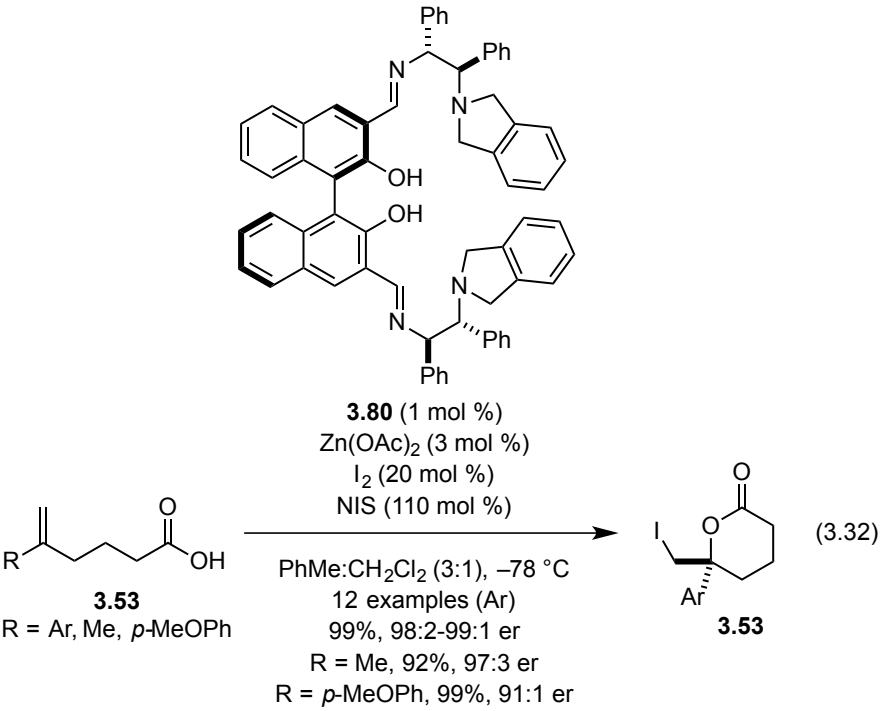


(3.30)

3.4.10 Arai

Arai and co-workers developed two organometallic-based catalysts for 6-exo iodocyclization reactions. The first involved ligand **3.79** and nickel acetate to catalyze the lactonization of **3.50** in the presence of iodine and NIS (Equation 3.31).[168] Other than demonstrating the effectiveness of ligand **3.79**, no advancement of substrate tolerance for 6-exo cyclizations of **3.50** was reported. The second method involved a tri-nuclear zinc complex with ligand **3.80** to catalyze the same type of 6-exo cyclization reaction with substrate **3.53** (Equation 3.32).[169] While this system provided little advantage over previously reported methodologies, it was noteworthy in that it worked extremely well on 4-methoxyphenyl- and methyl-substituted olefinic acids. Ligand **3.80** remains the only scaffold able to effect the transformation of substrate **3.53** (R = Me) with a synthetically useful enantioselectivity.

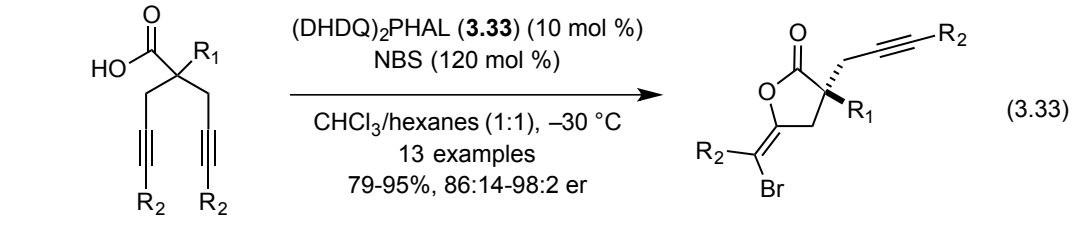




3.4.13 Hennecke

Hennecke disclosed a unique desymmetrization of prochiral diynes **3.81** using $(DHDQ)_2PHAL$ (**3.33**).[171] A number of derivatives were explored, and good to excellent yields and enantioselectivies were obtained (Equation 3.33). This reaction has been

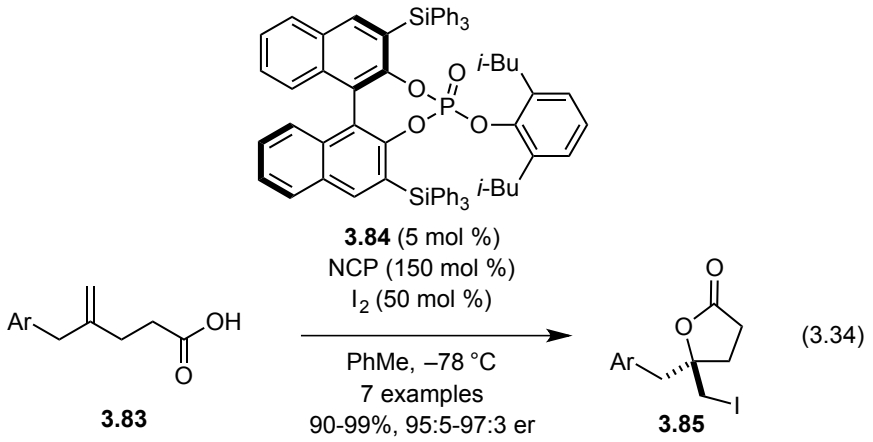
performed on gram scale with no loss in either yield or selectivity. Furthermore the alkyne could be reduced in the presence of the vinyl halide in 93% yield.



(3.33)

3.4.14 Ishihara

Ishihara reported the latest halolactonization reaction, wherein catalyst **3.84** promoted the iodolactonization of benzyl substited olefinic acids **3.83** with a high degree of enantioselectivity (Equation 3.34).[172] The substrates were new with respect to the previously reported methods, but perhaps the most interesting aspect was the use of half an equivalent of iodine to perform the transformation. *N*-Chlorophthalimide (NCP) is used as an oxidant in a redox cycle to generate two equivalents of "I^+" from one equivalent of iodine. While this method has yet to achieve success in the development of a general catalyst, it provides a foundation for future development wherein the byproducts of these reactions could be reduced.



3.4.15 Summary

While a number of high yielding and highly selective halolactonizations have been developed, there are still a myriad of improvements that need to be developed. One of the main drawbacks to the current methodology is the need for a different catalyst for each substrate and halogenating reagent. Ideally, one catalyst could perform the reaction for any substitution pattern on the olefin to produce any fluoro-, chloro-, bromo-, or iodolactone. Unfortunately for the methods discussed above, no catalyst has even begun to approach this ideal. In fact, only $(DHDQ)_2PHAL$ can promote more than one type of lactonization with respect to halogenating reagent. Additionally, the halolactonization reactions of alkyl-substituted olefinic acid derivatives are underrepresented and generally provide lower enantioselectivities with respect to the corresponding aryl derivatives; tri- and tetra-substituted olefinic aids remain all but absent in the literature. Finally, while two examples of halolactonizations that generate a stereogenic C-X bond were discussed, these reactions were unknown prior to our entrance into the field. Despite the shortcomings of the reported catalysts, the scaffolds disclosed thus far serve to rule out

what does not work and help to narrow the field for future designs that could meet the requirements for an ideal halolactonization catalyst.

3.5 Previous Work in the Martin Group

3.5.1 Catalyst Design

The Martin group was drawn to this field by the prospect of synthesizing bromophycolide A (**3.2**). Though bromophycolide A has yet to succumb to total synthesis, there is one asymmetric route to the carbocyclic skeleton.[224] It was imagined that halolactonization reactions could be used to introduce the macro-bromolactone and bromohydrin moiety of **3.2**. However, at the onset of this work (2010), the only halolactonization catalysts that had been reported were Borhan's **3.33**, Yeung's **3.59** and **3.60**, Tang's **3.55**, and Fujioka's **3.38** (Figure 3.6). All of these catalysts were limited to either aryl-substituted olefinic acids or enynes, thus they were useless in the planned approach toward bromophycolide A (**3.2**). Additionally, a catalytic, enantioselective bromo-polyene cyclization was envisaged to synthesize the bromo-cyclohexene moiety. While one stoichiometric, enantioselective polyene cyclization had been reported, [200] a catalytic enantioselective protocol remains unknown. Furthermore, besides the synthesis of bromophycolide and the development of polyenecyclizations, there were limitations within the halolactonization field that needed to be addressed: 1) Catalysts were limited to 5-aryl-5-hexenoic acids and *trans*-6-aryl-5-hexenoic acids, 2) No catalyst had been developed that could form a carbon halogen bond at an exocyclic stereogenic center, and 3) No catalyst could perform more than one type of halolactonization with respect to the halogen. Thus, a new catalyst(s) for both halolactonization and halopolyene cyclization reactions needed to be developed.

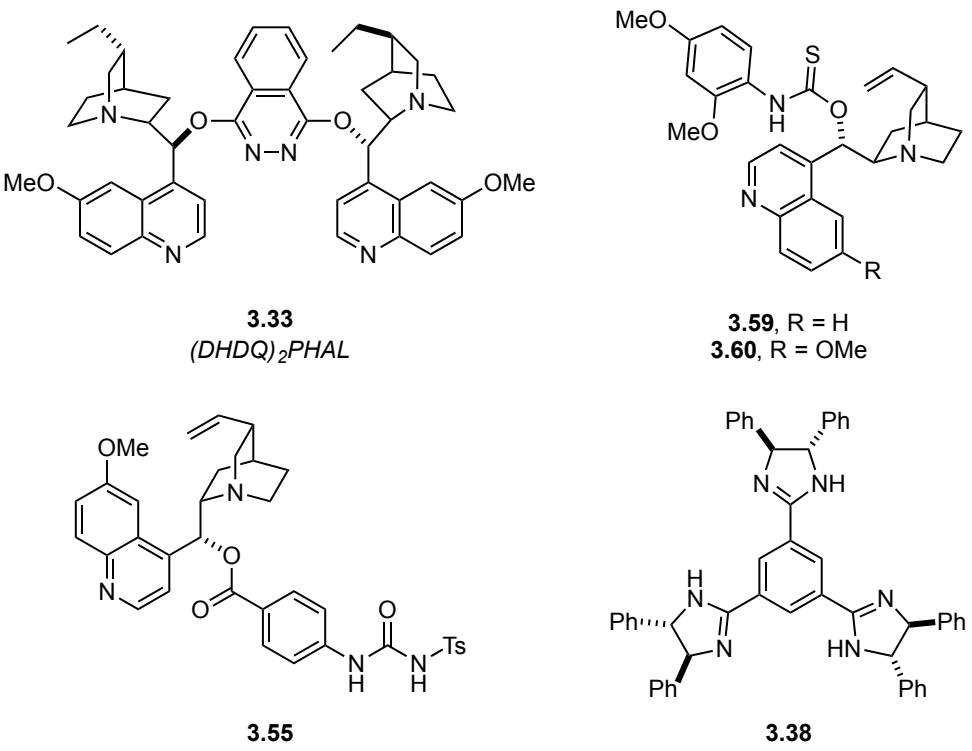


Figure 3.6 Known catalysts at the onset of our research

Because there were known catalysts that could promote halolactonization reactions, the group chose to learn from these catalysts in order develop a new catalyst. What was known from these successful catalysts was that they were bifunctional, including both a Lewis or Brønsted acid and a Lewis or Brønsted base. Consequently, it was decided that a new chiral scaffold capable of accepting two functional groups would be required. BINOL (**3.86**) was chosen as the catalyst scaffold because this backbone was unexplored in the realm of halocyclization reactions. Moreover, it is a privileged scaffold that is nearly ubiquitous in the field of enantioselective reactions, and it has two functional handles on which to attach a Lewis acid and a Lewis base functionality (Figure

3.7). With this idea in mind, the group set out to design and screen derivatives based on the general model **3.87**.

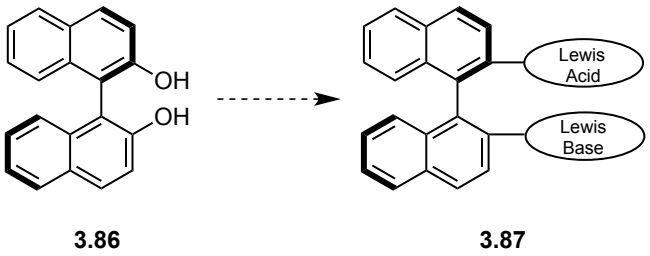
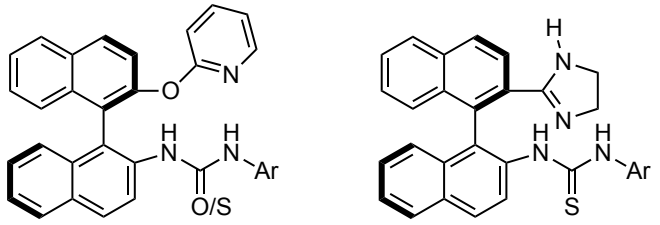


Figure 3.7 Strategy for BINOL as a catalyst scaffold

Based on the four successful catalyst designs reported thus far (Figure 3.6), it was reasoned that a basic nitrogen atom would be needed to coordinate the carboxylic acid, and a Lewis acidic functional group (urea, thiourea, carbamate, or thiocarbamate) would activate the halogenating reaction. A number of catalysts based on derivatives **3.89**, which contain a pyridine and a urea or thiourea were synthesized, but these designs provided the product lactones as racemic mixtures (Figure 3.8). As the pyridine moiety might not have be basic enough to coordinate the acid, the more basic imidazoline catalyst **3.90** was synthesized, but the product lactone was only obtained in up to 8% ee. Modeling catalyst **3.90** revealed that the imidizoline and thiourea were unable to adopt a conformation which would allow them to both participate in catalysis by coordinating both the acid and halogen source, thus a new design was needed to move the functionality away from the rigid BINOL scaffold. Additionally, the addition of steric bulk around the catalophore had been shown in the literature to enhance stereoselectivity,[225] so catalyst **3.92** was targeted, which borrowed a thiocarbamate from Yeung's design **3.59** and an amidine from Fujioka's design **3.38**. Unfortunately, the thiocarbamate moiety was unable

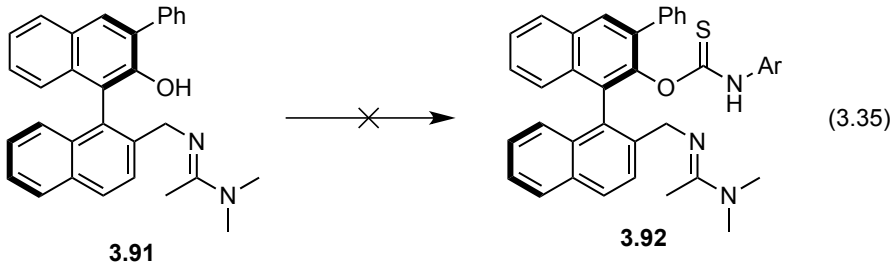
to be appended to **3.91** (Equation 3.35). As the phenyl moiety might have been blocking the naphthol, the synthesis of **3.94** was attempted, but **3.93** was unreactive as well (Equation 3.36).[226] Luckily, **3.91** was serendipitously discovered to provide bromolactones with a high degree of enantioselectivity.



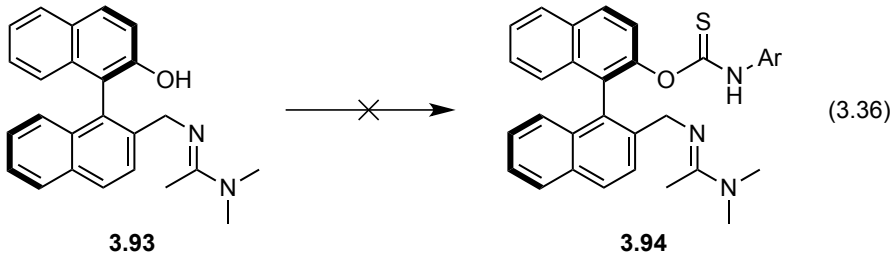
3.89
no enantioenrichment

3.90
no enantioenrichment

Figure 3.8 First and second generation catalyst designs **3.89** and **3.90**



3.91 **3.92** (3.35)



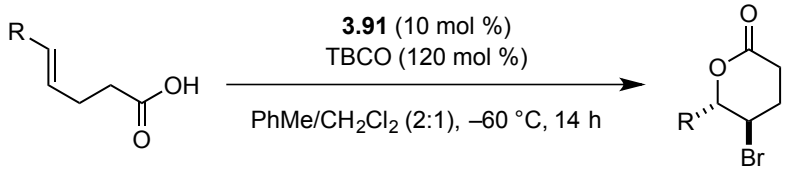
3.93 **3.94** (3.36)

3.5.2 Bromolactonization reactions

2,4,4,5-Tetrabromocyclohexadienone (TBCO) was found to be the optimum brominating reagent in preliminary experiments, with NBS and DBDMH reported to provide no reaction or low yields.[226] A solvent screen then revealed that a mixture (2:1) of toluene and methylene chloride provided the highest selectivity.[166]

In order to compare catalyst **3.91** to other catalysts, *trans*-6-aryl-5-hexenoic acids **3.28** were tested, revealing that catalyst **3.91** matched the best yields and enantioselectivities reported in the literature (Table 3.1). For 5-aryl-5-hexenoic acids **3.95**, it was found that the catalyst was competitive as well (Table 3.2, Entries A, B, and C), though catalyst **3.91**, like most other catalysts, lost efficiency on electron-rich aromatic-substituted acids (Table 3.2, Entry D). The ability to cyclize both of these substrates was a small victory, because no single catalyst had been reported to perform well on more than one type of substrate. Additionally, catalyst **3.91** was unfortunately inefficient in the bromolactonization of a tri-substituted olefinic acid (Table 3.2, Entry E); Fujioka's catalyst remains the only effective catalyst for this substrate class.

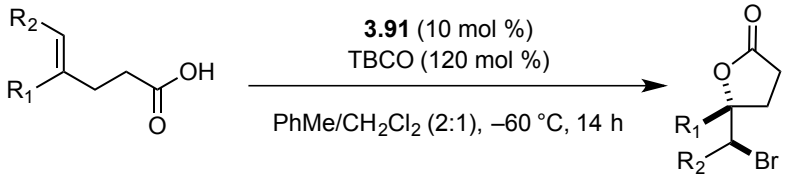
Table 3.1 Bromolactonization of *trans*-6-aryl-5-hexenoic acids



3.28 **3.63**

Entry	R	Yield (%)	er
A	Ph	94	98:2
B	1-Np	97	96:4
C	2-thienyl	92	94:6

Table 3.2 Bromolactonization of 5-aryl-5-hexenoic acids and a trisubstituted acid

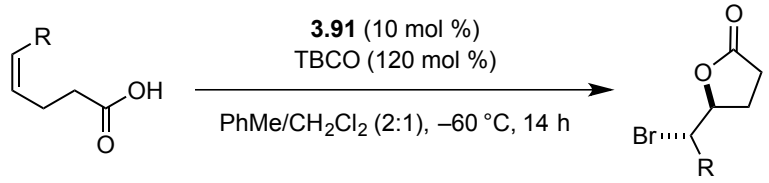


3.95 **3.96**

Entry	R_1	R_2	Yield	er
A	Ph	H	99	86:14
B	*m*-NC-Ph	H	89	91:9
C	*p*-NC-Ph	H	92	94:6
D	*p*-MeO-Ph	H	70	58:42
E	Me	Me	89	71:29

The bromocyclization of *cis*-alkyl olefinic acids **2.97**, which were unreported in the literature, was then attempted. It was found that catalyst **3.91** provided bromolactones **3.98** in excellent yields and enantioselectivities with branched alkyl olefinic acids (Table 3.3). This remarkable result was the first highly enantioselective bromolactonization of a Z-alkyl substituted olefinic acid, and thus the first bromolactonization that generated a C-Br bond at an exocyclic stereogenic center.

Table 3.3 Bromolactonization of 6-alkyl-5-hexenoic acids

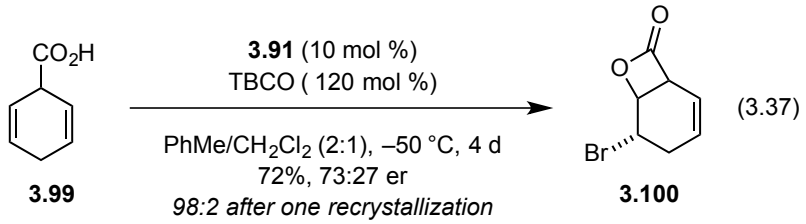


3.97 **3.98**

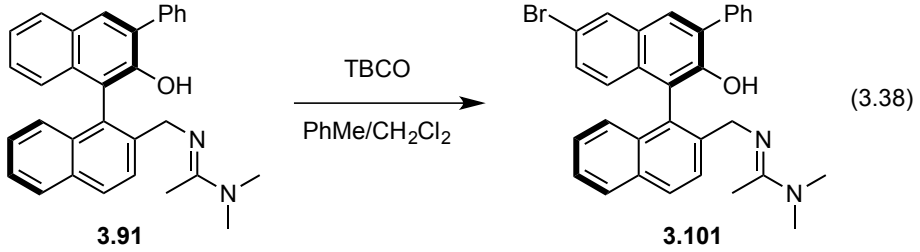
Entry	R	Yield (%)	er
A	Et	90	85:15
B	*i*-Bu	87	95:5
C	*i*-Pr	94	97:3
D	Cy	94	98.5:1.5
E	*t*-Bu	97	97:3

The prochiral diene **3.99** was then subjected to the bromolactonization conditions (Equation 3.37). Excitingly, bromolactone **3.100** was recovered in 72% yield and 73:27 er. After a single recrystallization, the enantioselectivity could be increased to 99:1. This reaction represented the first desymmetrization reaction via a halolactonization reaction. This reaction has since been performed on up to 2.5 g scale for our synthesis of the F ring

fragment of the natural product kibdelone C.[227] Additionally, this was the fourth type of substrate that was successful with catalyst **3.91**, whereas other catalysts only worked well on one type of substrate. It should be noted that during the course of the reaction, catalyst **3.91** was brominated to provide **3.101** (Equation 3.36). When **3.101** was subjected to the halolactonization reactions, the same yields and enantioselectivities that catalyst **3.91** provided were observed.



(3.37)



(3.38)

3.5.3 Working Model

Based on the results obtained thus far, the following working model was proposed for the induction of chirality from the catalyst to the substrate (Figure 3.9). Using *cis*-5-substituted-4-pentenoic acids as the model substrate, the naphthol moiety is thought to participate via a hydrogen bond interaction with the carboxylate while the amidine stabilizes the halonium ion prior to C-O bond formation. We posit this, because when the naphthol moiety was masked with a methyl group, no enantioselectivity was observed

(*vide infra*). Additionally, amidines are known to react with halogenating reagents to produce *N*-halo-amidines, which in turn react as brominating reagents themselves.[228,229] The substrate should favor alignment with the steric bulk away from the catalyst pocket, preferring **3.102** over **3.103**, thus transferring the chirality from the catalyst to the substrate to provide the enantioenriched lactone **3.98** instead of *epi*-**3.98**. However, the possibility that the amidine acts as the base while the naphoxide stabilizes the halonium as in **3.104** and **3.105** cannot be ruled out as this transition state ultimately leads to the same outcome.

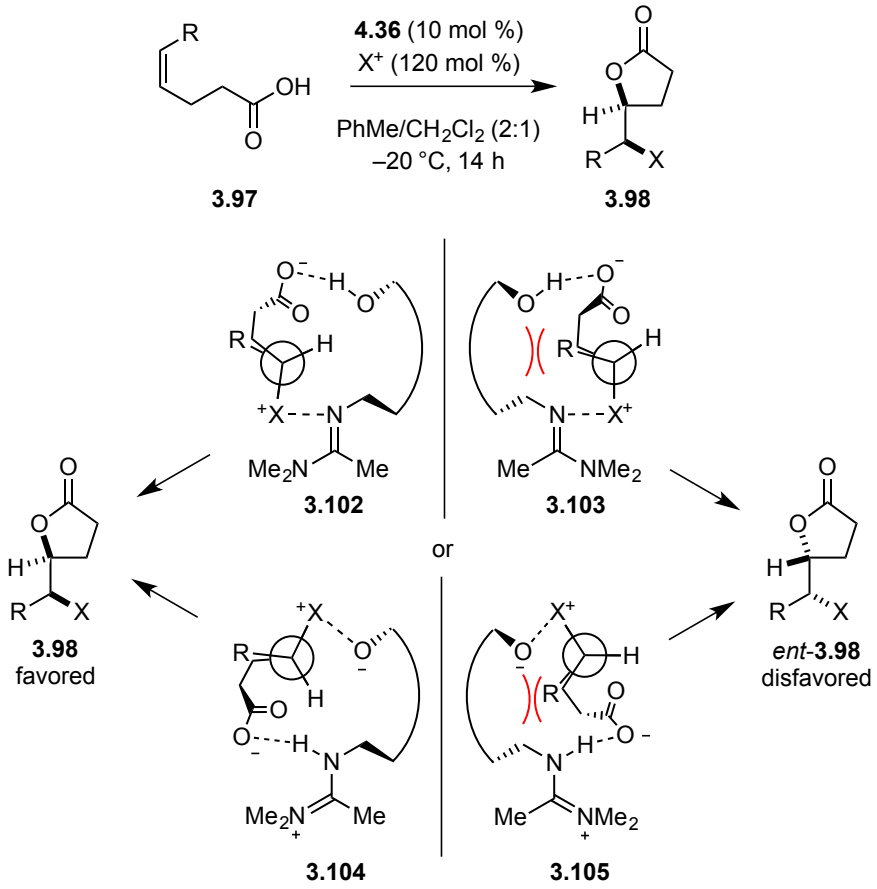


Figure 3.9 Working model for our bromolactonization reaction

3.5.4 Summary

At the conclusion of these initial studies on bromolactonization reactions, a catalyst was discovered that was more general than any of the previously reported catalysts, performing bromolactonizations on four different substrates rather than on only one. Catalyst **3.91** or **3.101**, for the first time, promoted the bromolactonization of alkyl olefinic acids generating a stereogenic C-Br bond exocyclic to the lactone. Furthermore, the catalyst desymmetrized a prochiral diene, which after a single recrystallization

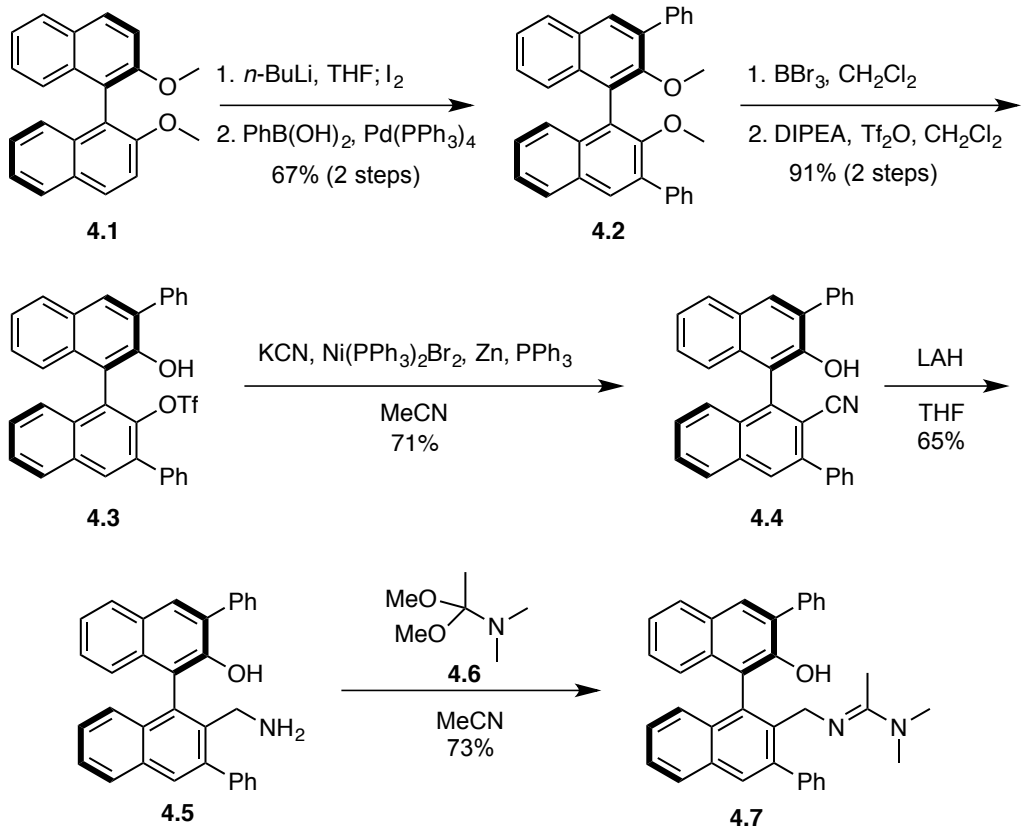
provided the desymmetrized product in 98:2 er. However, *trans*-alkyl olefinic acids yielded decreased enantioselectivities (ca. 70:30 er). Additionally, like all other reported catalysts, thus far catalyst **3.91** only worked for bromolactonization reactions. In our quest to discover a general halocyclization catalyst, we sought to be able to perform chloro-, iodo-, and/or fluorolactonization reactions, increase the enantioselectivity of problematic substrates, and hopefully perform a variety of other cyclizations (e.g. etherifications, aminocyclizations, halolactamization reactions, and polyene cyclizations). Thus, we set out to prepare derivatives of catalyst **3.91** to find the optimal catalyst design.

Chapter 4: Development and Application of New Halocyclization Catalysts

4.1 Catalyst Derivatives: Synthesis and Screening Bromolactonizations

4.1.1 Synthesis of Amidine Catalyst Derivatives

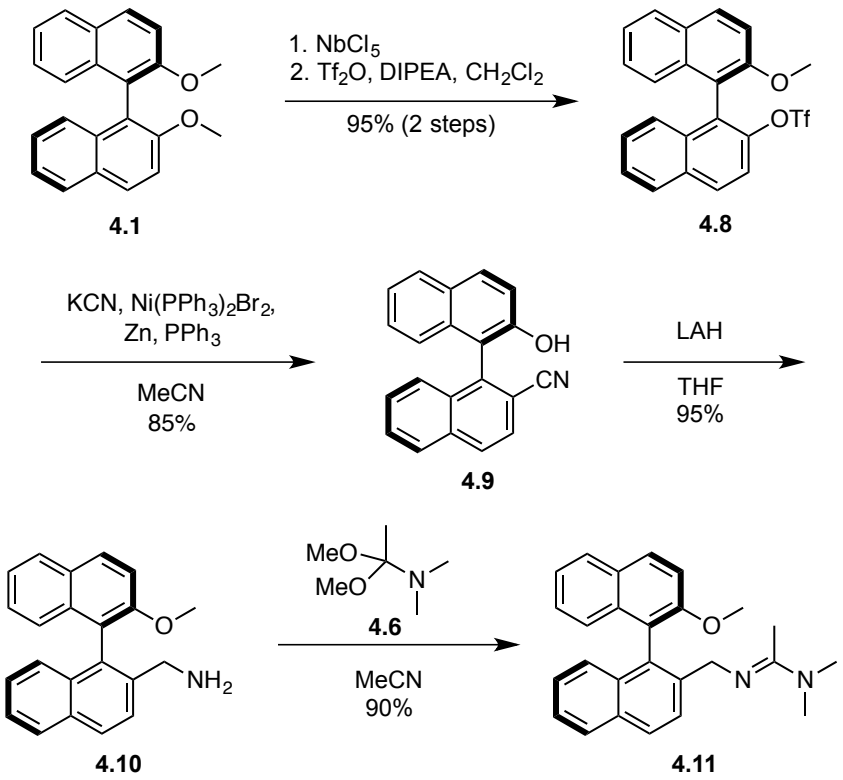
In the initial catalyst design, we had decided to include the phenyl group on the 3-position of the naphthol because literature precedent suggested that steric bulk around the catalaphore generally led to increased enantioselectivity.[225] Thus, we set out to prepare the 3,3'-disubstituted catalyst **4.7** in order to query if even more bulk would enhance the selectivity. The synthesis commenced from bis-methoxy BINOL **4.1**, which was iodinated and subsequently subjected to Suzuki cross-coupling conditions to provide **4.2** in 67% yield over two steps (Scheme 4.1).[230,231] Deprotection and triflation of **4.2** delivered **4.3** in 91% yield over two steps.[232] Cyanation of the triflate was accomplished by coupling with potassium cyanide in the presence of a nickel catalyst,[233,234] which was then reduced with lithium aluminum hydride to provide amine **4.5** in 35% yield over two steps. Finally, exposure of **4.5** to *N*,*N*-dimethylacetamide dimethylacetal (**4.6**) provided catalyst **4.7** in 73% yield. [166]



Scheme 9.1 Synthesis of bis-phenyl catalyst **4.7**

We had proposed that the naphthol/amidine-based catalysts were bifunctional (Section 3.5.3),[166] like most of the other successful halolactonization catalysts (Section 3.4). Specifically, we proposed that both the naphthol and the amidine were involved in determining the stereochemical outcome of the reaction, rather than relying on the amidine to function solely as a chiral base. Therefore, we sought to prepare analog **4.11** wherein the naphtoxy moiety had been masked (Scheme 4.2). Towards this end, bis-methoxy BINOL **4.1** was mono-demethylated with niobium pentachloride and treated with trifluoromethanesulfonic anhydride to provide **4.8** in 95% yield over two steps.[232,235] In an analogous sequence as above (Scheme 4.1), triflate **4.8** was coupled with potassium

cyanide, reduced, and treated with **4.6** to deliver catalyst **4.11**. We were then prepared to test our new catalyst derivatives.



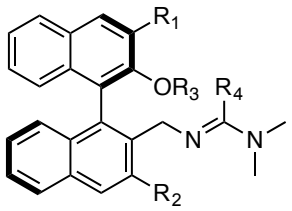
Scheme 4.2 Synthesis of catalyst derivative **4.11**

4.1.2 Comparison of Amidine-Based Catalyst Derivatives

Ultimately, a series of eight derivatives were prepared for testing (Table 4.1). These included the original catalyst **4.12** from the bromolactonization reactions (Section 3.5.2) and **4.13** and **4.14** to test the effect of increasing steric bulk near the naphthol moiety (R_1). Catalyst **4.15** was prepared to query if steric bulk was needed at all ($R_1 = R_2 = H$), while derivative **4.7** would increase the sterics at both the naphthol and the amidine ($R_1 = R_2 = Ph$). Catalysts **4.16** and **4.17** were used probe steric effects on the amidine

moiety (R_4 = Me, *t*-Bu, or Ph). Finally, we explored the importance of the naphthol by masking it as the methyl ether in catalyst **4.11** (R_3 = Me).

Table 4.1 List of catalyst derivatives

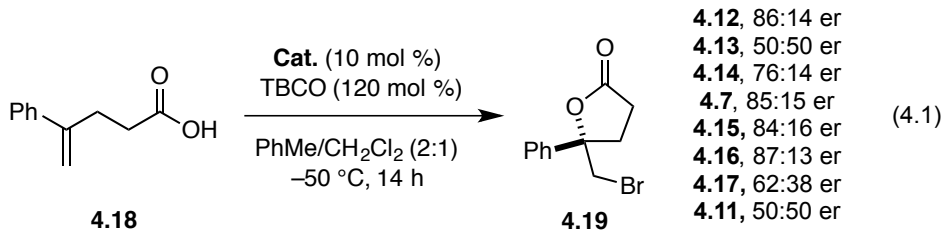


Entry	Catalyst	R_1	R_2	R_3	R_4
A[a]	**4.12**	Ph	H	H	Me
B[a]	**4.13**	2,4,6-(*i*-Pr)$_3$Ph	H	H	Me
C[b]	**4.14**	Si(Ph)$_3$	H	H	Me
D	**4.7**	Ph	Ph	H	Me
E[c]	**4.15**	H	H	H	Me
F[c]	**4.16**	H	H	H	Ph
G[c]	**4.17**	H	H	H	*t*-Bu
H	**4.11**	H	H	Me	Me

a) Daniel Paull. b) Chao Fang. c) Andrew Pansick

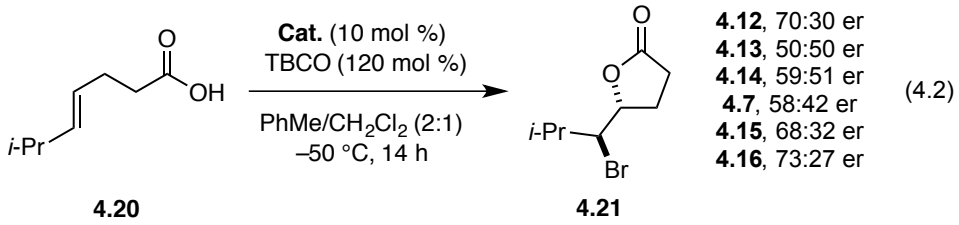
Our study began with acid **4.18**, one of the most common test substrates in the literature. As before, the original catalyst **4.12** delivered the product lactone **4.19** with 86:14 er (Equation 4.1). Catalysts **4.13** and **4.14** provided worse selectivity at 50:50 and 76:14 er respectively. We found that both the disubstituted catalyst **4.7** and the un-substituted catalyst **4.15** performed as well as the original catalyst **4.12**. Likewise, there was little difference between the methyl-substituted amidine **4.15** and phenyl-substituted

amidine **4.16**; however, we found that *tert*-butyl-substituted amidine catalyst **4.17** performed significantly worse at 62:38 er. Finally, as we hypothesized, blocking the naphthol moiety led to the recovery of *rac*-**4.19**, thus suggesting that our catalyst was indeed bifunctional.



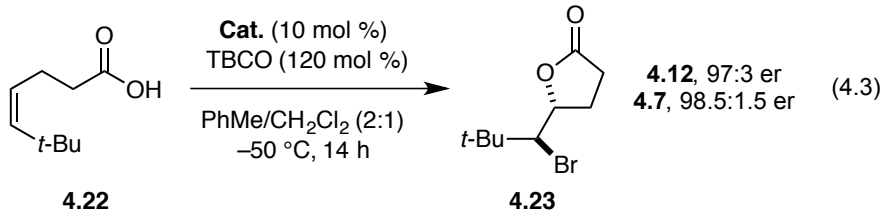
(4.1)

In our initial bromolactonization studies, catalyst **4.12** provided the worse selectivities (70:30 er) on *trans*-alkyl-substituted olefinic acids like **4.20**. We postulated that increased steric bulk might improve the enantioselectivity on this troublesome substrate (Equation 4.2). Unfortunately, we found that the entire series of bulky catalysts (**4.13**, **4.14**, **4.7**, and **4.15**) performed worse than catalyst **4.12**. Thus, it appeared that decreasing the steric interactions would lead to the increased selectivity; however, the un-substituted catalyst **4.16** provided only marginally improved enantioselectivity (73:27 er).



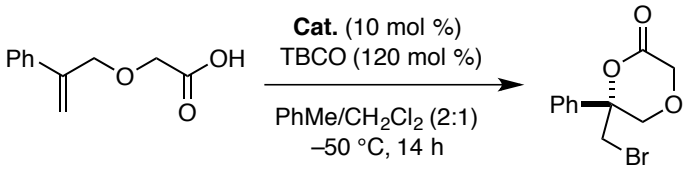
(4.2)

We continued our testing with *cis*-substituted olefinic acid **4.22** finding that the bis-phenyl catalyst **4.7** performed only slightly better than catalyst **4.12** (Equation 4.3). Both catalyst **4.7** and **4.12** delivered lactone **4.25** in similar selectivities (Equation 4.4). Finally, in the desymmetrizing lactonization of **4.36**, catalyst **4.12** was found to be the optimal catalyst (Equation 4.5). Thus, while the 3,3'-disubstituted catalyst **4.7** and the un-substituted catalyst **4.16** performed as well as **4.12** on most of the substrates, **4.12** was the most consistently selective across the range of substrates. Consequently, we chose to move forward with catalyst **4.12** for all further experiments involving hydroxy/amidine catalysis.



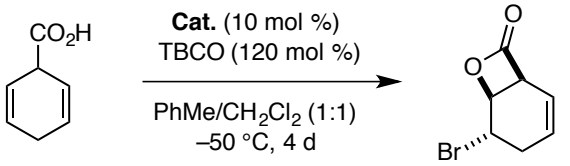
4.22 **4.23**

4.12, 97:3 er
4.7, 98.5:1.5 er (4.3)



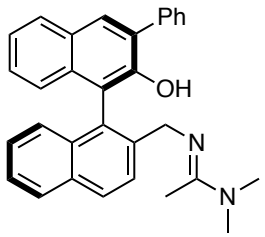
4.24 **4.25**

4.12, 85:15 er
4.7, 86:14 er (4.4)



4.26 **4.27**

4.12, 73:27 er
4.7, 66:34 er
4.15, 60:40 er (4.5)



4.12

Figure 4.1 Our most consistently selective bromolactonization catalyst **4.12**

4.1.3 Thiourea Catalyst Derivatives

Urea, thiourea, and thiocarbamate moieties were previously reported to be excellent functionalities on a number of successful organocatalysts for halocyclization reactions.[136] Thus, during the course of our screening, we posited that a thiourea moiety might be an appropriate functional group for our catalyst scaffold, either by acting as a Lewis acid to activate the halogenating reagent or as a Lewis base to transfer the halonium ion. Initially, a series of three aryl thiourea catalysts were prepared from precursor **4.28** by reaction with the appropriate isothiocyanate to provide **4.29**, **4.30**, and **4.31** (Figure 4.2).

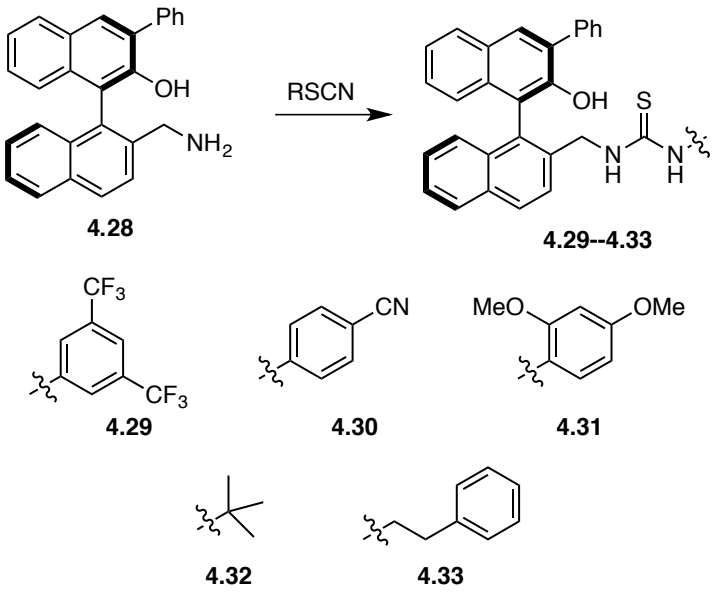
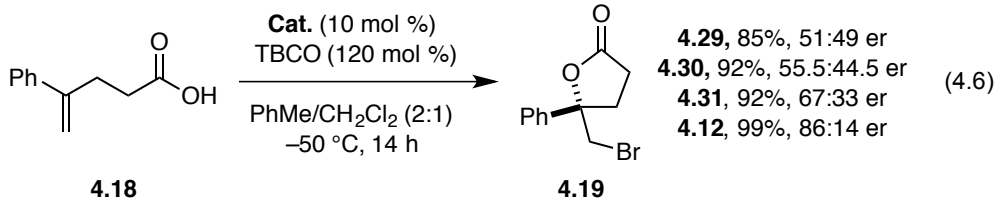
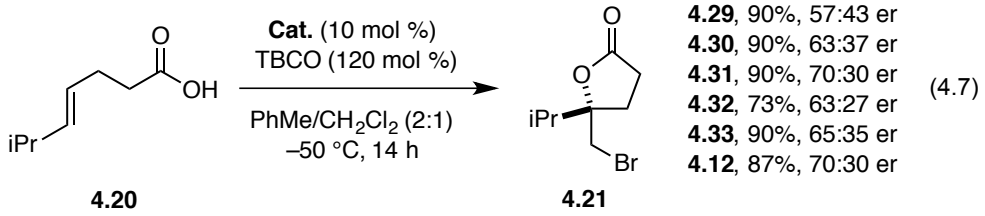


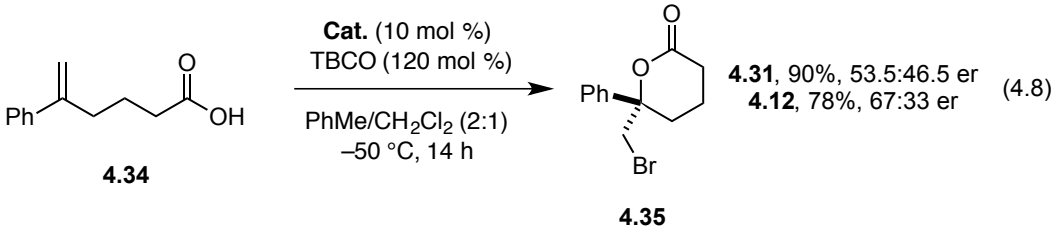
Figure 4.2 Thiourea based catalysts **4.29**-**4.33**

We found that the catalysts **4.29**, **4.30**, and **4.31** performed significantly worse than our best amidine catalyst **4.12** for the bromolactonization of acid **4.18** (Equation 4.6). As the thiourea catalysts did not perform as well at catalyst **4.12** on substrate **4.18**, the transition state must be unfavorable when the thiourea catalysts coordinate **4.18**. Thus, the transition state might in turn be favorable with the *trans*-alkyl olefinic acids, which were troublesome substrates with catalyst **4.12**. While no improvement was observed, catalyst **4.31** delivered lactone in 70:30 er, the same enantiomeric ratio that catalyst **4.12** afforded (Equation 4.7). Interestingly, in contrast to the normal trends in the literature,[136] the more electron-rich thiourea derivatives supplied the highest enantioselectivities. This suggests that the thiourea moiety was functioning as a Lewis base on our catalyst, rather than as a Lewis acid, which most other group propose. With this trend in mind, we synthesized the alkyl substituted thiourea derivatives **4.32** and **4.33**

(Figure 4.2), but these analogs failed to improve the selectivity (Equation 4.7). Finally, substrate **4.34**, another problematic substrate, was tested, but amidine **4.12** outperformed the best thiourea derivative **4.31**.







4.1.4 Summary

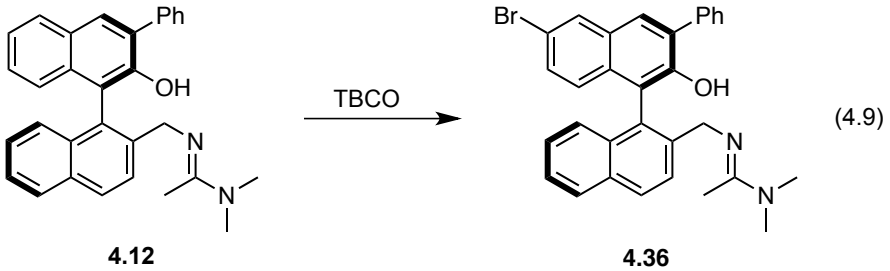
After extensive testing concluded that **4.12** was the most suitable catalyst for further development. However, it was slightly disappointing to discover that we had stumbled upon to the best catalyst design from the onset. Additionally, we learned via the use of catalyst **4.11** that the naphthol functionality is important in determining the stereochemical outcome of the bromolactonization reaction. With the most efficient

catalyst now known, we set out to explore the utility of catalyst **4.12** beyond bromolactonization reactions.

4.2 Development of Iodolactonization Reactions

4.2.1 Initial Discovery and Reaction Optimization

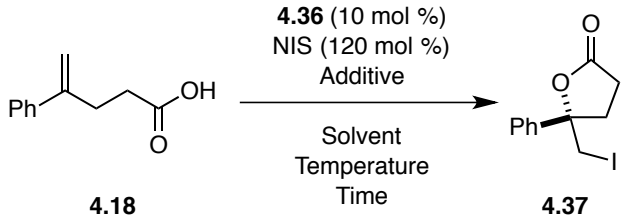
In early attempts, we found that iodolactonizations using catalyst **4.12** were sluggish. Remembering that during the course of the bromolactonization reaction, catalyst **4.12** was brominated to provide **4.36** led us to question whether **4.36** might be a better catalyst for iodolactonization reactions (Equation 4.9). While the reaction with catalyst **4.36** was slow at –50 °C, the temperature used for bromolactonization reactions, we found that at –20 °C in toluene/CH_2Cl_2 (2:1) that acid **4.18** suffered lactonization to provide **4.37** in 89% yield and 93:7 er (Table 4.2, entry A). To our delight, the iodolactonization provided a higher enantiomeric excess than the corresponding bromolactonization reaction (86:14 er). While it seemed intuitive that this iodolactonization should be feasible, at the time no reported catalyst was able to perform halolactonization reactions with more than one type of halogenating reagent. The fact that catalyst **4.36** could promote both iodo- and bromolactonization reactions was remarkable. We then set out to find the optimal conditions for iodolactonization.



4.12 **4.36** (4.9)

We began by changing the ratio of the solvents, finding the initial conditions of toluene/CH_2Cl_2 (2:1) to be optimal, although only marginally (Table 2.2, Entries A, B, C, and D). Next, temperature was investigated. No increase in selectivity was observed when the reaction was cooled to –40 °C; additionally, little erosion in selectivity was observed as the reaction was warmed to 0 °C (Table 2.2, Entries E, F, and G). At 0 °C, the product was obtained with a 90:10 er in only 45 min compared to a 93:7 er in 14 hours at –20 °C. These conditions (0 °C) are readily available to researchers without instrumentation to maintain a –20 °C bath overnight. Jacobsen previously reported that the inclusion of iodine as a co-catalyst improved the selectivity in his iodolactonizations,[150] so we added 10 mol % I_2 (Table 2.2, Entry H) and 1 mol % I_2 (Table 2.2, Entry I) but saw no improvement in enantioselectivity in either case. We later found that the reaction proceeded equally as well with only 5 mol % of catalyst (Table 2.2, Entry J), but we completed our studies with 10 mol % as most of the substrate exploration had already been completed when we tested the lower loading protocol.

Table 2.2 Optimization of the iodolactonization reaction



Entry	PhMe/CH_2Cl_2	Temp (°C)	Time (h)	Yield (%)[a]	er[b]
A[f]	2:1	–20	14	89	93:7
B[f]	1:0	–20	38	73	83:17
C[f]	1:1	–20	38	73	89:11
D[f]	1:2	–20	38	76	88:12
E	2:1	–40	38	86	93:7
F	2:1	–10	1.5	87	92:8
G	2:1	0	0.75	87	90:10
H[c]	2:1	–20	14	99	90:10
I[d]	2:1	–20	14	86	93:7
J[e]	2:1	–20	14	86	93:7

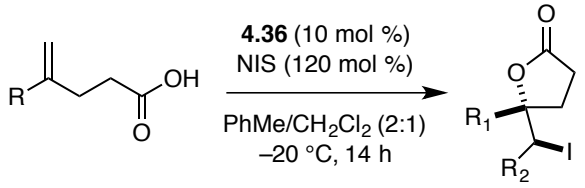
a) Isolated yield after column chromatography. b) er determined by chiral HPLC chromatography. c) with 10 mol % I_2. d) with 1 mol % I_2. e) reaction performs with 5 mol % catalyst. f) Chao Fang

4.2.2 Exploration of Iodolactonization Substrate Scope

4.2.2.1 Synthesis of Butyrolactones: 5-Exo-Iodolactonization Reactions

We began our exploration of the substrate scope by continuing with the 5-exo-iodolactonization reactions of geminally substituted olefinic acids. While electron-poor substrate **4.38** was lactonized to provide **4.42** with 90:10 er (Table 4.3, Entry D), the electron-rich **4.39** did not perform as well (Table 4.3, Entry C). This is presumably because the electron rich aromatic moiety can stabilize a carbocation at the benzylic position, which results in decreased selectivity as the carboxylate could attack from either face of the cation. We did find, in this case, that the addition of I_2 (10 mol %) improved the selectivity from 74:26 to 82:18 er for the lactonization of **4.39**. It remains unclear why I_2 helps in this case, though perhaps the iodonium ion derived from I_3^+ is further stabilized which attenuates ring opening to the carbocationic intermediate. We then tested alkyl substituted olefinic acids **4.40** and **4.41** and found that while methyl-substituted lactone **4.44** was obtained in only 65:35 er (Table 4.3, Entry D), catalyst **4.36** provided moderate selectivity with *tert*-butyl-substituted acid **4.41** (Table 4.3, Entry E).

Table 4.3 Iodolactonization of 4-substituted-4-pentenoic acid derivatives



4.18, 4.38-4.41 **4.37, 4.42-4.45**

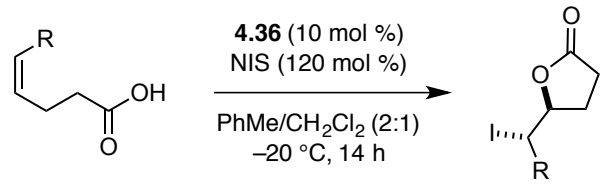
Entry	Acid	R	Product	Yield (%)[a]	er[b]-
A	**4.18**	Ph	**4.37**	89[d] (86)[c]	93:7 (93:7)[c]
B	**4.38**	*p*-NC-Ph	**4.42**	92[d]	90:10
C	**4.39**	*p*-MeO-Ph	**4.43**	90[e] (93)	74:26 (82:18)
D	**4.40**	Me	**4.44**	96[e]	65:35
E	**4.41**	*t*-Bu	**4.45**	91[e]	83:17

a) Isolated yield after column chromatography b) er determined by chiral HPLC chromatography c) Yields and er in parentheses obtained with the addition of I_2 (10 mol %) d) Daniel Paull e) Chao Fang

We continued our syntheses of butyrolactones with the lactonization reactions of *cis*-5-substituted-4-pentenoic acid derivatives (Table 4.4).[167] Across the board, for both alkyl- and aryl-substituted olefinic acids, we found that the lactones were obtained with the highest enantioselectivities of any substrate class. In the context of our working model (Section 3.5.3), this makes sense as the substrates can orient the two protons of the olefin towards the catalyst; whereas on other substrates, some amount of steric bulk will point in to the catalyst pocket. The 5-exo-cyclization pathway of the aryl-substituted olefinic acids **4.50**-**4.53** was interesting and initially counterintuitive, as one would predict a 6-endo cyclization based on the apparent electronic bias of the substrate. This can be explained through analysis of the transition state model (Figure 4.3). In order for the electronically preferred 6-endo-cyclization to occur, the π-system of aryl group needs

to be aligned to stabilize the positive charge as in **4.62**. However, this conformation induces $A^{1,3}$ strain between the aryl group and the aliphatic side chain, so it adopts conformation **4.64** to alleviate this strain leading to the kinetic 5-exo-cyclization product **4.65**.

Table 4.4 Iodolactonization of *cis*-5-substituted-4-pentenoic acid derivatives



4.46-4.53 **4.54-4.61**

Entry	Acid	R	Product	Yield[a]	er[b]
A	**4.46**	*i*-Pr	**4.54**	93	97:3
B	**4.47**	*i*-Bu	**4.55**	94[c]	98:2
C	**4.48**	*t*-Bu	**4.56**	99	97:3
D	**4.49**	Cy	**4.57**	97[d]	98.5:1.5
E	**4.50**	Ph	**4.58**	93[d]	98.5:1.5
F	**4.51**	*p*-NC-Ph	**4.59**	95[d]	99:1
G	**4.52**	*p*-Cl-Ph	**4.60**	89[d]	98:2
H	**4.53**	2-Np	**4.61**	94[d]	98:2

a) Isolated yield after column chromatography b) er determined by chiral HPLC chromatography c) Daniel Paull. d) Chao Fang

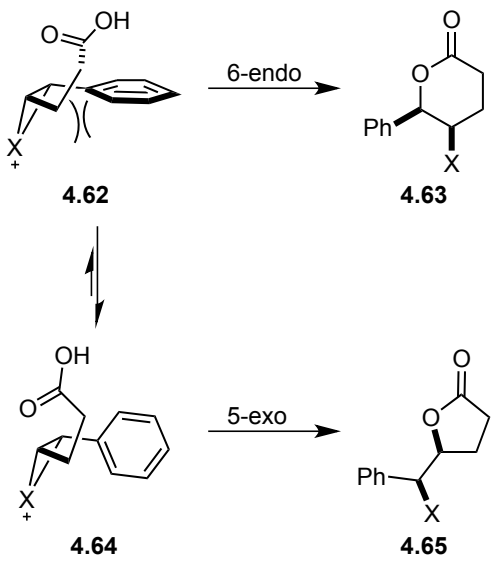
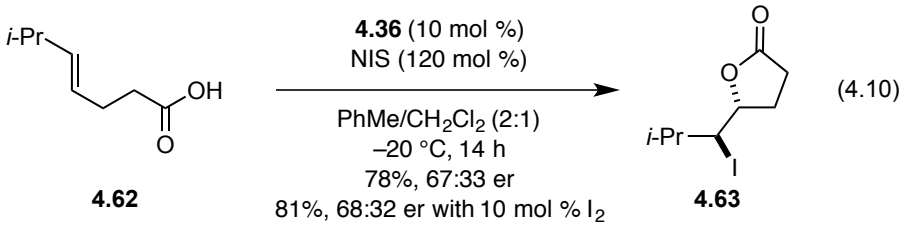
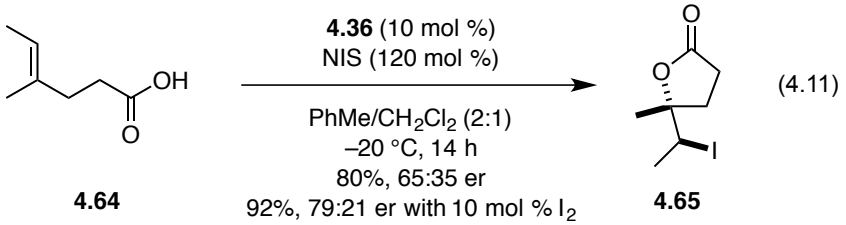


Figure 4.3 Cyclization pathways of the *cis*-5-aryl-substituted-4-pentenoic acids

We found iodolactonization of the *trans*-alkyl substituted olefinic acid **4.62** problematic (Equation 4.10), just like in the bromolactonization reactions. Intriguingly, acid **4.62** was the only substrate that provided lower enantioselectivity than the corresponding bromolactonization reaction. This low enantioselectivity was not improved with the inclusion of iodine. Another problematic substrate was tri-substituted acid **4.64**, which provided lactone **4.65** in only 65:35 er; however, unlike **4.62**, iodine did improve the selectivity up to 79:21 er. Thus, while iodine has not been found to be detrimental to any of the reactions, there was no clear trend to predict which substrates would benefit from the addition of iodine.

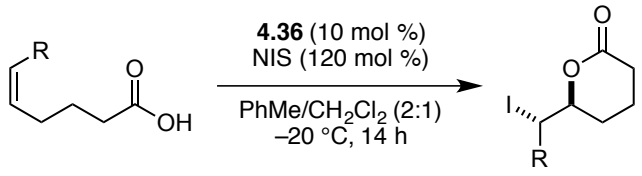




4.2.2.2 Synthesis of Valerolactones: 6-Exo-Iodolactonization Reactions

We then moved to the synthesis of valerolactones using our iodolactonization protocol. For *cis*-6-substituted-5-hexenoic acid derivatives **4.66-4.49** (Table 4.5), we observed similarly high yields and selectivities of the product lactones **4.70-4.73** as we did for the *cis*-substituted-5-exo substrates (Table 4.4). We then turned our attention to the geminally substituted substrates **4.72**-**4.74** (Table 4.6); however, we found the selectivities lacking; the selectivities were slightly enhanced with the inclusion of iodine. Finally, the tri-substituted olefinic acid **4.78** was subjected to the reaction conditions, but we saw only moderate levels selectivity, even with the inclusion of iodine (Equation 4.12).

Table 4.5 Iodolactonization of *cis*-6-substituted-5-hexenoic acids

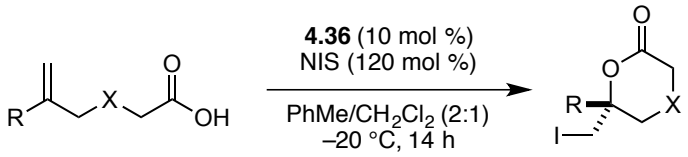


4.66-4.69 **4.70-4.71**

Entry	Acid	R	Product	Yield (%)[a]	er[b]
A	**4.66**	Ph	**4.70**	89[c]	99:1
B	**4.67**	*p*-NC-Ph	**4.71**	88[c]	99:1
C	**4.68**	2-Np	**4.72**	93[c]	98.5:1.5
D	**4.69**	*t*-Bu	**4.73**	98[c]	98:2

a) Isolated yield after column chromatography b) er determined by chiral HPLC chromatography. c) Chao Fang

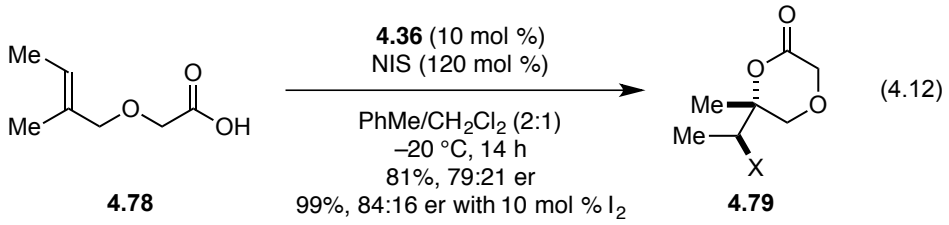
Table 4.6 6-Exo-iodolactonization reactions of geminally substituted acid derivatives



4.72-4.74 **4.75-4.77**

Entry	Acid	R	X	Product	Yield (%)[a]	er[b]
A	**4.72**	Ph	CH_2	**4.75**	98 (95)[c]	76:24 (85:15)[c]
B[d]	**4.73**	Me	CH_2	**4.76**	89 (90)	79:21 (80:20)
C	**4.74**	Ph	O	**4.77**	91 (89)	84:16 (90:10)

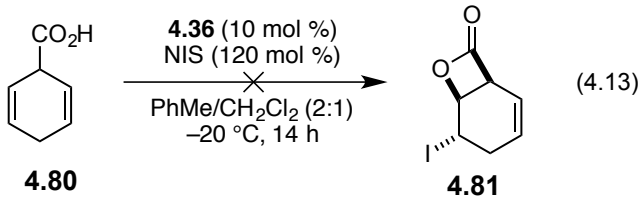
a) Isolated yield after column chromatography b) er determined by chiral HPLC chromatography c) Yields and er in parentheses obtained with the addition of I_2 (10 mol %) d) Chao Fang



(4.12)

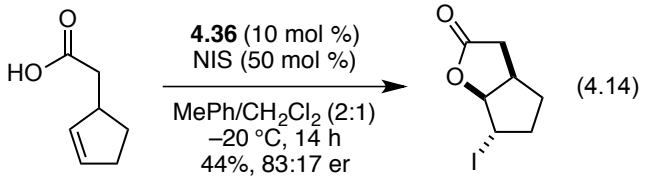
4.2.2.3 Desymmetrization, Kinetic Resolution, and Caprolactonization Reactions

Since a majority of the lactonization reactions worked better with NIS than TBCO, we thought that we might be able to perform the desymmetrization reaction with even better enantioselectivity. However, we found that while the reaction cleanly consumed diene **4.80** (Equation 4.13), the product **4.81** decomposed upon attempted isolation, even when shielded from light and oxygen.

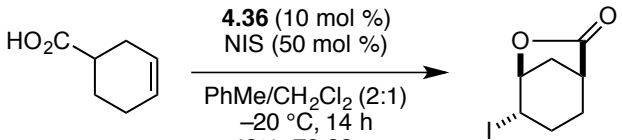


(4.13)

We saw an opportunity to develop a kinetic resolution of racemic olefinic acids, as at the time there were no reports of resolutions using halolactonization technology. To this end, olefinic acid **4.82** was subjected to iodolactonization with NIS (50 mol %) to provide iodolactone **4.83** in 44% yield in 83:17 er (Equation 4.14). Lactone **4.83** was used by Overman in the synthesis of (+)-sieboldine A and Helmchen in the synthesis of the jasmonoid family of natural products. [236-238] Similarly, cyclohexenoic acid **4.84** was subjected to the reaction conditions to furnish lactone **4.85** in 43% yield and 78:22 er. Martin used this lactone in his synthesis of (+)-phyllanthocin. [236]

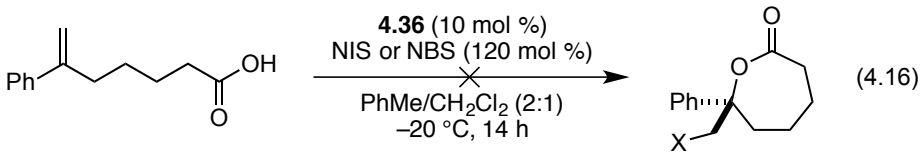


4.82 **4.83** (4.14)

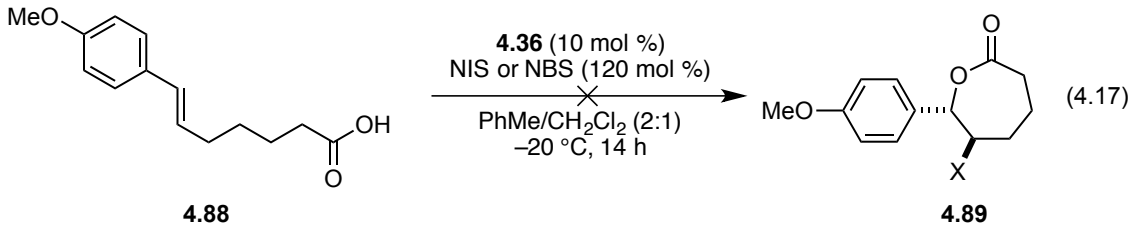


4.84 **4.85** (4.15)

In our attempts to expand the scope of the reaction further, we sought to synthesize caprolactones. To the best of our knowledge, this substrate class had not been attempted in the context of enantioselective halolactonization development. Unfortunately, both olefinic acid **4.86** and **4.88** failed to react. Acid **4.88** even failed to deliver the valerolactone product, though the electron rich aryl ring should have biased the substrate to the 7-endo cyclization pathway.



4.86 **4.87** (4.16)



4.2.4 Summary

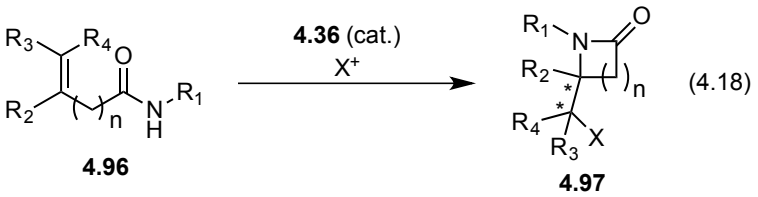
Through a systematic exploration of steric effects around our catalyst scaffold, we learned that catalyst **4.12** was the best catalyst for halolactonization reactions; however, in the development of an iodolactonization protocol we found reason to believe **4.36** to be the active catalyst. Furthermore, we extended the scope of the possible halolactonization reactions to iodolactonization reactions,[167] making catalyst **4.36** the first catalyst able to promote both iodo- and bromolactonization reactions. Finally, the substrate tolerance of catalyst **4.36** is extremely impressive. The range of substrates that **4.36** can lactonize with good to excellent enantioselectivities remains unrivaled. Due to the success of **4.36** in halolactonization reactions, we thought that we might be able to extend the utility of catalyst **4.36** further into a variety of halocyclization reactions.

4.3 BEYOND HALOLACTONIZATION REACTIONS

4.3.1 Halolactamization Reactions

A survey of the enantioselective halocyclization literature revealed that while numerous reactions have been developed, halolactamization reactions were absent (Equation 4.18). A number of halolactamization reactions that product racemic mixtures have been reported,[239-245] and one report of a diastereoselective halolactamization reaction using a chiral auxiliary exists.[246] Consequently, it was extremely surprising that this

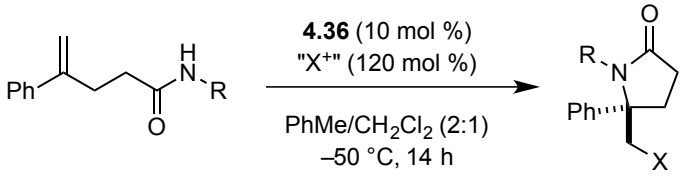
reaction had not been reported using catalyst control. Halolactams had been synthesized by oxidizing the product of an enantioselective haloaminations reactions,[185] but a direct reaction from an olefinic amide **4.96** would be ideal. Thus, we sought to extend the scope of our catalyst to this heretofore unexplored reaction type.



(4.18)

We chose to install an electron-withdrawing group on the amide nitrogen atom in order to increase the acidity of the substrate enough to coordinate to the catalyst, like we propose the olefinic acids do. To our delight, the reaction did progress when using mesyl **4.98**, tosyl **4.99**, and nosyl-sulfonimides **4.100**. Unfortunately, the enantioselectivities in these cyclizations were only moderate (ca. 70:30) (Table 4.7). During the course of these experiments, tried both NBS and DBDMH to effect the bromolactamization and found that the results were the same as TBCO (Table 4.7, Entries E and F). While the selectivities were somewhat lacking, to the best of our knowledge (ca. 2012) these reactions represented the first direct synthesis of enantioenriched halolactams, though Yeung was the first to report a bromolactamization protocol earlier this year, which provides halolactams in up to 95% ee.[247]

Table 4.7 Halolactamization reaction attempts



4.98-4.100 **4.101-4.104**

Entry	Amide	R	X^+	Product	Yield (%)[a]	er[b]
A	**4.98**	Ns	TBCO	**4.101**	85	71:29
B	**4.99**	Ts	TBCO	**4.102**	70	72:28
C	**4.100**	Ms	TBCO	**4.103**	70	71:29
D	**4.100**	Ms	NIS	**4.104**	70	71:29
E	**4.99**	Ts	NBS	**4.102**	90	70:30
F	**4.99**	Ts	DMDBH	**4.102**	80	72:28

a) Isolated yield after column chromatography b) er determined by chiral HPLC chromatography

We also explored the use of a Boc protected amide **4.105** for the halolactamization reactions (Equation 4.19). Interestingly, we isolated lactone **4.107** instead of the expected lactam **4.106** with the same enantioselectivity as the bromolactonization reaction (Equation 4.1). This type of cyclization was known in similar systems.[248] With this is mind we propose the following rationale for the high enantioselectivity for the lactones in comparison to the lactams. Once the acid has coordinated to the catalyst, the olefinic acids **4.108** and the Boc amide **4.109** cyclize from the coordinated position such that the carbonyl oxygen atom of the substrate acts as the nucleophile and ends up within the ring of the lactone (Figure 4.5). Conversely, the sulfonimides **4.110** must first release from the catalyst prior to C-N bond formation,

which may account for the decreased selectivity in the lactamization reactions. Though the reason why the sulfonimides release to form the lactams rather than cyclize to the imidate, which is hydrolyzed to the lacone, remains unknown.

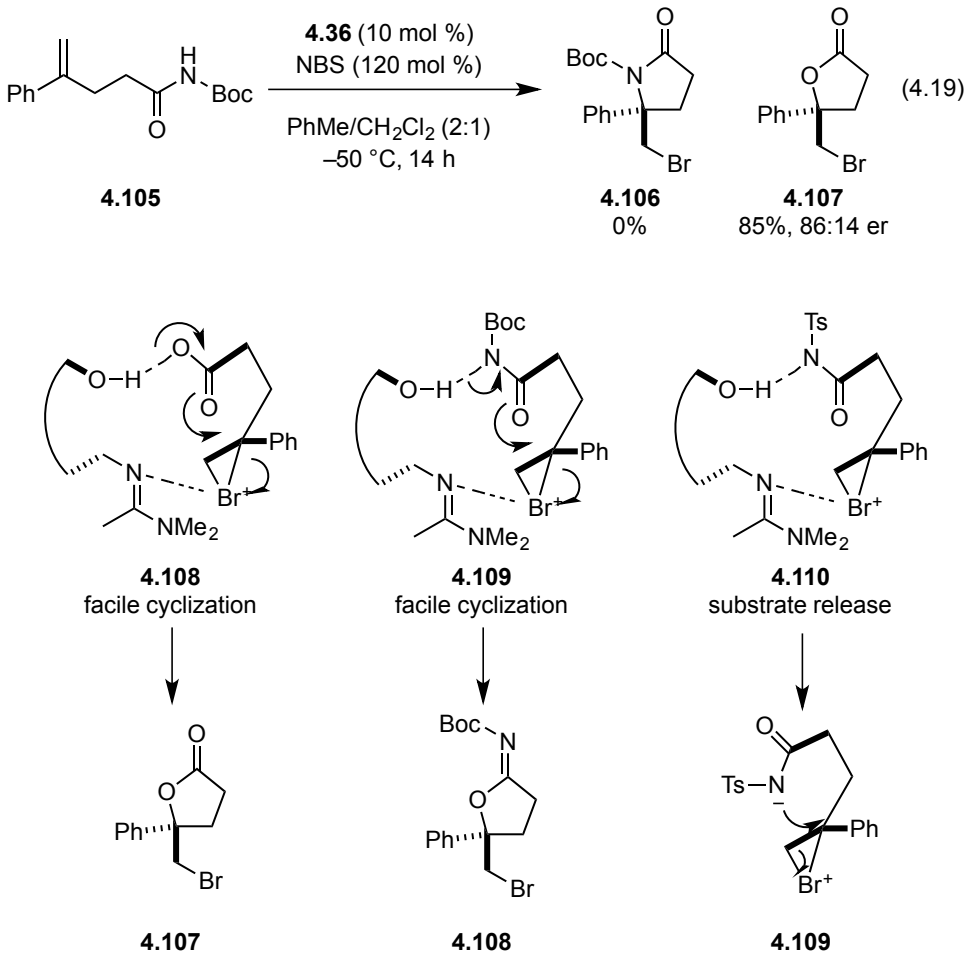
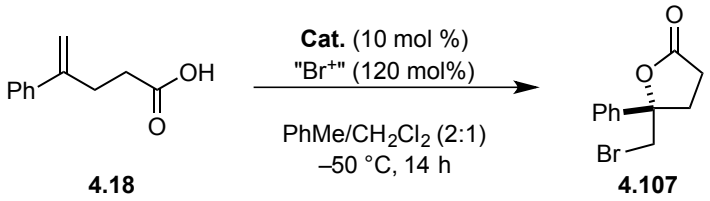


Figure 4.5 Lactonization pathways versus lactamization pathways

4.3.2 Extension of the Reagent Scope for Halolactonization Reactions

Because we found that the lactamization reactions proceeded with equal selectivities regardless of the halogenating reagents, we revisited the bromolactonization reactions. Whereas in preliminary studies, catalyst **4.12** was reported to only work with TBCO, we found that brominated catalyst **4.36** worked equally well with both NBS and DBDMH to provide lactone **4.107** (Table 4.8, Entries A and B). We reasoned that **4.36** may be a more reactive halogenating catalyst, which was why the bromolactonization studies with **4.12** were only successful with TBCO. Therefore, we retested **4.12** with NBS and DBDMH to find that the bromolactonization reactions were halogenating reagent independent with **4.12** as well (Table 4.8, Entries C, D, and E). Catalyst **4.36** was recovered from all three of the reactions. We also found the same results for the 6-endo cyclization reactions (Table 4.9). The fact that catalysts **4.12** and **4.36** are halogenating reagent independent makes these catalysts unique, as other catalysts in the literature only work well with a specific reagent, much like we initially thought **4.12** did.

Table 4.8 Bromolactonization reactions with various halogenating reagents

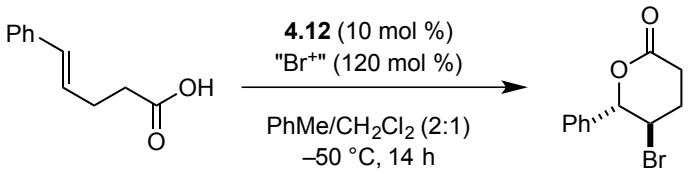


4.18 **4.107**

Entry	Catalyst	Br^+	Yield[a]	er[b]
A	**4.36**	NBS	95	87:13
B	**4.36**	DMDBH	90	87:13
C	**4.12**	TBCO	99	86:14
D	**4.12**	NBS	99	87:13
E	**4.12**	DMDBH	90	87:13

a) Isolated yield after column chromatography b) er determined by chiral HPLC chromatography

Table 4.9 6-Endo bromo lactonization reactions with various brominating reagents



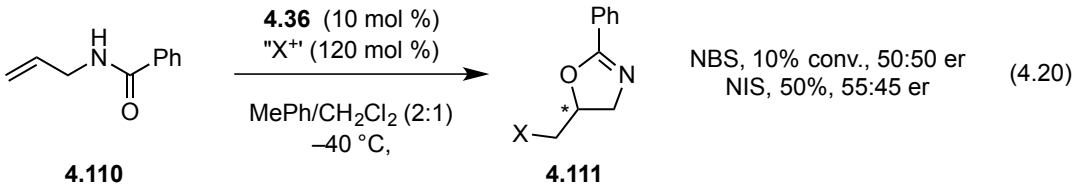
4.108 **4.109**

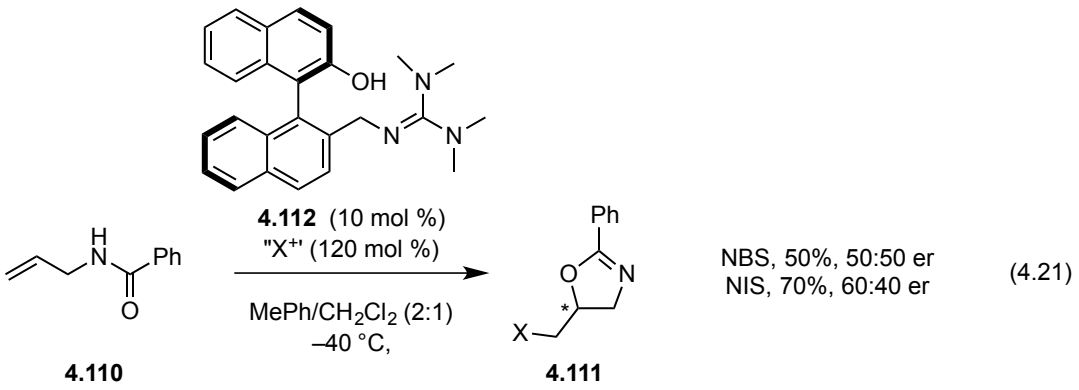
Entry	Br^+	Yield (%)[a]	er[b]
A	TBCO	94	98:2
B	NBS	92	99:1
C	DMDBH	92	99:1

a) Isolated yield after column chromatography b) er determined by chiral HPLC chromatography

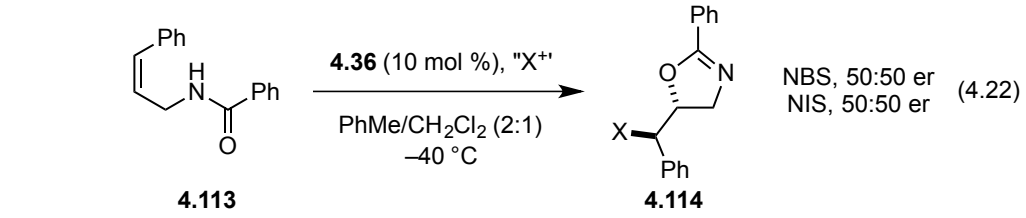
4.3.3 Halo-Oxazolination Reactions

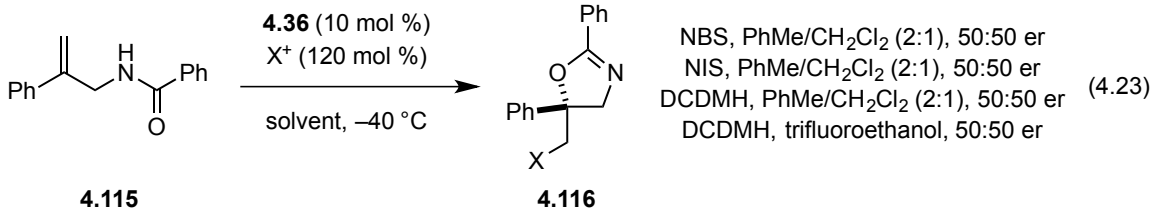
Since we hypothesized that the lactonization reactions worked so well because the substrate could cyclize from the coordinated transition state (Figure 4.5), we imagined that halo-oxazolination reactions of olefinic amides would work well. In initial experiments we found the cyclization of **4.110** to be sluggish and provide poor enantioselectivities (Equation 4.20). We thought that this could be due to the attenuated acidity of the amides in comparison to the acids and imides, so we attempted the cyclization with a more basic guanidine catalyst **4.112**. However, while the conversion increased, the selectivity remained about the same (Equation 4.21).





We attempted similar transformations on the *cis*-aryl substituted amide **4.113** as our *cis*-alkyl/aryl acids provided the highest enantioselectivities; however, we only isolated oxazoline **4.114** as a racemic mixture. Additionally, we tried the geminally substituted amide **4.115**, but observed no enantioenrichment in these attempts (Equation 4.23)





4.3.4 Summary

During the course of these studies, we found catalyst **4.36** to be the most remarkable catalyst in the halolactonization field. It was the first catalyst able to induce both bromo- and iodolactonization reactions with high enantiomeric excess. Catalyst **4.36** was the first catalyst reported that formed C-I bonds at exocyclic stereogenic centers. Furthermore, the range of substrates that **4.36** can lactonize with excellent enantioselectivities remains unrivaled.

While the enantioselectivities were lacking, this catalyst was, to the best of our knowledge, the first to provide enantioenriched halolactams from olefinic sulfonimides. During the course of the lactamization studies, we found that catalyst **4.36** is brominating reaction independent, which makes the catalyst unique. To our chagrin, **4.36** was ineffective at almost all other types of halocyclization reactions (oxazolination, etherification,[226] and aminocyclization[249]), thus we sought to develop a new BINOL-based catalyst that could further our development in the field.

4.4 Selenium-Based Chiral Lewis Base Catalysis for Halocyclizations

4.4.1 Inspiration

As chalcogens, specifically selenium, have been shown to be highly effective as achiral halogenation catalysts,[250-253] we thought that a chiral BINOL-based chalcogenide might be an excellent halocyclization catalyst. We tested dibenzylselenide in halo-aminocyclizations and etherification reactions to confirm the reports, and while the initial aminocyclization failed, the etherification progressed cleanly at –50 °C (Equations 4.24 and 4.25). This idea materialized as three independent strategies: the use of dibenzylselenide as a co-catalyst with **4.36**, the use of C_2-symmetric catalyst **4.121**, or the development of a new bifunctional catalyst **4.122** (Figure 4.6). With these ideas in mind, we set out to test our hypothesis in order of increasing difficulty with respect to catalyst synthesis.

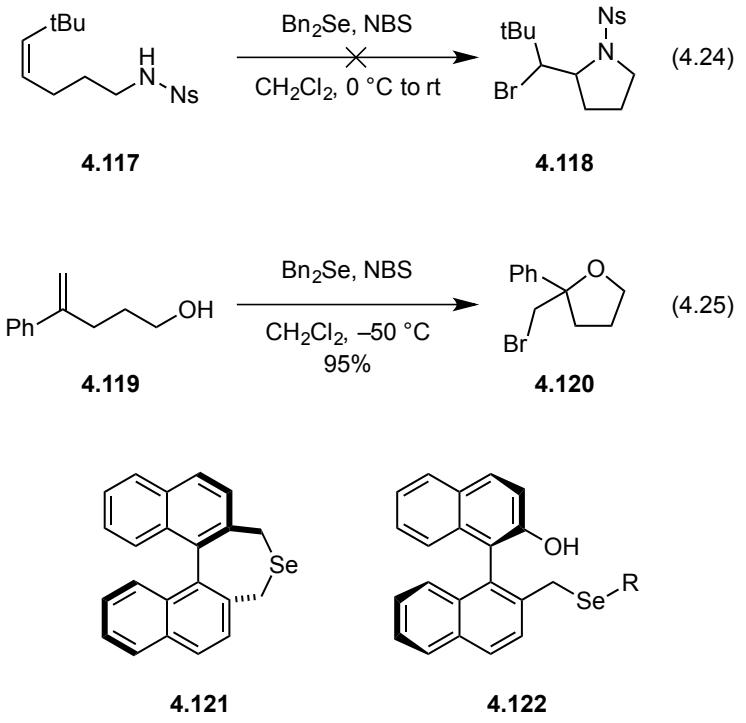
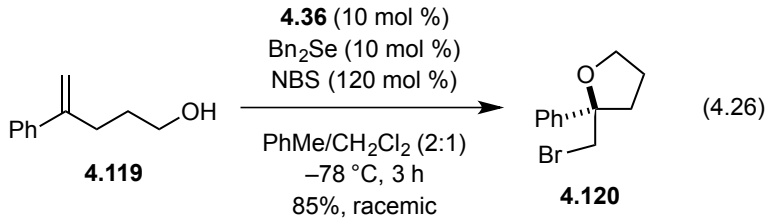


Figure 4.6 Selenide catalyst designs

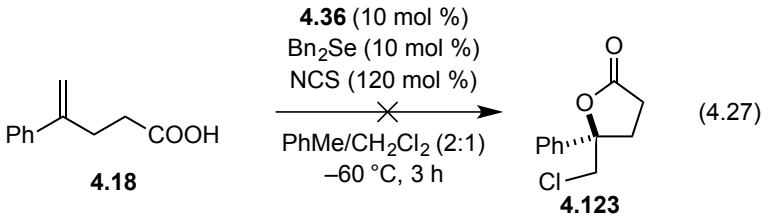
4.4.2 Selenide Co-Catalyst

The easiest possibly required the use of dibenzylselenide as a co-catalyst with **4.36**. Disappointingly, in the bromoetherification reaction using **4.119**, only *rac*-**4.120** was obtained (Equation 4.26). While the reaction did not occur in the absence of **4.36** or Bn_2Se, both reactions with and without **4.36** in the presence dibenzylselenide progressed at the same rate. Thus, we thought that **4.36** might not be involved at all in the catalysis. With this in mind, we turned our attention to chlorolactonization reactions, which had been unsuccessful with catalyst **4.36**. Since the chlorolactonization reaction did not progress with NCS, **4.36** with NCS, or Bn_2Se with NCS, we imagined that Bn_2Se might serve to provide a more reactive chlorinating reagent, Bn_2SeCl^+, *in situ*. If this reagent

could transfer the chloronium to **4.36** then perhaps a chlorolactonization reaction would be successful. Unfortunately, no reaction was observed (Equation 4.27).



(4.26)



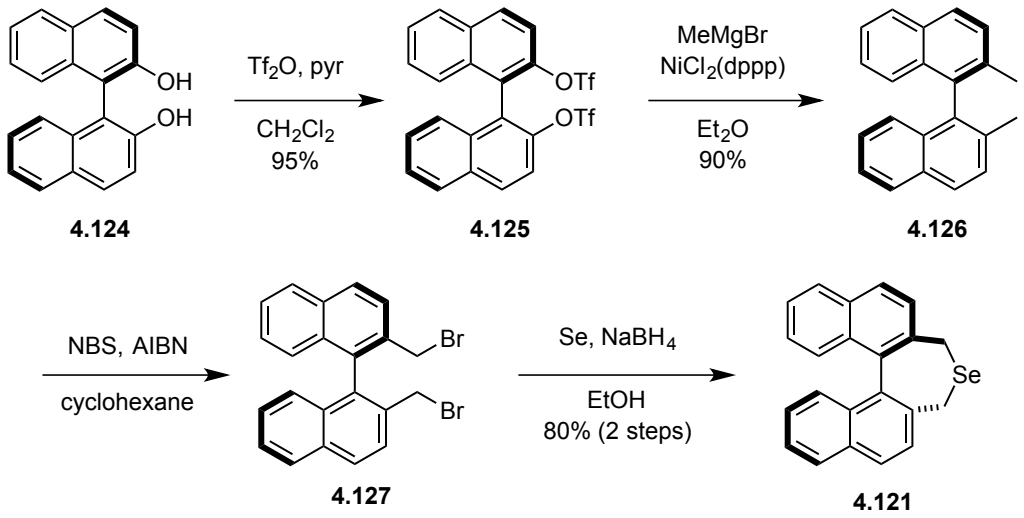
(4.27)

4.4.3 Monofunctional C_2-Symmetric Selenide Catalyst

Until recently, a survey of the literature suggested that bifunctional catalysts were required to obtain a high degree of enantioselectivity in halocyclization reactions; however, we thought that a C_2-symmetric catalyst like **4.121** might be able to differentiate between the faces of the olefin and provide enantioselectivity. Chiral selenide **4.121** has been used as a stoichiometric reagent for the oxidation of sulfides and resolution of ferrocenylphosphine compounds,[254,255] but its use as a catalyst in any context was heretofore unknown.

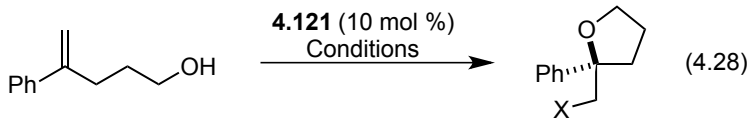
The synthesis commenced with the triflation of BINOL (**4.124**) to provide **4.125** in 95% yield. Cross-coupling with methylmagnesium bromide delivered **4.126** in 90% yield, and subsequent free radical bromination gave **4.127**. Finally, selenide formation

afforded **4.121** in 80% yield over two steps. We then set out to explore the effectiveness of this catalyst in halocyclization reactions.



Scheme 4.3 Synthesis of selenide **4.121**

In a variety of haloetherifications reactions, we found that while **4.121** cleanly provided the product tetrahydrofurans **4.128**, there was no enantioenrichment observed (Equation 4.28). We also screened these conditions in halopolyenecyclization reactions. Our rationale was based on Snyder's protocol for halopolyenecyclization reactions using bromodiethylsulfonium bromopentachloroantimonate (BDSB) (Equations 4.29 and 4.30).[256,257] As the halonium ion was delivered from a sulfonium reagent, we thought the selenonium intermediate would provide similar results. However, we were disappointed to find that we were unable to get the reactions to progress (Equations 4.31 and 4.32).

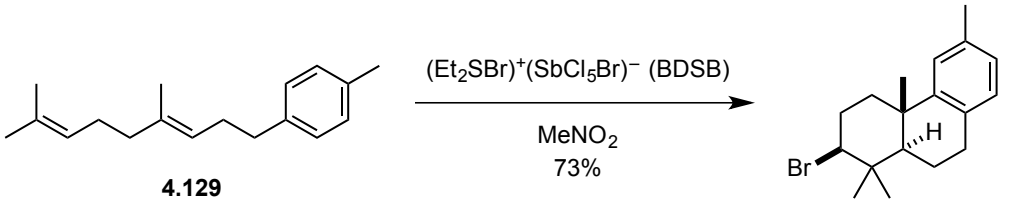


(4.28)

4.119 **4.128**

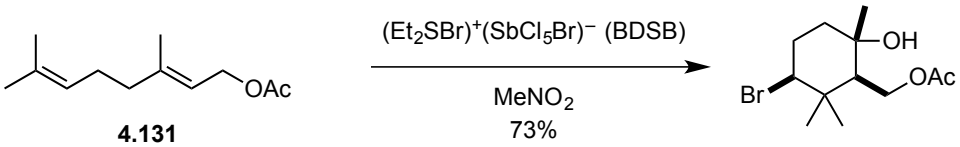
Conditions

NBS, CH_2Cl_2 (0.1 M), –78 °C, 1.5 h, 90%, racemic
NBS, CH_2Cl_2 (0.03 M), –78 °C, 2 h, 90%, racemic
NBS, PhMe/Ch_2Cl_2 (2:1) (0.03 M), –78 °C, 9 h, 80%, racemic
NBS, PhMe (0.03 M), –78 °C, 9 h, 15%, racemic
NIS, CH_2Cl_2 (0.03 M), –78 °C, NR
NCS, CH_2Cl_2 (0.03 M), –78 °C NR



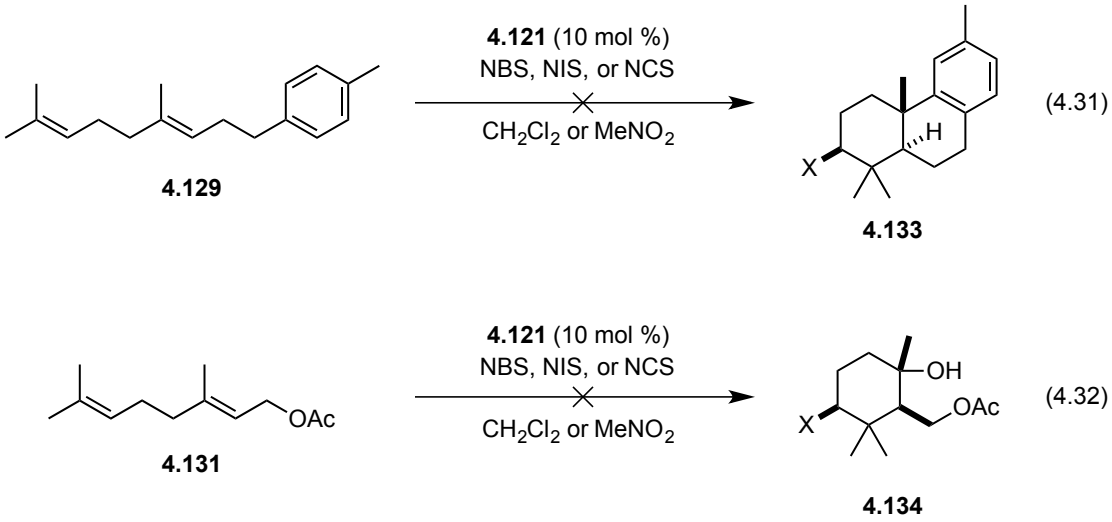
(4.29)

4.129 **4.130**

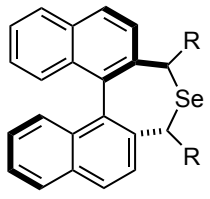


(4.30)

4.131 **4.132**

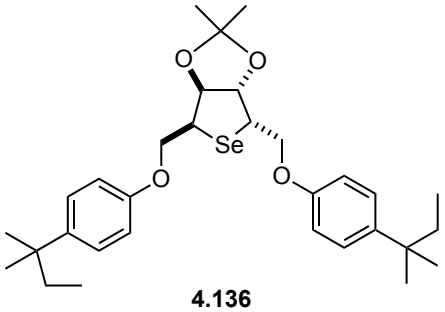


We imagined that we would be able to induce selectivity if we placed some steric bulk closer to the catalophore, represented by design **4.135**. As we were working on this C_2-catalyst design, Yeung reported his own C_2-symmetric catalyst **4.136** (Figure 4.8),[188] which confirmed the hypothesis we had planned to test with derivatives **4.135**. Yeung's protocol effected the bromo-aminocyclization of trisubstituted olefinic sulfonamides in good yields with good enantioselectivity (Equation 4.33). With this report, we decided to move away from the C_2-symmetric selenides, with hope that a bifunctional selenide catalyst would prove as effective in halocyclization reactions as our bifunctional catalyst **4.36** did.



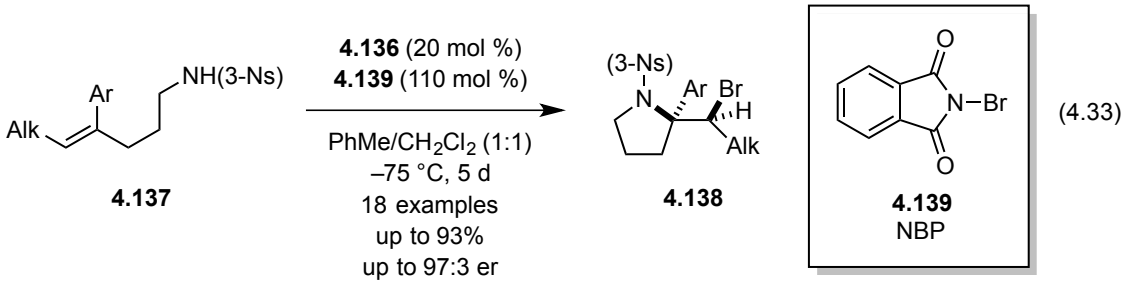
4.135

Figure 4.7 New C_2-symmetric catalyst design



4.136

Figure 4.8 Yeung's C_2-symmetric selenide catalyst

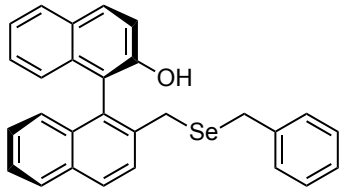


(4.33)

4.4.4 Bifuncational Selenide Catalyst

4.4.4.1 Synthesis of a Bifunctional Selenide Catalyst

Based on the success of our bifunctional catalyst **4.36**, we set out to synthesize catalyst **4.140** (Figure 4.9). We imagined that this catalyst might work much like catalyst **4.36**, wherein the catalyst would be brominated to provide **4.141** and subsequently deprotonated to provide **4.142** (Figure 4.10). Intermediate **4.142** then has a handle to hydrogen bond to the substrate as well as deliver the bromonium. With this in mind, we set out to prepare **4.140**.



4.140

Figure 4.9 Bifunctional selenide catalyst design

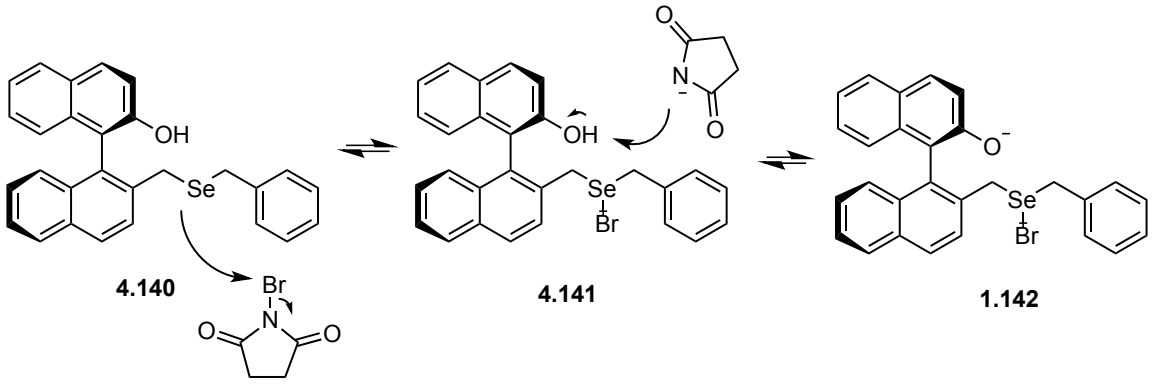
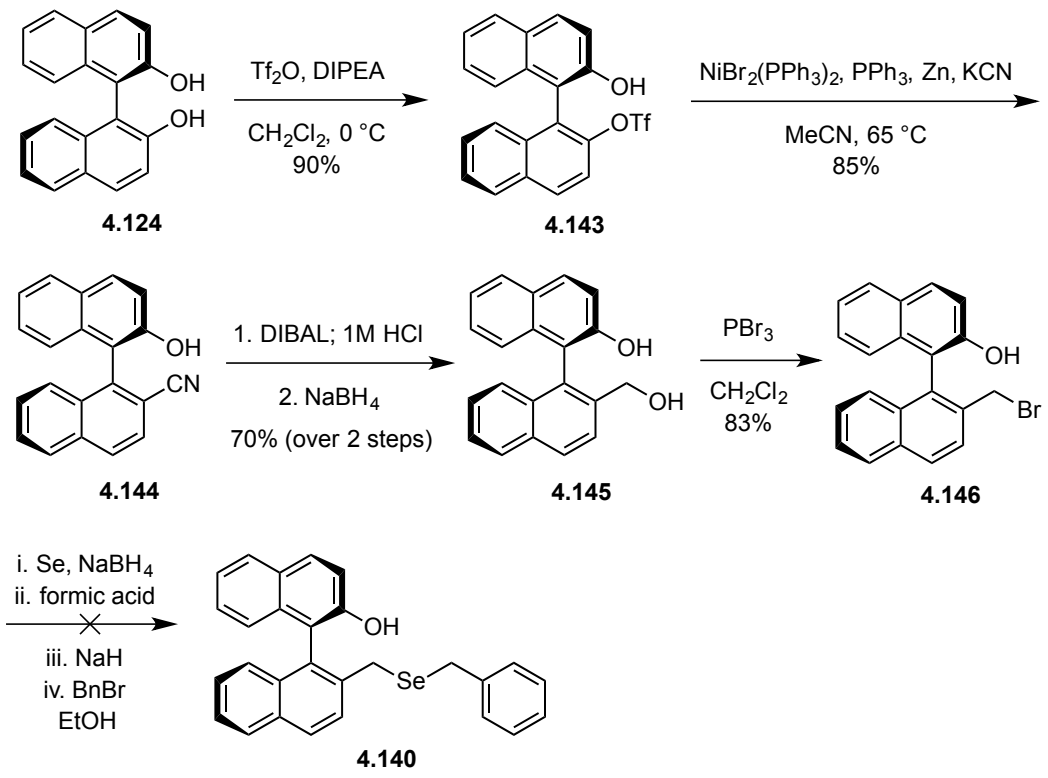


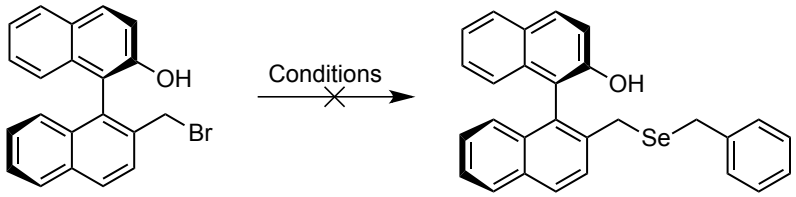
Figure 4.10 Rationale of bifunctionality in catalyst **4.140**

Toward this end, BINOL (**4.124**) was monotriflated to provide **4.134** and coupled with potassium cyanide to give **4.144** (Scheme 4.4). Two-step reduction of the nitrile moiety provided diol **4.145**,[258] which was brominated to provide the penultimate intermediate **4.146**. We were disappointed to find that while **4.146** was synthesized with ease, the final one-pot mixed selenide synthesis failed.[259] We then set out to find appropriate selenide forming conditions.



Scheme 4.4 Attempted synthesis of **4.140**

Generation of the mixed selenide from **4.146** and benzyl bromide failed to produce **4.140** (Equation 4.34). Reaction of **4.146** with sodium benzyl selenide, derived from the reduction of dibenzyldiselenide with zinc or sodium borohydride, led to no desired product formation.[260,261,262] Finally, although the literature suggested that free alcohols were tolerated in selenide formation reactions, *in situ* protection of the naphthol moiety prior to introduction of the zinc selenide failed as well. Mitsunobu-like selenide formation with *N*-(phenylseleno)phthalimide (NPSP, **4.148**) using Nicolauo's protocol also failed (Equation 4.35).[263,264] As the coupling of triflate **4.143** with potassium cyanide using a nickel catalyst proceeded with ease, we tried the known selenide cross-coupling conditions to no avail (Equation 4.36).[265]

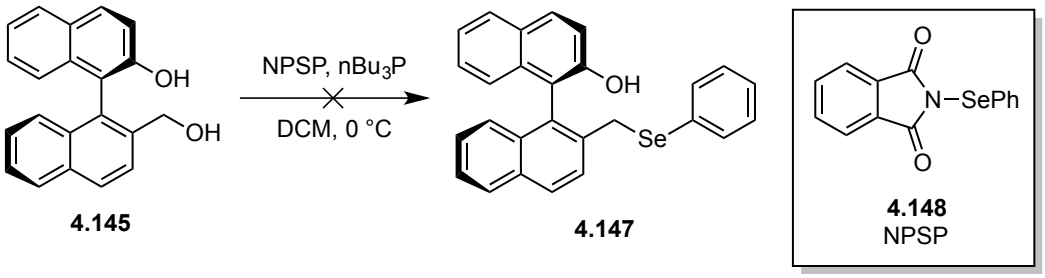


(4.34)

4.146 **4.140**

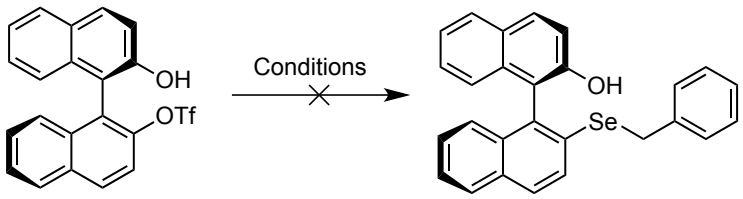
Conditions

1. Se, $NaBH_4$, EtOH; BnBr; **4.146**
2. $(BnSe)_2$, Zn, CH_2Cl_2, RT
3. $(BnSe)_2$, Zn, $AlCl_3$, MeCN/H_2O
4. $(BnSe)_2$, $NaBH_4$, EtOH
5. DIPEA, TMSCl; $(BnSe)_2$, Zn, CH_2Cl_2



(4.35)

4.145 **4.147** **4.148** NPSP



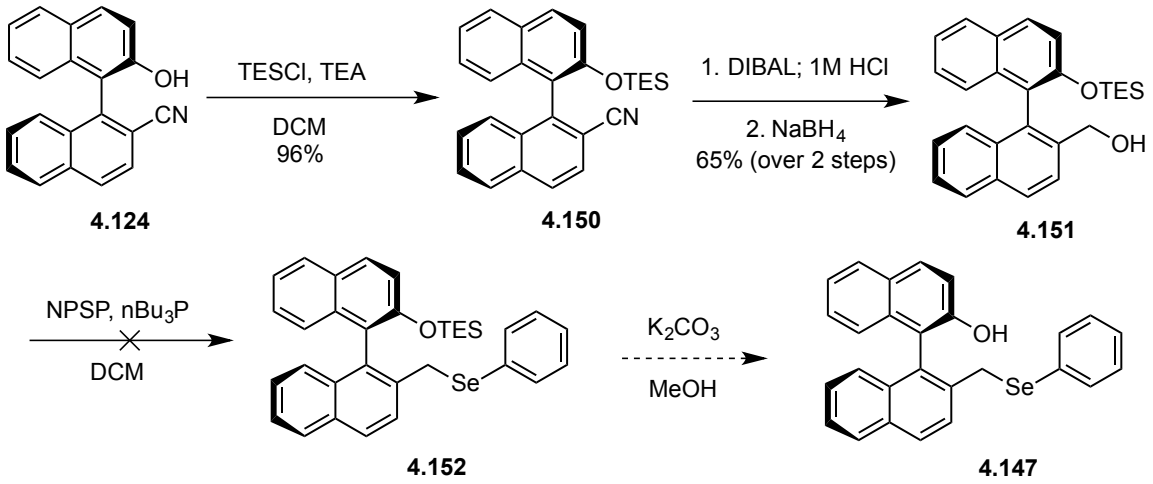
(4.36)

4.143 **4.149**

Conditions

$NiBr_2$, PPh_3, Zn, $(BnSe)_2$, DMF, 110 °C
$NiBr_2$, bpy, Zn, $(BnSe)_2$, DMF, 110 °C
$NiBr_2(PPh_3)_2$, PPh_3, Zn, $(BnSe)_2$, MeCN, 70 °C

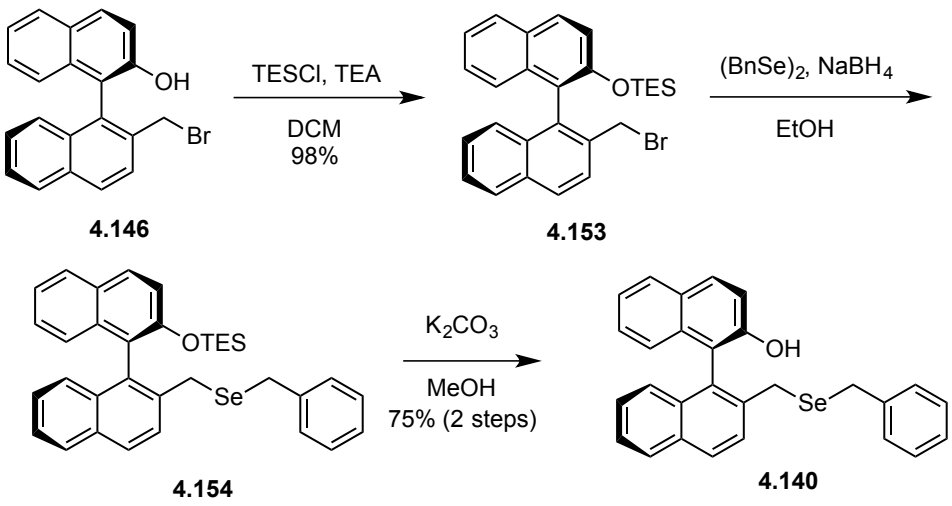
While the literature suggested that free alcohols were tolerated in these reactions and *in situ* protection of the naphthol had previously failed, we turned our attention to protecting the naphthol prior to the selenide formation. This strategy began by protecting nitrile **4.124** as the triethylsilylnaphthol **4.150** (Scheme 4.5). Two-step reduction of the nitrile group delivered **4.151** in 65% yield over two steps as well as the deprotected diol **4.145**. Unfortunately, treatment of **4.151** failed to provide the desired selenide **4.152**.



4.124 **4.150** **4.151** **4.152** **4.147**

Scheme 4.5 Attempted synthesis of **4.147**

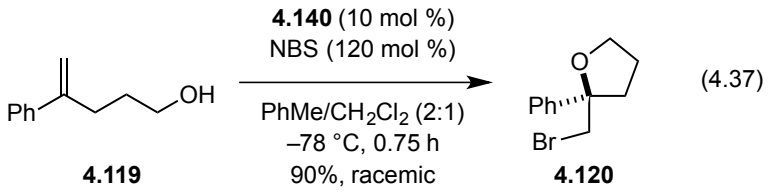
We then returned to the alkylation of metal selenides with a naphthyl halide. To this end, bromide **4.146** was protected as the triethylsilyl naphthol **4.153** in 93% yield (Scheme 4.6). We were pleased to find that upon exposure to sodium benzylselenide, derived from the reduction of dibenzyl diselenide with sodium borohydride, that **4.153** underwent selenation to provide selenide **4.154** in 75% yield. Finally, deprotection of the naphthol delivered our proposed catalyst **4.140**.



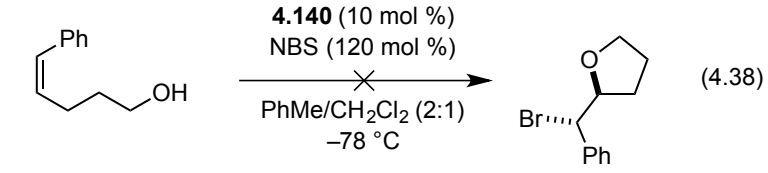
Scheme 4.6 Synthesis of catalyst **4.140**

4.4.4.2 Test Reactions with Bifunctional Selenide Catalyst 4.140

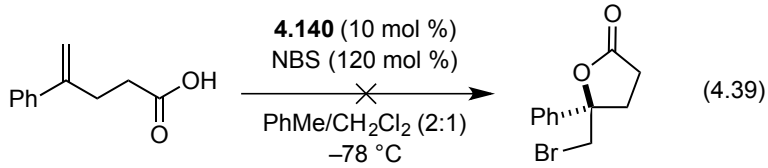
We were disappointed to find that that when **4.119** was subjected to bromoetherification with catalyst **4.140**, only *rac*-**4.120** was isolated in 90% yield (Equation 4.37). We attempted the cyclization of **4.155**, as the selectivities of the *cis*-substituted olefins provided the highest selectivities with **4.36**, but found that the cyclization returned starting material (Equation 4.38). This catalyst also failed to perform halolactonization reactions (Equations 4.39, 4.40, and 4.41). Though the cause of the deficiency in selectivity remains unknown, we propose that it arises from a lack of selectivity in the halogenation of the catalyst. Upon exposure to NBS, catalyst **4.140** might provide diastereomeric selenonium intermediates **4.160** and **4.161** (Equation 4.42). This problem is obviated in C_2-symmetric catalysts like **4.162** (Equation 4.43).



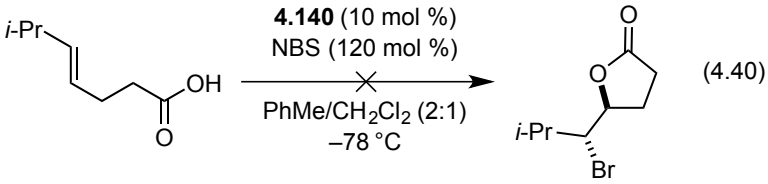
4.119 **4.120** (4.37)



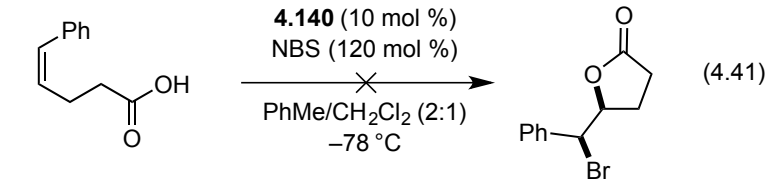
4.155 **4.156** (4.38)



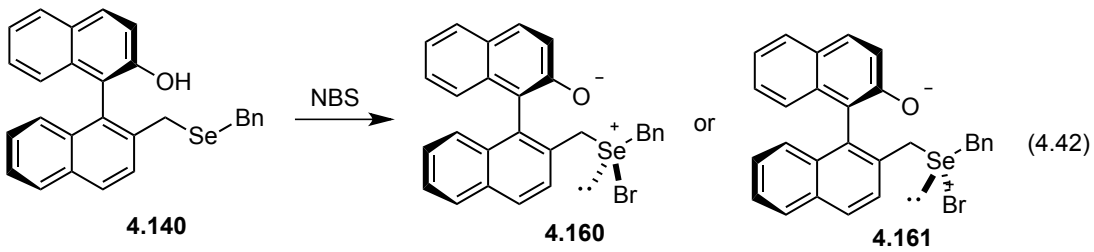
4.18 **4.157** (4.39)



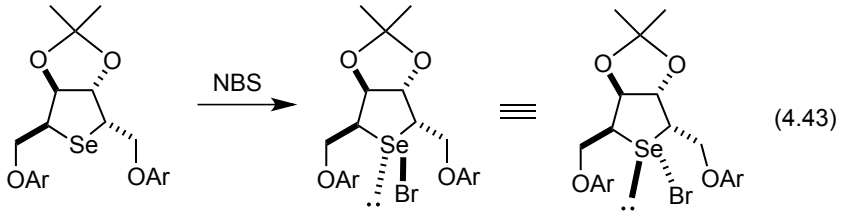
4.62 **4.158** (4.40)



4.66 **4.159** (4.41)



4.140 4.160 4.161 (4.42)



4.162 4.163 4.163 (4.43)

4.4.5 Summary

As both our newly designed selenide catalysts failed to induce enantioselective halocyclizations, we assessed the value of continuing to pursue this goal. Yeung had demonstrated the first C_2-symmetric selenide catalyst, so we decided that if we were to continue in this field that we would need to focus on the bifunctional selenides. However, as discussed above there are inherent problems with these catalyst designs. In order to find a feasible catalyst, numerous derivatives would need to be synthesized, resulting in a high-risk situation wherein a functional catalyst may never be found. We therefore decided to stop our pursuit of a chalcogen-based catalyst.

PROGRESS TOWARDS THE TOTAL SYNTHESIS OF JIADIFENOLIDE

Chapter 5: Jiadifenolide – Isolation and Previous Syntheses

5.1 ISOLATION

Natural products that promote the growth of neurons are quickly becoming a focus in the synthetic community as they could prove to be promising drug leads for the treatment of both acute and chronic neurological conditions.[266] These natural products either mimic or enhance the effect of neurotrophins, proteins responsible for the development and maintenance of neurons.[267] Unfortunately, these proteins are limited in their utility as drugs because they cannot be administered orally and present difficulty in crossing the blood-brain barrier. Therefore, in an ongoing search to find treatments for neurological diseases, such as Alzheimer's and Parkinson's disease, many groups are turning towards small molecules for inspiration.[268]

The *Illicium* sesquiterpenoids comprise jiadifenolide (**5.1**),[269] majucin (**5.2**),[270] jiadifenin (**5.3**),[271] anisatin (**5.4**),[272] and jiadifenoxolanes A/B (**5.5**/**5.6**)[269] among others (Figure 5.1). While anisatin (**5.4**) and the related molecules that bear a β-propiolactone moiety are toxic and lead to neurodegeneration,[269,272] the majucin-type *Illicium* sesquiterpenoids **5.1**, **5.2**, **5.3**, **5.5**, and **5.6**, which characterized by their γ-butyrolactone moeity, promote neurite outgrowth.[269] Due to their compact and complex architecture paired with their interesting neurological activity, this family of natural products has attracted significant attention from the synthetic community,[273] though jiadifenoxolanes A and B (**5.5** and **5.6**) have yet to succumb to total synthesis.

Jiadifenolide **(5.1**) is the most potent member of this family discovered to date, promoting neurite outgrowth in rat corticoid neurons at 10 nM concentrations in the

presence of nerve growth factor.[269] Additionally, it contains a densely functionalized cyclohexane moiety and seven contiguous stereocenters, which add a significant challenge to its synthesis. To date, Theodorakis,[274-276] Sorensen,[277] Paterson,[278] Shenvi,[279] and Zhang[280] have reported syntheses of jiadifenolide (**5.1**).

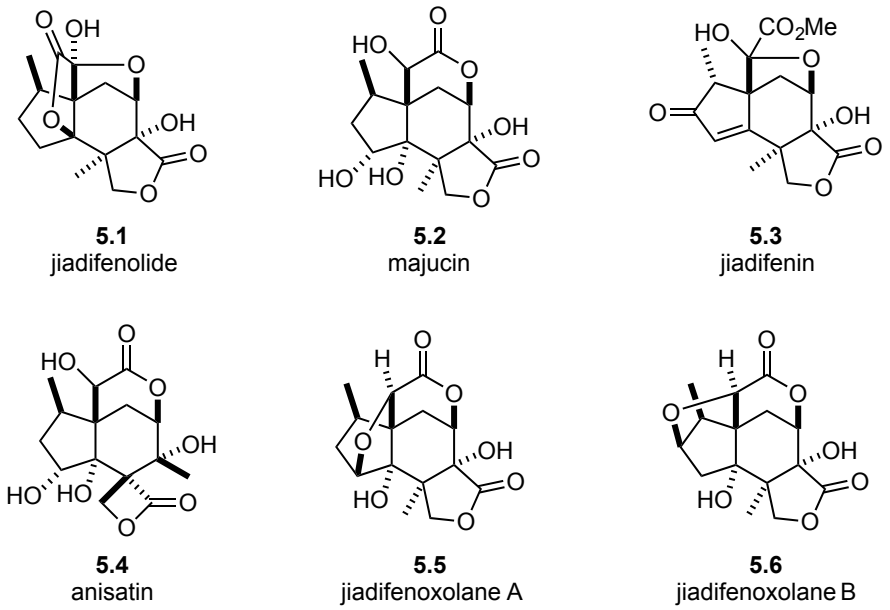


Figure 5.1 Representative members of the *Illicium* sesquiterpenoids.

5.2 PREVIOUS SYNTHESES OF JIADIFENOLIDE (5.1)

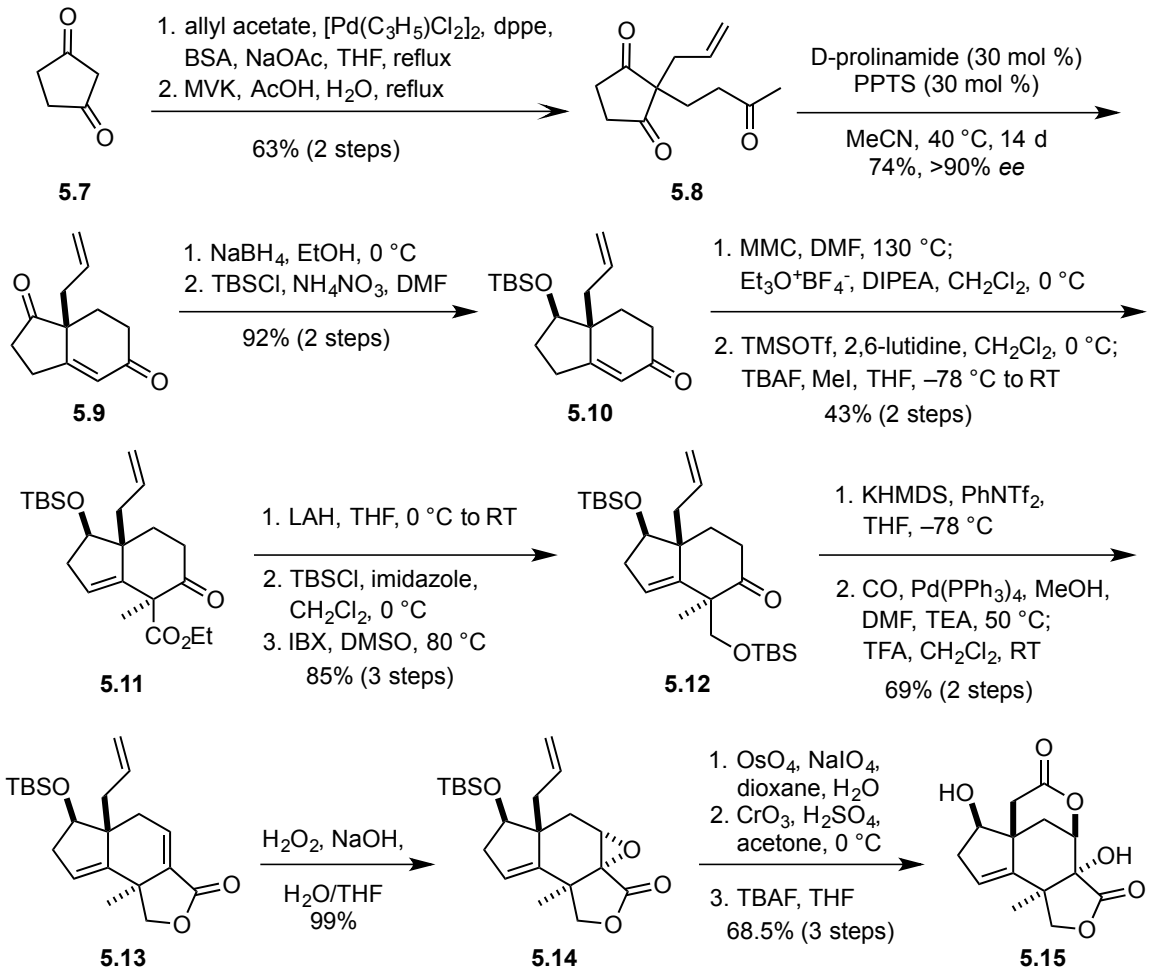
5.2.1 Theodorakis's Total Synthesis of (–)-Jiadifenolide

5.2.1.1 Synthesis of (–)-Jiadifenolide

Theodorakis began his synthesis with the preparation of trione **5.8** via a Tsuji allylation of dione **5.7** followed by a Michael addition into methyl vinyl ketone (MVK) to provide **5.8** in 63% yield over two steps (Scheme 5.1).[274] Treatment of **5.8** with D-prolinamide completed the two-pot Robinson annulation to afford enone **5.9** in 74% yield

with >90% ee. Stereoselective reduction followed by protection proceeded smoothly to afford **5.10**, which was subsequently subjected to a sequential carboxylation reaction using magnesium methyl carbonate (MMC) and methylation to give β-keto ester **5.11** in a modest 43% yield.

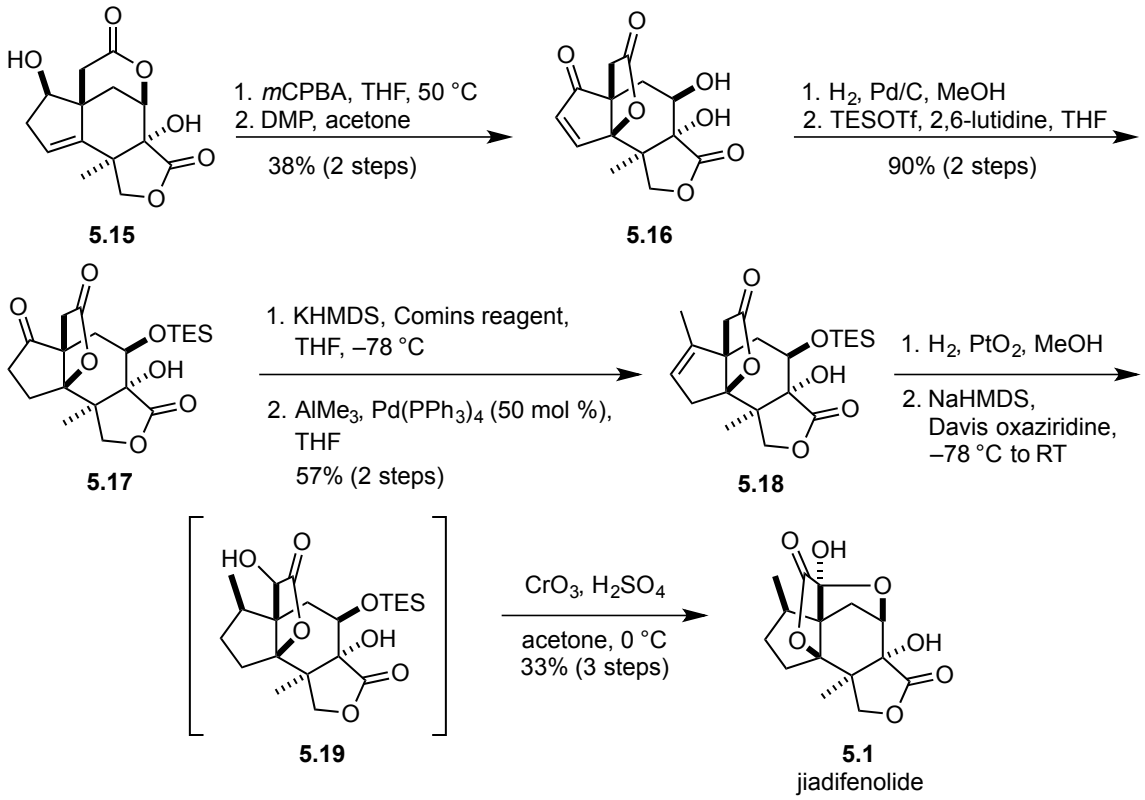
Focus then turned to the construction of the fused γ-butyrolactone and bridged δ-lactone moieties through elaboration of the β-keto ester and allyl functionalities. The lengthy sequence commenced with the reduction of both the ketone and the ester of **5.11** with lithium aluminum hydride, followed by protection of the primary alcohol and oxidation of the secondary alcohol. Ketone **5.12** was converted to a vinyl triflate, which allowed for the assembly of γ-lactone **5.13** via an intramolecular palladium-catalyzed carbonylative alkoxylation. Formation of the bridged δ-lactone proceeded through epoxide **5.14** followed by two additional oxidations. Finally, deprotection with tetrabutylammonium fluoride (TBAF) afforded tetracycle **5.15** in 19 steps and 7.2% overall yield from **5.7**. Intermediate **5.15** was then used to diverge to three of the *Illicium* sesquiterpenoid natural products: jiadifenolide (**5.1**), jiadifenin (**5.3**), and ODNM (**5.23**).



Scheme 5.1 Synthesis of key intermediate **5.15** by Theodorakis.

With their key intermediate **5.15** in hand, jiadifenolide (**5.1**) was a mere nine steps away (Scheme **5.2**). Rearranged tetracycle **5.16** was attained via a two-step oxidation procedure. In the event, **5.15** was epoxidized from the top face, which upon oxidation of the alcohol underwent isomerization and translactonization from the bridged δ-lactone to the fused γ-lactone **5.16**. Hydrogenation of the enone and protection of the secondary alcohol led to **5.17**, which was further transformed into a vinyl triflate and cross-coupled

with trimethyl aluminum to give **5.18**. Finally, a series of redox transformations delivered jiadifenolide (**5.1**) in 28 steps with an overall 0.47% yield.



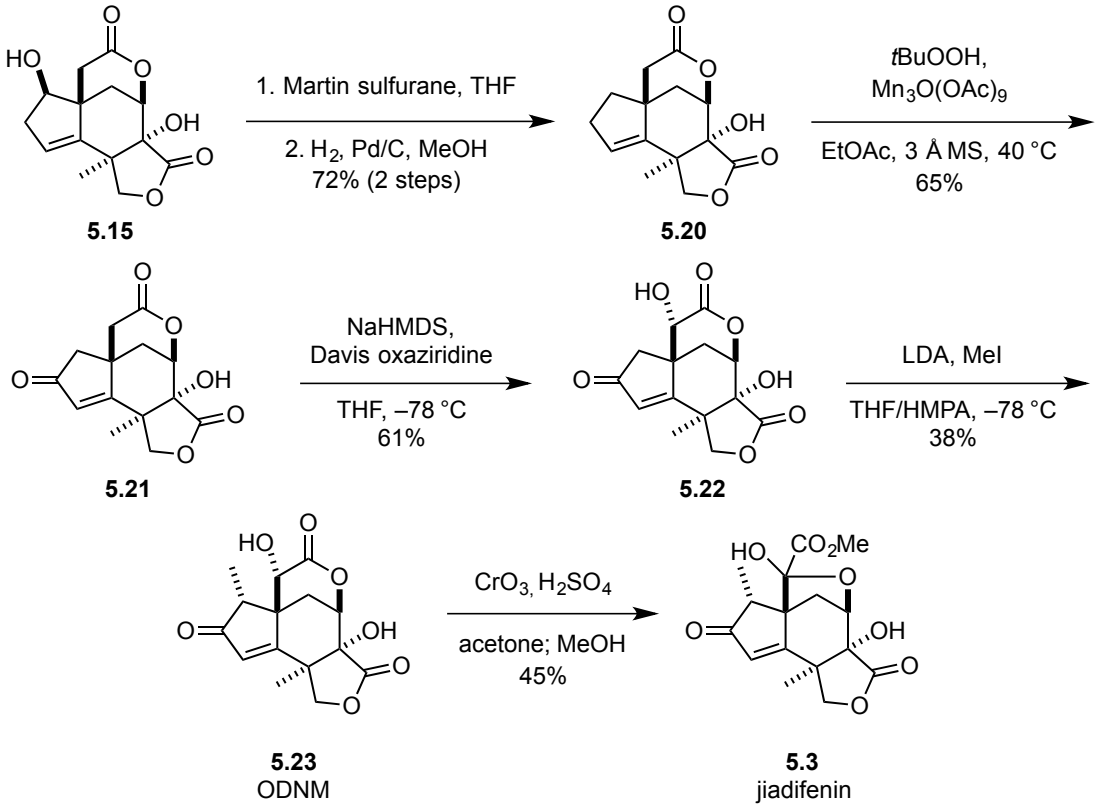
Scheme 5.2 Synthesis of jiadifenolide (**5.1**) by Theodorakis.

Overall, the Theodorakis synthesis of jiadifenolide (**5.1**) was lengthy and low yielding. Little innovative methodology was explored in a synthesis that relied on the time-tested Hajos-Parrish reaction as the key step. A lengthy sequence of redox transformations was required to install both lactone moieties that continued into another lengthy string of redox manipulations to furnish the target compound. Despite these shortcomings, this work realized the first total synthesis of jiadifenolide (**5.1**) and extra

value was found in the ability to diverge from intermediate **5.15** to two additional natural products, jiadifenin (**5.3**) and ODNM (**5.23**).

5.2.1.2 Divergence to Jiadifenin (5.3) and ODNM (5.23)

In addition to jiadifenolide (**5.1**), Theodorakis manipulated intermediate **5.15** into the related majucin-like *Illicium* sesquiterpenoids jiadifenin (**5.3**) and ODNM (**5.23**).[275] Toward that end, **5.15** was dehydrated with Martin sulfurane, and the resultant disubstituted olefin was selectively reduc098iuy- .ed to give **5.20**. Allylic oxidation proceeded in 65% yield to provide enone **5.21**, which upon exposure to excess NaHMDS and one equivalent of Davis's oxaziridine delivered α-hydroxy lactone **5.22**. Methylation of the cyclopentenone moiety afforded ODNM (**5.23**), and oxidative rearrangement of **5.23** provided jiadifenin (**5.3**). Again, much like the synthesis of jiadifenolide (**5.1**), the sequence is lengthy and low yielding. However, through these routes, they were able to synthesize enough material to perform biological testing of jiadifenolide (**5.3**), ODNM (**5.23**), and jiadifenin (**5.3**). The sequence was relatively straightforward and left a significant amount of room for innovation and improvement in both yield and step count.

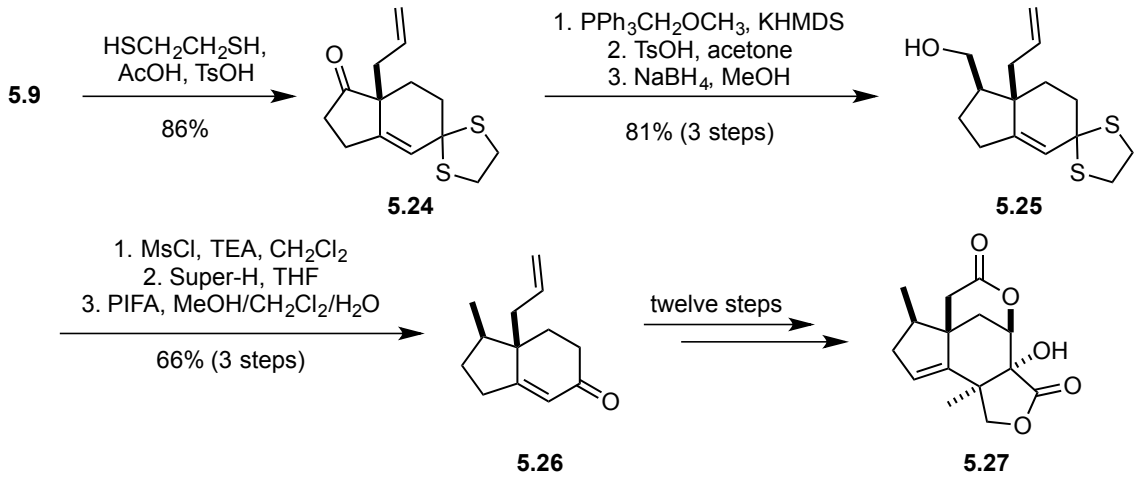


Scheme 5.3 Synthesis of ODNM (**5.23**) and jiadifenin (**5.3**) by Theodorakis

5.2.1.3 Second Generation Synthesis of the Tetracyclic Core

In order to address the step count issue, Theodorakis reported a second-generation approach to the *Illicium* sesquiterpenes.[276] This approach focused on early installation of the methyl group on the cyclopentane moiety, rather than the lengthy late stage installation used in the first synthesis (Scheme 5.2). First, enone **5.9** was protected as the allylic dithiane to provide **5.24**, which was subsequently converted to alcohol **5.25** in three steps (Scheme 5.4). In this sequence, the cyclopentanone was subjected to sequential Wittig olefination, hydrolysis, and reduction to furnish **5.25**. Mesylation followed by treatment with Super-Hydride® completed the installation of the methyl

group. Oxidative deprotection delivered enone **5.26** in 66% over three steps. Intermediate **5.26** was then subjected to a twelve-step sequence analogous to the previous route to deliver tetracycle **5.27** (Scheme 5.1). They concluded that tetracycle **5.27** could be a viable intermediate for diversity-oriented synthesis; however, this compound was not elaborated to any neurotropic molecule of natural or synthetic origin. With another straightforward, non-innovative synthesis that required 24 steps and did not result in the synthesis of any neurotropic molecules, Theodorakis again left room for improvements for future syntheses. In fact, it is difficult to assign any value to this second generation strategy at all.



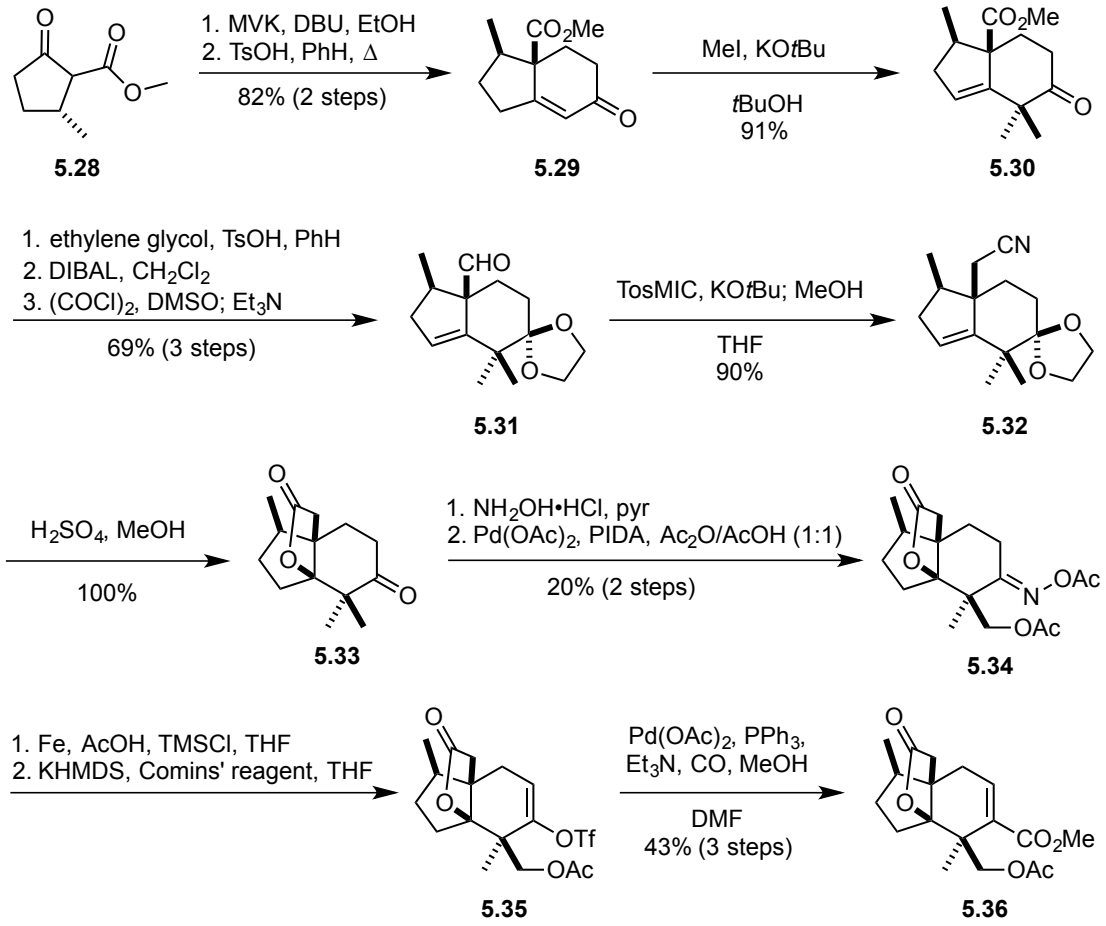
Scheme 5.4 Second-generation approach to the *Illicium* sesquiterpenes by Theodorakis.

5.2.2 Sorensen's Total Synthesis of (–)-Jiadifenolide

Sorensen began the synthesis of jiadifenolide (**5.1**) from chiral β-keto ester **5.28**, which was available in three steps from (+)-pulegone.[277] Robinson annulation of **5.28** with methyl vinyl ketone (MVK) provided bicycle **5.29** (Scheme 5.5), a similar opening

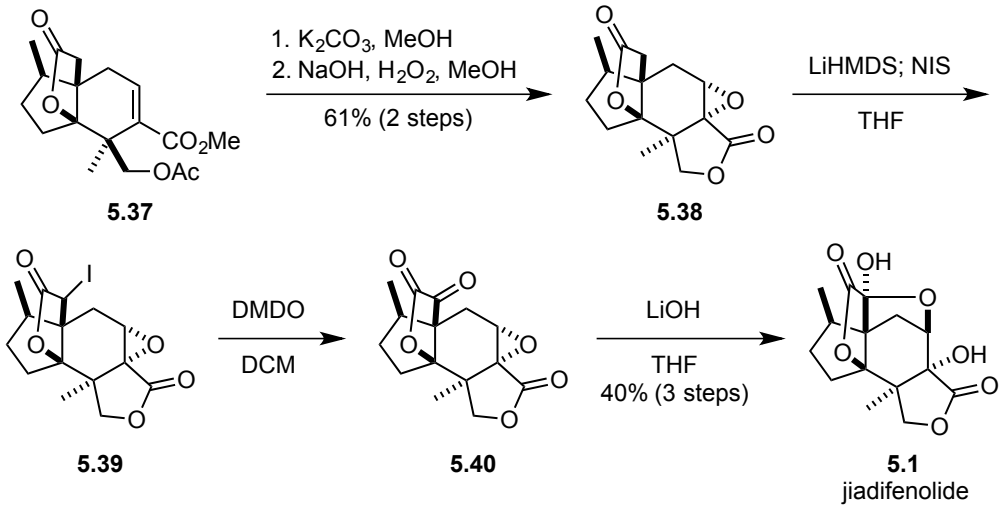
strategy to that of Theodorakis. Bismethylation with methyl iodide afforded **5.30** in 91% yield. Protection of the ketone of **5.30** followed by a redox sequence delivered aldehyde **5.31** from ester **5.30** in 91% yield over three steps. Homologation of the neopentyl aldehyde using the van Leusen protocol proceeded smoothly to provide nitrile **5.32** in 90% yield. Exposure of **5.32** to sulfuric acid in wet methanol delivered tricycle **5.33** in quantitative yield. Finally, condensation with hydroxylamine delivered key intermediate **5.34**, setting the stage for a daring diastereoselective C-H oxidation.

In the event, oxime **5.34** was subjected to Sanford's conditions to give **5.35**, albeit in a meager 22% yield.[281] In addition to the desired product **5.34**, both *epi*-**5.34** (22%) and bisacetoxy-**5.34** (yield not reported) were isolated. This represented the first application of the C-H oxidation protocol developed by Sanford in a total synthesis. To forge the southeastern γ-butyrolactone moiety, Sorensen borrowed a sequence from Theodorakis wherein the acetyl-oxime was reduced, converted to vinyl triflate **5.35**, and subjected to a palladium-catalyzed carbonylative methoxylation to provide enoate **5.36**.



Scheme 5.5 Synthesis of intermediate **5.36** by Sorensen

Upon sequential exposure to methoxide and basic peroxides, enoate **5.36** underwent lactonization and epoxidation to provide **5.38** in 61% yield. Oxidation to the penultimate intermediate **5.40** was accomplished in two steps via α-iodination followed by an iodoso-Pummerer reaction. Finally, treatment of **5.40** with lithium hydroxide completed the synthesis of jiadifenolide (**5.1**). Sorensen thus completed the second total synthesis of jiadifenolide in 21 steps with an overall 1% yield from known cyclopentanone **5.28**.

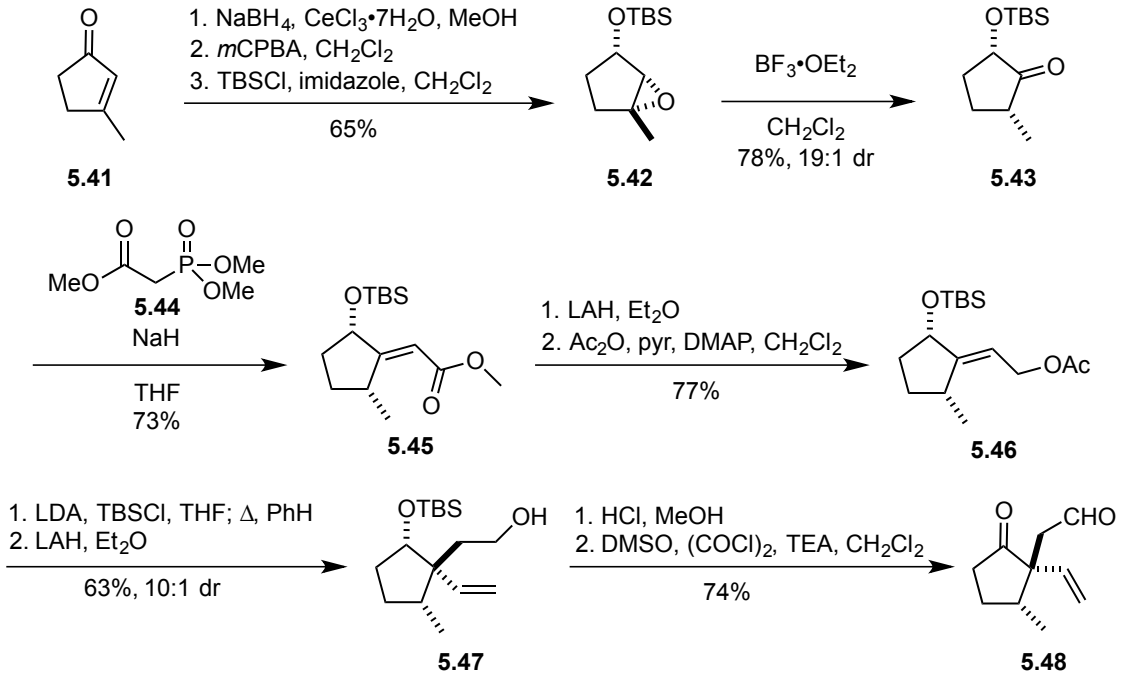


Scheme 5.6 Synthesis of jiadifenolide (**5.1**) by Sorensen.

The synthesis relied on a number of sequences similar to the strategy that Theodorakis utilized, including the opening Robinson annulation and palladium-catalyzed carbonylative methoxylation. The use of (+)-pulegone to set the stereochemistry, which we were exploring when Sorensen reported his synthesis, served him well. However, the key step involving the first application of the directed C-H oxidation developed by Sanford (Scheme 5.5) suffered from a complete lack of selectivity. Finally, the iodoso-Pummerer rearrangement proved to be a clever method for introducing the α-keto lactone. Overall, the synthesis was seven steps shorter than the route by Theodorakis, but again left significant room for improvement.

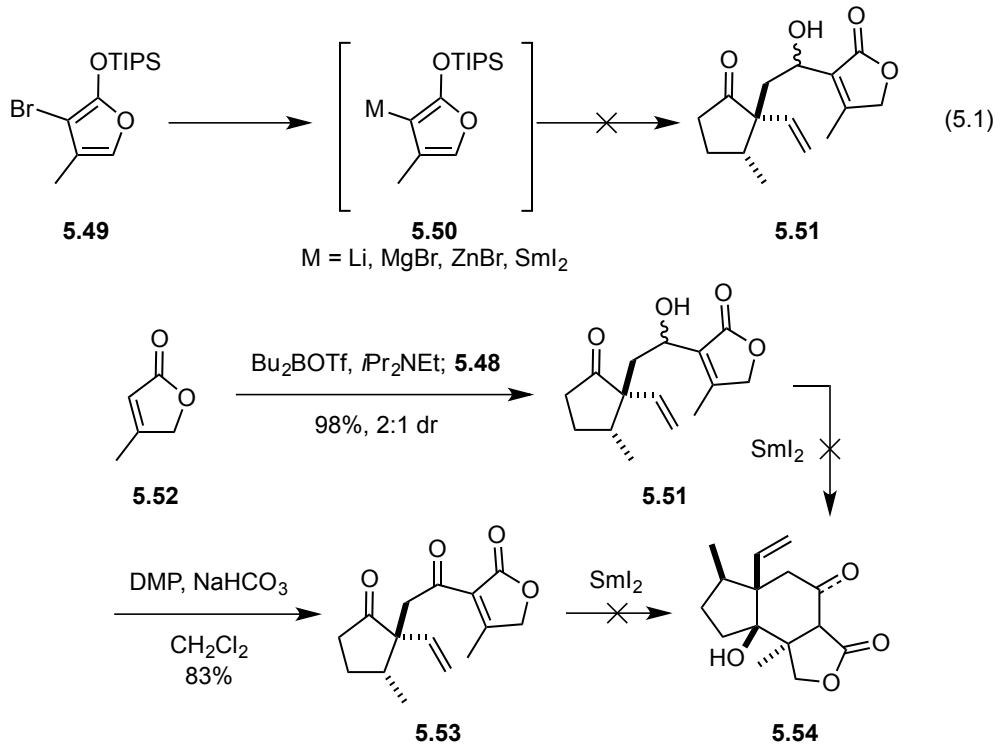
5.2.3 Paterson's Synthesis of (±)-Jiadifenolide

By comparison, the synthesis of jiadifenolide (**5.1**) by Paterson used a strikingly different approach than the two previous syntheses. Notably, his key step was similar to that which we had planned to utilize.[278] Beginning from cyclopentenone **5.41**, sequential Luche reduction, peracid oxidation, and protection delivered epoxide **5.42** in 65% yield (Scheme 5.7). Boron trifluoride diethyl etherate triggered a stereoselective Meinwald rearrangement of **5.42** to deliver ketone **5.43**, which was transformed into enoate **5.45** via a Horner-Wadsworth-Emmons olefination. Reduction and acylation delivered allylic acetate **5.46** setting the stage for a key Ireland-Claisen rearrangement. In the event, **5.46** was converted by action of LDA and TBSCl to a silyl ketene acetal, which underwent rearrangement upon heating. Reduction of the resultant acid provided alcohol **5.47** in 63% yield over two steps. Finally, hydrolysis of the silyl ether and bisoxidation using the Swern protocol gave rise to aldehyde **5.48**.



Scheme 5.7 Synthesis of aldehyde **5.48** by Paterson.

The next stage of the synthesis hinged upon coupling aldehyde **5.48** with a masked butenolide to form **5.51**. Unfortunately, despite extensive screening, they found that metallated furan **5.50** would not react with the homo-neopentyl aldehyde **5.48** (Equation 5.1). Luckily, they discovered that the extended boron enolate of **5.52** added smoothly into **5.48**, albeit with poor diastereoselectivity (Scheme 5.8). The stereoselectivity was thought not to be an issue as both diastereomers oxidized readily to provide **5.53** in 83% yield. However, when **5.53** was treated with samarium diiodide, tricycle **5.54** was never obtained. Additionally, neither diastereomer of alcohol **5.51** underwent cyclization when treated with samarium diioide.

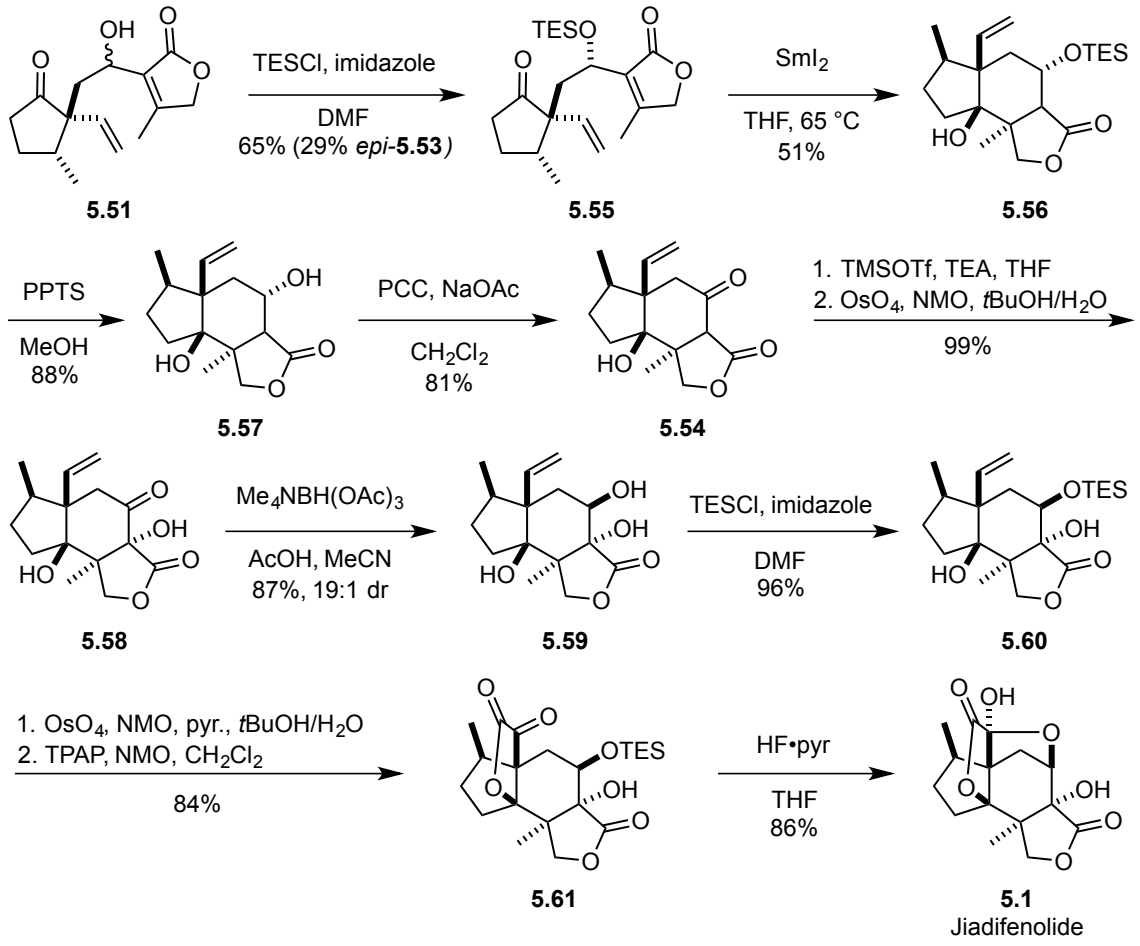


Scheme 5.8 Successful aldol and unsuccessful radical annulation by Paterson.

Undeterred by these results, both diastereomers of **5.51** were protected as the triethylsilyl ether ***5.55*** (and *epi*-***5.55***) and subjected individually to the cyclization conditions (Scheme 5.9). In the event, butenolide ***5.55*** underwent reductive annulation, which upon deprotection delivered tricycle ***5.57***. Despite extensive screening, the authors found that the reaction could only be taken to 51% completion with the remaining products being returned starting material and/or decomposition products upon forcing conditions; *epi*-***5.55*** was found to be unreactive.

With the key cyclization completed, the group began the final stage of forming the last two rings. Oxidation of alcohol ***5.57*** to β-keto ester ***5.54*** proceeded in 81% yield. The hydroxyl moiety of ***5.54*** was installed in two steps via oxidation of the silyl enol

ether of **5.54**. Directed reduction of **5.58** with ammonium triacetoxy borohydride delivered triol **5.59** in 87% yield with excellent diastereoselectivity. Protection of **5.59** as silyl ether **5.60** followed by two oxidations provided α-keto lactone **5.61** in 84% yield across two steps. Finally, deprotection of the silyl ether completed the synthesis of jiadifenolide (**5.1**).



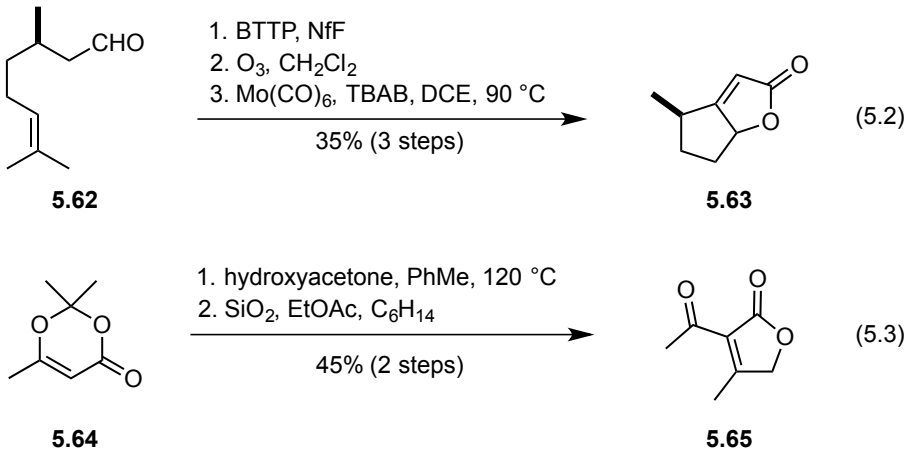
Scheme 5.9 Synthesis of jiadifenolide (**5.1**) by Patersen.

Paterson thus completed the total synthesis of **5.1** in 23 steps (27 steps including the synthesis of **5.49**) with a 1.8% overall yield. The synthesis was two steps longer (LLS) than the route by Sorensen, but it almost doubled the overall yield. While the synthesis by the Sorensen group closely resembled many sequences of the route taken by Theodorakis, Patersen managed to realize a unique route to jiadifenolide (**5.1**). Key sequences of the synthesis included the Luche reduction, directed epoxidation, and Meinwald rearrangement, which set the stereochemistry for the remainder of the synthesis. A crucial Johnson-Claisen rearrangement installed one of the two quaternary centers with ease. Finally, a reductive annulation induced by samarium diiodide, not too dissimilar from one we had planned (*vide infra*), formed the core tricycle of the molecule; however, since only one diastereomer cyclized with 51% conversion, this reaction was severely detrimental to the overall yield. While failing to best the step count of the synthesis by Sorensen, the route makes up for it in its innovation and by nearly doubling the overall yield. Yet, despite its successes with creative disconnects, this route still left room for improvements in both step count and yield.

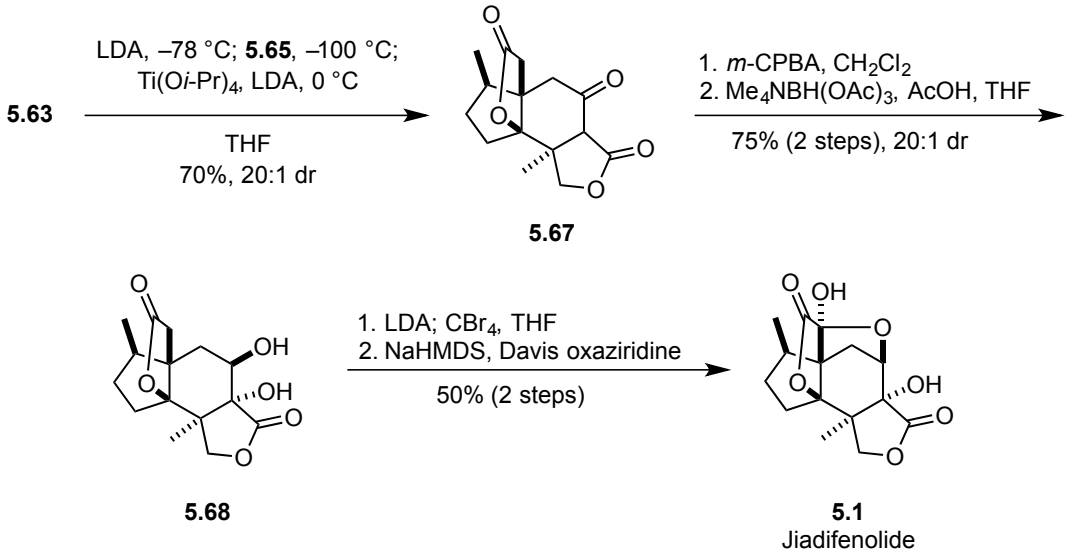
5.2.4 Shenvi's Total Synthesis of (–)-Jiadifenolide

Shenvi has realized the most concise and high yielding route to the natural product to date. Where as the previous syntheses were linear, resulting in >20 total steps (longest linear sequences), Shenvi reaped the rewards of convergence and audacious disconnects in his 10 step (eight LLS) synthesis of **5.1**.

The synthesis commenced from (*R*)-citronellal (**5.62**), which was dehydrated with *tert*-butylimino-tri(pyrrolidino)phosphorane (BTPP) and nonafluorobutanesulfonyl fluoride (NfF), ozonylized, and subjected to Pauson-Khand conditions to deliver bicyclic butenolide **5.63** in 35% yield (Equation 5.2). Known butenolide **5.65** was prepared in two steps from dioxalane **5.64** in 45% yield (Equation 5.3), setting the stage for an ambitious formal [4+2] cycloaddition.



In the event, **5.65** underwent Michael addition by the anion of **5.63**, which upon exposure to excess titanium tetrachloride and LDA succumbed to an intramolecular Michael addition to afford tetracycle **5.67** in 70% yield with 20:1 dr (Scheme 5.10). A series of redox transformations then delivered jiadifenolide (**5.1**) in four additional steps.



Scheme 5.10 Synthesis of jiadifenolide (**5.1**) by Shenvi.

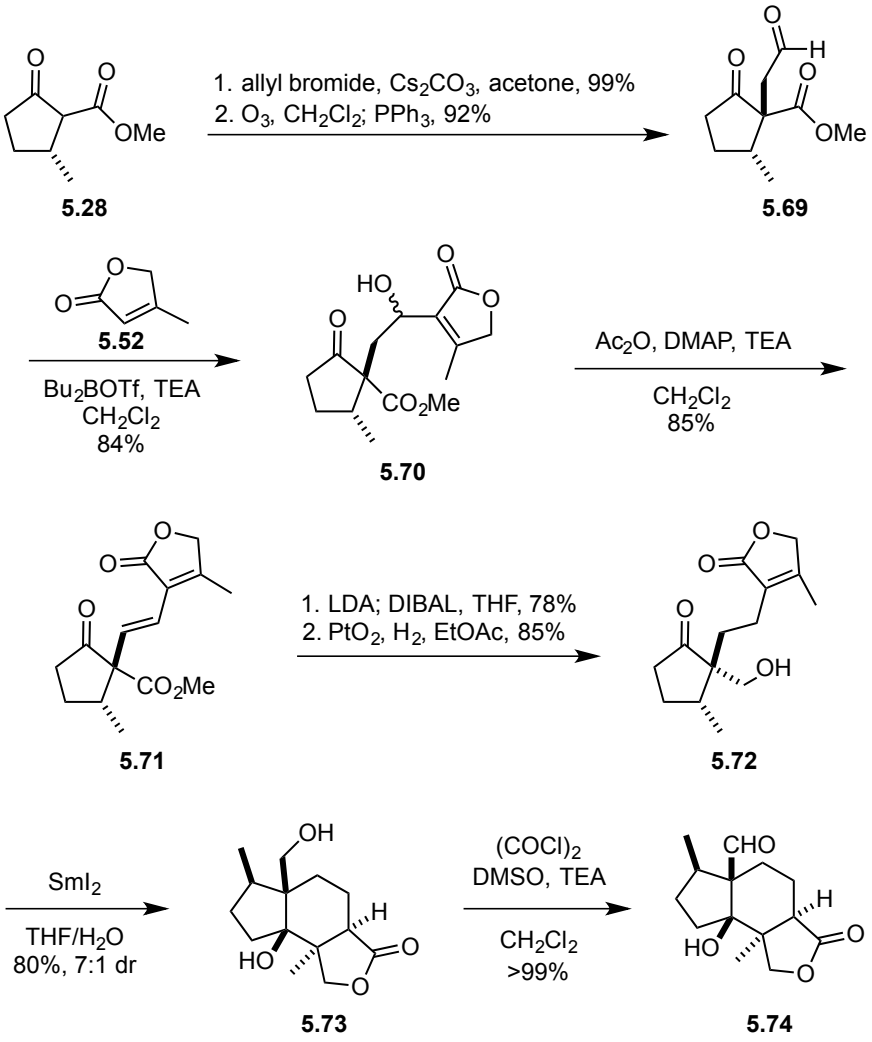
The brevity of this route allowed for the synthesis of more than a gram of jiadifenolide (**5.1**). The only major drawback to the sequence was the use super stoichiometric amounts of $Mo(CO)_6$ for the Pauhsen-Khand reaction. Though they served Shenvi well, the last four steps parallel similar transformations from the previous syntheses. Regardless of these minor shortcomings, the formal [4+2] cycloaddition (or Michael/Michael cascade) of the readily available butenolides **5.63** and **5.65** which swiftly constructed the core more than made up for the transition metal waste and the banal end game. By more than halving the step count and doubling the overall yield of

the previous reported syntheses, this remarkable route has raised the bar significantly for future attempts at the synthesis of **5.1**.

5.2.5 Zhang's Total Synthesis of (–)-Jiadifenolide

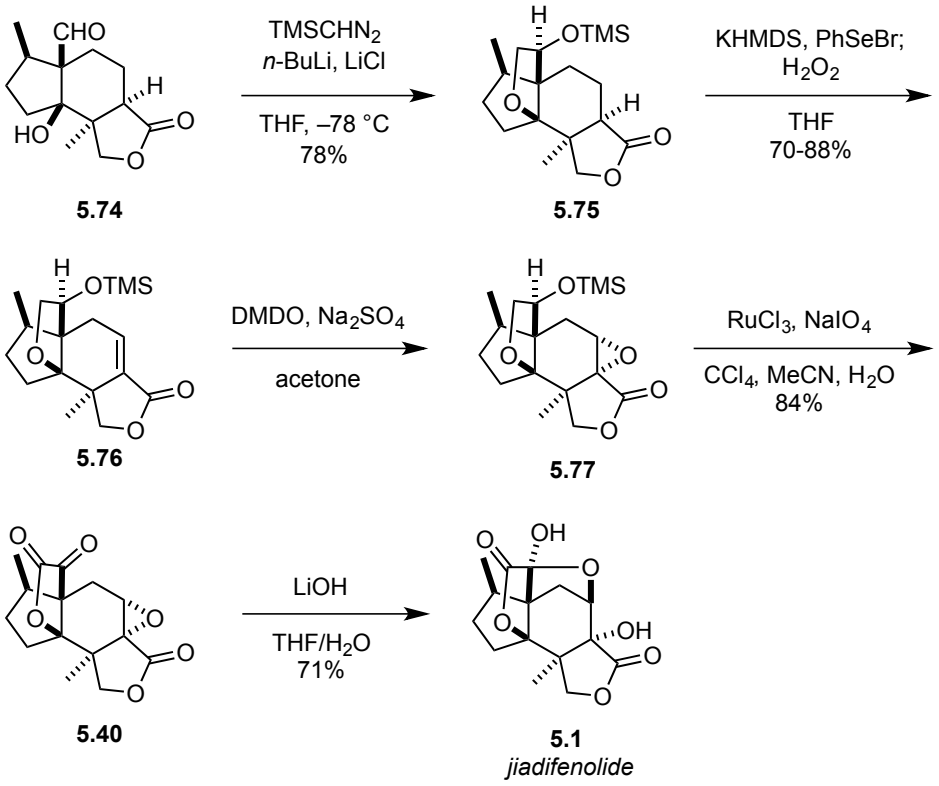
The Zhang group reported the most recent total synthesis of jiadifenolide in October of 2015.[280] The synthesis borrowed a number of strategies from both Sorensen and Paterson, as well as the use of similar late stage redox manipulations that all of the syntheses have utilized. The synthesis began from cyclopentanone **5.28**, the same starting material that Sorensen used, which was allylated and ozonolyzed to provide aldehyde **5.69** in 91% yield over two steps (Scheme 5.11). Aldehyde **5.69** was subjected to the same aldol conditions that Paterson used to afford butenolide **5.70** in 84% yield as a mixture (1:1) of diastereomers. As Paterson had previously demonstrated that only one diastereomer cyclized in a moderate 50% yield (Scheme 5.9), Zhang decided to remove the hydroxyl group in effort to increase the efficiency of the reductive cyclization.

Toward this end, the hydroxyl group of **5.70** was eliminated to afford **5.71**. The butenolide and cyclopentanone carbonyl groups of **5.71** were protected as the enolates, the ester was reduced by action of DIBAL, and then hydrogenation afforded alcohol **5.72**. Samarium diiodide induced a reductive annulation of **5.72** to provide tricycle **5.73** in 80% yield as a mixture (7:1) of diastereomers. Though removal of the hydroxyl group did increase the yield of the reductive cyclization, the diastereoselectivity suffered. Finally, the alcohol was oxidized using the Swern protocol to deliver key intermediate **5.74**.



Scheme 5.11 Zhang's synthesis of intermediate **5.74**

A formal [4+1] cycloaddition was effected with trimethylsilyldiazomethane to afford tetracycle **5.75**. Selenide oxidation provided **5.76**, which was oxidized with dimethyldioxirane (DMDO) to deliver epoxide **5.77**. Oxidation of the tetrahydrofuran moiety with ruthenium trichloride provided α-keto lactone **5.40**, which upon treatment with lithium hydroxide completed the synthesis of jiadifenolide **5.1**.



Scheme 5.12 Zhang's synthesis of jiadifenolide (5.1)

Zhang thus completed the fifth total synthesis of jiadifenolide in 13 steps with a 7.9% overall yield from known **5.28**. The synthesis relied on a number of similar strategies that have been previously reported including the use of pulegone as a starting material to prepare **5.28**, the installation of the butenolide through an aldol reaction, the samarium mediated reductive cyclization, and the late-stage oxidative manipulations to complete the core. During the course of this work, Zhang did develop a new formal [4+1] cycloaddition with trimethylsilyldizomethane to synthesize tetrahydrofurans. This methodology was further explored and found to be generally applicable to a number of

substrates. Though Zhang was unable to best Shenvi's step count, he more than doubled the overall yield. This synthesis is currently the highest yielding synthesis of **5.1** to date.

5.2.6 Summary of Previous Syntheses

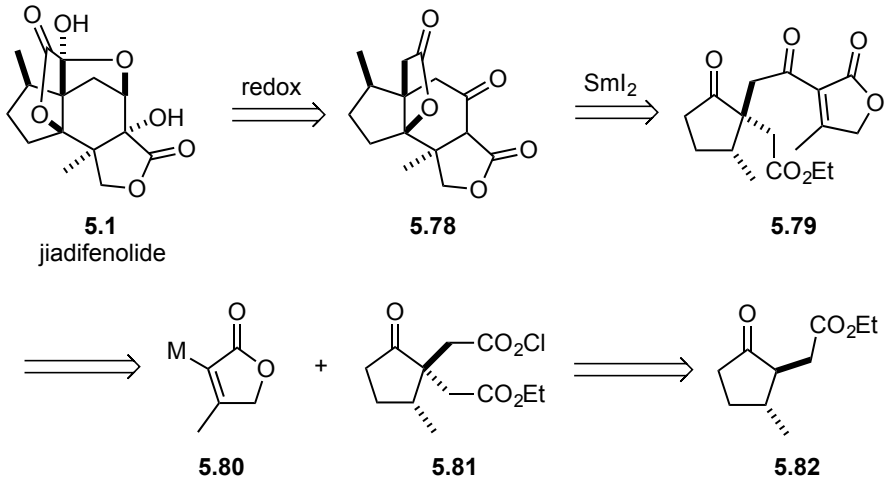
Jiadifenolide (**5.1**) has been synthesized five times since its isolation in 2009 (Table 5.1). Theodorakis's synthesis, though it was the first, lacked innovation and was exceedingly lengthy. As a result, were we to complete our route, we undeniably stood to compete with him in terms of step count and innovation; however, during the course of our study, Sorensen and Patersen both reported syntheses that included key strategies central to our route (the use of pulegone and the reductive annulation). Despite these disappointing revelations, both of these syntheses were lengthy as well, so we continued to press forward via a modified route to the target molecule (*vide infra*). Yet, Shenvi's elegant 10 step total synthesis ultimately befell our goal of realizing the most concise synthesis of jiadifenolide (**5.1**). Zhang's recent report of the highest yielding synthesis of **5.1** to date ultimately foiled our plans of testing the reductive annulation with the hydroxyl group removed.

Table 5.1 Total syntheses of jiadifenolide (**5.1**)

Group	Year	(+)/(–)/(±)	Steps	Yield (%)
Theodorakis	2011	(–)	28	0.5
Sorensen	2014	(–)	21	0.9
Patersen	2014	(±)	23	1.8
Shenvi	2015	(–)	10	4.1
Zhang	2015	(–)	13	7.9

5.3 Past Martin Group Efforts Towards Jiadifenolide

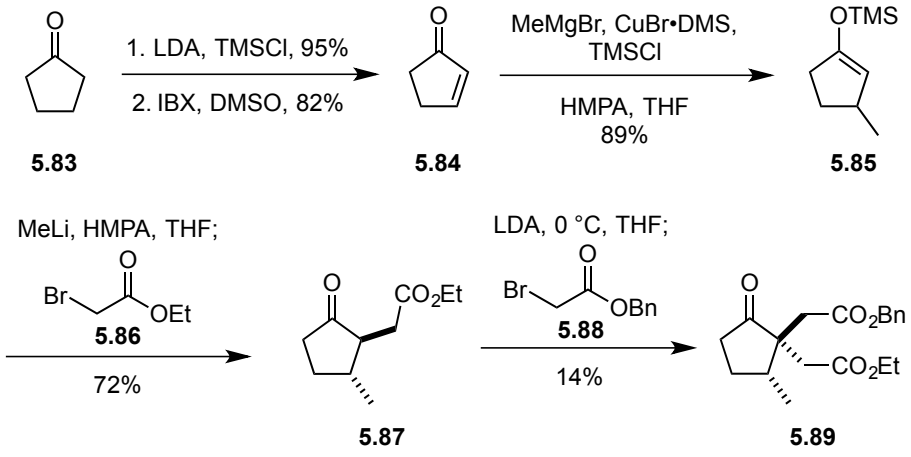
The Martin group began their efforts towards jiadifenolide (**5.1**) in 2011, shortly before Theodorakis reported the first total synthesis. Much like the other total syntheses (*vide supra*), it was envisaged that **5.1** could be disconnected to **5.78** through a series of late stage redox manipulations (Scheme 5.13). Tetracycle **5.78** would be made from **5.79** via a reductive annulation with concomitant lactonization. Butenolide **5.79** would be formed through an acylation of synthon **5.80** with **5.81**. Acyl chloride **5.81** would be attained through a series of manipulation after alkylation of the thermodynamic enolate of **5.82**, which in turn could be made from a conjugate addition/alkylation reaction with cyclopentenone. This synthesis could potentially be completed in as few as 16 steps.



5.1 jiadifenolide **5.78** **5.79** **5.80** **5.81** **5.82**

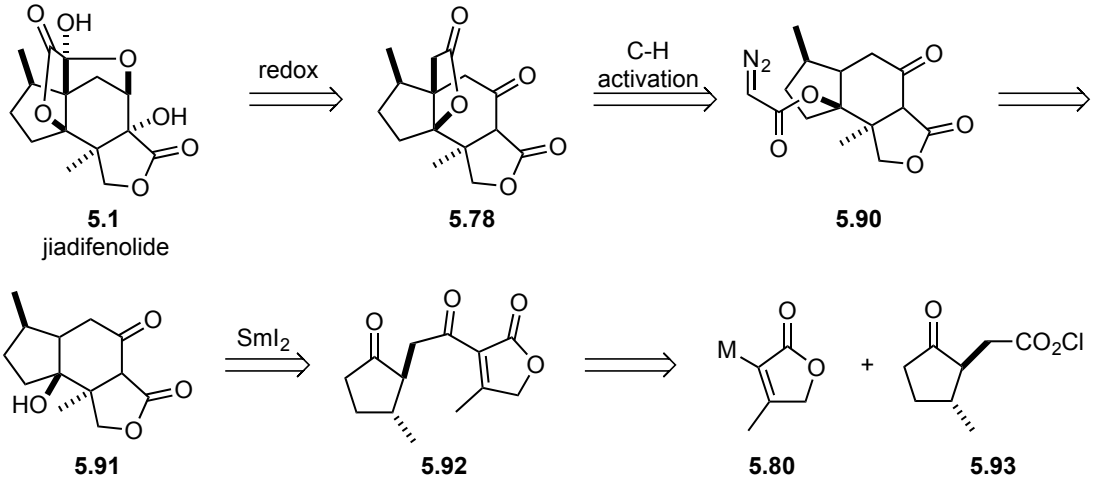
Scheme 5.13 Martin group first generation retrosynthesis of **5.1**

With the desired sequence outlined, work began to assemble butenolide **5.79** in effort to test the reductive cyclization reaction.[282] Due to the relative expense of cyclopentenone (**5.84**), synthesis began from cyclopentanone (**5.83**) (Scheme 5.14). The silyl enol ether of **5.83** was oxidized with 2-iodoxybenzoic acid (IBX) to deliver cyclopentenone (**5.84**) in 78% yield (two steps).[283] One-pot conjugate addition and alkylation of **5.84** proved to be difficult, thus the task was completed in two steps. First, conjugate addition in the presence of chlorotrimethylsilane provided silyl enol ether **5.85**,[284] which upon deprotection with methyllithium in the presence of 20 equivalents of **5.86** delivered ketoester **5.87** in 72% yield. Unfortunately, despite extensive attempts at optimization, alkylation of the thermodynamic enolate of **5.87** failed to deliver synthetically useful amounts of **5.89**. Unable to acquire enough material to continue the synthesis, attention was turned to an alternate route to the natural product.



Scheme 5.14 Martin group synthesis of diester **5.89**

The second approach was designed to circumvent the problems associated with the alkylation of cyclopenatanone **5.87** (Scheme 5.15). Still relying on a late stage redox strategy, the synthesis was still planned to progress through tetracycle **5.78**. However, to remove the need for the second alkylation, the fused lactone moiety would need to be installed after the reductive cyclization; thus, they imagined that lactone **5.78** could be formed via rhodium catalyzed C-H activation of diazoester **5.90**. Reductive cyclization of **5.92** could provide tricycle **5.91**, and a similar acylation strategy would be used on a simpler cyclopentanone derivative **5.93** to access butenolide **5.92**.

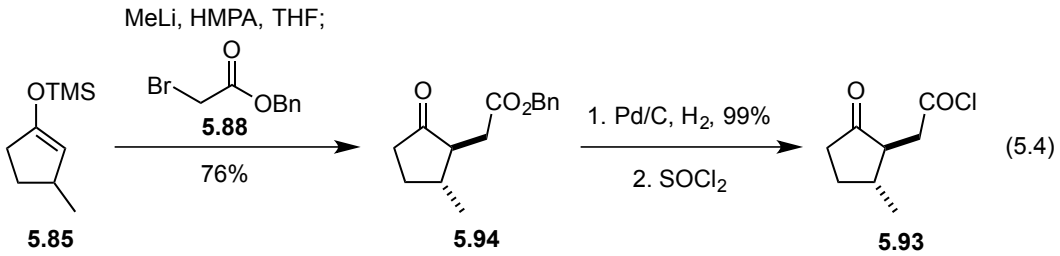


5.1 jiadifenolide | **5.78** | **5.90**

5.91 | **5.92** | **5.80** | **5.93**

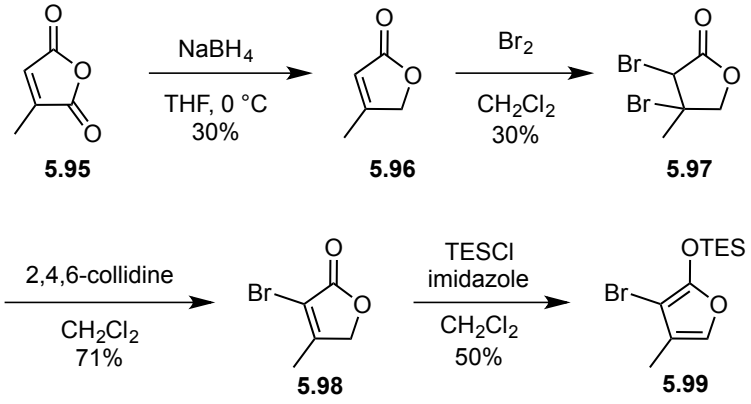
Scheme 5.15 Martin group second generation retrosynthesis of **5.1**

In the event, deprotection of silyl enol ether **5.85** with methyllithium in the presence of **5.88** delivered **5.94** in 76% yield (Equation 5.4). Hydrogenolysis of the benzyl ester followed by treatment with thionyl chloride provided **5.93**, setting the stage for acylation with metallo-butenolide **5.80**.

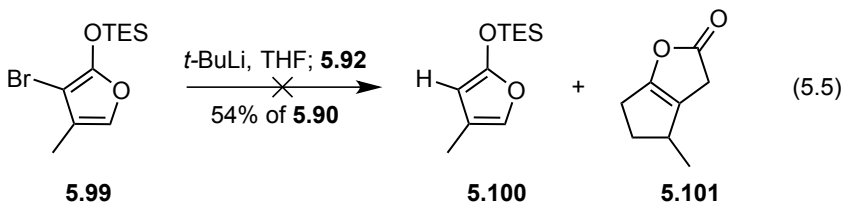


(5.4)

Bromofuran **5.99** was targeted as an equivalent of **5.80** (Scheme 5.14). Thus, citraconic anhydride (**5.95**) was selectively reduced to butenolide **5.96** in 30% yield (Scheme 5.14).[285] Bisbromination of **5.96** yielded **5.97**, which underwent elimination in the presence of 2,4,6-collidine to provide α-bromobutenolide **5.98**.[286] Finally, protection of **5.98** as the silyloxyfuran delivered the latent nucleophile **5.99**. With both **5.92** and **5.99** in hand, the key reductive cyclization substrate was only one step away. Furan **5.99** was metallated with *tert*-butyllithium followed by addition of acyl chloride **5.92** (Equation 5.5); unfortunately, **5.92** was prone to self-acylation and only bicycle **5.101** was recovered. Because it was not possible to access the reductive cyclization substrate **5.92**, it was necessary to re-evaluate the routes to either **5.79** or **5.92**.



Scheme 5.16 Synthesis of bromofuran **5.99**

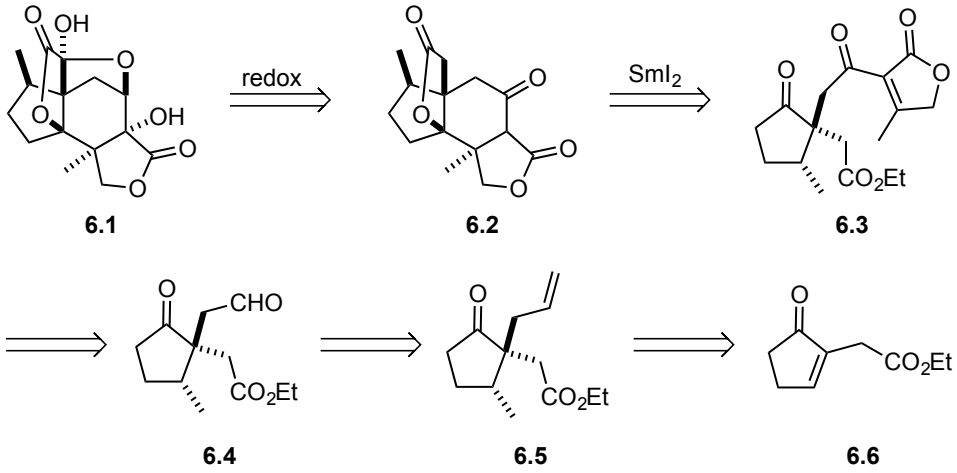


5.99 **5.100** **5.101**

Chapter 6: Progress Towards the Total Synthesis of Jiadifenolide

6.1 Revised Strategy

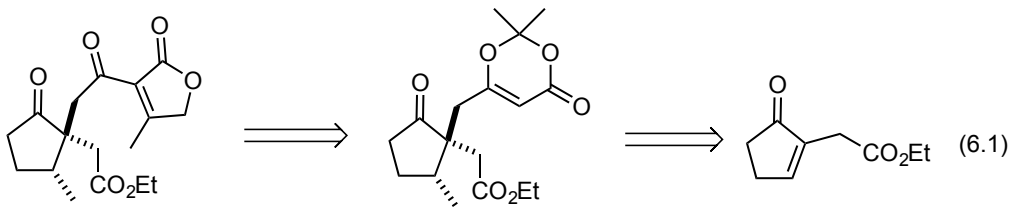
In an effort to remove the problematic alkylation (Scheme 5.2) and acylation reactions (Equation 5.5), we reassessed our approach to jiadifenolide (**6.1**). We still sought to utilize the yet untested mid- and end-game strategies that were previously planned, which once again led us from **6.1** to **6.2** to **6.3** (Scheme 6.1). However, instead of using an acyl chloride, we would progress through aldehyde **6.4**, which would be accessible via oxidative cleavage of olefin **6.5**. We reasoned that the cyclopentanone **6.5** would arise from conjugate addition and allylation of cyclopentenone **6.6**, thereby eliminating the need to generate the thermodynamic enolate prior to a second alkylation.



Scheme 6.1 Revised retrosynthesis of jiadifenolide (**6.1**)

We then saw an opportunity to reduce the step count by removing redox manipulations that would be required to progress from **6.5** to **6.3**. This possibility would manifest by forming the butenolide from dioxenone **6.7** (Equation 6.1).[287] We envisaged

that dioxenone **6.7** would also be derived from a conjugate addition and alkylation of **6.6**. This simple change would, if reduced to practice, lower the total step count from sixteen to eleven total steps barring any unforeseen complications.

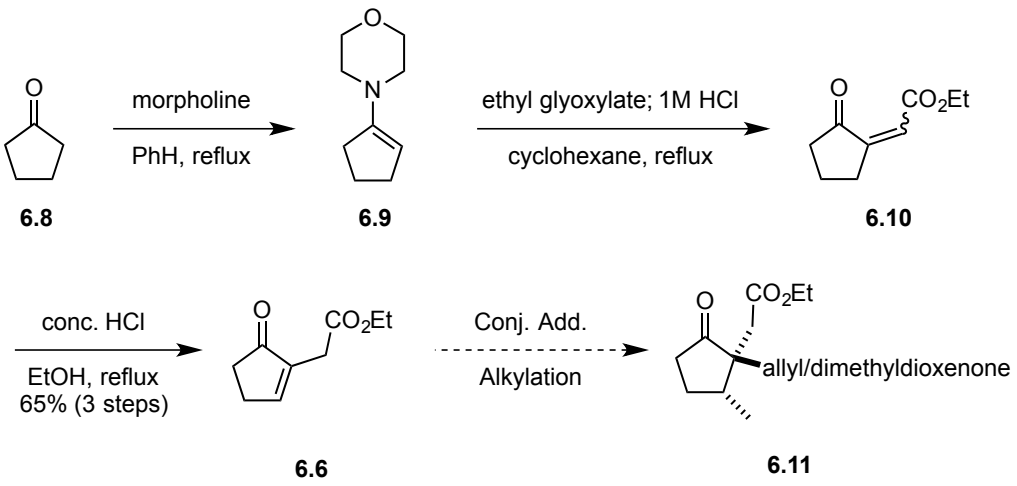


6.3 **6.7** **6.6**

6.2 Conjugate Addition/Alkylation Route

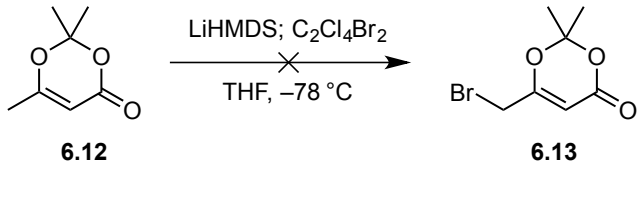
6.2.1 Synthesis of Starting Materials

With our plan laid out, we sought to push forward to the key reductive cyclization of butenolide **6.3**. Cyclopentanone (**6.8**) was condensed with morpholine under Dean-Stark conditions to yield enamine **6.9**,[288] which was condensed with ethyl glyoxylate and hydrolyzed to provide enoate **6.10** (Scheme 6.2). Acid catalyzed isomerization of **6.10** provided cyclopentenone **6.6** in 65% yield over three steps.[289] This method is readily scalable to provide multi-gram quantities of **6.6**.

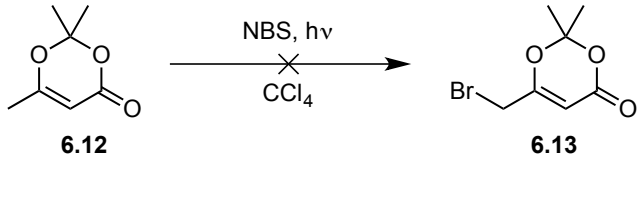


Scheme 6.2 Synthesis of cyclopentenone **6.6**

With enone **6.6** in hand, we turned our attention to the synthesis of a dioxenone electrophile. Following the literature procedure,[290,291] trimethyldioxenone **6.12** was sequentially treated with LiHMDS and 1,2-dibromotetrachloroethane; however, instead of the desired product **6.13**, only polybrominated products and starting material were recovered (Equation 6.2). An alternate procedure for the synthesis of **6.13** via radical bromination with NBS was tested as well, but only starting material was recovered (Equation 6.3).[292]

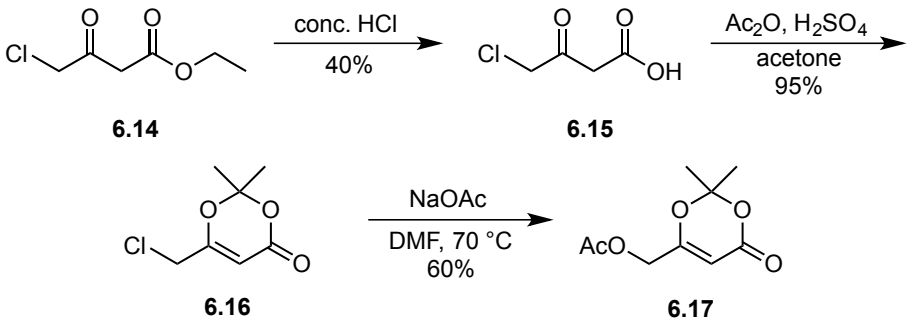


(6.2)



(6.3)

As the direct synthesis of **6.13** proved difficult, we decided to target acetate **6.17**. Beginning the synthesis with **6.14** with the halide installed would facilitate the synthesis, as installation of a halide on dioxenone **6.12** was difficult. Additionally, as conjugate addition/alkylation sequences on α-substituted cyclopentenones have been shown to be problematic,[275,276,293-298] we decided that a Tsuji-Trost allylation with acetate **6.13** might be more suitable, reasoning that the more reactive allyl cation should be more reactive with less basic and reactive enolate species, thus attenuating polymerization, polyalkylation, and enolate isomerization. Toward this end, ethyl 4-chloroacetoacetate (**6.14**) was hydrolyzed with concentrated HCl to provide **6.15** in 40% yield.[299] Treatment of **6.15** with acetic anhydride, sulfuric acid, and acetone delivered chlorodioxenone **6.16**, which underwent nucleophilic displacement of the chloride by sodium acetate to give **6.17**.[300,301] With both enone **6.6** and acetate **6.17** in hand, we moved forward to test the unknown Tsuji-Trost reaction.

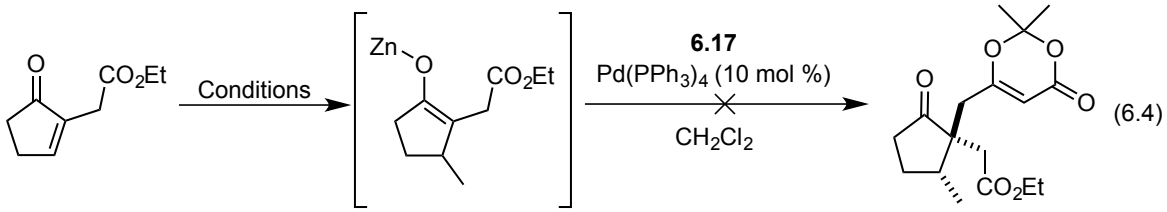


Scheme 6.3 Synthesis of dioxenone acetate **6.17**

6.2.2 Conjugate Addition/Alkylation Attempts

6.2.2.1 Dioxenone Route

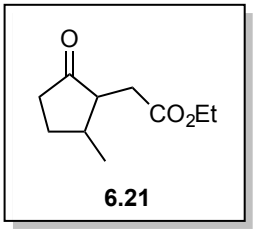
We first attempted to convert **6.6** directly to **6.7** via a one-pot conjugate addition/Tsuji allylation. When enone **6.6** was exposed to dimethylzinc in the presence of catalytic copper (II) triflate, complete consumption of the starting material was observed after eleven days (Equation 6.4).[302] Conditions reported to provide a faster reaction using copper (I) thiophene-2-carboxylate (CuTC) failed to yield any conjugate addition adduct.[303,304] Despite zinc enolates having been demonstrated to be effective nucleophiles in Tsuji allylations,[303] the reactivity of **6.17** in transition metal-mediated allylation processes was unknown. Unfortunately, only the conjugate addition adduct **6.21** was recovered from the reaction after treating **6.18** with **6.17** and palladium (Equation 6.4). We then turned our attention to a two-step conjugate addition and Tsuji-Trost reaction via a silyl enol ether.



Condtiions

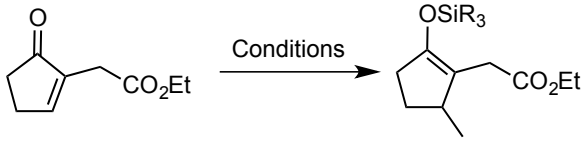
Me_2Zn (150 mol %), $Cu(OTf)_2$ (2.5 mol %), $P(OEt)_3$ (5 mol %), CH_2Cl_2, –20 °C to rt, NR

Me_2Zn (150 mol %), CuTC (2.5 mol %), $P(OEt)_3$ (5 mol %), CH_2Cl_2, –20 °C to rt, >99%



While not immediately successful, conditions to perform the conjugate addition to enone **6.6** were quickly realized (Table 6.1). We found that conditions developed by Bergdahl for conjugate addition to cyclopentenones using monoorganocuprates were unsuccessful on the α-substituted cyclopentenone **6.6** (Table 6.1, Entries A and B).[284,305,306] We next attempted to effect the same transformation with a Gilman reagent and chlorotrimethylsilane, but only achieved 50% conversion in 4 h (Table 6.1, Entry C).[307] We found that by increasing the equivalents of the Gilman reagent, we could consistently effect the desired transformation with complete consumption of starting material in 30 min (Table 6.1, Entry D). Additionally, we found that use of copper cyanide, although it slowed the reaction, provided similar results (Table 6.1, Entry E). Despite the swift reaction times and lack of by-products, silica gel chromatography of the crude reaction mixtures resulted in hydrolysis of approximately 60% of the product. Fortunately, switching to chlorotriethylsilane resulted in less hydrolysis, and we were able to isolate **6.20** in 70% yield (Table 6.1, Entry F). Through further experimentation, we found that lowering the equivalents of chlorotriethylsilane affected neither the yield nor reaction time.

Table 6.1 Optimization of the conjugate addition to enone **6.6**



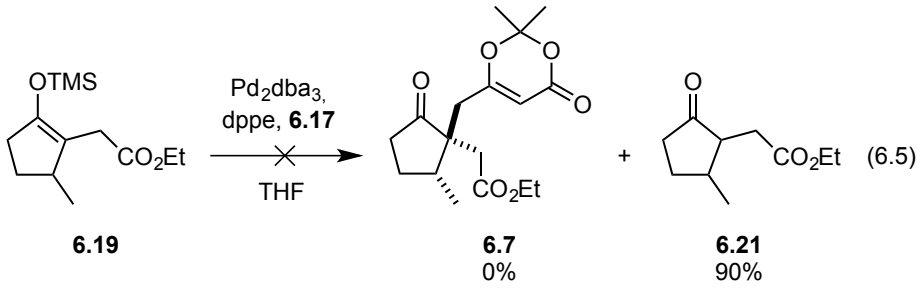
6.6

6.19, R = Me
6.20, R = Et

Entry	Cu (equiv.)	MeLi (equiv.)	TMSX (equiv.)	Solvent	Conv. (%)
A	CuBr•DMS (1.3)	MeLi (1.25)	TMSI (1.25)	THF	NR
B	CuBr•DMS (1.3)	MeLi (1.25)	TMSI (1.25)	THF/HMPA	NR
C	CuBr•DMS (1.2)	MeLi (2.4)	TMSCl (4)	THF	50
D	CuBr•DMS (1.8)	MeLi (3.7)	TMSCl (4)	THF	100 (40)*
E	CuCn (1.8)	MeLi (3.7)	TMSCl (4)	THF	100 (50)*
F	CuBr•DMS (1.8)	MeLi (3.7)	TESCl (4)	THF	100 (70)*
G	CuBr•DMS (1.8)	MeLi (3.7)	TESCl (1.2)	THF	100 (71)*

*Yields in parentheses are isolated yields after silica gel chromatography

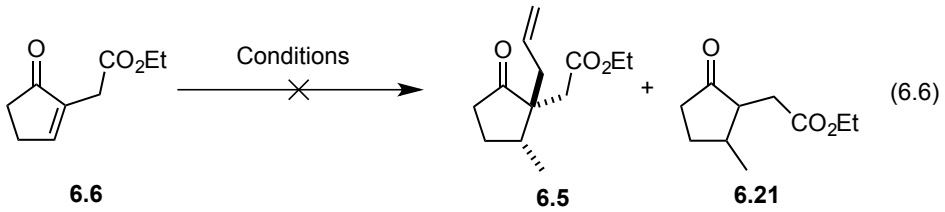
We then began to explore the use of nucleophile **6.19** in Tsuji-Trost reactions. However, while substituted silyl enol ethers are known to react with allyl cationic species derived from allyl acetates and palladium,[308] we once again observed no desired product formation and isolated only **6.21** from the reaction (Equation 6.5). As dioxenone **6.17** had not been used in Tsuji-type allylation reactions, we turned our attention to standard allylation conditions with hopes to return to **6.17** upon success with known electrophiles.



6.2.2.2 Allylation Route

We first attempted to prepare cyclopentanone **6.5**, via a one-pot conjugate addition/allylation sequence that we had initially planned to use with **6.7**. We found that allylation of a zinc enolate derived from a copper-catalyzed conjugate addition of dimethylzinc only led to formation of the conjugate addition adduct **6.21** (Equation 6.6). Use of conditions developed by Alexakis for the catalytic conjugate addition of Grignard reagents to cyclohexenones provided mainly polymerized material due to the more reactive magnesium enolate reacting with **6.6**.[309,310] We found minor success with the copper-mediated conjugate addition followed by allyl tosylate, but we recovered the product in only 40% yield as an inseparable mixture (1:1.6) of diastereomers (Equation 6.7). At the time, the stereochemistry of the major isomer was unknown, though we now know that the major was in fact the desired isomer (shown) of **6.5**.

We then turned to the alkylation of silyl enol ethers. Attempts to unmask the latent nucleophile with methyllithium were unsuccessful (Equation 6.8), as were attempts to allylate using silver trifluoroacetate (Equation 6.9).[311] We then attempted a Tsuji-Trost reaction with the silyl enol ether **6.20**; however, like we observed with the dioxenone acetate (Equation 6.5), we only recovered the hydrolyzed starting material **6.21** (Equation 6.10).



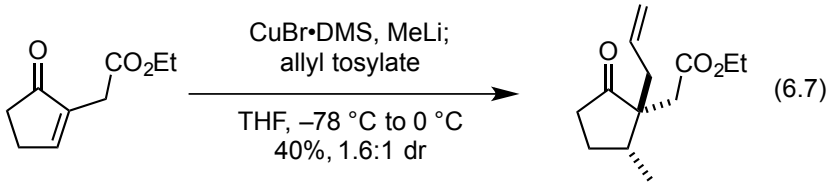
6.6 **6.5** **6.21** (6.6)

Conditions

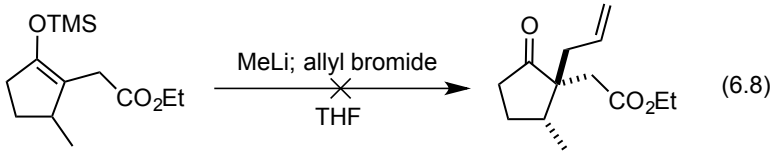
$Cu(OTf)_2$, $P(OEt)_3$, Me_2Zn, CH_2Cl_2, –20 °C, 11 d; allyl iodide, HMPA, 0 °C, no alkylation

$Cu(OTf)_2$, MeMgBr, Et_2O, –30 °C, polymerization

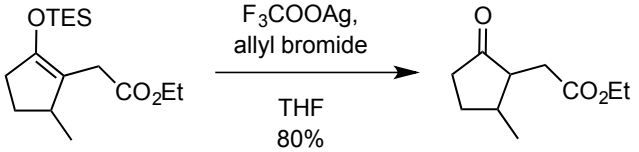
CuTC, $P(OEt)_3$, Me_2Zn, MTBE, 0 °C, rsm



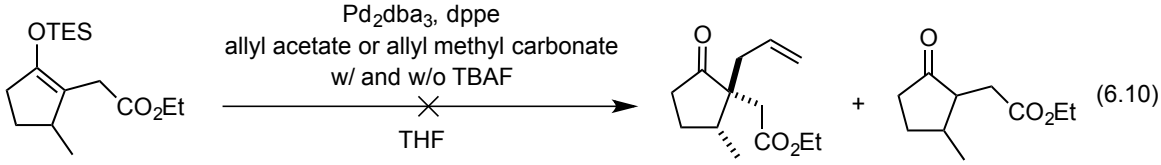
6.6 **6.5** (6.7)



6.20 **6.5** (6.8)



6.20 **6.21** (6.9)



6.20

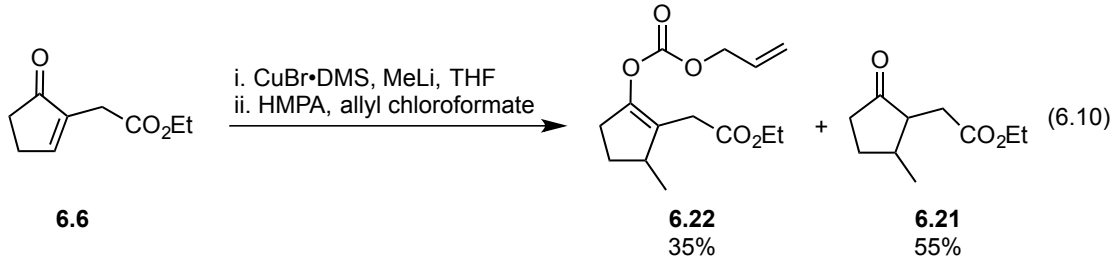
6.5
not observed

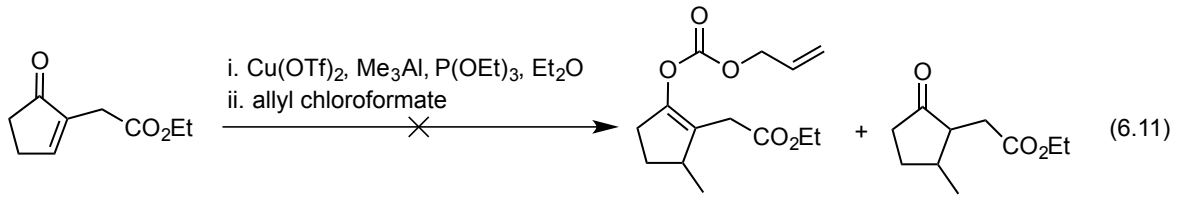
6.21
80-95%

(6.10)

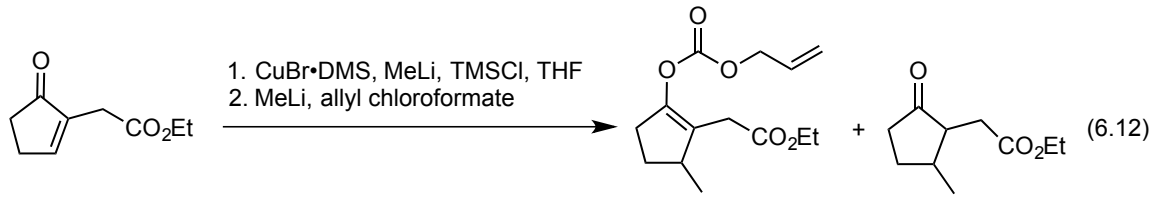
6.2.2.3 Vinylcarbonate Route

We reasoned that if we used an intramolecular Tsuji allylation that the hydrolysis would be less of a problem as it had been demonstrated that these intramolecular reactions could tolerate water;[312] however, this is most likely influenced by the ligands on palladium and whether attack on the allyl palladium cation is inner-sphere or outer-sphere. Unfortunately, preparation of the vinyl carbonate **6.22** proved to be low yielding. Copper-mediated conjugate addition followed by allyl chloroformate provided **6.22** in 35% yield with the remainder of the material being the conjugate addition adduct **6.21** (Equation 6.10). Copper-catalyzed addition of trimethylaluminum, which we hoped would provide a more reactive enolate, failed to provide any of the desired adduct **6.22** (Equation 6.11).[313,314] Attempts to transmetallate the copper enolate with methyllithium was less efficacious than use of the copper enolate (Equation 6.12). Activation of the aluminum enolate with methyllithium to give the alanate provided the vinyl carbonate in 36% yield (Equation 6.13). Finally, use of Stoltz's conditions to prepare vinyl carbonates from silyl enol ethers were unsuccessful (Equation 6.14).[315,316] Despite our inability to prepare **6.22** in high yield, we had enough material to attempt preliminary studies on the Tsuji allylation. However, we once again received hydrolyzed product upon exposure of **6.22** to the reaction conditions (Equation 6.15).

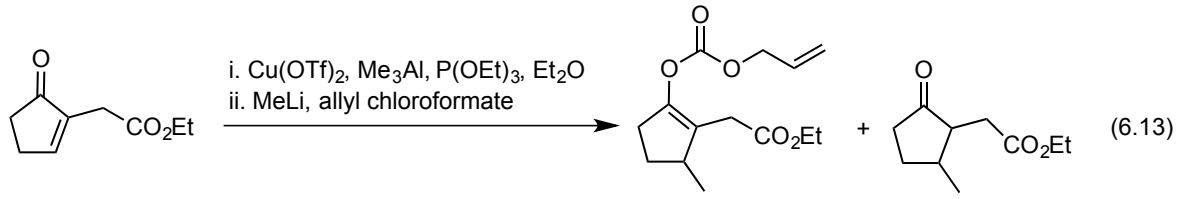




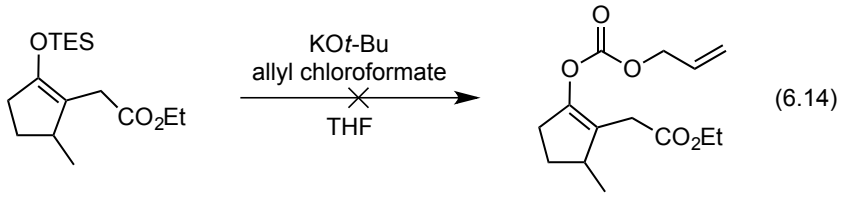
6.6 **6.22** 0% + **6.21** 40% (6.11)



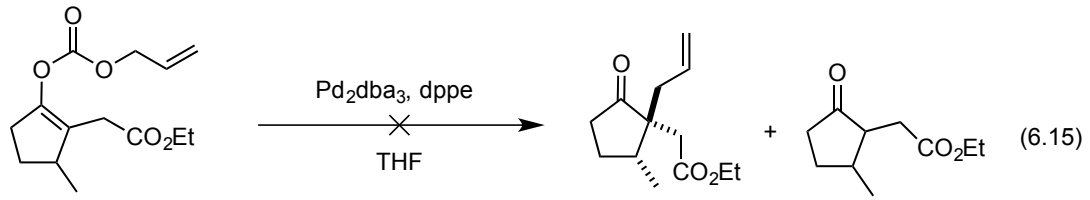
6.6 **6.22** 25% + **6.21** 60% (6.12)



6.6 **6.22** 36% + **6.21** 40% (6.13)



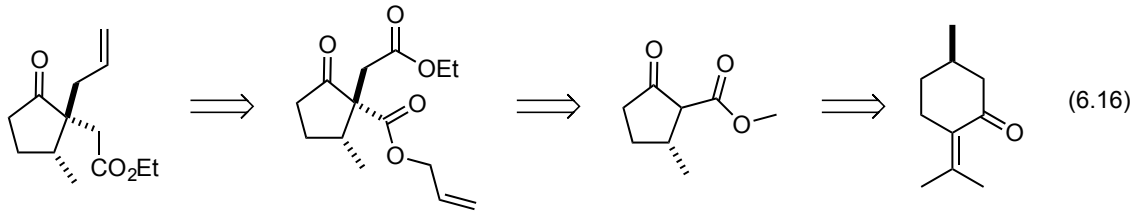
6.20 **6.22** (6.14)



6.22 **6.5** *not observed* **6.21** 88%

6.3 THIRD GENERATION STRATEGY: STEREOSELECTIVE SYNTHESIS

We thought that the desired ketone **6.5** could be attained via a Tsuji-Trost reaction of β-keto ester **6.23** (Equation 6.16). Alkylation and esterification of methyl β-keto ester **6.24** would allow access to **6.23**, and we found that **6.24** could be prepared as a single enantiomer in three steps from (+)-pulegone (**6.25**). This new route not only removes the conjugate addition/allylation sequence required in the previous route, but also shortens the route and allows for an enantioselective synthesis of **5.1**. During the course of our studies on this route, Sorensen disclosed his synthesis of jiadifenolide (**5.1**) which also began from pulegone (**6.25**).[277]

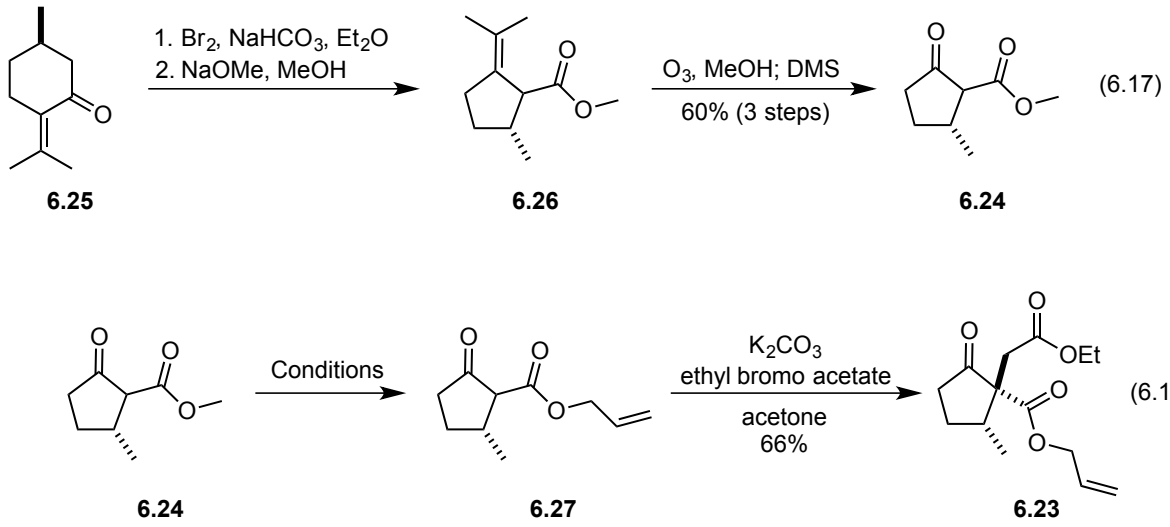


6.5 **6.23** **6.24** **6.25**

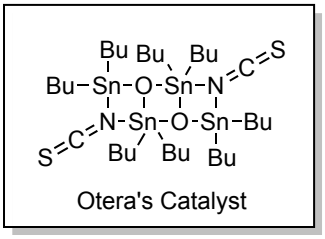
6.3.1 Synthesis of Tsuji-Trost Substrate 6.23

The route began from (+)-pulegone (**6.25**), which was smoothly transformed into ester **6.26** via bromination and Favorski rearrangement (Equation 6.17). Ozonolysis of the resulting olefin then delivered β-keto ester **6.24** in 60% yield over three steps.[317-319]

Elaboration of **6.24** to the desired substrate **6.23** took place over two steps (Equation 6.18). Transesterification of **6.24** with allyl alcohol using DMAP and 4 Å molecular sieves proved to be low yielding,[320] as did use of Otera's catalyst (Equation 6.18). [321,322] We then found that heating **6.24** in the presence of DMAP and allyl alcohol with azeotropic removal of methanol provided **6.27** in moderate yield.[323] Finally, treatment of **6.27** with potassium carbonate and ethyl bromoacetate delivered **6.23** in 66% yield, and the stereochemistry was assigned based on analogy to the reported literature.[324]



Conditions
DMAP (1.5 eq), allyl alcohol (3 eq), 4 Å MS, 32%
Otera's catalyst (0.1 eq), allyl alcohol (10 eq), toluene, Δ, 44%
DMAP (0.2 eq), allyl alcohol (5 eq), cyclohexane, 80 °C, 65%

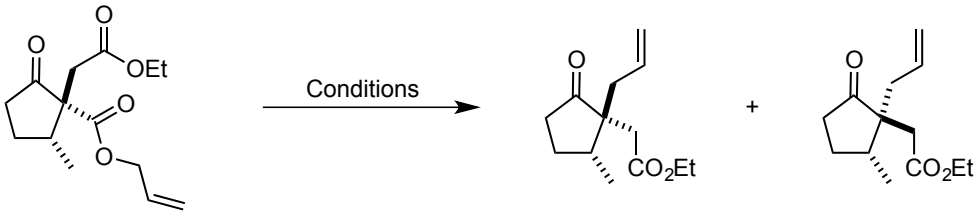


6.3.2 Decarboxylative Allylation Reactions with 6.23

With β-keto ester **6.23** in hand, we set out the test the palladium mediated decarboxylative allylation. In the event, **6.23** was exposed to Pd_2dba_3 and dppe in THF to provide allyl cyclopentenone **6.5** as the sole product, but as a mixture (1:1.4) of diastereomers as determined by ^1H NMR of the crude reaction mixture (Table 6.2, Entry A). The stereochemistry of the two diastereomers was determined by 1D and 2D NOESY experiments, wherein an NOE between the methyl group protons and the protons of the allyl group could be observed (Figure 6.2). Despite the poor diastereoselectivity, we were pleased to find that the reaction proceeded smoothly with no by-products. Although there was no information regarding diastereoselective Tsuji allylations of cyclopentanones and little information was available on diastereoselective Tsuji reactions in general,[325-329] the panoply of information on Tsuji-Trost reactions in the literature made us confident that we would find suitable conditions for the transformation.

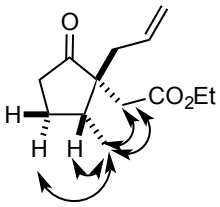
Shown in Table 6.2, switching to $Pd(PPh_3)_4$ in THF proved to be detrimental to the stereoselectivity (Entry B). Furthermore, it seemed that solvent was not a major contributing factor to the poor selectivity (Entry C). It had been shown in the literature that the addition of lithium chloride enhanced diastereoselectivity in select cases, possibly due to disruption of the ion pair.[330,331] Unfortunately, we found that lithium chloride completely shut down the reaction (Entry D).

Table 6.2 Initial studies of the palladium mediated decarboxylative allylation of **6.27**.

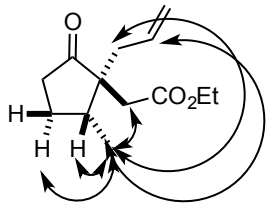


6.27 **6.5** ***epi*-6.5**

Entry	Metal	Ligand/Additive	Solvent (0.03 M)	dr (**6.5**:*epi*-**6.5**)
A	Pd_2dba_3	dppe	THF	1.4:1
B	$Pd(PPh_3)_4$	–	THF	1.1:1
C	$Pd(PPh_3)_4$	–	PhMe	1.2:1
D	$Pd(PPh_3)_4$	LiCl	THF	NR



6.5
NOE between both protons of the ester and methyl
No NOE between allylic protons or vinyl protons and methyl



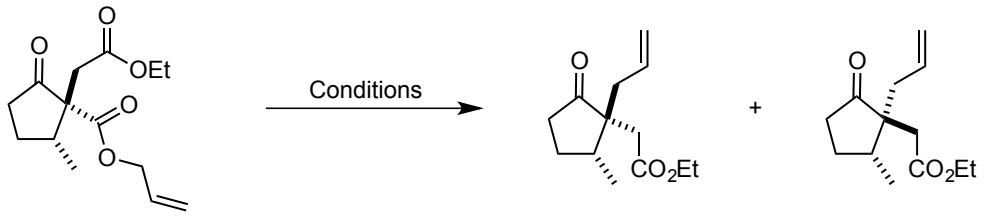
***epi*-6.5**
NOE between both allylic protons and methyl
NOE between one vinyl proton and methyl
NOE between one ester proton and methyl

Figure 6.1 NOE correlations for **6.5** and *epi*-**6.5**

As the rate-determining step of the decarboxylative Tsuji-Trost reaction is believed to be decarboxylation,[332] we envisioned that slowing down the C-C bond forming step would likely be difficult; however, if possible, this would hopefully provide some enhancement of the diastereoselectivity. It had been demonstrated that the electronics of the phosphine ligands influenced the rate of the reactions,[333] presumably by either stabilizing or destabilizing the allyl palladium cation intermediate; however, the ligand electronics may only change the rate of decarboxylation. Accordingly, we screened a number of ligands with differing electronic character.

As demonstrated in Table 6.3, ligand electronics did have a profound effect on the reaction, but it was not a desirable one. We noted in the above reactions that dibenzylideneacetone co-elutes with the product, so we switched to palladium acetate for the following experiments. The electron-deficient perfluorotriphenylphosphine shut down the reaction completely (Entry A), as did triphenylphosphite and tricyclohexylphosphine (Entries B and C). We were pleased to find that *rac*-BINAP not only promoted the reaction but also increased the dr to 1:1.6, the best selectivity observed thus far (Entry D). While not yet synthetically useful, it was certainly a step in the right direction. We also tested triphenylphosphite and perfluorotriphenylphosphine with palladium dibenzylidene acetone to exclude the possibility that palladium acetate did not form the active palladium (0) catalyst with the different phosphines, but received the same results as with palladium acetate (Entries E and F).

Table 6.3 Screening ligand electronics in the allylation of **6.27**



6.27 **6.5** ***epi*-6.5**

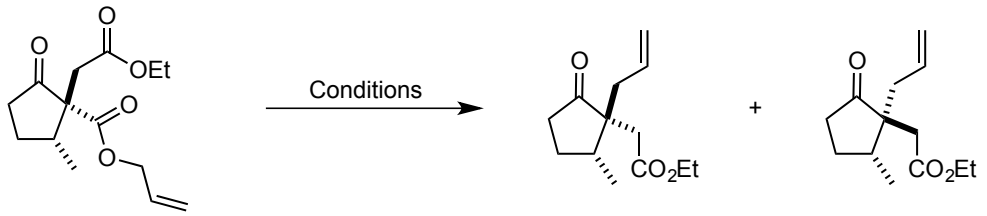
Entry	Metal	Ligand/Additive	Solvent (0.03 M)	dr (**6.5**:*epi*-**6.5**)
A	$Pd(OAc)_2$	$P(C_6F_5)_3$	THF	NR (rt, 40 °C)
B	$Pd(OAc)_2$	$P(OPh)_3$	THF	NR (rt, 40 °C)
C	$Pd(OAc)_2$	$P(C_6H_{11})_3$	THF	NR (rt, 40 °C)
D	$Pd(OAc)_2$	*rac*-BINAP	THF	1.6:1 (40 °C)
F	Pd_2dba_3	$P(C_6F_5)_3$	THF	NR (rt, 40 °C)
G	Pd_2dba_3	$P(OPh)_3$	THF	NR (rt, 40 °C)

Based on the results obtained thus far, we began screening bidentate ligands. The rationale being that if a ligand dissociated from the metal during the course of the reaction, more transition states would be possible due to the open coordination site and less steric bulk in the local environment. Having the phosphines tethered should keep as many coordination sites occupied on the catalyst as possible.

We previously tested dppe and obtained the product cleanly with a 1:1.4 dr (Table 6.2, Entry A). Thus we expanded our testing to the other bidentate phosphines. As shown in Table 6.4, lengthening the alkyl tether from ethyl (dppe) to propyl (dppp) and butyl

(dppb) did nothing to improve the diastereoselectivity of the reaction (Entries A and B). Furthermore, bis(diphenylphosphino)ferrocene (dppf) and xantphos returned similar results as the other achiral bidentate phosphines. In reviewing all of the results, *rac*-BINAP had performed the best, thus we queried if better selectivity might be achieved with an enantiopure ligand.

Table 6.4 Screening bidentate ligands for the allylation of **6.27**



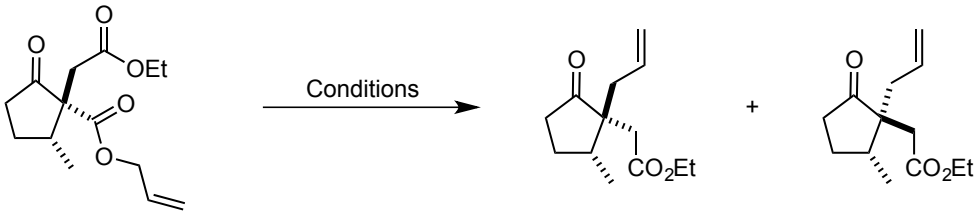
6.27 **6.5** ***epi*-6.5**

Entry	Metal	Ligand	Solvent (0.03)	dr (**6.5**:*epi*-**6.5**)
A	Pd_2dba_3	dppp	THF	1.4:1
B	Pd_2dba_3	dppb	THF	1.3:1
C	Pd_2dba_3	dppf	THF	1.4:1
D	Pd_2dba_3	xantphos	THF	1.3:1

As shown in Table 6.5, (*R*)-T-BINAP reversed the stereoselectivity of the reaction (Entry A); however, we were disappointed to find that (*S*)-T-BINAP did not improve the selectivity over *rac*-BINAP (Entry B). We switched solvents from THF to toluene in order to test any effect that had with a chiral ligand (Entries C and D). While we did find that the active catalyst formed slower in toluene and required elevated temperatures

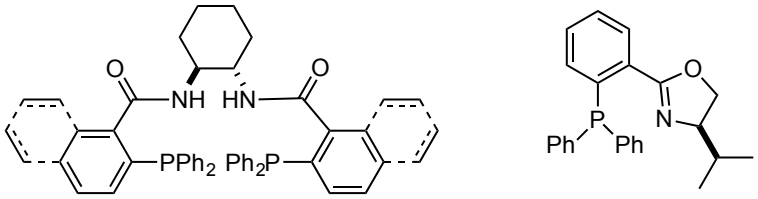
(Entry C), no enhanced selectivity was observed. Additionally, when we formed the catalyst at 60 °C and cooled the reaction back to room temperature prior to addition of the substrate, we saw little change in the selectivity (Entry D). The ligands designed by Trost have been shown to be extremely effective in enantioselective Tsuji-Trost allylations for a number of substrates,[324,334-337] as well as one diastereoselective prenylation.[327] Despite the success with other substrates, we were disappointed to find that the reactions returned starting material, even upon heating (Entries E, F, G, and H). The PHOX ligands have been explored extensively in a wide variety of applications since their introduction by Pfaltz,[338] Helmchen,[339] and Williams.[340] During the past ten years, Stoltz has pioneered these ligands use in a variety of decarboxylative allylation reactions with a high degree of enantioselectivity.[315,316,329,341-347] More importantly for us, he has shown that these ligands were useful in diastereoselective allylations of cyclohexanones.[329,344] Although he had reported that the enantioselective allylation of cyclopentanones was problematic,[315] based on those examples, we should at least expect to see diastereoselectivities greater than 2:1, provided that we did not have a mismatched substrate and ligand. Unfortunately, we once again found that the ligands were unsuccessful with all reactions returning starting material in both THF and toluene, even at elevated temperatures (Entries I, J, K, and L).

Table 6.5 Screening chiral ligands for the allylation of **6.27**



6.27 **6.5** ***epi*-6.5**

Entry	Metal	Ligand	Solvent (0.03 M)	dr (**6.5**:*epi*-**6.5**)
A	Pd_2dba_3	(R)-T-BINAP	THF	1:1.2
B	Pd_2dba_3	(S)-T-BINAP	THF	1.7:1
C	Pd_2dba_3	(S)-T-BINAP	PhMe	1.7:1 (60 °C)
D	Pd_2dba_3	(S)-T-BINAP	PhMe	1.8:1 (rt)
E	Pd_2dba_3	R,R-naph-Trost	THF	NR
F	Pd_2dba_3	S,S-naph-Trost	THF	1:1.2
G	Pd_2dba_3	R,R-Trost	THF	NR
H	Pd_2dba_3	R,R-Trost	PhMe	NR
I	Pd_2dba_3	S-*i*Pr-PHOX	THF	NR
J	Pd_2dba_3	R-*i*Pr-PHOX	THF	NR
K	Pd_2dba_3	S-*i*Pr-PHOX	PhMe	NR
L	Pd_2dba_3	R-*i*Pr-PHOX	PhMe	NR



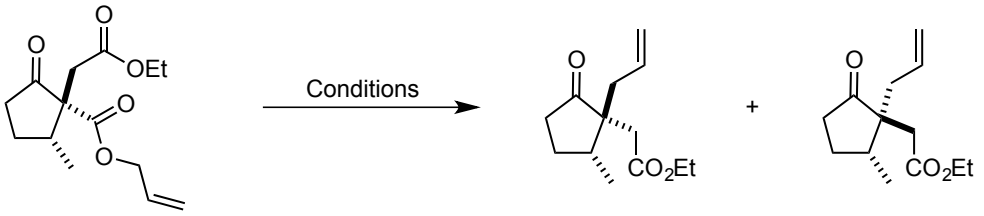
6.28
Trost

6.29
i-Pr-PHOX (Stoltz)

Figure 6.2 Chiral ligands for Tsuji-Trost allylations

Unfortunately, we had thus far been unable to improve the stereoselectivity using tactics frequently utilized in the literature. One condition that is not frequently changed during the course of reaction optimization for similar reactions is concentration. Most reactions, especially enantioselective variants of the decarboxylative allylations, are run at 0.03 or 0.05 M. Although it is only a slight enhancement, we found that increasing the concentration incrementally from 0.03 to 1 M led to a slight increase in the stereoselectivity (Table 6.6). We then tested (*S*)-T-BINAP at 1 M concentration. Indeed, combining the two best conditions so far increased the dr consistently to 1:2 with an average of an 85% yield. While not a complete solution, it was a step in the right direction.

Table 6.6 Changing concentration for the allylation of **6.27**



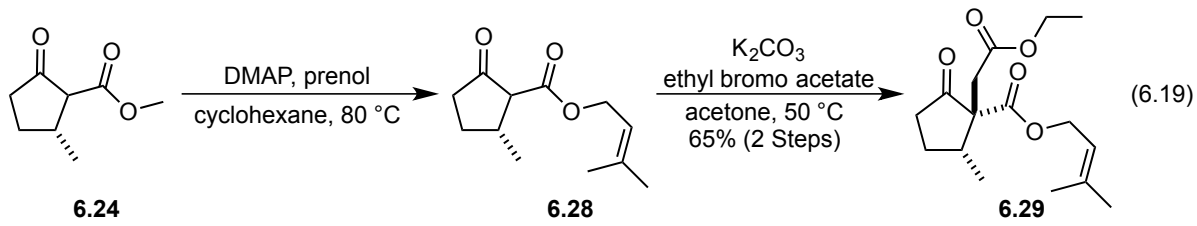
6.27 **6.5** ***epi*-6.5**

Entry	Metal	Ligand	THF (M)	dr (**6.5**:*epi*-**6.5**)
A	$Pd(PPh_3)_4$	–	0.03	1.1:1
B	$Pd(PPh_3)_4$	–	0.1	1.2:1
C	$Pd(PPh_3)_4$	–	0.5	1.4:1
D	$Pd(PPh_3)_4$	–	1.0	1.4:1
E	Pd_2dba_3	(S)-T-BINAP	1.0	2:1

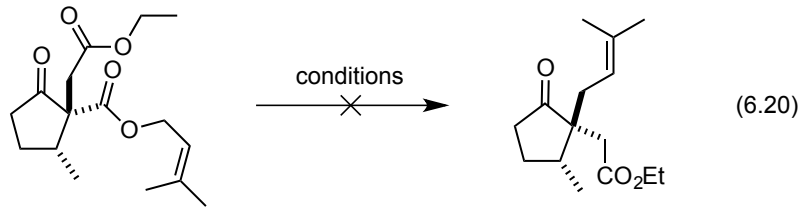
6.3.3 Various Tsuji-Trost Attempts: New Substrates and Catalysts

As we found minimal success by varying ligands and solvents, we envisaged that perhaps increasing the size of the latent electrophile could lead to enhanced stereoselectivity. Thus, we sought to synthesize prenyl β-keto ester **6.29**. The synthesis was straightforward and was performed in an analogous manner as **6.27**. Known methyl β-keto ester **6.24** underwent transesterification with prenyl alcohol to provide **6.28** (Equation 6.19). Upon treatment of **6.28** with potassium carbonate and ethyl bromoacetate, **6.29** was formed in 65% yield over two steps. With substrate **6.29** in hand, we were excited to see what effect the increased size of the electrophilic prenyl palladium cation would have on the diastereoselectivity. Despite our best efforts, the substrate failed to produce any product when subjected to the reaction conditions, and we exclusively

recovered starting material (Equation 6.20). It was known in the literature that prenyl β-keto esters generally react slower than their corresponding allyl substrates, but it is unclear at this point why β-keto ester **6.29** is unreactive.



6.24 **6.28** **6.29** (6.19)

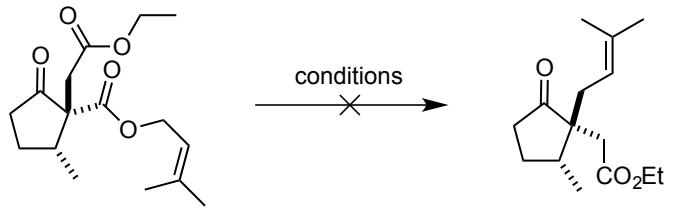


6.29 **6.30** (6.20)

Conditions
$Pd(PPh_3)_4$, THF (RT, 40 °C), RSM
$Pd(PPh_3)_4$, PhMe (RT, 40 °C, 60 °C, 100 °C), RSM
Pd_2dba_3, (R)-T-BINAP, THF (RT, 40 °C), RSM
Pd_2dba_3, (S)-T-BINAP, THF (RT, 40 °C), RSM
Pd_2dba_3, (R)-T-BINAP, PhMe (RT, 40 °C, 60 °C, 100 °C), RSM
Pd_2dba_3, (S)-T-BINAP, PhMe (RT, 40 °C, 60 °C, 100 °C), RSM

With many options involving palladium exhausted, we moved on to other metals known to promote this reaction. It had been demonstrated in the literature that iridium,[341] rhodium,[348-350] molybdenum, and tungsten promote Tsuji-Trost reactions.[351] In fact, it is believed that the octahedral transition metal complexes $Mo(CO)_n(L)_{6-n}$ and $W(CO)_n(L)_{6-n}$ (n = 3,4, or 6) impart better selectivity, in some cases, than the square planar or tetrahedral palladium catalysts due to their larger size.[351] However, we were disappointed

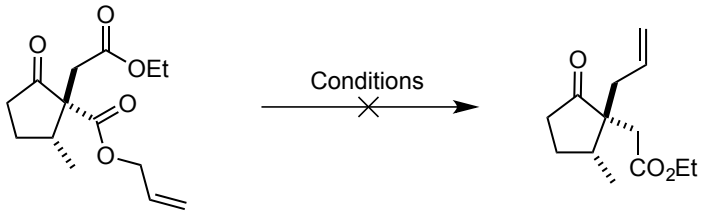
to find that for both prenyl substrate **6.29** and allyl substrate **6.27**, only starting material was recovered from the reactions (Equations 6.21 and 6.22).



(6.21)

6.29 **6.30**

Conditions
$Mo(CO)_3(MeCN)_3$, THF, RSM
$W(CO)_3(MeCN)_3$, bpy, THF, RSM
$Rh(PPh_3)_3Cl$, THF, RSM
$[Rh(CO)_2Cl]_2$, THF, RSM
$Mo(CO)_6$, THF, µW, RSM
$Mo(CO)_6$, PhMe, µW, RSM



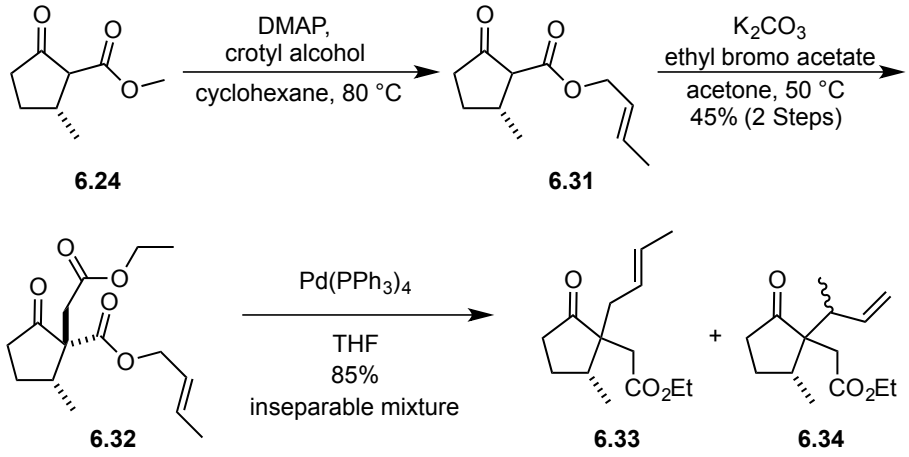
(6.22)

6.27 **6.5**

Conditions
$[Ir(COD)Cl]_2$, $P(OPh)_3$, THF, RSM
$Rh(PPh_3)_3Cl$, THF, RSM
$[Rh(CO)_2Cl]_2$, THF, RSM
$[Rh(CO)_2Cl]_2$, DMF, RSM
$Mo(CO)_3(EtCN)_3$, THF, RSM
$Mo(CO)_3(EtCN)_3$, PhMe, RSM
$Mo(CO)_6$, THF, µW, RSM

As the prenyl substrate failed to react, we decided to explore the crotyl analog **6.32**. If the sterics associated with the tri-substituted olefin were a problem for substrate **6.29**, perhaps the disubstituted croyl variant **6.32** would react. The synthesis of **6.32** followed the same route as both the allyl substrate **6.27** and the prenyl substrate **6.29**.

Sequential esterification and alkylation provided **6.32** in 45% yield over two steps (Scheme 6.4). However, we were disappointed to find that while the decarboxylative allylation proceeded in 85% yield, we received an intractable mixture of diastereomers of both the linear **6.33** and branched addition products **6.34**.

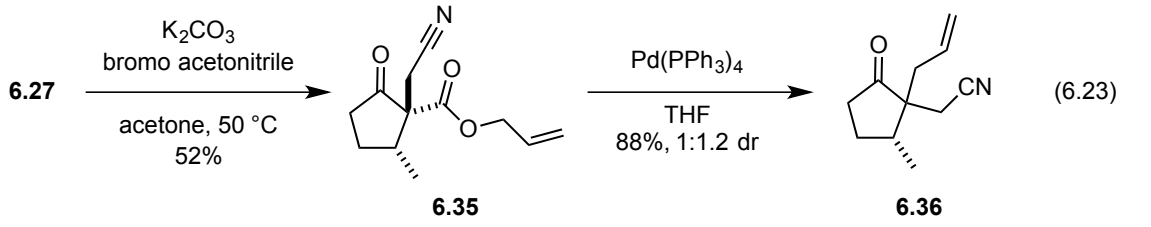


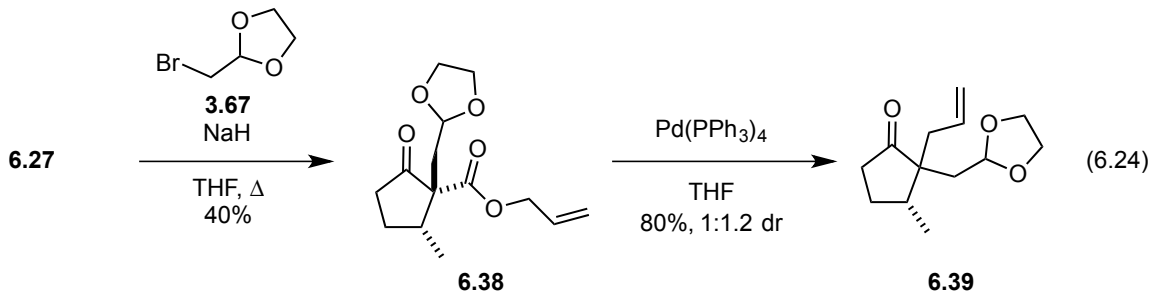
Scheme 6.4 Attempted decarboxylative allylation of prenyl substrate **6.32**

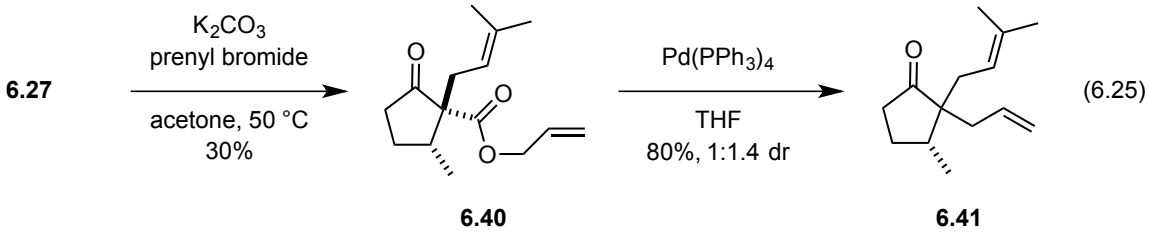
We reasoned that the ester moiety in **6.27** could be problematic if it formed an unfavorable chelate with the catalyst during the course of the reaction. Indeed, there was a single example in the literature of an enantioselective decarboxylative allylation on a cyclohexanone wherein a chelate was proposed, but Trost reasoned that this chelate was favorable.[352] As there was no information available on chelate effects in diastereoselective Tsuji allylations or on cyclopentanones, we chose to explore the reaction of masked ester functionalities that would not be able to chelate.

The syntheses of the target molecules were again straightforward, involving alkylation of the allyl β-keto ester **6.27** and the stereochemistry was once again assigned based on an analogous example in the literature.[324] When the ester was masked as a nitrile

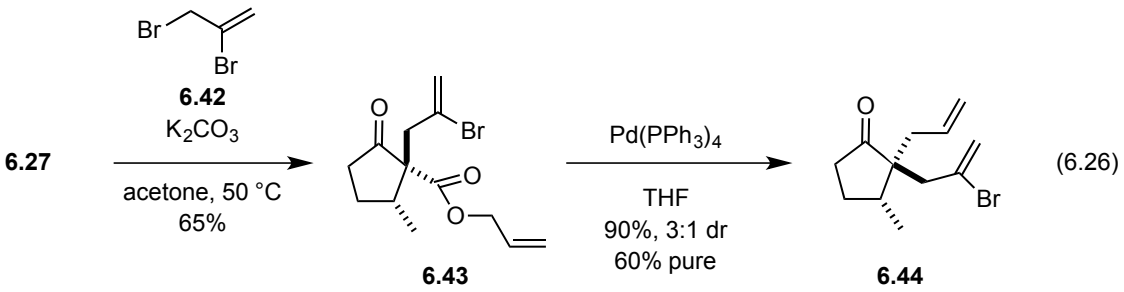
in **6.35**, we observed no enhancement in stereoselectivity (Equation 6.23). We thought that perhaps increasing the size of the masked ester could benefit the diastereoselectivity, but again found no enhancement with the use of acetal **6.38** (Equation 6.24). Only a marginal increase in selectivity was obtained when using the prenylated substrate **6.40** (Equation 6.25). Finally, we achieved the highest diastereoselectivity thus far when the ester was masked as a vinyl bromide (Equation 6.26); however, upon analysis of **6.44** with both 1D and 2D NOESY experiments, we found that the stereochemistry was opposite to that which we had expected and desired as there was an NOE between the methyl protons and every position of the allyl group and no NOE between the methyl group protons and the bromoallyl group (Figure 6.3). In an attempt to achieve an equal but opposite result, we prepared vinyl chloride **6.45** (Equation 6.27); however, we found the substrate unreactive.



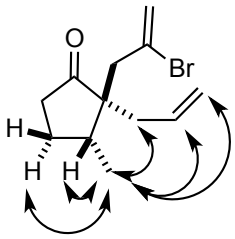




6.40 **6.41**

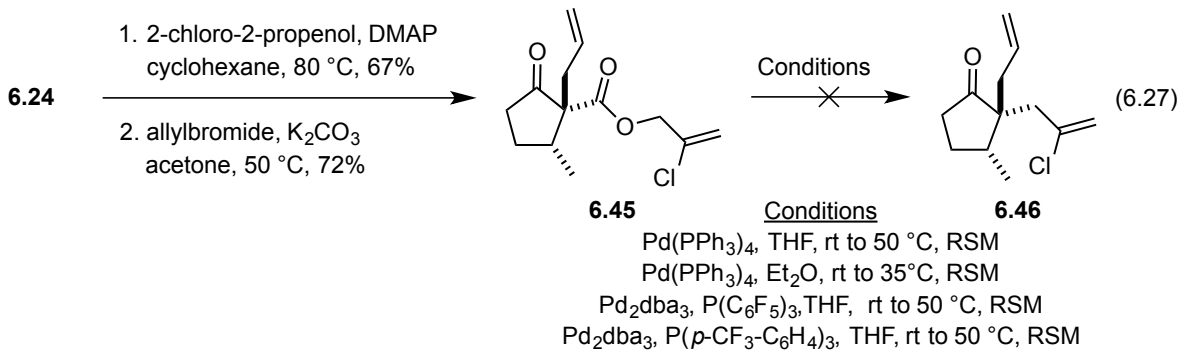


6.43 **6.44**



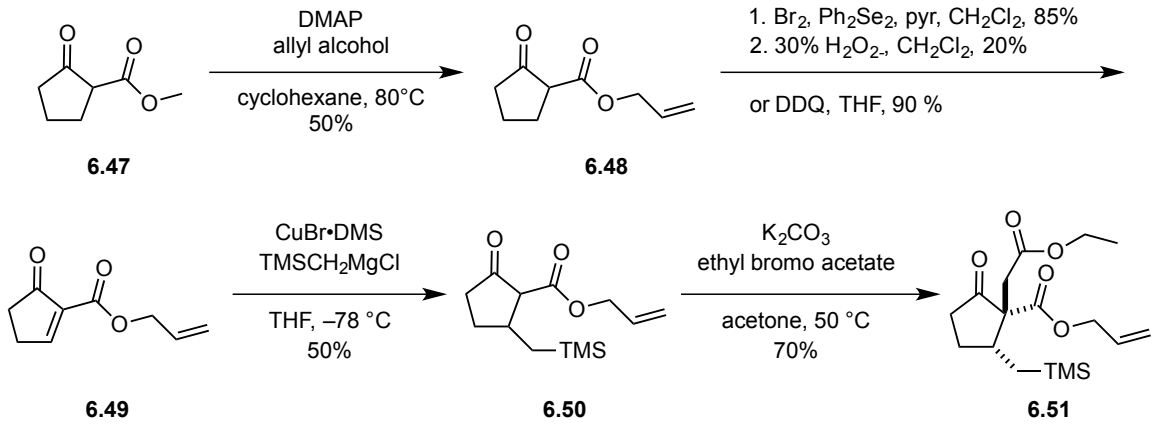
6.44
NOE between the Me group and all positions of the allyl group
No NOE between the Me group and the bromoallyl group

Figure 6.3 NOE correlations of **6.44**

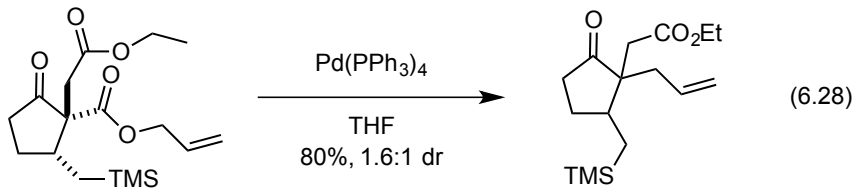


As varying the substituents on the α-position of the cyclopentanone had no beneficial effect, we reasoned that the methyl group was not providing enough steric differentiation between the two faces of the enolate. Thus, we turned our attention to increasing the size of the β-substituent via a removable functionality. Toward this end, cyclopentanone **6.47** was esterified to provide **6.48** (Scheme 6.5). Despite literature precedent,[353] we found the oxidation of **6.48** to **6.49** via a selenide low yielding because the product was not stable to the reaction conditions. This was not surprising,[85] and we were pleased to find that dehydrogenation with DDQ proceeded smoothly in 90% yield.[354] Conjugate addition to **6.49** provided a moderate amount of **6.50**, which was alkylated under standard conditions to provide **6.51**. However, when **6.51** was subjected to decarboxylative allylation conditions, we found minimal improvement over the methyl variant (Equation 6.28); the stereochemistry was not assigned as the selectivity was not synthetically useful. This is most likely due to the position of the silyl group relative to the enolate (Figure 6.2), which we believe to favor **6.53** over **6.54** due to minimization of steric interactions between the TMS group and the ester side chain. We believed that the diastereoselectivity could therefore be improved by using the dithiane derivative **6.55**, which would be required to have one of the sulfur atoms near the enolate (Figure 6.3);

however, attempts at the synthesis of **6.55** were unsuccessful due to non-productive decomposition of the starting material under the reaction conditions (Equation 6.29).[355]



Scheme 6.5 Synthesis of TMS derivative **6.51**



(6.28)

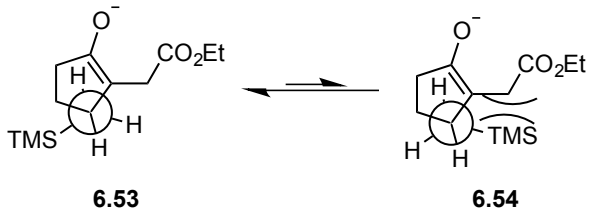


Figure 6.2 Conformational analysis of the enolate of **6.51**

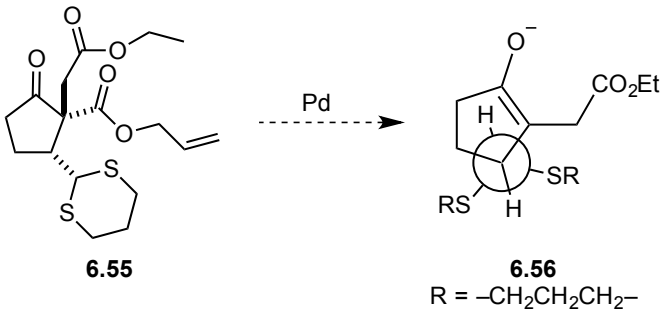
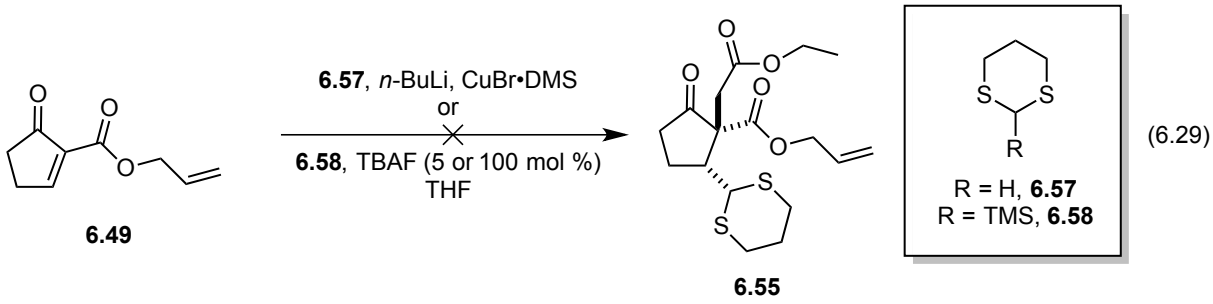


Figure 6.3 Analysis of enolate **6.56**

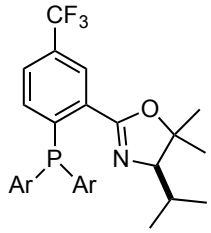


(6.29)

6.3.4 Stoltz's Electron Deficient PHOX ligand

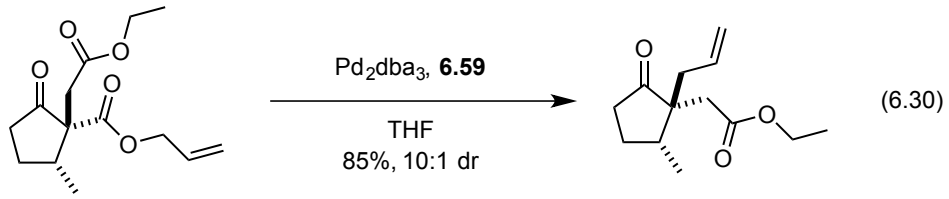
During the course of our studies on diastereoselective decarboxylative allylations of cyclopentanones, Stoltz reported a new electron deficient PHOX ligand **6.59** (Figure 6.4).[356-359] In addition to promoting Tsuji allylations with challenging substrates, this ligand generally provided higher enantioselectivities with all substrates. We were excited to try this new ligand with our substrate, despite the failure of the standard PHOX ligand **6.29** in previous attempts (Table 6.5, Entries I, J, K, and L). In the event, we found that when **6.27** was exposed to the reactions conditions, we recovered **6.5** in 85% yield and 10:1 dr! To the best of our knowledge, this reaction represents the first diastereoselective decarboxylative allylation on a cyclopentanone. In fact, while Stoltz has reported excellent enantioselectivities with cyclobutanones,[343] cyclohexanones,[315] and cycloheptanones,[360] cyclopentanones have been troublesome for their group in the past;

making this perhaps one of the first highly stereoselective Tsuji allylations of a cyclopentanone in general.



6.59
Ar = *p*-CF_3-C_6H_4
(R)-(p-CF_3)$_3$-i-PrPHOX^{Me2}

Figure 6.4 Stoltz's trifluoromethyl PHOX ligand



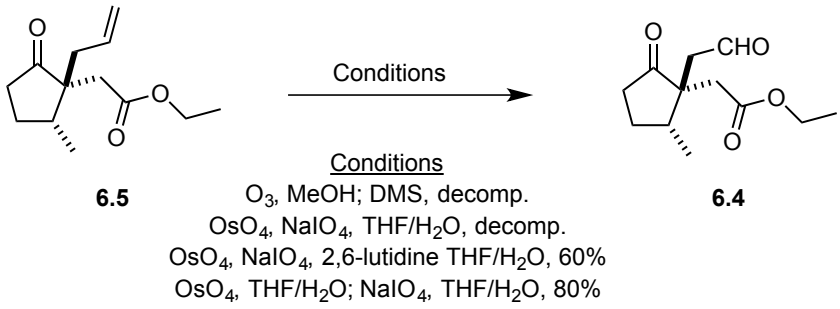
6.27 **6.5**

6.3.5 Attempts to Elaborate Cyclopentanone 6.5

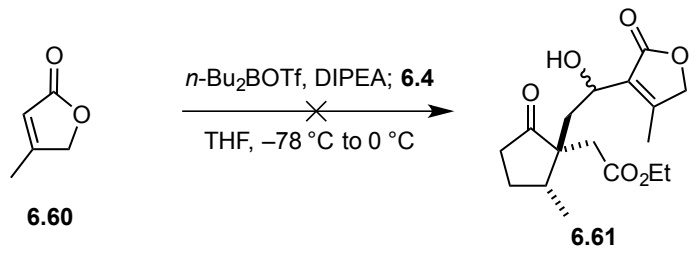
6.3.5.1 Additions to Aldehyde 6.4

Having access to **6.5** with synthetically useful diastereoselectivity, we had only to elaborate **6.5** to **6.3** in order to test the key reductive cyclization reaction. We found that the olefin of **6.5** underwent oxidative cleavage under standard Johnson-Lemiuex conditions, though the two-pot procedure consistently provided higher yields (Equation 6.31). We soon found, like Paterson reported,[278] that the homo-neopentyl aldehyde **6.4** was unreactive. Our first attempt involved the only conditions reported to work on a

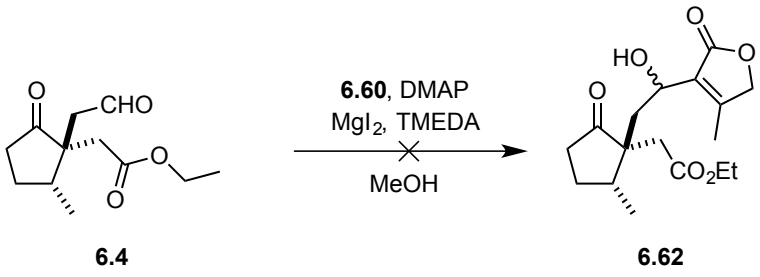
similar system;[278] however, the boron enolate of **6.60** failed to add to aldehyde **6.4** (Equation 6.32). We then attempted a Baylis-Hilman reaction with **6.60** and **6.62**, which could be converted to the butenolide via ring closing metathesis, but both attempts failed to deliver the desired product (Equations 6.32 and 6.33). Because Paterson demonstrated that a related keto-butenolide did not undergo the radical addition (Section 5.5),[278] we decided to remove the oxygen atom from our substrate.



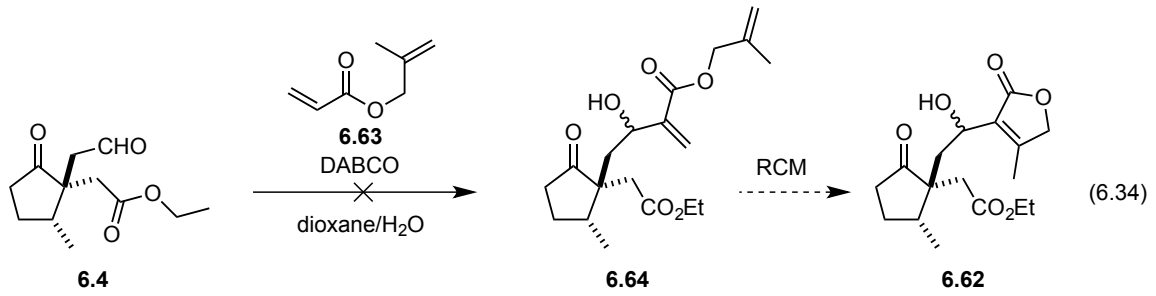
(6.31)



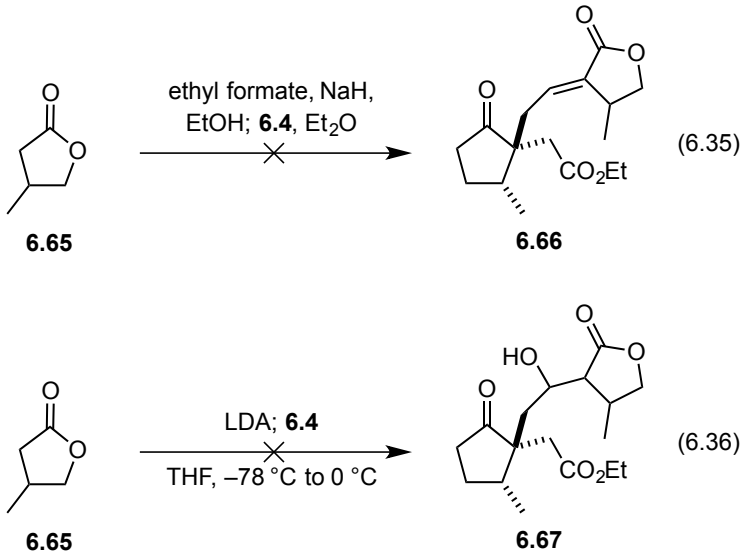
(6.32)

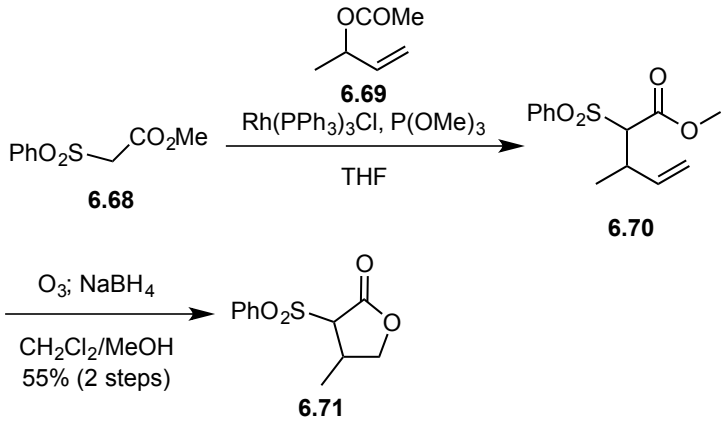


(6.33)

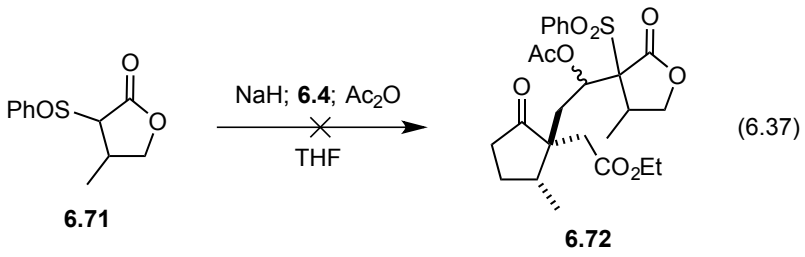


Toward this end, we attempted an aldol condensation of **6.4** with **6.65**, but no product was observed (Equation 6.35). Additionally, the lithium enolate derived from **6.65** failed to react with aldehyde **6.4** (Equation 6.36). We thought that perhaps a Julia olefination of **6.4** could provide access to **6.66**, so we prepared **6.71** via a known three-step procedure (Scheme 6.6).[361] However this too failed to add into the aldehyde. Most of the above reactions returned starting material, presumably because the nucleophile deprotonated our electrophile, though non-productive decomposition of the starting material could be achieved with more forcing conditions.





Scheme 6.6 Synthesis of lactone **6.71**

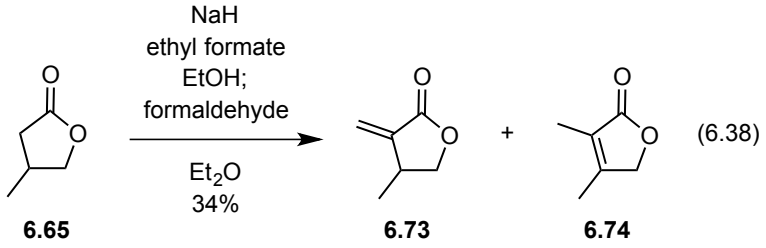


(6.37)

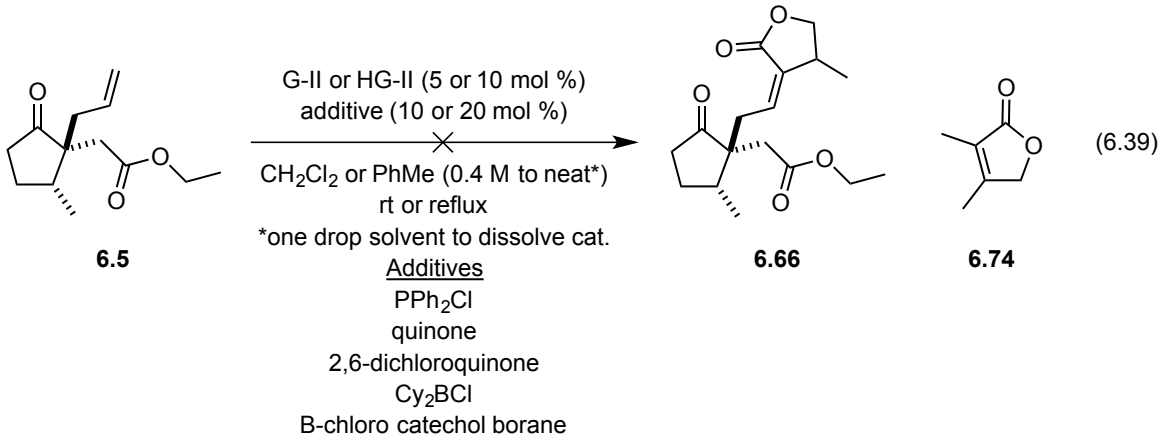
6.3.5.2 Cross Metathesis Attempts

As we no longer required the oxygen atom that had proved problematic for Patersen, we reasoned that the step count could be reduced if olefin **6.5** were directly converted to **6.66** via cross metathesis. Lactone **6.65** was converted to α-methylene-γ-butyrolactone **6.73** via condensation with formaldehyde (Equation 6.38),[362] though the yield of the lactone was low due to olefin isomerization to the butenolide **6.74**. With both **6.73** and **6.5** in hand, we attempted cross metathesis. Both Howell and Cossy have reported conditions for the cross metathesis of unsubstituted α-methylene-γ-butyrolactones using additives to suppress olefin isomerization.[363,364] However, we were disappointed to find that none of the additives suppressed olefin migration for substituted

methylene lactone **6.73**, leading to the recovery of **6.74**, starting material, and dimerized starting material (Equation 6.39). The Johnson group has also reported that they were unable to reproduce the Howell and Cossy protocols.[365]



(6.38)



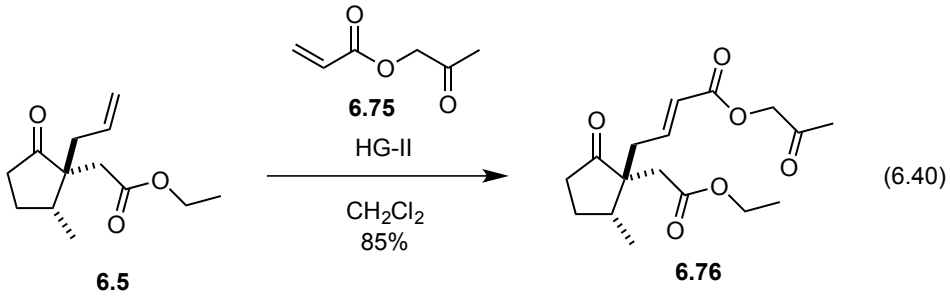
(6.39)

Undeterred by this failure, we turned our attention to cross metatheses involving non-isomerizable olefins that could in turn be elaborated to the required butenolide. We were pleased to find that cross metathesis of **6.75**, available from acryloyl chloride and hydroxyacetone,[366] proceeded smoothly to provide **6.76** in 85% yield (Equation 6.40). With **6.76** in hand, we had only to perform a 1,4-reduction and aldol reaction to give **6.77**, which could be dehydrated to provide the key intermediate for reductive

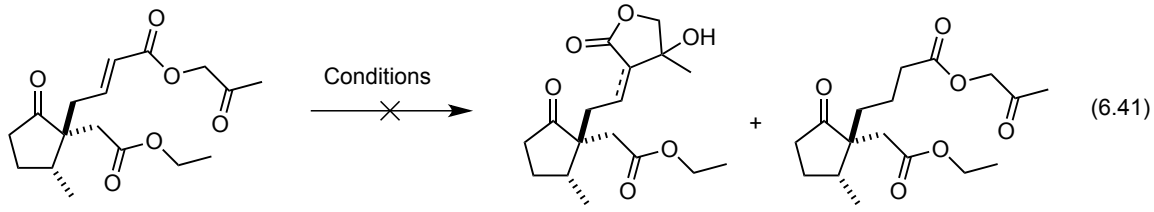
cyclization. Unfortunately, nickel hydride,[367] Stryker's reagent,[368] catechol borane with and without Wilkenson's catalyst,[369] copper hydrides,[370-372] and ruthenium hydrides[373] all failed to deliver **6.77** though they did hydrogenate the enoate to give **6.78**.

Though similar reactions have been reported to work beautifully on enones and enals, the hydrogen-mediated reductive aldol reactions developed by Krische also failed to promote the hydrogenative aldol reaction of enoate **6.76** delivering only **6.78**.[374-377] We were later informed, as the reactions were not reported in the literature, that these were the same results that they had obtained when attempting hydrogen-mediated reductive aldol reactions with acrylates and crotonates. Additionally, a Kulinkovich-like reaction failed, and Baylis-Hilman reactions failed to give the unsaturated product.

Samarium diiodide has been utilized in a similar fashion to form cyclopentanones,[378-381] so we believed the method could be applicable to the synthesis of butyrolactones. However, both sets of conditions only provided the reductive cleavage product **6.79** (Equation 6.42). We thought that perhaps **6.78** could be converted to the appropriate intermediate **6.77**, but all attempts to perform a base-mediated aldol cyclization were unsuccessful (Equation 6.43), most likely due to the need for the deprotonation to occur at the second least acid position of the molecule. Finally, we attempted intermolecular reductive aldol reaction with **6.80** to no avail (Scheme 6.7).



(6.40)



(6.41)

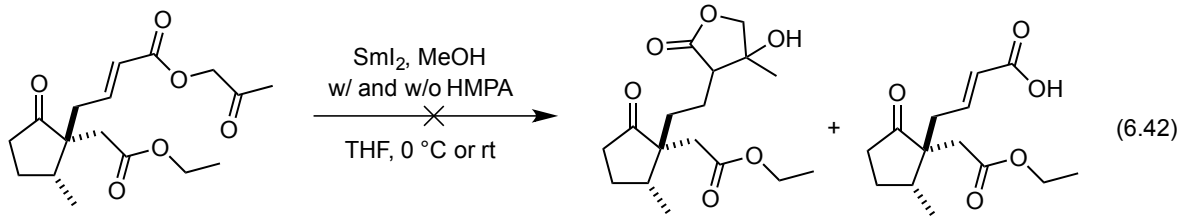
6.76

6.77
not observed

6.78
isolated under reductive conditions

Conditions

Et_2Zn, $Ni(acac)_2$, THF, 0 °C to rt
Stryker's reagent, PhMe, –40 °C
catecholborane, THF, rt
Wilkinson's catalyst, catecholborane, THF, 0 °C
$Cu(OAc)_2$, dppf, $SiEt_3H$, KO*t*Bu, THF
CuCl, $PhMe_2SiH$, DMF
$RuCl_3$, $SiEt_3H$, THF
$Rh(cod)_2OTf$, PPh_3, K_2CO_3, H_2, DCE
$Rh(cod)_2$, PPh_3, KOAc, H_2, DCE
$Rh(cod)_2$, P(*p*-CF_3-Ph)$_3$, KOAc, H_2, DCE
$Rh(cod)_2OTf$, PPh_3, K_2CO_3, H_2, DCE, 60 °C (pre-heated)
Ti(O*i*Pr)$_4$, CyMgCl, TBME, –40 °C
DABCO, MeOH
DABCO, dioxane

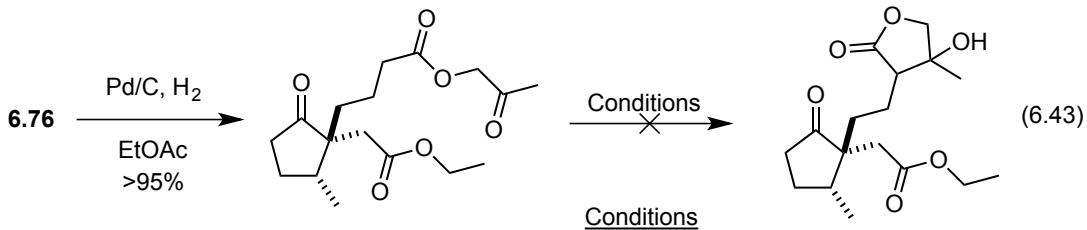


(6.42)

6.76

6.77
not observed

6.79
quantitative



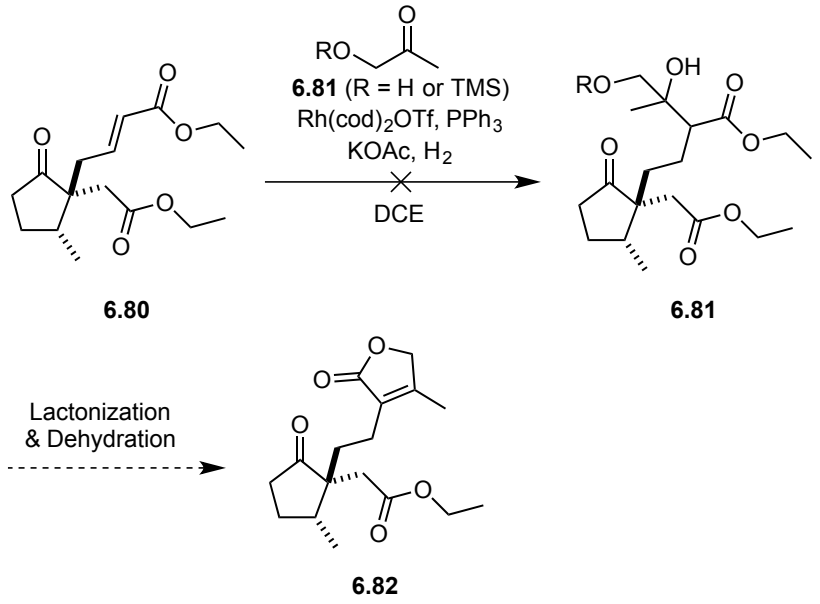
(6.43)

6.78

Conditions

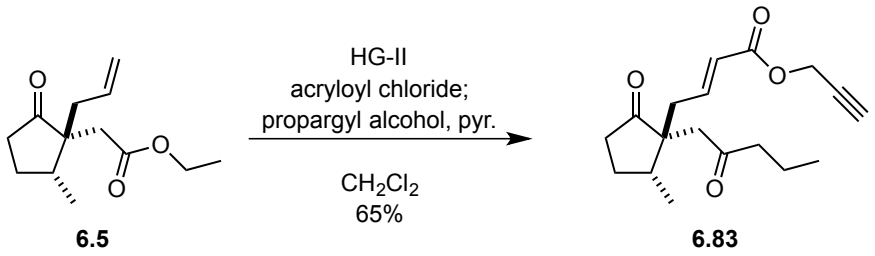
DBU, MeCN
NaH, DMSO
LDA (0.95 equiv.), THF

6.77

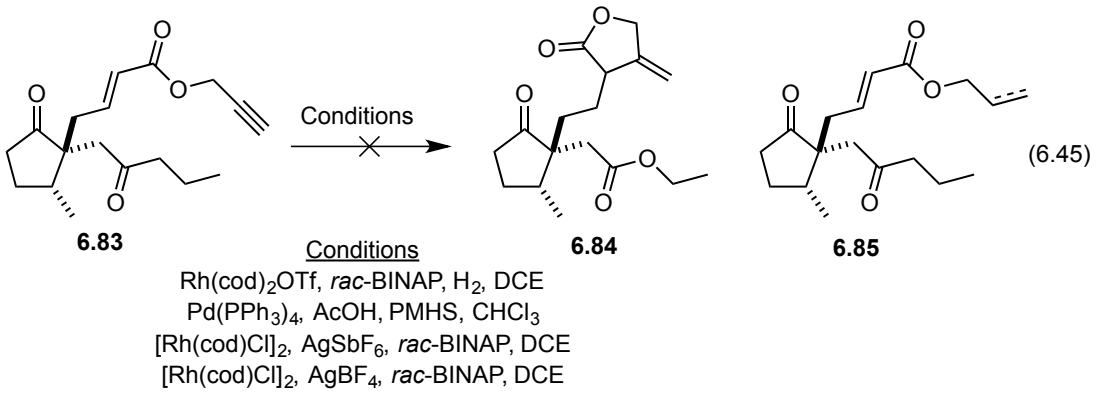


Scheme 6.7 Intermolecular reductive aldol reaction of **6.80**

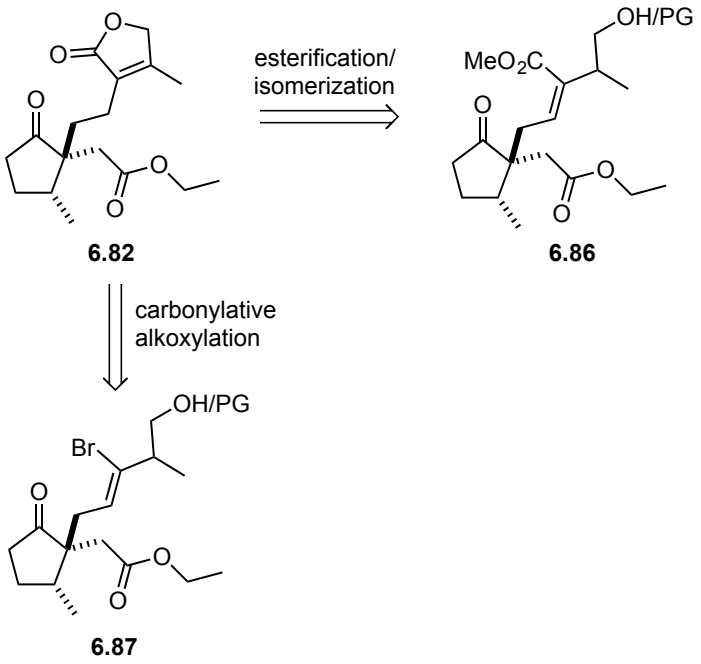
Next, we focused on the reductive cycloisomerization of propargyl enoates. Substrate **6.83** was readily accessible via cross metathesis with acryoyl chloride followed by propargyl alcohol (Equation 6.44).[382] Although reductive cycloisomerization of allyl ynoates had been explored,[383] we were unable to effect the desired transformation on propargyl enoate **6.83** (Equation 6.45). In all cases either partially hydrogenated or fully hydrogenated **6.85** was recovered.



(6.44)

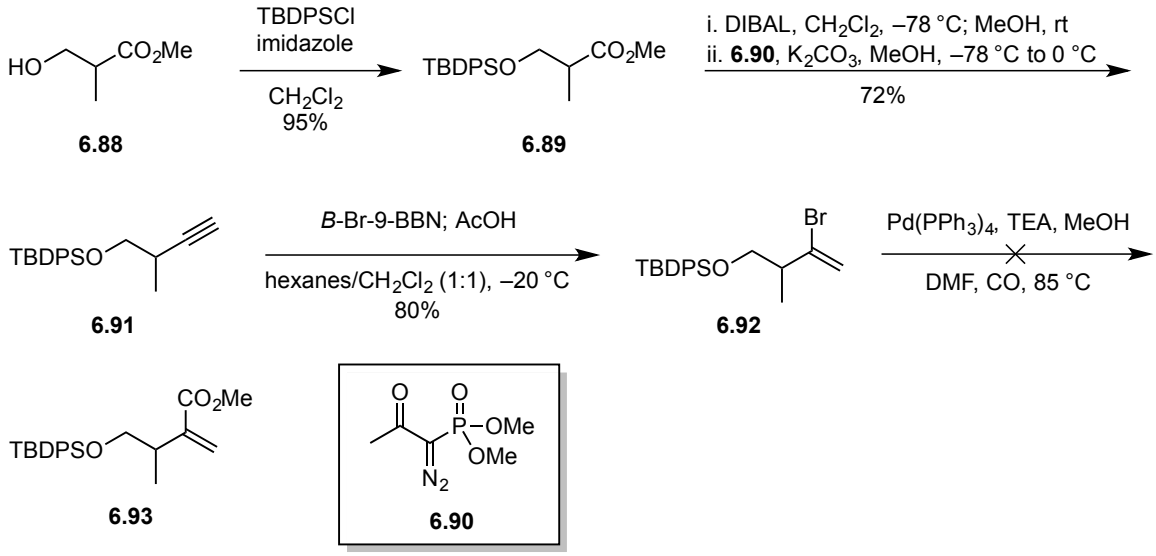


As the unprecedented reductive aldol and cycloisomerization reactions were proving difficult, we decided to reassess how we might attach the butenolide. Our new strategy would rely on more reliable methods to form the butenolide after the cross metathesis; however, this strategy would require unprecedented cross metatheses. We imagined that **6.82** could be synthesized through enoate **6.86** via a standard esterification reaction followed by isomerization, but the cross metathesis with the requisite sterically conjested enoate would likely be challenging (Scheme 6.8). Alternatively, we could use a carbonylative alkoxylation on vinyl halide **6.87** to install the butenolide, though this would require the cross metathesis of a vinyl halide, a reaction for which there is little precedent.[384] Despite the potential obstacles, we moved forward with our alternate plans.

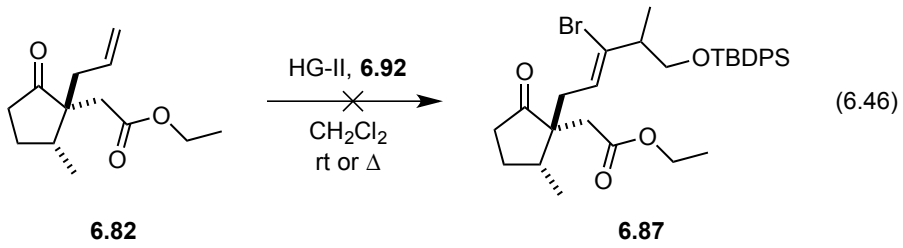


Scheme 6.8 Alternate strategies to access butenolide **6.82**

We imagined that both vinyl bromide **6.92** and enoate **6.93** could be synthesized via the same route. Hydroxy ester **6.88** was protected as silyl ether **6.89** and subjected to a one-pot reduction/Ohira-Bestmann reaction to provide alkyne **6.91** in 72% yield (Scheme 6.9).[385] Bromination of the alkyne proceeded in 80% yield to deliver **6.92**; however, we were unable to successfully prepare **6.93** via a carbonylative coupling. With vinyl bromide **6.92** in hand, we attempted cross metathesis with **6.82**, but were unable to produce the desired product **6.87** (Equation 6.46). We then turned our attention to an alternate preparation of **6.93**.

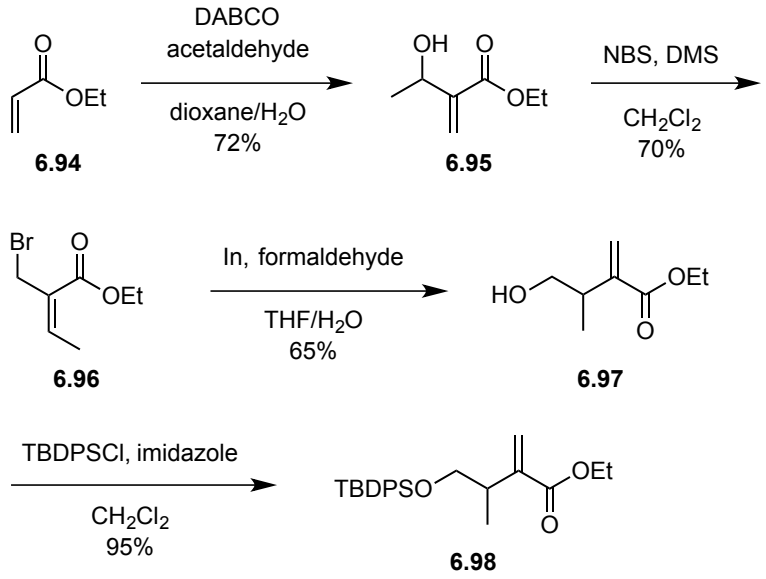


Scheme 6.9 Synthesis of vinyl bromide **6.92**

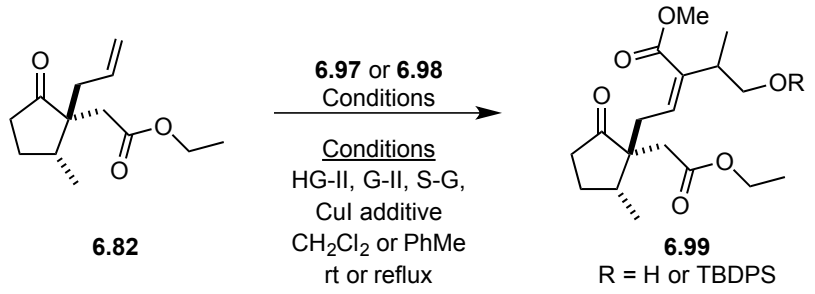


(6.46)

Toward this end, ethyl acrylate (**6.94**) was subjected to Baylis-Hillman conditions to produce **6.95** in 72% yield (Scheme 6.10).[386] Bromination of **6.95** delivered **6.96**, and subsequent indium-mediated allylation of formaldehyde provided **6.97** in 65% yield. The hydroxyl group was then protected to afford enoate **6.98**. We were disappointed to find that neither **6.97** nor **6.98** would undergo cross metathesis with **6.82** under a variety of conditions, even with Stewart-Grubbs catalyst (Equation 6.47).[387]



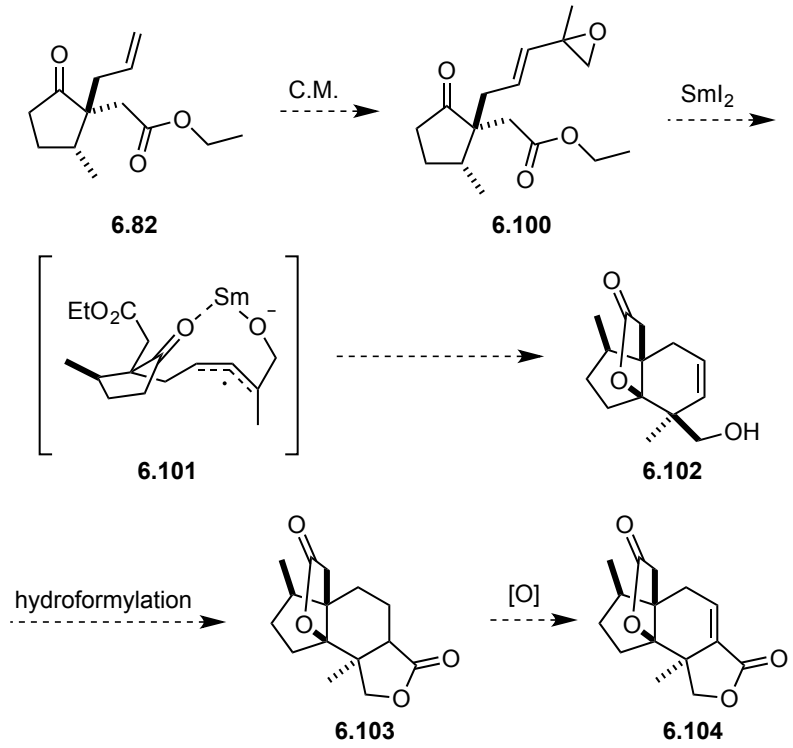
Scheme 6.10 Synthesis of enolates **6.97** and **6.98**



(6.47)

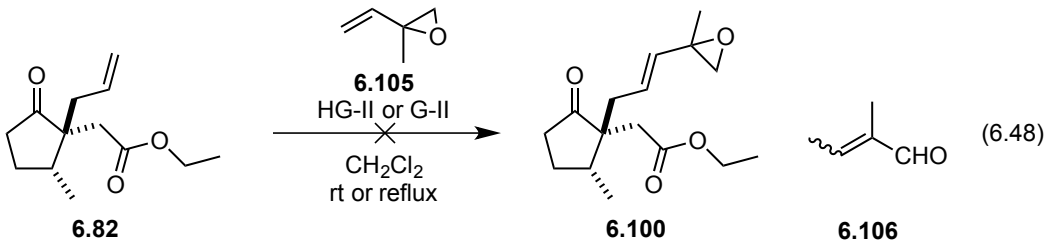
With our plans once again foiled, we decided to attempt an entirely new approach. This route would rely on installation of the southeastern γ-butyrolactone moiety after the reductive cyclization reaction. We imagined that cross metathesis would provide allylic epoxide **6.100**, which we could subject to a samarium-mediated reduction cyclization to provide **6.102**. Allylic epoxides have been shown to undergo a similar intermolecular samarium-mediated *tert*-(hydroxy)-prenylation of ketones and aldehydes.[388] We

envisaged that chelation of the samarium alkoxide and ketone in intermediate **6.101** would control the diastereoselectivity. Finally, hydroformylation would install the lactone,[389] and an oxidation to the α-methylene lactone **6.104** would allow us to continue forward to jiadifenolide (**6.1**). At the very least, **6.104** would represent a formal synthesis of **5.1** by intercepting a late-stage intermediate in Sorensen's synthesis.[277]

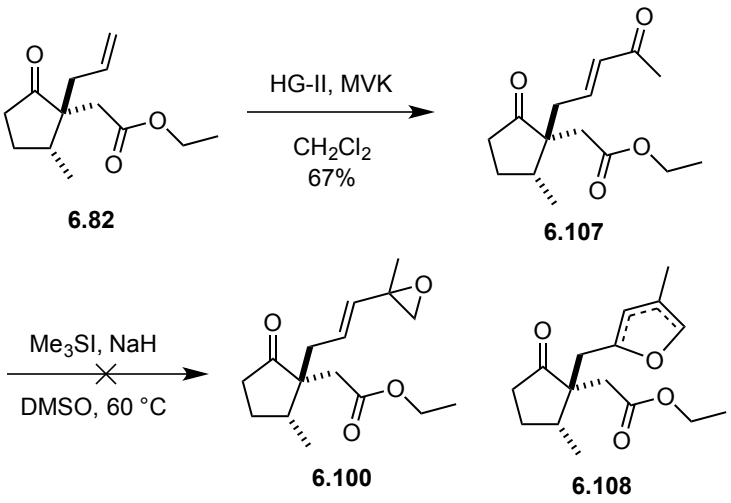


Scheme 6.11 Second alternate strategy to approach the core structure

Unfortunately, simply performing the cross metathesis with allylic epoxide **6.105** proved fruitless, as the epoxide was immediately isomerized to aldehyde **6.106** (Equation 6.48). This was unfortunate, though not unexpected, as similar results have been observed in transition metal reactions employing **6.106**.[390] In order to mediate this unwanted isomerization, we tried a two-step protocol. Cross metathesis of **6.82** with methyl vinyl ketone (MVK) proceeded smoothly to deliver enone **6.107** in 67% yield (Scheme 6.12). However, we again failed to reach our goal, as the desired product **6.100** isomerized to a dihydrofuran **6.108** during the course of the reaction with trimethylsulfonium iodide. Because of the failures with the cross metathesis routes, we once again redesigned our strategy.



6.82 **6.100** **6.106** (6.48)



Scheme 6.12 Attempted synthesis of **6.100**

6.3.5.3 Latest Strategy and Future Directions

As we have thus been unable to progress forward via cross metathesis attempts, we decided to attempt to install the butenolide moiety during the decarboxylative allylation reaction. Ideally, this could be accomplished through the use of **6.109**, which could undergo a Tsuji allylation to deliver **6.82** after isomerization of the olefin (Equation 6.49). However, as the olefin isomerization preceded cross metathesis in previous attempts, we decided to target an intermediate that could be readily manipulated after the allylation. Stoltz recently reported a fluoride-triggered allylation of (trimethylsilyl)ethyl esters like **6.110** (Equation 6.50),[391] and we imagined that this methodology would serve us well here, though it should be noted that it had never been tested on cyclopentanones or on electrophiles as complicated as we wished to employ. With this strategy, we would require electrophile **6.112**, **6.113**, or **6.114** (Figure 6.5). Thus, we set out to synthesize **6.110** and the requisite electrophiles.

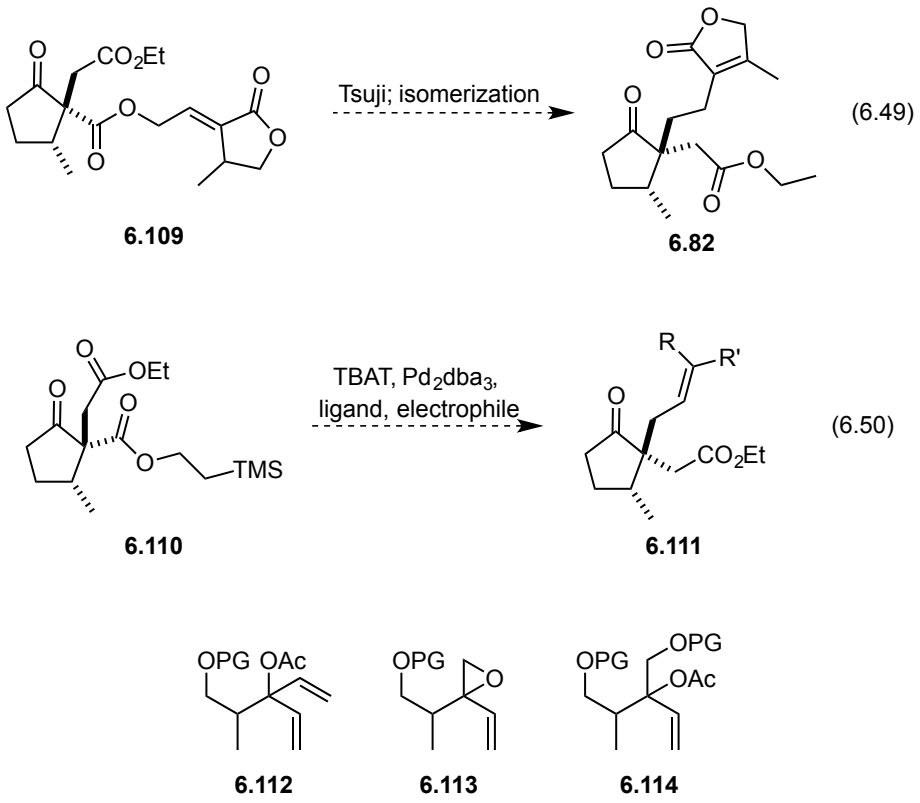
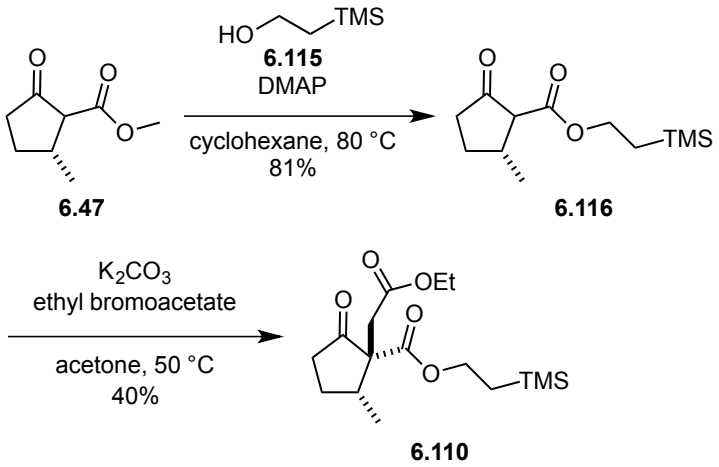


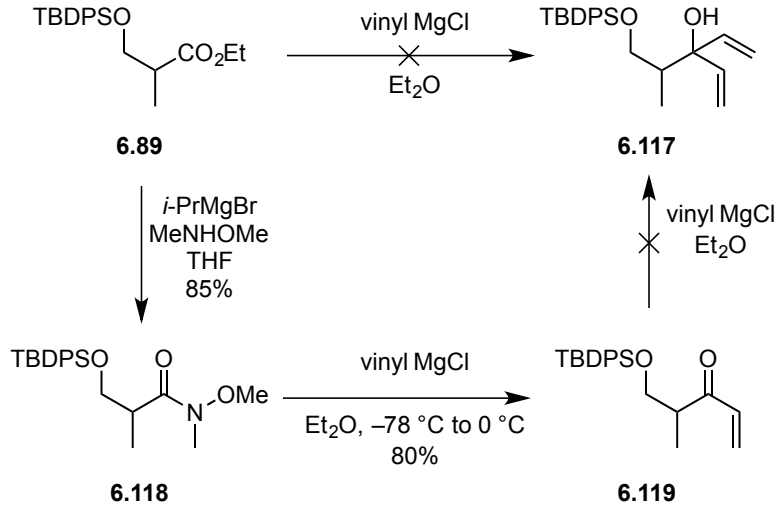
Figure 6.5 Electophiles for the intermolecular Tsuji allylation

β-Keto ester **6.110** was readily available via an analogous route used for the preparation of the allylation precursors. Esterification of **6.47** with alcohol **6.115** provided the silyl-ethyl ester **6.116**, and alkylation with ethyl bromoacetate gave **6.110** (Scheme 6.13). We had only to synthesize the necessary electrophiles to test our new route, though we did not foresee the imminent complications.

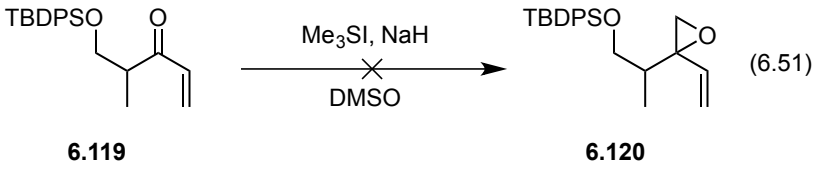


Scheme 6.13 Synthesis of pronucleophile **6.110**

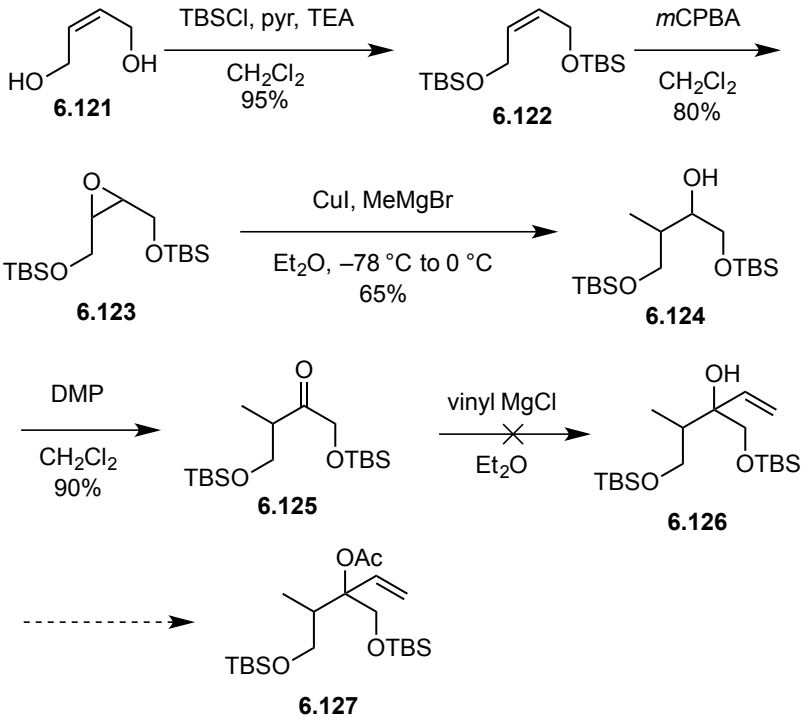
The most interesting allylic electrophile imagined was **6.117**, which had never been tested by Stoltz. We thought we would be able to synthesize **6.117** by the addition of excess vinylmagnesium chloride to **6.89**, but were unable to isolate any of the desired product (Scheme 6.14). We imagined that we would have better luck via a sequential addition of vinyl Grignard, so we prepared the Weinreb amide **6.118**. The first addition of vinylmagnesium chloride proceeded smoothly to afford enone **6.119** in 80% yield; however, we were once again unable to isolate **6.117** after addition of vinyl Grignard into **6.119**. The starting material was quickly consumed during the course of the reaction, but we imagine that the doubly allylic alcohol was especially prone to ionization, which precluded our attempted isolation. We then turned our attention to allylic epoxide **6.120**, but were unable to effect a Corey-Chaykovsky reaction on substrate **6.119** (Equation 6.51).



Scheme 6.14 Attempted synthesis of diene **6.117**

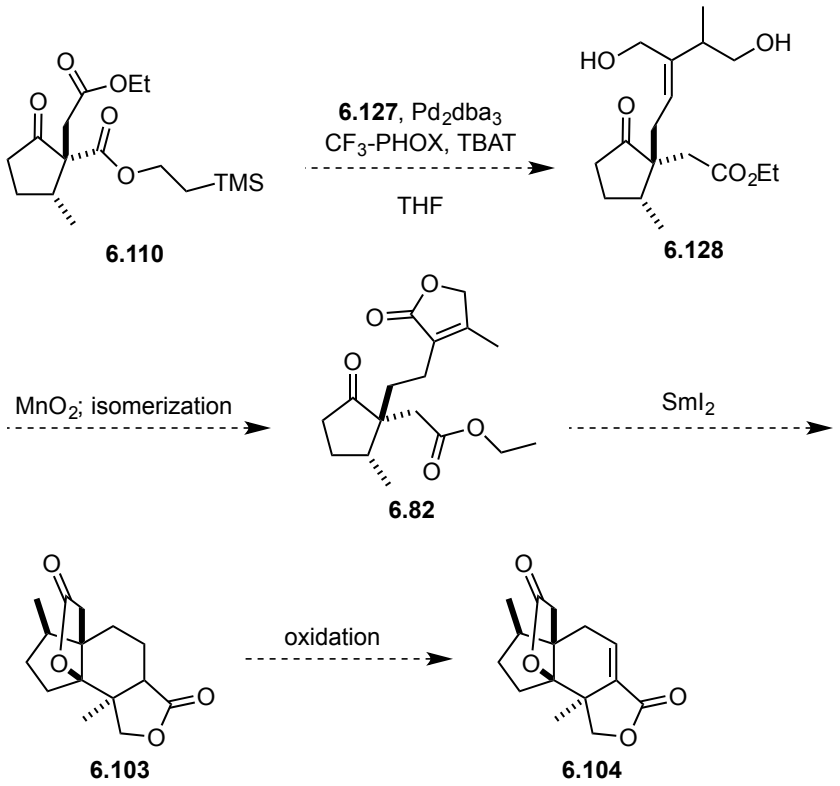


Lastly, we turned our attention to a more traditional Tsuji electophile, allylic acetate **6.127**. The synthesis commenced from diol **6.121**, which was protected and epoxidized to provide **6.123** in 76% yield over two steps (Scheme 6.15). Nucleophilc opening of the epoxide delivered alcohol **6.124**, and oxidation with Dess-Martin periodinane afforded ketone **6.125**. Unfortunately, preliminary attempts to add a Grignard reagent into the ketone have precluded further work on this route. Future attempts will include less basic nucleophiles, such as cerates and vinylzinc species. Once the addition is complete, we have only to acylate **6.126** to provide our requiste electrophile **6.127**.



Scheme 6.15 Towards allylic acetate **6.127**

The synthesis will then progress by testing the decarboxylative allylation of **6.127** with **6.110**, which with any luck should provide **6.128**, as we believe the silyl groups will be deprotected during the course of the reaction (Scheme 6.16). From that point, allylic oxidation proceeding with concomitant lactonization would afford lactone **6.82** after isomerization. Finally, we will be able to test the proposed reductive cyclization. If successful, we would be but one oxidation away from a formal synthesis of jiadifenolide (**6.1**).[277]



Scheme 6.16 Planned end-game for the formal synthesis of **6.1**

6.4 SUMMARY

Through our continued studies towards the synthesis of jiadifenolide (**6.1**), we developed a strategy to use (+)-pulegone (**6.25**) to access a chiral trisubstituted cyclopentenone **6.5**, thereby eliminating the need to either generate thermodynamic enolates or perform conjugate addition/alkylation reactions on cyclopentenones, both of which are known to be problematic. Unfortunately, this strategy was reported by Sorensen while we were pursuing **6.1**.[277] Additionally, with the use of Stoltz's electron-deficient PHOX ligand (**6.59**), we were able to effect a diastereoselective Tsuji-Trost allylation on a cyclopentanone. To the best of our knowledge, this represents the first

diastereoselective Tsuji allylation on a cyclopentanone, and one of the first diastereoselective allylation reactions of a non-multicyclic substrate. Unfortunately, our inability to install the butenolide moiety via known methodology and attempts at unprecedented reductive aldol and cycloisomerization reactions has thus far precluded our attempts to both test the proposed radical annulation and complete the synthesis of **6.1**. However, during the course of our work, Patersen reported a similar radical annulation in his synthesis of **6.1**,[278] thereby suggesting that were we to complete the installation of the butenolide, the annulation would be possible. Future work will continue with the attempts to install the butenolide through a Tsuji allylation.

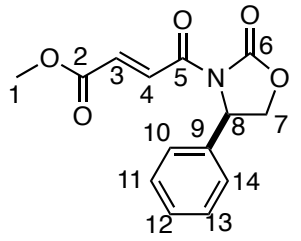
Chapter 7: Experimental Procedures

7.1 General Experimental

Tetrahydrofuran and diethyl ether were dried by filtration through two columns of activated, neutral alumina according to the procedure described by Grubbs.[392] Methanol, acetonitrile and dimethylformamide were dried by filtration through two columns of activated molecular sieves, and toluene was dried by filtration through one column of activated, neutral alumina followed by one column of Q5 reactant. Benzene was distilled from sodium and benzophenone. Methylene chloride, diisopropylamine, triethylamine, and diisopropylethylamine were distilled from calcium hydride immediately prior to use. Pyridine was distilled from potassium hydroxide (KOH) and calcium hydride and stored over KOH pellets. Dioxane was distilled from sodium metal and benzophenone prior to use. All solvents were determined to have less than 50 ppm H_2O by Karl Fischer coulometric moisture analysis. All reagents were reagent grade and used without purification unless otherwise noted. All reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon in glassware that was flame dried. Solutions were degassed using three freeze-thaw cycles under vacuum. Reaction temperatures refer to the temperature of the cooling/heating bath. Volatile solvents were removed under reduced pressure using a Büchi rotary evaporator at 25–30 °C. Thin layer chromatography performed using run on pre-coated plates of silica gel with a 0.25 mm thickness containing 60F-254 indicator (Merck). Chromatography was performed using forced flow (flash chromatography) and the indicated solvent system on 230-400 mesh silica gel (E. Merck reagent silica gel 60) according to the method of Still,[393] unless otherwise noted.

Infrared (IR) spectra were obtained either neat on sodium chloride or as solutions in the solvent indicated and reported as wavenumbers (cm^{-1}). Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained at the indicated field as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are referenced to the deuterated solvent and are reported in parts per million (ppm, δ) downfield from tetramethylsilane (TMS, δ = 0.00 ppm). Coupling constants (*J*) are reported in Hz and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, overlapping multiplets of magnetically nonequivalent protons; br, broad; app, apparent.

7.2 EXPERIMENTAL PROCEDURES

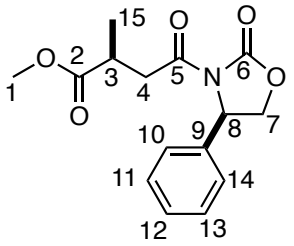


2.31

(*R*,*E*)-Methyl 4-oxo-4-(2-oxo-4-phenyloxazolidin-3-yl)but-2-enoate (2.31). (JCH-I-181). A solution of methyl fumarate (**2.29**) (2.66 g, 20.4 mmol) and pivaloyl chloride (2.70 g, 2.76 mL, 22.5 mmol) in THF (40 mL) was cooled to –20 °C. Triethylamine (4.13 g, 5.68 mL, 40.8 mmol) was added dropwise, and the mixture was stirred 1.5 h at –20 °C. The cooling bath was removed, and the solution was allowed to warm to room temperature. Solid LiCl (0.953 g, 22.5 mmol) and (*R*)-phenyl-oxazolidone **2.30** (5.00 g, 30.6 mmol) were added portionwise, and the reaction was stirred 12 h. H_2O (10 mL) and EtOAc (50 mL) were added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with 1 M HCl (1 x 25 mL), saturated Na_2CO_3 (2 x 50 mL), saturated brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography, eluting with hexanes/ethyl acetate (3:1) to provide 3.25 g (58%) of the chiral methyl fumarate **2.31** as a white solid: mp 92-94 °C; ^{1}H NMR (400 MHz) δ 8.17 (d, *J* = 15.7 Hz, 1 H), 7.43 (comp, 5 H), 6.87 (d, *J* = 15.7 Hz, 1 H), 5.50 (dd, *J* = 4.0, 8.9 Hz, 1 H), 4.76 (t, *J* = 8.9 Hz, 1 H), 4.36 (dd, *J* = 4.0, 8.9 Hz, 1 H), 3.81 (s, 3 H); ^{13}C NMR (100 MHz) δ 165.1, 163.1, 153.2, 138.2, 133.8, 132.2, 129.1,

128.8, 125.9, 70.2, 57.7, 52.2; IR (neat) 1780, 1727, 1690, 1387, 1341, 1306, 1279, 1196 cm^{-1}; HRMS (CI) *m/z* 275.0869 [$C_{14}H_{13}NO_5$ (M+1) requires 275.0794].

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 15.7 Hz, 1 H, C3-H), 7.31-7.43 (comp, 5 H, C10-H, C11-H, C12-H, C13-H, and C14-H), 6.87 (d, *J* = 15.7 Hz, 1 H, C4-H), 5.50 (dd, *J* = 4.0, 8.9 Hz, 1 H, C7-H_a), 4.76 (t, *J* = 9.0 Hz, 1 H, C8-H), 4.36 (dd, *J* = 4.0, 8.9 Hz, 1 H, C7-H_b), 3.81 (s, 3 H, C1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1 (C2), 163.1 (C5), 153.2 (C6), 138.2 (C9), 133.8 (C3), 132.2 (C4), 129.1 (C11 and C13), 128.8 (C12), 125.9 (C10 and C14), 70.2 (C7), 57.7 (C1), 52.2 (C8).

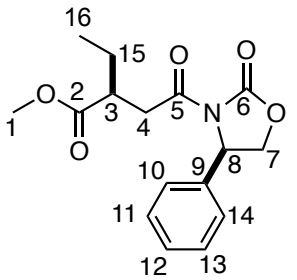


2.32

(*S*)-Methyl 2-methyl-4-oxo-4-((*R*)-2-oxo-4-phenyloxazolidin-3-yl) butanoate (2.32). (JCH-I-277) A suspension of $(CuI)_4(DMS)_3$ (prepared according to House)[394] (0.405 g, 1.71 mmol) in THF (8.6 mL) was prepared and cooled to –78 °C, whereupon MeLi (1.31 M in hexanes, 1.2 mL, 1.59 mmol) was added dropwise. The resulting orange solution was stirred for 40 min at –78 °C. Iodotrimethylsilane (0.33 g, 0.25 mL, 1.65 mmol) was added dropwise, and stirring was continued for 30 min. A solution of chiral fumarate **2.31** (0.337 g, 1.22 mmol) in THF (1.75 mL) was added dropwise, and

the reaction was stirred for 6 h at –78 °C. Triethylamine (0.620 g, 0.836 mL, 6.12 mmol) was added, and the reaction was stirred 1 h. Saturated NH_4Cl (10 mL) was added, and the cooling bath was removed. Upon reaching room temperature, the septum was removed, and the solution was stirred until a homogeneous blue solution was obtained. The reaction mixture was poured into H_2O (10 mL) and ethyl acetate (10 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified via flash chromatography, eluting with hexanes/ethyl acetate (5:1) to provide 0.521 g (86%) of **2.32** as a white solid: mp 77-78 °C; ^{1}H NMR (400 MHz) δ 7.40-7.27 (comp, 5 H), 5.42 (dd, *J* = 3.9, 8.7 Hz, 1 H), 4.70 (t, *J* = 8.7 Hz, 1 H), 4.27 (dd, *J* = 3.9, 8.7 Hz, 1 H), 3.55 (s, 3 H), 3.44 (dd, *J* = 7.5, 17.8 Hz, 1 H), 3.04-2.90 (comp, 2 H), 1.21 (d, *J* = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz) δ 175.5, 170. 8, 153.6, 138.6, 128.9, 128.4, 125.5, 70.0, 57.3, 51.6, 38.9, 34.9, 16.8; IR (neat) 1781,1733, 1707, 1386 cm^{-1}; HRMS (CI) *m/z* 291.1107 [$C_{15}H_{17}NO_5$ (M+1) requires 291.1107].

NMR Assignments: ^{1}H NMR (400 MHz) δ 7.40-7.27 (comp, 5 H, C10-H, C11-H, C12-H, C13-H, and C14-H), 5.42 (dd, *J* = 3.9, 8.7 Hz, 1 H, C7-H_a), 4.70 (t, *J* = 8.7 Hz, 1 H, C8-H), 4.27 (dd, *J* = 3.9, 8.7 Hz, 1 H, C7-H_b), 3.55 (s, 3 H, C1-H), 3.44 (dd, *J* = 7.5, 17.8 Hz, 1 H, C3-H), 3.04-2.90 (comp, 2 H), 1.21 (d, *J* = 7.5 Hz, 3 H, C15-H); ^{13}C NMR (100 MHz) δ 175.5 (C2), 170.8 (C5), 153.6 (C6), 138.6 (C9), 128.9 (C11 and C13), 128.4 (C12), 125.5 (C10 and C14), 70.0 (C8), 57.3 (C1), 51.6 (C7), 38.9 (C3), 34.9(C4), 16.8 (C15).

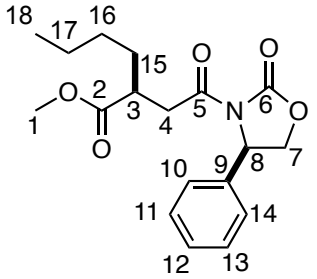


2.33

(*S*)-Methyl 2-ethyl-4-oxo-4-((*R*)-2-oxo-4-phenyloxazolidin-3-yl)butanoate (2.33). (JCH-I-113) Compound **2.33** was prepared on 1.25 mmol via the same method as **2.32**, employing *n*-BuLi in place of MeLi. Isolated 0.210 mg (72 %) of **2.33** as a white solid: mp 80-81 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) 7.26-7.41 (comp, 5 H), 5.42 (dd, *J* = 3.84, 8.70 Hz, 1 H), 4.70 (t, *J* = 8.97 Hz, 1 H), 4.26 (dd, *J* = 4.10, 8.97 Hz, 1 H), 3.42 (dd, *J* = 9.73, 18.19 Hz, 1 H), 3.04 (dd, J = 4.61, 18.19 Hz, 1 H), 2.77-2.86 (m, 1 H), 1.55-1.72 (comp, 2 H), 0.92 (t, *J* = 7.43 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 174.9, 171.1, 153.7, 138.6, 129.0, 128.5, 125.6, 70.0, 57.4, 51.5, 41.8, 37.0, 24.8, 11.4; IR (neat) 1782, 1733, 1707 1386, 1197 cm^{-1}; HRMS (CI) *m/z* 306.1340 [$C_{16}H_{20}NO_5$ (M + 1) requires 306.1340].

NMR Assignments: ^{1}H NMR (300 MHz, $CDCl_3$) 7.26-7.41 (comp, 5 H, C10-H, C11-H, C12-H, C13-H, and C14-H), 5.42 (dd, *J* = 3.84, 8.70 Hz, 1 H, C7-H), 4.70 (t, *J* = 8.97 Hz, 1 H, C8-H), 4.26 (dd, *J* = 4.10, 8.97 Hz, 1 H, C7-H), 3.42 (dd, *J* = 9.73, 18.19 Hz, 1 H, C5-H), 3.04 (dd, *J* = 4.61, 18.19 Hz, 1 H, C5-H), 2.77-2.86 (m, 1 H, C3-H), 1.55-1.72 (comp, 2 H, C15-H), 0.92 (t, *J* = 7.43 Hz, 3 H, C16-H); ^{13}C NMR (75 MHz, $CDCl_3$) 174.9 (C2), 171.1 (C7), 153.7 (C6), 138.6 (C9), 129.0 (C11 and C13), 128.5

(C12), 125.6 (C10 and C14), 70.0 (C7), 57.4 (C1), 51.5 (C8), 41.8 (C3), 37.0 (C4), 24.8 (C15), 11.4 (C16).

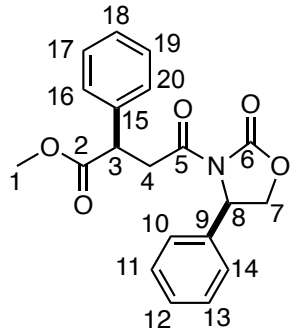


2.34

(*S*)-methyl 2-(2-oxo-2-((*R*)-2-oxo-4-phenyloxazolidin-3-yl)ethyl)hexanoate (2.34). (JCH-II-075) Compound **2.34** was prepared on 1 mmol via the same method as **2.32**, employing *n*-BuLi in place of MeLi. Isolated 0.275 g (83%) of **2.34** as a clear oil. ^{1}H NMR (300 MHz) δ 7.43-7.29 (m, 5 H), 5.44 (dd, *J* = 8.8, 4.3 Hz, 1 H), 4.72 (t, *J* = 8.8 Hz, 1 H), 4.31-4.26 (m, 1 H), 3.54 (s, 3 H), 3.43 (dd, *J* = 18.0, 9.6 Hz, 1 H), 3.06 (dd, *J* = 18.0, 4.3 Hz, 1 H), 2.92-2.82 (m, 1 H), 1.67-1.48 (m, 3 H), 1.30-1.28 (m, 3 H), 0.89-0.87 (m, 3 H); ^{13}C NMR (75 MHz): δ 175.4, 171.5, 154.0, 138.9, 129.1, 126.0, 77.7, 70.4, 57.8, 51.9, 40.8, 37.8, 31.8, 29.4, 22.7, 14.1; IR (neat) 2957, 2861, 1785, 1733, 1704, 1386 cm^{-1}; HRMS (CI) *m/z* 334.1656 [$C_{16}H_{20}NO_5$ (M + 1) requires 336.1654].

NMR Assignments: ^{1}H NMR (300 MHz) δ 7.43-7.29 (m, 5 H, C10-H, C11-H, C12-H, C13-H, and C14-H), 5.44 (dd, *J* = 8.8, 4.3 Hz, 1 H, C7-H_a), 4.72 (t, *J* = 8.8 Hz, 1 H, C8-H), 4.31-4.26 (m, 1 H, C7-H_b), 3.54 (s, 3 H, C1-H), 3.43 (dd, *J* = 18.0, 9.6 Hz, 1 H, C4-H_a), 3.06 (dd, *J* = 18.0, 4.3 Hz, 1 H, C4-H_b), 2.92-2.82 (m, 1 H, C3-H), 1.67-1.48 (m, 3 H, C16-H and C17-H), 1.30-1.28 (m, 3 H, C16-H and C17-H), 0.89-0.87 (m, 3 H,

C20-H); ^{13}C NMR (75 MHz): δ 175.4 (C2), 171.5 (C5), 154.0 (C6), 138.9 (C9), 129.1 (C11 and C13), 126.0 (C10 and C14), 77.7 (C12), 70.4 (C8), 57.8 (C1), 51.9 (C7), 40.8 (C4), 37.8 (C3), 31.8 (C15), 29.4 (C16), 22.7 (C17), 14.1 (C18)

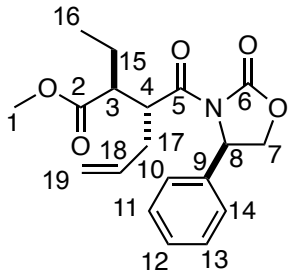


2.35

(*R*)-methyl 4-oxo-4-((*R*)-2-oxo-4-phenyloxazolidin-3-yl)-2-phenylbutanoate (2.35). (JCH-II-064) Compound **2.35** was prepared on 1 mmol via the same method as **2.32**, employing PhLi in place of MeLi. Isolated 0.290 g (82%) of compound **2.35** as a clear oil. ^{1}H NMR (300 MHz) δ 7.46-7.29 (m, 9 H), 7.27-7.26 (m, 1 H), 5.58 (dd, *J* = 11.2, 4.4 Hz, 1 H), 5.37 (dd, *J* = 8.8, 3.5 Hz, 1 H), 4.58 (t, *J* = 8.8 Hz, 1 H), 4.21 (dd, *J* = 8.8, 3.4 Hz, 1H), 3.53 (s, 3 H), 3.27 (dd, *J* = 17.3, 11.2 Hz, 1 H), 2.62 (dd, *J* = 17.3, 4.4 Hz, 1 H); ^{13}C NMR (125 MHz) δ 172.5, 171.5, 153.0, 138.9, 136.9, 129.9, 129.1, 128.8, 128.6, 128.5, 128.3, 128.1, 127.8, 125.7, 70.0, 58.1, 51.7, 44.8, 38.6, 29.7; IR (neat) 2922, 2852, 1781, 1735, 1699, 1383, 1192 cm^{1}; HRMS (CI) *m/z* 354.1336 [$C_{20}H_{20}NO_5$ (M + 1) requires 354.1341].

NMR Assignments: ^{1}H NMR (300 MHz) δ 7.46-7.29 (m, 9 H, C10-H, C11-H, C12-H, C13-H, C14-H, C16-H, C17-H, C18-H, C19-H, or C20-H), 7.27-7.26 (m, 1 H,

C10-H, C11-H, C12-H, C13-H, C14-H, C16-H, C17-H, C18-H, C19-H, or C20-H), 5.58 (dd, J = 11.2, 4.4 Hz, 1 H, C7-H_a), 5.37 (dd, J = 8.8, 4.4 Hz, 1 H, C7-H_b), 4.58 (t, J = 8.8 Hz, 1 H, C8-H), 4.21 (dd, J = 8.8, 3.4 Hz, 1H, C5-H), 3.53 (s, 3 H, C1-H), 3.27 (dd, J = 17.3, 11.2 Hz, 1 H, C4-H_a), 2.62 (dd, J = 17.3, 4.4 Hz, 1 H, C4-H_b); ^{13}C NMR (125 MHz) δ 172.5 (C2), 171.5 (C5), 153.0 (C6), 138.9 (C15 or C9), 136.9 (C15 or C9)), 129.9 (C13), 129.1 (C11), 128.8 (C20), 128.6 (C19), 128.5 (C18), 128.3 (C17), 128.1 (C16), 127.8 (C14), 125.7 (C13), 70.0 (C12), 58.1 (C1), 51.7 (C8), 44.8 (C7), 38.6 (C3), 29.7 (C4)



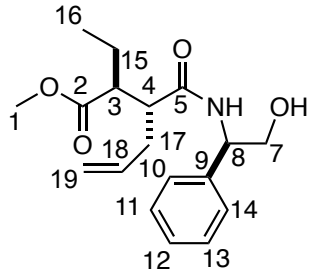
2.47

Methyl (2*S*,3*R*)-2-ethyl-3-((*R*)-2-oxo-4-phenyloxazolidine-3-carbonyl)hex-5-enoate (**2.47**). (JCH-I-210) *n*-Butyllithium (2.5 M solution in hexanes, 0.7 mL, 1.8 mmol) was added to a solution of hexamethyldisilazane (0.31 g, 1.9 mmol) in THF (1.9 M) at –78 °C. The solution was stirred for 15 min at –78 °C, 30 min at 0 °C, and then cooled to –78 °C. Hexamethylphosphoramide (0.47 g, 2.6 mmol) was added to the solution, and succinate **2.33** (0.36 g, 0.85 mmol) in THF (1.6 mL) was added dropwise. The solution was stirred for 1 h at –78 °C, whereupon allyl iodide (0.44 g, 2.6 mmol) was

added. The reaction was stirred for 6 h, whereupon 1 M HCl (2.5 mL) was added and the reaction was allowed to warm to room temperature. The mixture was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude reaction mixture purified via column chromatography, eluting with hexanes/EtOAc (8:1 → 6:1) to provide 0.10 g (34%) of **2.47** as a clear colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.26 (m, 5H), 5.48 (dddd, *J* = 17.0, 10.2, 7.6, 6.7 Hz, 1 H), 5.42 (dd, *J* = 8.7, 3.7 Hz, 1 H), 4.77 (ddt, *J* = 10.2, 1.8, 0.9 Hz, 1 H), 4.72 (dq, *J* = 17.0, 1.5 Hz, 1 H), 4.67 (t, *J* = 8.9 Hz, 1 H), 4.30 (td, *J* = 8.5, 4.7 Hz, 1 H), 4.26 (dd, *J* = 8.9, 3.8 Hz, 1 H), 2.65 (ddd, *J* = 10.7, 8.5, 3.8 Hz, 1 H), 2.32-2.27 (m, 1 H), 2.23-2.19 (m, 1 H), 1.67-1.60 (m, 1 H), 1.55-1.48 (m, 1 H), 0.85 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (150 MHz; $CDCl_3$): δ 174.4, 173.4, 153.3, 138.9, 133.7, 129.0 (2C), 128.7, 126.2 (2C), 117.7, 69.6, 57.9, 51.6, 49.0, 44.1, 34.9, 23.5, 11.9; IR (film, NaCl) 2968, 1779, 1733, 1701, 1384, 1195, 1168 cm^{-1}; HRMS (ESI) *m/z* 368.1498 [$C_{19}H_{25}NO_5Na^+$ $(M + Na)^+$ requires 368.1474].

NMR Assignments: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.26 (m, 5H, C10-H, C11-H, C12-H, C13-H, and C14-H), 5.48 (dddd, *J* = 17.0, 10.2, 7.6, 6.7 Hz, 1 H, C18-H), 5.42 (dd, *J* = 8.7, 3.7 Hz, 1 H, C19-H_a), 4.77 (ddt, *J* = 10.2, 1.8, 0.9 Hz, 1 H, c19-H_b), 4.72 (dq, *J* = 17.0, 1.5 Hz, 1 H, C7-H_a), 4.67 (t, *J* = 8.9 Hz, 1 H, C8-H), 4.30 (td, *J* = 8.5, 4.7 Hz, 1 H, C17-H_a), 4.26 (dd, *J* = 8.9, 3.8 Hz, 1 H, C7-H_b), 2.65 (ddd, *J* = 10.7, 8.5, 3.8 Hz, 1 H, C17-H_b), 2.32-2.27 (m, 1 H, C3-H), 2.23-2.19 (m, 1 H, C4-H), 1.67-1.60 (m, 1 H, C5-H), 1.55-1.48 (m, 1 H, C15-H), 0.85 (t, *J* = 7.4 Hz, 3 H, C16-H); ^{13}C NMR (150 MHz; $CDCl_3$): δ 174.4 (C2), 173.4 (C5), 153.3 (C6), 138.9 (C18), 133.7 (C19), 129.0

(C11 and C13), 128.7 (C9), 126.2 (C10 and C14), 117.7 (C12), 69.6 (C8), 57.9 (C1), 51.6 (C7), 49.0 (C3), 44.1 (C4), 34.9 (C17), 23.5 (C15), 11.9 (C16)

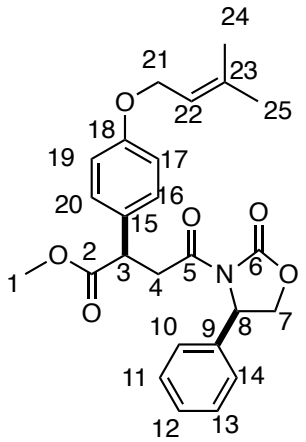


2.51

Methyl (2*S*,3*R*)-3-(((*R*)-2-hydroxy-1-phenylethyl)carbamoyl)-2-methylhex-5-enoate (**2.51**). (JCH-I-219) Imide **2.47** (0.070 g, 0.203 mmol) was dissolved in a mixture of THF (1 mL) and MeOH (0.04 mL) and cooled to –78 °C. Lithium borohydride (2 M in THF, 1 mL, 2.0 mmol) was added, and the reaction was transferred to a 0 °C bath and stirred for 1 h. The reaction was quenched with sat. aq. Rochelle's salt (3 mL), the ice bath was removed, and the reaction was stirred 1 h at room temperature. EtOAc (5 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified via column chromatography, eluting with hexanes/EtOAc (4:1 → 3:2) to provide 0.064 g (81%) of **2.51** as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5 H), 6.44 (d, *J* = 7.2 Hz, 1 H), 5.64 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1 H), 5.08 (dt, *J* = 7.1, 5.0 Hz, 1 H), 5.04-4.94 (m, 2H), 3.87 (d, *J* = 5.0 Hz, 2 H), 3.70 (s, 3 H), 2.64 (td, *J* = 9.5, 4.3 Hz, 1 H), 2.49 (td, *J* = 9.5, 4.3 Hz, 1 H), 2.4-2.33 (m, 1 H), 2.14-2.07 (m, 1 H), 1.70-1.54 (m, 2 H), 0.89 (t, *J* =

7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 173.2, 138.7, 134.8, 128.8 (2C), 127.9, 126.8 (2 C), 117.57, 117.51, 66.5, 55.9, 51.7, 49.58, 49.44, 35.5, 23.8, 11.9; IR (film) 3298, 2935, 2877, 1733, 1645, 1541, 1733, 1645, 1541, 1272, 1166, 700 cm^{-1}; HMRS (ESI) *m/z* 342.1670 [$C_{18}H_{25}NO_4Na^+$ $(M + Na)^+$ requires 342.1676].

NMR Assignments: ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5 H, C10-H, C11-H, C12-H, C13-H, and C14-H), 6.44 (d, *J* = 7.2 Hz, 1 H), 5.64 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1 H), 5.08 (dt, *J* = 7.1, 5.0 Hz, 1 H, C18-H), 5.04-4.94 (m, 2H, C7-H), 3.87 (d, *J* = 5.0 Hz, 2 H, C19-H), 3.70 (s, 3 H, C1-H), 2.64 (td, *J* = 9.5, 4.3 Hz, 1 H, C8-H), 2.49 (td, *J* = 9.5, 4.3 Hz, 1 H, C3-H), 2.4-2.33 (m, 1 H, C4-H_a), 2.14-2.07 (m, 1 H, C4-H_b), 1.70-1.54 (m, 2 H, C15-H), 0.89 (t, *J* = 7.4 Hz, 3 H, C16-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7 (C2), 173.2 (C5), 138.7 (C18), 134.8 (C19), 128.8 (C9), 127.9 (C10 and C14)), 126.8 (C12), 117.57 (C11 or C13), 117.51 (C11 or C13), 66.5 (C8), 55.9 (C1), 51.7 (C7), 49.58 (C4), 49.44 (C3), 35.5 (C17), 23.8 (C15), 11.9 (C16)

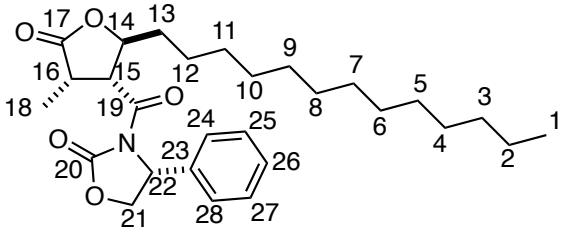


2.52

Methyl-(2*S*,3*R*)-2-ethyl-3-(((*R*)-2-hydroxy-1-phenylethyl)carbamoyl)hex-5-enoate (**2.52**). (JCH-I-148) *n*-BuLi (2.54 M in hexanes, 0.37 mL, 0.90 mmol) was added dropwise to a solution of aryl bromide **2.56** (0.22 g, 0.91 mmol) in THF (2.0 mL) at –78 °C, and the solution was stirred 15 min. The resulting solution was added via cannula to a suspension of $(CuI)_4(DMS)_3$ (0.22 g, 0.95 mmol) in THF (2.8 mL) at –78 °C, and the resulting black solution was stirred 20 min. Iodotrimethylsilane was added dropwise to the reaction and stirring continued for 5 min. A solution of fumarate **2.31** (0.20 g, 0.73 mmol) in THF (1.0 mL) was added dropwise, and the reaction was stirred 6 h at –78 °C. Triethylamine (1.8 g, 17.9 mmol) was added, and was stirred for 1 h, whereupon sat. NH_4Cl (10 mL) was added. The reaction was warmed to room temperature, the septum was removed, and the solution was stirred until a homogenous blue solution was attained. The reaction was diluted with H_2O (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified via column

chromatography, eluting with hexanes/ethyl acetate (3:1) to afford 0.179 (56%) of **2.52** as a white solid: mp 120–122 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27-7.40 (comp, 5 H), 7.19 (d, *J* = 8.7 Hz, 2 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 5.46-5.49 (m, 1 H), 5.40 (dd, *J* = 3.9, 8.8 Hz, 1 H), 4.66 (t, *J* = 8.8 Hz, 1 H), 4.48 (d, *J* = 6.8 Hz, 2 H), 4.25 (dd, *J* = 3.9, 8.8 Hz, 1 H), 4.06 (dd, *J* = 5.2, 9.7 Hz, 1 H), 3.84 (dd, *J* = 9.7, 18.2 Hz, 1 H), 3.51 (s, 3 H), 3.29 (dd, *J* = 5.2, 18.2 Hz, 1 H), 1.79 (s, 3 H), 1.73 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.4, 170.8, 158.4, 153.7, 138.6, 138.4, 129.5, 129.2, 128.9, 128.6, 125.7, 119.6, 114.9, 70.2, 64.8, 57.5, 52.2, 45.7, 39.5, 25.8, 18.2; IR (film, NaBr) 2917, 1781, 1733, 1704, 1611, 1511 cm^{-1}; HRMS (ESI) *m/z* 460.1733 [$C_{25}H_{27}NO_6Na^+$ (M + Na) requires 460. 1731].

NMR Assignments: ^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.27-7.40 (comp, 5 H, C10-H, C11-H, C12-H, C13-H, and C14-H), 7.19 (d, *J* = 8.7 Hz, 2 H, C17-H and C19-H), 6.84 (d, *J* = 8.8 Hz, 2 H, C16-H and C20-H), 5.46-5.49 (m, 1 H, C3-H), 5.40 (dd, *J* = 4, 8.8 Hz, 1 H, C7-H), 4.66 (t, J = 8.8 Hz, 1 H, C8-H), 4.48 (d, J = 6.8 Hz, 2 H, C21-H), 4.25 (dd, *J* = 3.9, 8.8 Hz, 1 H, C7-H), 4.06 (dd, *J* = 5.2, 9.7 Hz, 1 H, C22-H), 3.84 (dd, *J* = 9.7, 18.2 Hz, 1H, C4-H), 3.51 (s, 3 H, C1-H), 3.29 (dd, *J* = 5.2, 18.2 Hz, 1 H, C4-H), 1.79 (s, 3 H, C24-H or C25-H), 1.73 (s, 3 H, C24-H or C25-H); ^{13}C NMR: ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.3 (C2), 170.8 (C5), 158.3 (C18), 153.6 (C6), 138.6 (C9), 138.3 (C23), 129.5 (C16 and C20), 129.1 (C11 and C13), 128.9 (C12), 128.6 (C15), 125.7 (C10 and C14), 119.6, 114.9 (C17 and C19), 70.1 (C7), 64.7 (C21), 57.5 (C8), 52.1 (C1), 45.7 (C3), 39.5 (C4), 25.8 (C24 or C25), 18.1 (C24 or C25).

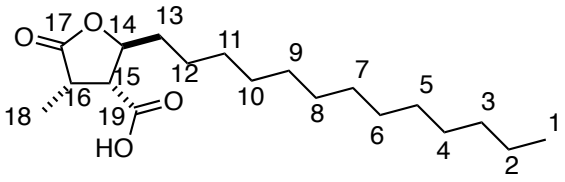


2.60

(*R*)-3-((2*S*,3*R*,4*S*)-4-Methyl-5-oxo-2-tridecyltetrahydrofuran-3-carbonyl)-4-phenyloxazolidin-2-one (2.60). (JCH-II-033) A solution of **2.32** (0.250 g, 0.858 mmol) in CH_2Cl_2 (1 mL) was cooled to 0 °C, whereupon dibutylboron triflate (0.354 g, 1.29 mmol) was added dropwise. Hünig's base (0.184 g, 0.250 mL, 1.29 mmol) was added and the solution was stirred for 30 min at room temperature and then cooled to –78 °C. A solution of freshly distilled tetradecanal (0.220 g, 0.260 mL, 1.03 mmol) in methylene chloride (0.2 mL) was added dropwise, and the solution was stirred for 20 min at –78 °C and then at 0 °C for 15 h. A solution of MeOH/H_2O_2 (30% in H_2O) (2:1, 1 mL) was added, and the mixture was stirred 1 h. The layers were separated, and the aqueous layer was extracted with methylene chloride (3 x 2 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure yielding a clear oil. Purification by recrystallization from methyl *tert*-butyl ether yielded 0.217 g (54%) of **2.60** as a white solid: mp 107-108 °C; ^{1}H NMR (600 MHz) δ 7.41-7.34 (comp, 5 H), 5.43 (dd, *J* = 3.5, 8.9 Hz, 1 H,), 4.79-4.74 (comp, 2 H), 4.43 (dd, *J* = 3.5, 8.9 Hz, 1 H), 4.21 (dd, *J* = 7.5, 9.2 Hz, 1 H), 3.21 (dq, *J* = 7.5, 9.2 Hz, 1 H), 1.69-1.58 (comp, 2 H), 1.39-1.26 (comp, 22 H), 0.88 (t, *J* = 6.9 Hz, 3 H), 0.80 (d, *J* = 7.5 Hz, 3 H); ^{13}C NMR (150 MHz) δ 177.2, 169.3, 153.2, 138.3, 129.3, 129.3, 126.6, 79.1, 70.2, 57.8,

49.3, 37.7, 34.7, 29.7, 29.7, 29.7, 29.6, 29.6, 29.6, 29.5, 29.4, 29.4, 29.4, 29.3, 29.1, 25.5, 24.7, 22.7, 14.1, 11.6; IR (neat) 2917, 2848, 1787, 1758, 1696, 1382, 1204 cm^{-1} ; HRMS (CI) *m/z* 472.3063 [$C_{28}H_{42}NO_5$ (M+1) requires 472.30].

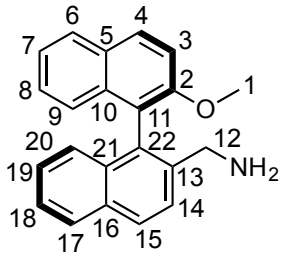
NMR Assignments: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41-7.34 (comp, 5 H, C24-H, C25-H, C26-H, C27-H, and C28-H), 5.43 (dd, *J* = 3.5, 8.9 Hz, 1 H, C21-H_a), 4.79-4.74 (comp, 2 H, C22-H and C14-H), 4.43 (dd, *J* = 3.5, 8.9 Hz, 1 H, C21-H_b), 4.21 (dd, *J* = 7.5, 9.2 Hz, 1 H, C15-H), 3.21 (dq, *J* = 7.5, 9.2 Hz, 1 H, C16-H), 1.69-1.58 (comp, 2 H, C13-H), 1.39-1.26 (comp, 22 H, C2 – C12-H), 0.88 (t, *J* = 6.97 Hz, 3 H, C1-H), 0.80 (d, *J* = 7.5 Hz, 3 H, C18-H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.2 (C17), 169.3 (C19), 153.2 (C6), 138.3 (C23), 129.3 (C25 and C27), 129.3 (C28 and C24), 126.6 (C26), 79.1 (C14), 70.2 (C21), 57.8 (C22), 49.3 (C15), 37.7 (C16), 34.7, 29.6 (C12), 29.6 (C11), 29.5 (C10), 29.4 (C9), 29.4 (C8), 29.4 (C7), 29.3 (C6), 29.1 (C5), 25.5 (C4), 24.7 (C3), 22.7 (C2), 14.1 (C1), 11.6 (C18)



2.61

(2*S*,3*R*,4*S*)-4-methyl-5-oxo-2-tridecyltetrahydrofuran-3-carboxylic acid (dihydroprotolichesterinic acid) (2.61). (JCH-II-042) To a solution of **2.60** (0.243 g, 0.515 mmol) in THF/H_2O (4:1, 4.2 mL) at 0 °C was added H_2O_2 (30% in H_2O, 2.1 mmol, 0.25 mL) and LiOH•H_2O (0.032 g, 0.773 mmol). The flask was removed from the cooling bath and stirred at room temperature for 5 h. The reaction was quenched with 10% aqueous $Na_2S_2O_3$ (2 mL). The THF was removed under reduced pressure. The pH was adjusted to pH = 12 with 3 M NaOH and extracted with EtOAc (3 x 3 mL). The pH of the aqueous layer was then adjusted to pH = 1 with 1 M HCl, and the mixture was extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield 0.142 g (85%) of **2.61** as a white solid: mp 105-106 °C (lit. 106 °C);[96] $[\alpha]_D^{22}$ = –51.1° (c = 1.75, $CHCl_3$) [lit. $\alpha]_D^{20}$ = –49.5° (c = 1.75, $CHCl_3$)];[96] ^{1}H NMR (600 MHz) δ 4.65 (comp, 1 H), 3.10-3.08 (comp, 1 H), 2.97 (dq, *J* = 8.8, 7.5 Hz, 1 H), 1.70-1.61 (comp, 2 H), 1.41-1.28 (comp, 25 H), 0.88 (t, *J* = 6.9 Hz, 3 H)**;** ^{13}C NMR (150 MHz) δ 177.9, 174.8, 80.0, 50.2, 36.7, 34.5, 31.9, 29.7, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4 29.3, 25.4, 22.7, 14.1, 11.5; IR (neat) 2955, 2919, 2852, 1765, 1726, 1698 cm^{-1}; HRMS (ESI) *m/z* 349.2350 [$C_{19}H_{34}O_4$ (M+Na) requires 349.2349].

NMR Assignment: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.65 (comp, 1 H, C14-H), 3.10-3.08 (comp, 1 H, C15-H), 2.97 (dq, *J* = 8.8, 7.5 Hz, 1 H, C16-H), 1.70-1.61 (comp, 2 H, C13-H), 1.41-1.28 (comp, 25 H, C2-H, C3-H, C4-H, C5-H, C6-H, C7-H, C8-H, C9-H, C10-H, C11-H, C12-H, and C18-H), 0.88 (t, *J* = 6.96 Hz, 3 H, C1-H)**;** ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.9 (C17 or C19), 174.8 (C13 or C19), 80.0 (C15), 50.2 (C16), 36.7 (C14), 34.5 (C13), 31.9 (C12), 29.7 (C11), 29.7 (C10), 29.7 (C9), 29.6 (C8), 29.6 (C7), 29.5 (C6), 29.4 (C5), 29.3 (C4), 25.4 (C3), 22.7 (C4), 14.1 (C18 or C1), 11.5 (C18 or C1)

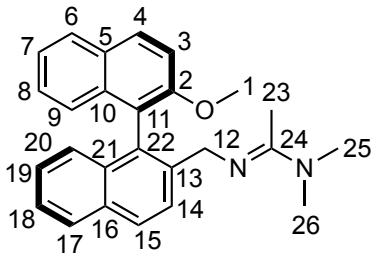


4.10

***R*-(2'-Methoxy-[1,1'-binaphthalen]-2-yl)methanamine (4.10).** (JCH-II-090) *R*-(2'-Methoxy-[1,1'-binaphthalen]-2-yl)methanamine (**4.9**) (available in four steps from (R)-BINOL)[234,232,235] (0.250 g, 0.808 mmol) was dissolved in THF (8 mL) and cooled to 0 °C. Lithium aluminum hydride (0.250 g, 6.5 mmol) was added portionwise, and the reaction was stirred until the starting material was consumed as indicated by thin layer chromatography. Water (0.25 mL) was added, followed by 3 N NaOH (0.25 mL), then water (0.75 mL). The reaction was stirred 1 h, then vacuum filtered and concentrated under reduced pressure to provide 0.240 g (95%) of **4.10** as a colorless oil: ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.98 (dd, *J* = 12.1, 8.7 Hz, 2 H), 7.87 (t, *J* = 8.9 Hz, 2 H), 7.68 (d, *J* = 8.5 Hz, 1 H), 7.44 (d, *J* = 9.1 Hz, 1 H), 7.40 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1 H), 7.31 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1 H), 7.22-7.16 (m, 2 H), 7.09 (dd, *J* = 8.5, 0.8 Hz, 1 H), 6.94 (dd, *J* = 8.5, 0.8 Hz, 1 H), 3.74 (s, 3 H), 3.54 (d, *J* = 1.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 139.7, 134.0, 133.1, 132.7, 131.7, 129.7, 129.0, 128.4, 128.0, 126.7, 126.5, 126.11, 126.04, 125.3, 125.0, 123.7, 120.9, 113.5, 56.4, 45.1; IR (NaCl, film) 3055, 3006, 2934, 2839, 1621, 1592, 1507, 1462, 1432, 1353, 1333, 1265, 1261, 1147, 1083 cm^{-1}; HRMS (ESI) *m/z* 336.1364 [$C_{22}H_{19}NO$ (M+Na) requires 336.1359].

NMR Assignments: ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 12.1, 8.7 Hz, 2 H), 7.87 (t, *J* = 8.9 Hz, 2 H), 7.68 (d, *J* = 8.5 Hz, 1 H), 7.44 (d, *J* = 9.1 Hz, 1 H), 7.40 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1 H), 7.31 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1 H), 7.22-7.16 (m, 2 H), 7.09 (dd, *J* = 8.5, 0.8 Hz, 1 H), 6.94 (dd, *J* = 8.5, 0.8 Hz, 1 H), 3.74 (s, 3 H), 3.54 (d, *J* = 1.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 139.7, 134.0, 133.1, 132.7, 131.7, 129.7, 129.0, 128.4, 128.0, 126.7, 126.5, 126.11, 126.04, 125.3, 125.0, 123.7, 120.9, 113.5, 56.4, 45.1

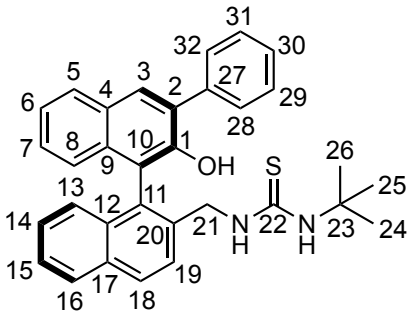


4.12

***N*'-((2'-Methoxy-[1,1'-binaphthalen]-2-yl)methyl)-*N*,*N*-dimethylacetimidamide (4.12).** (JCH-II-092) *N*,*N*'-dimethylacetamide dimethyl acetal (0.019 g, 0.021 mL, 0.14 mmol) was added to a solution of amine **4.10** (0.040 g, 0.13 mmol) in acetonitrile (0.25 mL) and stirred 2 h. The solvent was removed under reduced pressure and the crude reaction mixture was purified via flash column chromatography, eluting with CH_2Cl_2/MeCN/MeOH/NEt_3 (80:15:4:1) to provide 0.040 g (80%) of **4.11** as an amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 9.0 Hz, 1 H), 7.96 (d, *J* = 8.6 Hz, 1 H), 7.89-7.85 (m, 2 H), 7.79 (d, *J* = 8.6, 1 H), 7.46-7.40 (m, 2 H), 7.30 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1 H), 7.22-7.16 (m, 2 H), 7.11 (dd, *J* = 8.5, 0.6 Hz, 1 H), 6.89 (dd, *J* = 8.5, 0.6 Hz, 1 H), 4.42 (s, 2 H), 3.76 (s, 3 H), 1.98-1.97 (m, 6 H), 1.64 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 175.9, 163.6, 154.3, 133.60, 133.46, 133.0, 132.7, 131.8, 130.3, 128.94, 128.87, 128.18, 128.12, 127.0, 126.4, 126.10, 125.92, 125.4, 124.7, 123.8, 119.4, 113.2, 56.2, 46.4, 40.8, 22.3, 14.8, 1.9; IR (NaCl, film) 3415, 1645, 1592, 1558, 1508, 1265, 1251 cm^{-1}; HRMS (ESI) *m/z* 383.2120 [$C_{26}H_{26}N_2O$ (M+Na) requires 383.2118].

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 9.0 Hz, 1 H), 7.96 (d, *J* = 8.6 Hz, 1 H), 7.89-7.85 (m, 2 H), 7.79 (d, *J* = 8.6, 1 H), 7.46-7.40 (m, 2 H), 7.30 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1 H), 7.22-7.16 (m, 2 H), 7.11 (dd, *J* = 8.5, 0.6 Hz, 1 H),

6.89 (dd, *J* = 8.5, 0.6 Hz, 1 H), 4.42 (s, 2 H), 3.76 (s, 3 H), 1.98-1.97 (m, 6 H), 1.64 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 175.9, 163.6, 154.3, 133.60, 133.46, 133.0, 132.7, 131.8, 130.3, 128.94, 128.87, 128.18, 128.12, 127.0, 126.4, 126.10, 125.92, 125.4, 124.7, 123.8, 119.4, 113.2, 56.2, 46.4, 40.8, 22.3, 14.8, 1.9

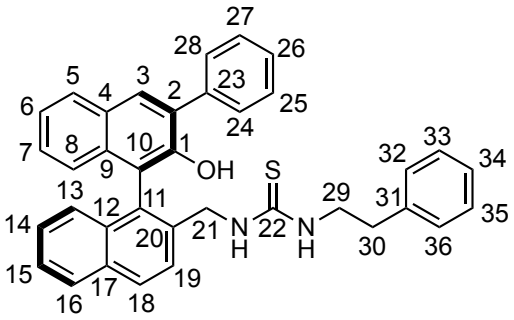


4.32

1-(*tert*-Butyl)-3-((2'-hydroxy-3'-phenyl-[1,1'-binaphthalen]-2-yl)methyl)thiourea (4.32). (JCH-II-194) *tert*-Butyl isothiocyanate (0.015 g, 0.13 mmol) was added to a solution of **4.28** (0.50 g, 0.13 mmol) in CH_2Cl_2 (0.65 mL), and the solution was stirred for 2.5 h. H_2O (1 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 1 mL), and the combined organic layers were washed with brine (3 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified via column chromatography, eluting with CH_2Cl_2 on SiO_2 (12 mL) to provide 0.038 g (60%) of **4.32** as a tan foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.5 Hz, 1 H), 7.94 (d, *J* = 6.7 Hz, 2 H), 7.90-7.88 (m, 1 H), 7.83 (d, *J* = 8.5 Hz, 1 H), 7.68-7.65 (m, 2 H), 7.49 (ddd, *J* = 8.0, 5.6, 3.7 Hz, 3 H), 7.42-7.38 (m,

1H), 7.36-7.29 (m, 3 H), 7.24-7.20 (m, 1 H), 6.94 (d, J = 8.1 Hz, 1 H), 5.86 (d, *J* = 0.5 Hz, 1 H), 5.78-5.74 (m, 1 H), 4.77-4.71 (m, 1 H), 4.65-4.60 (m, 1 H), 1.16 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9, 148.2, 138.3, 137.0, 135.6, 133.44, 133.27, 132.8, 130.9, 130.46, 130.27, 129.65, 129.60, 129.56, 129.53, 129.1, 128.8, 128.43, 128.28, 128.24, 128.0, 127.15, 127.03, 126.95, 126.4, 125.9, 124.22, 124.14, 118.1, 117.8, 29.3; IR (NaCl, film) 3410, 3058, 2964, ,2925, 2853, 1697, 1649, 1538, 1455, 1427, 1360, 1196 cm^{-1}; HRMS (ESI) *m/z* 513.1971 [$C_{32}H_{30}N_2OS$ (M+Na) requires 513.1971].

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.5 Hz, 1 H), 7.94 (d, *J* = 6.7 Hz, 2 H), 7.90-7.88 (m, 1 H), 7.83 (d, *J* = 8.5 Hz, 1 H), 7.68-7.65 (m, 2 H), 7.49 (ddd, *J* = 8.0, 5.6, 3.7 Hz, 3 H), 7.42-7.38 (m, 1H), 7.36-7.29 (m, 3 H), 7.24-7.20 (m, 1 H), 6.94 (d, J = 8.1 Hz, 1 H), 5.86 (d, *J* = 0.5 Hz, 1 H), 5.78-5.74 (m, 1 H), 4.77-4.71 (m, 1 H), 4.65-4.60 (m, 1 H), 1.16 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9, 148.2, 138.3, 137.0, 135.6, 133.44, 133.27, 132.8, 130.9, 130.46, 130.27, 129.65, 129.60, 129.56, 129.53, 129.1, 128.8, 128.43, 128.28, 128.24, 128.0, 127.15, 127.03, 126.95, 126.4, 125.9, 124.22, 124.14, 118.1, 117.8, 29.3

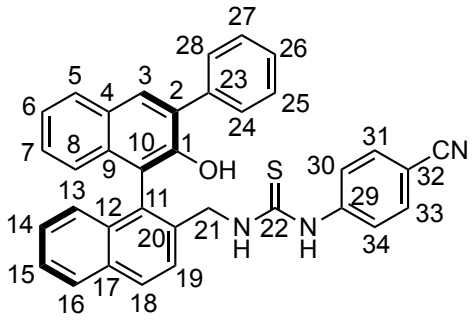


4.33

1-((2'-Hydroxy-3'-phenyl-[1,1'-binaphthalen]-2-yl)methyl)-3-phenethylthiourea (4.33). (JCH-II-195) (2-Isothiocyanatoethyl)benzene (0.021 g, 0.13 mmol) was added to a solution of **4.28** (0.50 g, 0.13 mmol) in CH_2Cl_2 (0.65 mL), and the solution was stirred for 2.5 h. H_2O (1 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 1 mL), and the combined organic layers were washed with brine (3 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified via column chromatography, eluting with CH_2Cl_2 on SiO_2 (14 mL) to provide 0.060 g (86%) of **4.32** as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.5 Hz, 1 H), 7.94 (d, *J* = 9.9 Hz, 2 H), 7.88 (dd, *J* = 8.2, 0.3 Hz, 1 H), 7.76-7.73 (m, 1 H), 7.65 (dt, *J* = 8.1, 1.6 Hz, 2 H), 7.52-7.47 (m, 3 H), 7.44-7.39 (m, 1 H), 7.34-7.26 (m, 3 H), 7.19-7.14 (m, 2 H), 6.91-6.88 (m, 2 H), 6.81 (d, *J* = 8.4 Hz, 1 H), 5.58-5.54 (m, 1 H), 5.11-5.07 (m, 1 H), 4.41-4.31 (m, 2 H), 2.67-2.56 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 134.4, 133.7, 133.1, 132.9, 130.9, 130.52, 130.36, 130.12, 130.02, 129.86, 129.55, 129.48, 129.2, 128.92, 128.89, 128.67, 128.53, 128.48, 128.46, 128.41, 128.33, 128.28, 128.14, 127.22, 127.14, 127.03, 126.93, 126.48, 126.41, 125.89, 125.74, 125.0, 124.3, 124.0, 36.2, 34.9, 32.4; IR (NaCl, film) 3397, 3059, 1706,

1650, 1554, 1497, 1454, 1427, 1360, 1260 cm^{-1}; HRMS (ESI) *m/z* 561.1970 [$C_{36}H_{30}N_2OS$ (M+Na) requires 561.1971].

NMR Assignments: ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.5 Hz, 1 H), 7.94 (d, *J* = 9.9 Hz, 2 H), 7.88 (dd, *J* = 8.2, 0.3 Hz, 1 H), 7.76-7.73 (m, 1 H), 7.65 (dt, *J* = 8.1, 1.6 Hz, 2 H), 7.52-7.47 (m, 3 H), 7.44-7.39 (m, 1 H), 7.34-7.26 (m, 3 H), 7.19-7.14 (m, 2 H), 6.91-6.88 (m, 2 H), 6.81 (d, *J* = 8.4 Hz, 1 H), 5.58-5.54 (m, 1 H), 5.11-5.07 (m, 1 H), 4.41-4.31 (m, 2 H), 2.67-2.56 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 134.4, 133.7, 133.1, 132.9, 130.9, 130.52, 130.36, 130.12, 130.02, 129.86, 129.55, 129.48, 129.2, 128.92, 128.89, 128.67, 128.53, 128.48, 128.46, 128.41, 128.33, 128.28, 128.14, 127.22, 127.14, 127.03, 126.93, 126.48, 126.41, 125.89, 125.74, 125.0, 124.3, 124.0, 36.2, 34.9, 32.4.

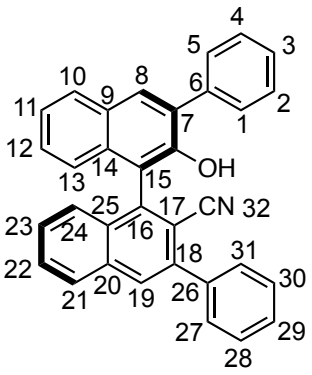


4.30

1-(4-cyanophenyl)-3-((2'-hydroxy-3'-phenyl-[1,1'-binaphthalen]-2-yl)methyl)thiourea (4.30). (JCH-II-167) 4-Isothiocyanatobenzonitrile (0.021 g, 0.13 mmol) was added to a solution of **4.28** (0.50 g, 0.13 mmol) in CH_2Cl_2 (0.70 mL), and the solution was stirred for 2 h. H_2O (1 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 1 mL), and the combined organic layers were washed with brine (3 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified via column chromatography, eluting with CH_2Cl_2/MeOH (97:3) on SiO_2 (16 mL) to provide 0.060 g (85%) of **4.30** as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 1 H), 7.94-7.92 (m, 2 H), 7.86 (t, *J* = 9.0 Hz, 2 H), 7.58-7.47 (m, 7 H), 7.36-7.28 (m, 3 H), 7.21-7.19 (m, 2 H), 7.14 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1 H), 6.96-6.94 (m, 1 H), 6.86 (dd, *J* = 8.3, 0.6 Hz, 1 H), 5.03-4.90 (m, 1 H), 4.40 (dd, *J* = 14.1, 4.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 136.63, 136.61, 136.3, 133.60, 133.52, 131.5, 130.4, 130.0, 129.71, 129.55, 129.31, 129.27, 129.13, 128.53, 128.38, 128.36, 128.27, 127.27, 127.24, 127.07, 126.6, 125.8, 124.4, 124.2, 123.21, 123.19, 38.6; IR (NaCl, film) 3398, 3057, 2226, 1605, 1507, 1425, 1360,

1318, 1257, 1195 cm^{-1}; HRMS (ESI) *m/z* 558.1610 [$C_{35}H_{25}N_2OS$ (M+Na) requires 558.1611.

NMR Assignments: ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 1 H), 7.94-7.92 (m, 2 H), 7.86 (t, *J* = 9.0 Hz, 2 H), 7.58-7.47 (m, 7 H), 7.36-7.28 (m, 3 H), 7.21-7.19 (m, 2 H), 7.14 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1 H), 6.96-6.94 (m, 1 H), 6.86 (dd, *J* = 8.3, 0.6 Hz, 1 H), 5.03-4.90 (m, 1 H), 4.40 (dd, *J* = 14.1, 4.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 136.63, 136.61, 136.3, 133.60, 133.52, 131.5, 130.4, 130.0, 129.71, 129.55, 129.31, 129.27, 129.13, 128.53, 128.38, 128.36, 128.27, 127.27, 127.24, 127.07, 126.6, 125.8, 124.4, 124.2, 123.21, 123.19, 38.6

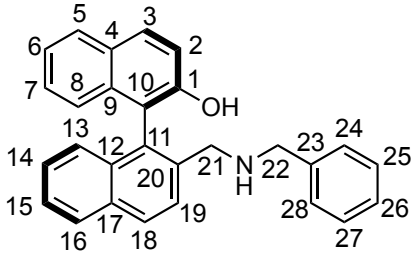


4.4

2'-Hydroxy-3,3'-diphenyl-[1,1'-binaphthalene]-2-carbonitrile (4.4). Triflate **4.3** (0.329 g, 0.577 mmol), $Ni(PPh_3)_2Br_2$ (0.085 g, 0.115 mmol), triphenylphosphine (0.085 g, 0.324 mmol), potassium cyanide (0.075 g, 1.15 mmol), and zinc powder (0.030 g, 0.461 mmol) were placed in a pear shaped flask. The flask was evacuated under high vacuum and placed under a nitrogen atmosphere three times. Dry, degassed acetonitrile (1 mL) was introduced, and the reaction was stirred at room temperature until it turned red (5-10 min). The flask was transferred to a 65 °C bath and was stirred for 4 h. (Do not monitor reaction by TLC; the reaction turned a slightly different shade of red with some solid material in it as the reaction completes.) The reaction was removed from bath, and the solids were removed by vacuum filtration through a pad of celite. The pad was washed with ether (5 mL) and concentrated under reduced pressure. The crude product was purified via flash chromatography (8:1 hexanes/ethyl acetate) to provide 0.124 g (48%) of **4.4** as an amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1 H), 8.02-7.97 (comp, 2 H), 7.91 (d, J = 8.0 Hz, 1 H), 7.79-7.62 (comp, 5 H), 7.56-7.36 (comp, 9 H), 7.32-7.28 (m, 1 H), 7.04 (d, J = 8.4 Hz, 1 H), 5.36 (s, 1 H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 148.5, 142.3, 140.4, 138.7, 136.4, 134.9, 133.2, 131.2, 130.3, 129.4, 129.3, 129.2, 128.9, 128.3, 127.7, 127.2, 126.9, 124.14, 124.11, 117.6, 116.7, 112.3; IR (NaCl, film) 3534, 3369, 3058, 2927, 2225, 1495, 1450, 1427, 1260, 1239 cm^{-1}; HRMS (ESI) *m/z* 470.1514 [$C_{33}H_{22}N_2NaO$ (M+Na) requires 470.1515].

NMR Assignments: ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1 H), 8.02-7.97 (comp, 2 H), 7.91 (d, *J* = 8.0 Hz, 1 H), 7.79-7.62 (comp, 5 H), 7.56-7.36 (comp, 9 H), 7.32-7.28 (m, 1 H), 7.04 (d, *J* = 8.4 Hz, 1 H), 5.36 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 142.3, 140.4, 138.7, 136.4, 134.9, 133.2, 131.2, 130.3, 129.4, 129.3, 129.2, 128.9, 128.3, 127.7, 127.2, 126.9, 124.14, 124.11, 117.6, 116.7, 112.3



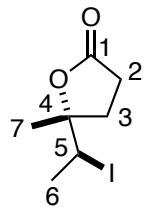
2'-((Benzylamino)methyl)-[1,1'-binaphthalen]-2-ol. (JCH-III-128) A solution of 2'-(aminomethyl)-[1,1'-binaphthalen]-2-ol (0.50 g, 0.17 mmol) and benzaldehyde (0.20 g, 0.19 mmol) in ethanol (0.7 mL) was heated at 70 °C for 10 h. The reaction was cooled to room temperature, whereupon sodium borohydride (0.13 g, 0.24 mmol) was added. The reaction was stirred for 3 h, whereupon H_2O (1.5 mL) was added, and the ethanol was removed under reduced pressure. The aqeous layer was extracted with EtOAc (3 x 1.5 mL), and the combined organic layers were washed with brine (4 mL), dried

($MgSO_4$), and concentrated under reduced pressure. The residue was purified via column chromatography, eluting with hexanes/EtOAc (2:1 → 1:2) on SiO_2 (15 mL) to provide 0.40 g (61%) of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.85 (comp, 5 H), 7.54 (d, *J* = 8.4 Hz, 1 H), 7.48-7.34 (comp, 3 H), 7.34-7.25 (comp, 5 H), 7.21-7.17 (m, 1 H), 7.14-7.10 (m, 1 H), 7.04-7.02 (m, 1 H), 6.70-6.78 (m, 1 H), 3.81-3.67 (comp, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 138.1, 135.8, 134.3, 133.7, 133.6, 133.4, 129.6, 129.1, 128.7, 128.64, 128.63, 128.4, 127.8, 127.5, 127.3, 127.2, 127.0, 126.4, 126.0, 125.9, 125.3, 123.1, 121.8, 120.7, 53.5, 52.9; IR (NaCl, film) 3056, 2926, 2853, 1618, 1591, 1505, 1455, 1434, 1343, 1272, 1233 cm^{-1}; HRMS (ESI) *m/z* 390.1858 [$C_{28}H_{23}NO$ (M+H) requires 390.1852].

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.85 (comp, 5 H), 7.54 (d, *J* = 8.4 Hz, 1 H), 7.48-7.34 (comp, 3 H), 7.34-7.25 (comp, 5 H), 7.21-7.17 (m, 1 H), 7.14-7.10 (m, 1 H), 7.04-7.02 (m, 1 H), 6.70-6.78 (m, 1 H), 3.81-3.67 (comp, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 138.1, 135.8, 134.3, 133.7, 133.6, 133.4, 129.6, 129.1, 128.7, 128.64, 128.63, 128.4, 127.8, 127.5, 127.3, 127.2, 127.0, 126.4, 126.0, 125.9, 125.3, 123.1, 121.8, 120.7, 53.5, 52.9

General procedure for iodolactonizations:

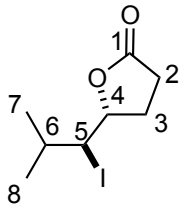
NIS (1.2 mmol) and I_2 (0.010 mmol), if used, were added in one portion to a solution of catalyst (0.010 mmol) and the appropriate olefinic acid (0.10 mmol) in a mixture (2:1) of toluene (2 mL) and CH_2Cl_2 (1 mL) at –20 °C with stirring. The reaction was stirred for 14 h, whereupon a solution of saturated sodium thiosulfate (1 mL) was added. The reaction was removed from the bath, and the stirring was continued for 0.5 h. The reaction mixture was transferred to a separatory funnel and extracted with Et_2O (3 x 3 mL). The combined organic extracts were washed with 5% Na_2CO_3 (5 mL), saturated brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified via flash chromatography eluting with hexanes/EtOAc.



4.65

(*R*)-5-((*S*)-1-Iodoethyl)-5-methyldihydrofuran-2(3*H*)-one (4.65). (JCH-II-190) 0.1 mmol scale; purified via column chromatography, eluting with hexanes/EtOAc (6:1) on SiO_2 (6 mL). Isolated 0.020 g (80%) as a clear, colorless oil: ^{1}H NMR (300 MHz; $CDCl_3$): δ 4.29 (q, *J* = 7.0 Hz, 1 H), 2.70-2.64 (m, 2 H), 2.35-2.13 (m, 2 H), 1.97 (d, *J* = 7.0 Hz, 3 H), 1.59 (s, 3 H). ^{13}C NMR (75 MHz; $CDCl_3$): δ 176.1, 88.7, 34.8, 34.6, 29.7, 23.6, 21.7; IR (neat) 2978, 2931, 1777, 1240, 1176, 1073 cm^{-1}; HRMS (ESI) *m/z* 276.9695 [$C_7H_{11}O_2INa$ (M+Na) requires 276.9696]; HPLC (259 nm): Whelk-O1 (20% *i-PrOH* / hexanes, 1.2 mL/min) 14.4 min (minor), 17.3 min (major); 66:34 er (without I_2), 79:21 er (with 10 mol % I_2).

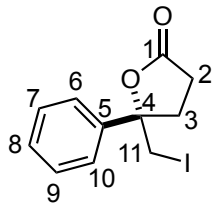
NMR Assignment: ^{1}H NMR (300 MHz; $CDCl_3$): δ 4.29 (q, *J* = 7.0 Hz, 1 H, C5-H), 2.70-2.64 (m, 2 H, C2-H), 2.35-2.13 (m, 2 H, C3-H), 1.97 (d, *J* = 7.0 Hz, 3 H, C6-H), 1.59 (s, 3 H, C7-H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 176.1 (C1), 88.7 (C4), 34.8 (C5), 34.6 (C2), 29.7 (C3), 23.6 (C6), 21.7 (C7)



4.63

(*R*)-5-((*S*)-1-Iodo-2-methylpropyl)dihydrofuran-2(3*H*)-one (4.63). (JCH-II-209) 0.1 mmol scale; purified via column chromatography, eluting with hexanes/EtOAc (5:1) on SiO_2 (6 mL): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66–4.58 (m, 1 H), 4.08 (dd, *J* = 10.0, 2.8 Hz, 1 H), 2.64–2.45 (comp, 3 H), 2.23–2.16 (m, 1 H), 1.57–1.45 (m, 1 H), 0.97 (d, *J* = 6.4 Hz, 3 H), 0.92 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 80.6, 51.4, 30.1, 29.9, 29.1, 23.6, 19.0; IR (neat) 1783 cm–1; HRMS (ESI) *m/z* 290.9851 [$C_8H_{13}O_2INa$ (M+Na) requires 290.9852]; HPLC (259 nm): OD-H (0.75% *i*-PrOH / hexanes, 1.0 mL/min) 26.5 min (major), 28.2 min (minor); 67:33 er (without I_2), 68:32 (with 10 mol % I_2).

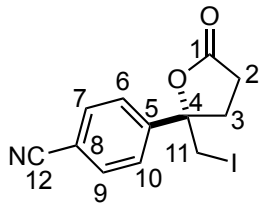
NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66–4.58 (m, 1 H, C4-H), 4.08 (dd, *J* = 10.0, 2.8 Hz, 1 H, C5-H), 2.64–2.45 (comp, 3 H, C-2H and C3-H_a), 2.23–2.16 (m, 1 H, C3-H_b), 1.57–1.45 (m, 1 H, C6-H), 0.97 (d, *J* = 6.4 Hz, 3 H, C7-H or C8-H), 0.92 (d, *J* = 6.4 Hz, 3 H, C7-H or C8-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6 (C1), 80.6 (C4), 51.4 (C2), 30.1 (C6), 29.9 (C7), 29.1 (C8), 23.6 (C3), 19.0 (C5)



4.37

(*S*)-5-(Iodomethyl)-5-phenyldihydrofuran-2(3*H*)-one (4.37). (JCH-II-185) 0.1 mmol scale; purified via column chromatography, eluting with hexanes/EtOAc (6:1) on SiO_2 (6 mL): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.33 (m, 5 H), 3.65 (d, *J* = 11.1 Hz, 1 H), 3.61 (d, *J* = 11.1 Hz, 1 H), 2.83-2.68 (comp, 2 H), 2.66-2.45 (comp, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 140.6, 128.8, 128.6, 124.8, 86.0, 33.9, 29.2, 16.2; IR (neat) 2924, 2853, 1779, 1448, 1151, 700 cm–1; HRMS (CI) *m/z* 302.9881 [$C_{11}H_{12}O_2I$ (M+H) requires 302.9882]; HPLC (214 nm): ODH (5% *i*-PrOH / hexanes, 1.0 mL/min) 19.0 min (minor), 23.8 min (major); 93:7 er (without I_2), 98:2 (with 10 mol % I_2), 81.5:18.5 (with 100 mol % I_2).

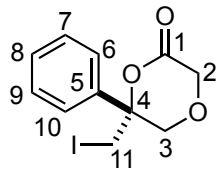
NMR Assignments: ^{1}H NMR (CDCl3, 300 MHz) δ 7.42-7.33 (m, 5 H, C6-H, C7-H, C8-H, C9-H, and C10-H), 3.65 (d, *J* = 11.1 Hz, 1 H, C11-H_a), 3.61 (d, *J* = 11.1 Hz, 1 H, C11-H_b), 2.83-2.68 (comp, 2 H, C2-H), 2.66-2.45 (comp, 2 H, C3-H); ^{13}C NMR (CDCl3, 75 MHz) δ 175.3 (C1), 140.6 (C5), 128.8 (C6 and C10 or C7 and C9), 128.6 (C6 and C10 or C7 and C9), 124.8 (C8), 86.0 (C4), 33.9 (C2), 29.2 (C2), 16.2 (C11)



4.38

(*S*)-4-(2-(Iodomethyl)-5-oxotetrahydrofuran-2-yl)benzonitrile (4.38). (JCH-II-208) 0.1 mmol scale; purified via column chromatography, eluting with hexanes/EtOAc (6:1) on SiO_2 (6 mL): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2 H), 7.54 (d, *J* = 8.4 Hz, 2 H), 3.60 (s, 2 H), 2.85–2.74 (comp, 2 H), 2.64–2.51 (comp, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 145.9, 132.6, 125.8, 118.1, 112.7, 85.3, 33.8, 29.0, 14.6; IR (neat) 2921, 2230, 1783, 1413, 1164, 1028, 841 cm–1; HRMS (CI) *m/z* 327.9835 [$C_{12}H_{11}NO_2I$ (M+H) requires 327.9835]; HPLC (231 nm): Whelk-O1 (3% CH3CN / 20% *i*-PrOH /hexanes, 1.2 mL/min) 17.5 min (minor), 20.2 min (major); 90:10 er (without I_2), 94:6 er (with 10 mol % I_2)

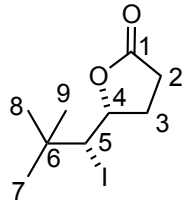
NMR Assignments: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2 H, C6-H and C10-H), 7.54 (d, *J* = 8.4 Hz, 2 H, C7-H and C9-H), 3.60 (s, 2 H, C11-H), 2.85–2.74 (comp, 2 H, C2-H), 2.64–2.51 (comp, 2 H, C3-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4 (C1), 145.9 (C8), 132.6 (C6 and C10), 125.8 (C5), 118.1 (C7 and C9C12)), 112.7 (, 85.3 (C4), 33.8 (C2), 29.0 (C3), 14.6 (C11)



4.75

(*R*)-6-(Iodomethyl)-6-phenyl-1,4-dioxan-2-one (4.75). (JCH-II-210) 0.1 mmol scale; purified via column chromatography, eluting with hexanes/EtOAc (6:1) on SiO_2 (6 mL): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.35 (comp, 5 H), 4.43 (d, *J* = 17.7 Hz, 1 H), 4.32 (d, *J* = 12.9 Hz, 1 H), 4.28 (d, *J* = 17.7 Hz, 1 H), 4.19 (d, *J* = 12.9 Hz, 1 H), 3.70 (d, *J* = 11.2 Hz, 1 H), 3.66 (d, *J* = 11.2 Hz, 1 H); 13C NMR (100 MHz, $CDCl_3$) δ 166.0, 138.0, 129.0, 128.9, 125.1, 83.0, 69.6, 65.4, 10.7; HRMS (CI) *m/z* 317.9753 [$C_{11}H_{11}IO_3$ (M+H) requires 317.8753]; HPLC (210 nm): Whelk-O1 (20% *i*-PrOH / hexanes, 1.2 mL/min) 19.5 min (minor), 24.3 min (major); 84:16 er (without I_2), 90:10 er (with 10 mol % I_2).

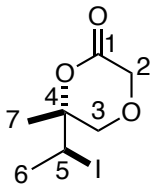
NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.35 (comp, 5 H, C6-H, C7-H, C8-H, C9-H, and C10-H), 4.43 (d, *J* = 17.7 Hz, 1 H, C2-H_a), 4.32 (d, *J* = 12.9 Hz, 1 H, 3-H_a), 4.28 (d, *J* = 17.7 Hz, 1 H, C2-H_b), 4.19 (d, *J* = 12.9 Hz, 1 H, C3-H_b), 3.70 (d, *J* = 11.2 Hz, 1 H, C11-H_a), 3.66 (d, *J* = 11.2 Hz, 1 H, C11-H_b); $_{13}$C NMR (100 MHz, $CDCl_3$) δ 166.0 (C1), 138.0 (C5), 129.0 (C7 and C9), 128.9 (C6 and C10), 125.1 (C8), 83.0 (C4), 69.6 (C4), 65.4 (C3), 10.7 (C11)



4.56

(*R*)-5-((*R*)-1-Iodo-2,2-dimethylpropyl)dihydrofuran-2(3*H*)-one (4.56). (JCH-II-240) 0.1 mmol scale; purified via column chromatography, eluting with hexanes/EtOAc (7:1) on SiO_2 (6 mL): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (t, *J* = 7.5 Hz, 1 H), 4.06 (s, 1 H), 2.75–2.65 (m, 1 H), 2.56–2.31 (comp, 2 H), 2.13– 2.01 (m, 1 H), 1.18 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 77.7, 60.0, 36.6, 29.6, 29.5, 27.8; IR (neat) 2960, 1768, 1463, 1352, 1176, 914 cm–1; HRMS (CI) *m/z* 283.0196 [$C_7H_{11}IO_2$ (M+H) requires 283.0195]; HPLC (259 nm): Whelk-O1 (20% *i*-PrOH / hexanes, 1.2 mL/min) 11.1 min (minor), 15.4 min (major); 97:3 er (without I_2), 98:2 er (with 10 mol % I_2).

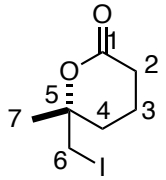
NMR Assignments: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (t, *J* = 7.5 Hz, 1 H, C4-H), 4.06 (s, 1 H, C5-H), 2.75–2.65 (m, 1 H, C2-H_a), 2.56–2.31 (comp, 2 H, C2-H_b and C3-H_a), 2.13– 2.01 (m, 1 H, C3-H_b), 1.18 (s, 9 H, C7-H, C8-H, and C9-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6 (C1), 77.7 (C4), 60.0 (C6), 36.6 (C2), 29.6 (C3), 29.5 (C7, C8, and C9), 27.8 (C5).



4.77

(*R*)-6-((*S*)-1-Iodoethyl)-6-methyl-1,4-dioxan-2-one (4.77). (JCH-II-183) 0.1 mmol scale; purified via column chromatography, eluting with hexanes/EtOAc (6:1) on SiO_2 (6 mL), isolated 0.026 g (81%) as a clear, colorless oil: 1H NMR (300 MHz; $CDCl_3$): δ 4.41 (q, *J* = 7.1 Hz, 1 H), 4.31 (s, 2 H), 4.05 (d, *J* = 12.6 Hz, 1 H), 3.96 (dd, *J* = 56.7, 12.6 Hz, 2 H), 3.87 (d, *J* = 12.6 Hz, 1 H), 2.02 (d, *J* = 7.1 Hz, 3 H), 1.61 (s, 3 H); ^{13}C NMR (75 MHz; CDCl3): δ 166.6, 84.1, 71.8, 65.5, 28.2, 22.5, 19.0; IR (neat) 2985, 2932, 2872, 1749, 1273, 1102 cm^{-1}; HRMS (ESI) *m/z* 292.9644 [$C_7H_{11}INaO_2$ (M+Na) requires 292.9645]; HPLC (259 nm): Whelk-O1 (20% *i-PrOH* / hexanes, 1.2 mL/min) 10.7 min (minor), 12.8 min (major); 79:21 er (without I_2), 84:16 er (with 10 mol % I_2).

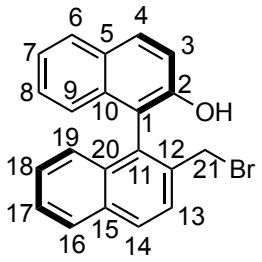
NMR Assignment: 1H NMR (300 MHz; $CDCl_3$): δ 4.41 (q, *J* = 7.1 Hz, 1 H, C5-H), 4.31 (s, 2 H, C2-H), 4.05 (d, *J* = 12.6 Hz, 1 H, C6-H), 3.96 (dd, *J* = 56.7, 12.6 Hz, 2 H, C3-H), 2.02 (d, *J* = 7.1 Hz, 3 H, C6-H), 1.61 (s, 3 H, C7-H); ^{13}C NMR (75 MHz; CDCl3): δ 166.6 (C1), 84.1 (C4), 71.8 (C2) , 65.5 (C3), 28.2 (C5), 22.5 (C6), 19.0 (C7).



4.73

(*R*)-6-(Iodomethyl)-6-methyltetrahydro-2*H*-pyran-2-one (4.73). (JCH-II-207) 0.1 mmol scale; purified via column chromatography, eluting with hexanes/EtOAc (6:1) on SiO_2 (6 mL), isolated 0.024 (89%) as clear, slightly yellow oil. ^{1}H-NMR (300 MHz; $CDCl_3$): δ 3.4 (dd, J = 10.5, 14.5 Hz, 2 H), 2.62-2.42 (m, 2 H), 2.16-2.02 (m, 1 H), 1.95-1.82 (m, 3 H), 1.59 (s, 3 H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 170.4, 81.9, 31.9, 29.4, 26.5, 16.9, 15.3; IR (neat) 2955, 1730, 1275, 1215, 1183, 1050 cm^{-1}; HRMS (CI) *m/z* 254.9872 [$C_7H_{11}IO_2$ (M+H) requires 254.9882]; 79:21 er (without I_2), 80:20 er (with I_2).

NMR Assignment: ^{1}H NMR (300 MHz; CDCl3): δ 3.4 (dd, J = 10.5, 14.5 Hz, 2 H, C6-H), 2.62-2.42 (m, 2 H, C2-H), 2.16-2.02 (m, 1 H, C3-H_a), 1.95-1.82 (m, 3 H, C4-H and C3-H_b), 1.59 (s, 3 H, C7-H); ^{13}C NMR (75 MHz; CDCl3): δ 170.4 (C1), 81.9 (C5), 31.9 (C6), 29.4 (C2), 26.5 (C3), 16.9 (C4), 15.3 (C7).

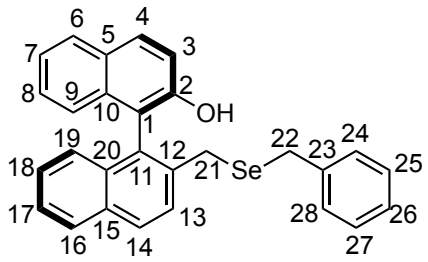


4.146

(*R*)-2'-(bromomethyl)-[1,1'-binaphthalen]-2-ol (4.146). (JCH-III-223) Phosphorous tribromide (0.45 g, 0.17 mmol) was added to a solution of **4.145** in CH_2Cl_2 (0.66 mL) at 0 °C, and the solution was stirred for 20 min. The reaction was poured into H_2O (1.5 mL) and extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were washed with brine (8 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified via column chromatography, eluting with hexanes/EtOAc (7:3) to provide 0.050 g (83%) of **4.146** as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 1 H), 7.95 (app t, *J* = 8.8, 7.2 Hz, 2 H), 7.88 (d, *J* = 11.2 Hz, 1 H), 7.77 (d, *J* = 9.2 Hz, 1 H), 7.54-7.50 (m, 1 H), 7.38-7.30 (comp, 3 H), 7.26-7.22 (comp, 2 H), 6.93 (d, *J* = 8.4 Hz, 1 H), 4.32 (dd, *J* = 10.0, 38.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCL_3$) δ 151.3, 136.5, 133.7, 133.4, 132.9, 130.5, 130.3, 130.0, 129.0, 128.2, 128.1, 127.9, 127.4, 127.0, 126.9, 126.1, 124.4, 123.7, 117.8, 115.7, 31.9; IR (NaCl, film) 3054, 2926, 2853, 2357, 1620, 1596, 1506, 1380 cm^{-1}; HRMS (ESI) *m/z* 361.0230 [$C_{21}H_{14}BrO$ (M–H) requires 361.0233].

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 1 H), 7.95 (app t, *J* = 8.8, 7.2 Hz, 2 H), 7.88 (d, *J* = 11.2 Hz, 1 H), 7.77 (d, *J* = 9.2 Hz, 1 H),

7.54-7.50 (m, 1 H), 7.38-7.30 (comp, 3 H), 7.26-7.22 (comp, 2 H), 6.93 (d, *J* = 8.4 Hz, 1 H), 4.32 (dd, *J* = 10.0, 38.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCL_3$) δ 151.3, 136.5, 133.7, 133.4, 132.9, 130.5, 130.3, 130.0, 129.0, 128.2, 128.1, 127.9, 127.4, 127.0, 126.9, 126.1, 124.4, 123.7, 117.8, 115.7, 31.9

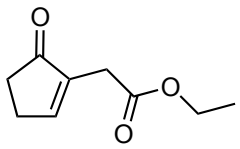


4.140

2'-((Benzylselanyl)methyl)-[1,1'-binaphthalen]-2-ol (4.140). (JCH-III-291/292/293) Triethylamine (0.33 g, 0.32 mmol) and chlorotriethylsilane (0.37 g, 0.32 mmol) were added to a solution of **4.146** (0.090 g, 0.25 mmol) in CH_2Cl_2 (7 mL), and the solution was stirred for 1 h. The reaction mixture was washed with 1 M HCl (5 mL), H_2O (5 mL), bring (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure to provide crude **4.153**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.85 (comp, 4 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.45-7.42 (m, 1 H), 7.34-7.31 (m, 1 H), 7.25-7.19 (comp, 3 H), 7.16 (d, *J* = 8.0 Hz, 1 H), 7.06 (d, *J* = 7.6 Hz, 1 H), 4.37 (s, 2 H), 0.58 (t, *J* = 8 Hz, 9 H), 0.46-0.29 (comp, 6 H).

Degassed ethanol (12 mL) was added to a stirred mixture of dibenzyl diselenide (0.14 g, 0.84 mmol) and sodium borohydride (0.032 g, 0.84 mmol) and stirring was

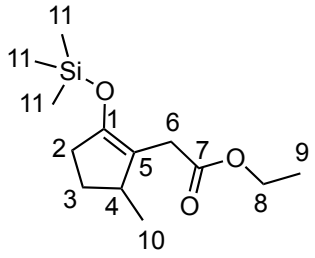
continued until a clear, colorless solution was obtained; stirring was continued for an additional 15 min. A solution of **4.153** (0.08 g, 1.68 mmol) in degassed ethanol (2 mL) was added, and the reaction was stirred for 7 h. The reaction was concentrated, and the residue was dissolved in methanol (1 mL), whereupon K_2CO_3 (0.25 g, 0.17 mmol) was added. The reaction was stirred for 1 h, then diluted with EtOAc (4 mL). The organic layer was washed with 1 M HCl (3 mL), brine 3 mL), dried ($MgSO_4$), and concentrated under reduced pressure to provide crude **4.140**. The crude product was purified with column chromatography eluting with hexanes/EtOAc (15:1) on SiO_2 (15 mL) to provide 0.048 g (75%) of **4.140** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.86 (comp, 4 H), 7.54-7.51 (m, 1 H), 7.47-7.44 (m, 1 H), 7.36-7.27 (comp, 3 H), 7.23-7.15 (comp 5 H), 7.03-6.95 (comp, 3 H), 3.61-3.44 (comp, 4 H); IR (NaCl, film) 3402, 3056, 2924, 2851, 1619, 1596, 1506, 1379, 1344 cm^{-1}; HRMS (CI) *m/z* 454.0837 [$C_{28}H_{22}OSe$ (M+H) requires 454.0836].



6.6

Ethyl 2-(5-oxocyclopent-1-en-1-yl)acetate (6.6). (JCH-IV-111 and JCH-IV-113) Prepared via Barco's procedure.[289] A solution of 4-(cylopent-1-en-1-yl)morpholine (**6.9**) (prepared via condensation of morpholine and cyclopentane[288]) (10 g, 65 mmol) and ethyl glyoxylate (8 g, 78 mmol) in cyclohexane (100 mL) was prepared in a round-bottom flask equipped with a Dean-Stark trap and heated under reflux for 20 h. The solution was cooled to 40 °C (internal temperature) and 6 M HCl (12 mL) was added. The solution was stirred 2 h at 40 °C and cooled to room temperature. Water (50 mL) was added, and the layers were separated. The aqueous layer was extracted with toluene (2 x 50 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide 10.5 g (96%, >95% pure by ^{1}H NMR) of ethyl 2-(2-oxocyclopentylidene)acetate (**6.10**) as a brown oil.

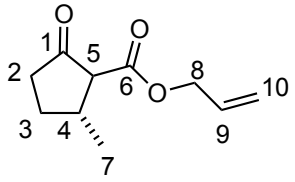
Ethyl 2-(2-oxocyclopentylidene)acetate (**6.10**) (10.5 g, 61.8 mmol) was dissolved in EtOH (125 mL) and concentrated HCl (4 mL) was added. The solution was heated under reflux for 9 h. The reflux condenser was replaced with a distillation head and the EtOH, H_2O, and HCl were removed via distillation to provide 10.5 g (>99%, >95% pure by ^{1}H NMR) of **6.6** as a brown oil. The spectra were consistent with reported literature values.[395] The oil was distilled prior to use in subsequent reactions; bp = 70-71 °C at 0.1 mm Hg.



6.19

Ethyl 2-(5-methyl-2-((trimethylsilyl)oxy)cyclopent-1-en-1-yl)acetate (6.19). (JCH-IV-119). Methyllithium (1.43 mmol, 1.46 M) was added dropwise to a suspension of CuBr•DMS (0.146 g, 0.713 mmol) in THF (1.80 mL) at –78 °C. The reaction was stirred 1 h, whereupon a solution of enone **6.6**[289] (0.100 g, 0.595 mmol) and chlorotrimethylsilane (0.259 g, 2.38 mmol) in THF (0.60 mL) was added with stirring. After 0.5 h, the reaction was poured into water (10 mL), and the resultant mixture was extracted with ether (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography, eluting with hexanes/ethyl acetate (10:1) on 40 mL SiO_2 to provide 0.057 g (36%) of **6.19** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (q, *J* = 7.1 Hz, 2 H), 3.17 (d, *J* = 15.7 Hz, 1 H), 2.84 (d, *J* = 15.7 Hz, 1 H), 2.71-2.66 (m, 1 H), 2.30-2.26 (m, 2 H), 2.12-2.03 (m, 1 H), 1.39-1.30 (m, 1 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 0.18 (s, 9 H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 171.9, 149.4, 114.6, 60.2, 37.3, 32.4, 30.5, 29.3, 19.9, 14.2, 0.5; IR (film, NaCl) 2956, 1738, 1783, 1253 846 cm^{-1}; HRMS (CI) *m/z* 256.1492 [$C_{13}H_{24}O_3Si$ (M+1) requires 256.1495].

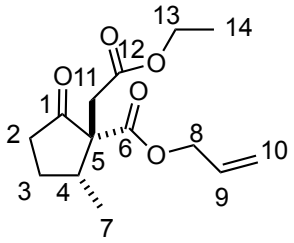
NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.11 (q, *J* = 7.1, 2 H, C8-H), 3.17 (d, *J* = 15.7 Hz, 1 H, C6-H_a), 2.84 (d, *J* = 15.7 Hz, 1 H, C6-H_b), 2.71-2.66 (m, 1 H, C4-H), 2.30-2.26 (m, 2 H, C2-H), 2.12-2.03 (m, 1 H, C3-H_a), 1.39-1.30 (m, 1 H, C3-H_b), 1.24 (t, *J* = 7.1, 3 H, C9-H), 0.98 (d, *J* = 6.8, 3 H, C10-H), 0.18 (s, 9 H, C11-H); ^{13}C NMR (100 MHz; $CDCl_3$): δ 171.9 (C7), 149.4 (C1), 114.6 (C5), 60.2 (C8), 37.3 (C4), 32.4 (C3), 30.5 (C2), 29.3 (C6), 19.9 (C10), 14.2 (C9), 0.5 (C11).



6.27

Allyl (2*R*)-2-methyl-5-oxocyclopentane-1-carboxylate (6.27). (JCH-IV-273) A solution of methyl (2*R*)-2-methyl-5-oxocyclopentane-1-carboxylate (**6.24**)[318] (2.00 g, 12.8 mmol), DMAP (0.39 g, 3.2 mmol), and allyl alcohol (7.43 g, 128 mmol) in cyclohexane (25 mL) was heated at 80 °C with continuous removal of solvent (vigreux column with Claisen head) until methanol and cyclohexane were no longer condensing in the collection vessel. After removal of methanol and some cyclohexane, the temperature was raised to 105 °C and the cyclohexane and most of the allyl alcohol was removed by distillation. The crude product was purified by column chromatography eluting with hexanes/EtOAc (15:1) on silica gel (260 mL) to provide 1.6 g (69%) of **6.27** as a colorless oil: ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.99-5.85 (m, 1 H), 5.34 (dq, *J* = 17.2, 1.5 Hz, 1 H), 5.24 (dt, *J* = 10.5, 1.2 Hz, 1 H), 4.70-4.59 (comp, 2 H), 2.79 (d, *J* = 11.4 Hz, 1 H), 2.67-2.55 (m, 1 H), 2.48-2.27 (comp, 2 H), 2.20 (dddd, *J* = 12.6, 8.4, 6.4, 2.0 Hz, 1 H), 1.48 (dtd, *J* = 12.6, 11.2, 8.6 Hz, 1 H), 1.19 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 211.6, 168.8, 131.8, 118.4, 65.8, 63.0, 38.7, 36.4, 29.3, 19.3; IR (film, NaCl) 2961, 2875, 1756, 1728, 1295, 1192, 1129 cm^{-1}; HRMS (CI) *m/z* 183.1021 [$C_{10}H_{15}O_3$ (M+1) requires 183.1021].

NMR Assignments: ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.99-5.85 (m, 1 H, C9-H), 5.34 (dq, *J* = 17.2, 1.3 Hz, 1 H, C10-H_{cis}), 5.24 (dt, *J* = 10.5, 1.3 Hz, 1 H, C10-H_{trans}), 4.70-4.59 (comp, 2 H, C8-H), 2.79 (d, *J* = 11.4 Hz, 1 H, C5-H), 2.67-2.55 (m, 1 H, C2-H_a), 2.48-2.27 (comp, 2 H, C2-H_b, C3-H_a), 2.20 (dddd, *J* = 12.6, 8.4, 6.4, 2.0 Hz, 1 H, C4-H), 1.48 (dtd, *J* = 12.6, 11.2, 8.6 Hz, 1 H, C3-H_b), 1.19 (d, *J* = 6.4 Hz, 3 H, C7-H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 211.6 (C1), 168.8 (C6), 131.8 (C9), 118.4 (C10), 65.8 (C8), 63.0 (C5), 38.7 (C2), 36.4 (C4), 29.3 (C3), 19.3 (C7).

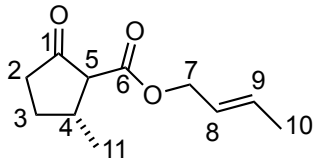


6.23

Allyl (1*R*,2*R*)-1-(2-ethoxy-2-oxoethyl)-2-methyl-5-oxocyclopentane-1-carboxylate (6.23). (JCH-IV-186) A suspension of allyl carboxylate **6.27** (1.2 g, 8.2 mmol), ethyl bromoacetate (2.7 g, 16.5 mmol), and K_2CO_3 (3.4 g, 25.0 mmol) in acetone (40 mL) was heated at 55 °C for 12 h. The reaction was cooled to room temperature and partitioned between Et_2O (200 mL) and H_2O (160 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 x 150 mL). The combined organic extracts were washed with brine (300 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude product was purified via column chromatography eluting

with hexanes/EtOAc (12:1) on SiO_2 (250 mL) to provide 1.2 g (60%) of **6.23** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1 H), 5.29 (dq, *J* = 17.2, 1.3 Hz, 1 H), 5.24 (dq, *J* = 10.4, 1.3 Hz, 1 H), 4.63-4.52 (comp, 2 H), 4.12-4.04 (comp, 2 H), 3.12 (d, *J* = 17.9 Hz, 1 H), 2.82 (d, *J* = 17.9 Hz, 1 H), 2.59-2.49 (m, 3 H), 2.15-2.08 (m, 1 H), 1.89-1.78 (m, 1 H), 1.25-1.21 (t, *J* = 7.2 Hz, 3 H), 1.03 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 215.2, 170.8, 169.3, 131.3, 119.1, 65.8, 60.77, 60.76, 39.2, 38.1, 35.9, 28.3, 15.4, 14.1; IR (film, NaCl) 2962, 2881, 1730, 1215, 1158, 1120 cm^{-1}; HRMS (CI) *m/z* 269.1388 [$C_{14}H_{21}O_5$ (M+1) requires 269.1389].

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1 H, C9-H), 5.29 (dq, *J* = 17.2, 1.3 Hz, 1 H, C10-H_{cis}), 5.24 (dq, *J* = 10.4, 1.3 Hz, 1 H, C10-H_{trans}), 4.63-4.52 (comp, 2 H, C8-H), 4.12-4.04 (comp, 2 H, C13-H), 3.12 (d, *J* = 17.9 Hz, 1 H, C11-H_a), 2.82 (d, *J* = 17.9 Hz, 1 H, C11-H_b), 2.59-2.49 (m, 3 H, C2-H, C3-H), 2.15-2.08 (m, 1 H, C4-H), 1.89-1.78 (m, 1 H, C3-H), 1.25-1.21 (t, *J* = 7.2 Hz, 3 H, C14-H), 1.03 (d, *J* = 6.7 Hz, 3 H, C7-H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 215.2 (C1), 170.8 (C6 or C12), 169.3 (C6 or C12), 131.3 (C9), 119.1 (C10), 65.8 (C5), 60.77 (C8 or C13), 60.76 (C8 or C13), 39.2 (C2), 38.1 (C4), 35.9 (C3), 28.3 (C11), 15.4 (C7 or C14), 14.1 (C7 or C14).

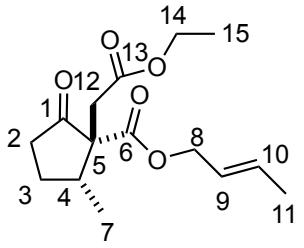


6.31

(*E*)-But-2-en-1-yl (2*R*)-2-methyl-5-oxocyclopentane-1-carboxylate (6.31). (JCH-IV-274). A solution of methyl (2*R*)-2-methyl-5-oxocyclopentane-1-carboxylate (**6.24**) (0.50 g, 3.2 mmol), DMAP (0.97 g, 0.80 mmol), and *E*-crotyl alcohol (2.3 g, 32.0 mmol) in cyclohexane (6.5 mL) was heated at 80 °C with continuous removal of solvent (vigreux column with Claisen head) until methanol and cyclohexane were no longer condensing in the collection vessel. After removal of methanol and some cyclohexane, the temperature was raised to 105 °C and the cyclohexane and most of the crotyl alcohol was removed by distillation. The crude product was purified by column chromatography, eluting with hexanes/EtOAc (15:1) to provide 0.30 g (50%) of **6.31** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84-5.74 (m, 1 H), 5.62-5.53 (m, 1 H), 4.58-4.55 (m, 2 H), 2.75 (d, *J* = 11.3 Hz, 1 H), 2.65-2.53 (m, 1 H), 2.45-2.21 (comp, 2 H), 2.20-2.14 (m, 1 H), 1.72-1.70 (m, 3 H), 1.51-1.39 (m, 1 H), 1.16 (d, *J* = 6.5 Hz, 3 H); ^{13}C (100 MHz, $CDCl_3$) δ 211.8, 168.9, 131.6, 124.7, 65.9, 63.1, 38.7, 36.4, 29.3, 19.3, 17.8; IR (NaCl, film) 2960, 2875, 1755, 1729, 1456, 1380, 1332 cm^{-1}; HRMS (CI) *m/z* 197.1177 [$C_{11}H_{17}O_3$ (M+1) requires 197.1178].

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84-5.74 (m, 1 H, C8-H), 5.62-5.53 (m, 1 H, C9-H), 4.58-4.55 (m, 2 H, C7-H), 2.75 (d, *J* = 11.3 Hz, 1 H, C5-H),

2.65-2.53 (m, 1 H, C4-H)), 2.45-2.21 (comp, 2 H, C2-H), 2.20-2.14 (m, 1 H, C3-H_a), 1.72-1.70 (m, 3 H, C10-H), 1.51-1.39 (m, 1 H, C3-H_b), 1.16 (d, J = 6.5 Hz, 3 H, C11-H); ^{13}C (100 MHz, $CDCl_3$) δ 211.8 (C1), 168.9 (C6), 131.6 (C8), 124.7 (C9), 65.9 (C7), 63.1 (C5), 38.7 (C2), 36.4 (C4), 29.3 (C3), 19.3 (C10), 17.8 (C11)

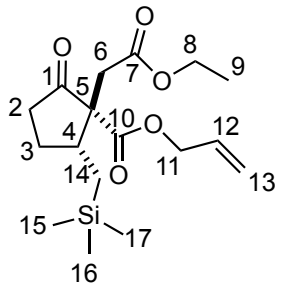


6.32

(*E*)-But-2-en-1-yl (1*R*,2*R*)-1-(2-ethoxy-2-oxoethyl)-2-methyl-5-oxocyclopentane-1-carboxylate (6.32). (JCH-IV-278) A suspension of crotyl carboxylate **6.31** (0.260 g, 1.32 mmol), ethyl bromoacetate (0.441 g, 2.64 mmol), and K_2CO_3 (0.547 g, 3.96 mmol) in acetone (7 mL) was heated at 55 °C for 12 h. The reaction was cooled to room temperature and partitioned between Et_2O (20 mL) and H_2O (16 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude product was purified by column chromatography eluting with hexanes/EtOAc (12:1) to provide 0.290 g (77%) of **6.32** as a colorless oil: ^{1}H NMR (400 MHz; $CDCl_3$): δ 5.81-5.72 (m, 1 H), 5.56-5.48 (m, 1 H), 4.58-4.52 (m, 1 H), 4.49-4.43 (m, 1 H), 4.12-4.04 (comp, 2 H), 3.11 (d, J = 17.9 Hz, 1 H), 2.81 (d, J = 17.9 Hz, 1 H), 2.59-2.45 (comp, 3 H), 2.14-2.07 (m, 1 H), 1.89-

1.78 (m, 1 H), 1.72-1.69 (m, 3 H), 1.23 (t, J = 7.1 Hz, 3 H), 1.02 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz; $CDCl_3$): δ 215.4, 170.9, 169.5, 132.1, 124.3, 65.9, 60.8, 60.7, 39.2, 38.1, 35.9, 28.2, 17.8, 15.4, 14.1; IR (film, NaCl) 2963, 1754, 1731, 1215, 1159 cm $^{-1}$; HRMS (CI) m/z 283.1542 [$C_{15}H_{23}O_5$ (M+1) requires 283.1545].

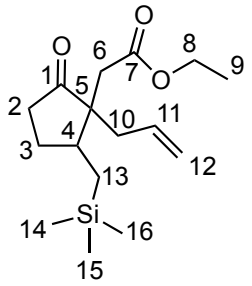
NMR Assignments: ^{1}H NMR (400 MHz; $CDCl_3$): δ 5.81-5.72 (m, 1 H, C9), 5.56-5.48 (m, 1 H, C10), 4.58-4.52 (m, 1 H, C8-H_a), 4.49-4.43 (m, 1 H, C8-H_b), 4.12-4.04 (comp, 2 H, C14), 3.11 (d, J = 17.9 Hz, 1 H, C12-H_a), 2.81 (d, J = 17.9 Hz, 1 H, C12-H_b), 2.59-2.45 (comp, 3 H, C2-H and C4-H), 2.14-2.07 (m, 1 H, C3-H_a), 1.89-1.78 (m, 1 H, C3-H_b), 1.72-1.69 (m, 3 H, C11-H), 1.23 (t, J = 7.1 Hz, 3 H, C15-H), 1.02 (d, J = 6.9 Hz, 3 H, C7-H); ^{13}C NMR (100 MHz; $CDCl_3$): δ 215.4 (C1), 170.9 (C6), 169.5 (C13), 132.1 (C9), 124.3 (C10), 65.9 (C5), 60.8 (C8), 60.7 (C14), 39.2 (C12), 38.1 (C2), 35.9 (C4), 28.2 (C11), 17.8 (C3) , 15.4 (C7), 14.1 (C15).



6.51

Allyl-1-(2-ethoxy-2-oxoethyl)-2-oxo-5-((trimethylsilyl)methyl)cyclopentane-1-carboxylate (6.51). (JCH-V-115) A suspension of **6.50** (0.040 g, 0.160 mmol), ethyl bromoacetate (0.530 g, 0.320 mmol), and K_2CO_3 (0.088 g, 0.640 mmol) in acetone (1 mL) was heated at 55 °C for 12 h. The reaction was cooled to room temperature and partitioned between Et_2O (2 mL) and H_2O (1 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 x 2 mL). The combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude product was purified by column chromatography eluting with hexanes/EtOAc (5:1) on SiO_2 (40 mL) to provide 0.038 g (70%) of **6.51** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddt, J = 17.1, 10.5, 5.8, 1 H), 5.32-5.23 (m, 2 H), 4.64-4.54 (m, 2 H), 4.09 (q, *J* = 7.1, 2 H), 3.11 (d, *J* = 17.7, 1 H), 2.79 (d, *J* = 17.7, 1 H), 2.62-2.47 (m, 3 H), 2.20-2.12 (m, 1 H), 1.87-1.76 (m, 1 H), 1.23 (t, *J* = 7.1, 3 H), 0.79 (dd, *J* = 14.3, 2.5, 1 H), 0.34 (dd, *J* = 14.3, 12.4, 1 H), 0.03 (s, 9 H); ^{13}C (100 MHz, $CDCl_3$) δ 216.0, 171.8, 170.3, 132.3, 119.9, 66.7, 63.2, 61.7, 42.0, 39.3, 36.6, 29.5, 18.8, 15.1, 0.0; IR (NaCl, film) 2953, 1754, 1733, 1373, 1249, 1223, 1175, 1025 cm^{-1}; HRMS (ESI) *m/z* 363.1599 [$C_{17}H_{28}O_5Si$ (M+Na) requires 363.1598].

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddt, J = 17.1, 10.5, 5.8, 1 H, C12-H), 5.32-5.23 (m, 2 H, C13-H), 4.64-4.54 (m, 2 H, C11-H), 4.09 (q, J = 7.1, 2 H, C8-H), 3.11 (d, J = 17.7, 1 H, C6-H_a), 2.79 (d, J = 17.7, 1 H, C6-H_b), 2.62-2.47 (m, 3 H, C2-H and C4-H), 2.20-2.12 (m, 1 H, C3-H_a), 1.87-1.76 (m, 1 H, C3-H_b), 1.23 (t, J = 7.1, 3 H, C9-H), 0.79 (dd, J = 14.3, 2.5, 1 H, C14-H_a), 0.34 (dd, J = 14.3, 12.4, 1 H C14-H_b), 0.03 (s, 9 H, C15-H, C16-H, and C17-H); ^{13}C (100 MHz, $CDCl_3$) δ 216.0 (C1), 171.8 (C10), 170.3 (C7), 132.3 (C11), 119.9 (C13), 66.7 (C5), 63.2 (C11), 61.7 (C8), 42.0 (C2), 39.3 (C2), 36.6 (C3), 29.5 (C6), 18.8 (C9), 15.1 (C14), 0.0 (C15, C16, and C17)

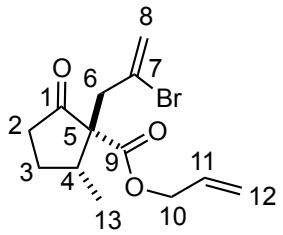


6.52

Ethyl 2-(1-allyl-2-oxo-5-((trimethylsilyl)methyl)cyclopentyl)acetate (6.52). (JCH-V-127) Ester **6.51** (0.025 g, 0.073 mmol) was added to a solution of $Pd(PPh_3)_4$ (0.008 g, 0.007 mmol) in THF (3 mL). The reaction was stirred for 12 h, whereupon it was concentrated under reduced pressure to provide crude **6.52** as a mixture (1:1.6) of diastereomers. The crude product was purified via column chromatography eluting with hexanes/Et_2O (5:1) on SiO_2 (15 mL) to provide 0.18 g (80%) of **6.52** as a mixture (1:1.6) of diastereomers. ^1H NMR (600 MHz, $CDCl_3$) δ 5.72-5.65 (m, 0.6 H), 5.62-5.55 (m, 0.3 H), 5.06-4.98 (m, 2 H), 4.11-4.00 (m, 2 H), 2.75 (d, *J* = 16.7 Hz, 0.6 H), 2.45-2.37 (m, 1.8 H), 2.34-2.28 (m, 1.6 H), 2.27-2.22 (m, 1 H), 2.15-2.00 (m, 3 H), 1.54-1.48 (m, 1 H), 1.22-1.19 (m, 3 H), 0.68-0.63 (m, 1 H), 0.53-0.49 (m, 0.6 H), 0.41-0.36 (m, 0.4 H), 0.01 (bs, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.1, 219.9, 171.6, 171.4, 133.4, 133.2, 118.9, 118.6, 60.6, 60.4, 53.4, 53.2, 39.7, 39.5, 38.2, 37.8, 37.7, 37.2, 35.2, 27.8, 27.2, 17.4, 16.3, 14.2, 14.11, 14.0, -0.72, -0.89; IR (NaCl, film) 2958, 2904, 1730, 1462, 1279 cm^{-1}; HRMS (ESI) *m/z* 319.1703 [$C_{17}H_{28}O_3Si$ (M+Na) requires 319.1700].

NMR Assignments: ^1H NMR (600 MHz, $CDCl_3$) δ 5.72-5.65 (m, 0.6 H, C11-H_{major}), 5.62-5.55 (m, 0.3 H, C11-H_{minor}), 5.06-4.98 (m, 2 H, C12-H), 4.11-4.00 (m, 2 H, C8-H), 2.75 (d, *J* = 16.7 Hz, 0.6 H, C6-H_a major), 2.45-2.37 (m, 1.8 H), 2.34-2.28 (m, 1.6

H,), 2.27-2.22 (m, 1 H, C4-H), 2.15-2.00 (m, 3 H, C3H_a, C10-H), 1.54-1.48 (m, 1 H, C3-H_b), 1.22-1.19 (m, 3 H, C9-H), 0.68-0.63 (m, 1 H, C13-H_a), 0.53-0.49 (m, 0.6 H, C13-H_b $_{major}$), 0.41-0.36 (m, 0.4 H, C-13$_{b\ minor}$), 0.01 (bs, 9 H, C14-H, C15-H, and C16-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.1 ($C1_{minor}$), 219.9 ($C1_{major}$), 171.6 ($C7_{minor}$), 171.4 ($C7_{major}$), 133.4 ($C11_{minor}$), 133.2 ($C11_{major}$), 118.9 ($C12_{minor}$), 118.6 ($C11_{major}$), 60.6 ($C5_{minor}$), 60.4 ($C5_{major}$), 53.4 ($C8_{minor}$), 53.2 ($C8_{major}$), 39.7, 39.5, 38.2, 37.8, 37.7, 37.2, 35.2, 27.8, 27.2, 17.4, 16.3, 14.2 , 14.11 ($C9_{minor}$), 14.0 ($C9_{major}$), -0.72 (C14, C15, and $C16_{minor}$), -0.89 (C14, C15, and $C16_{major}$)

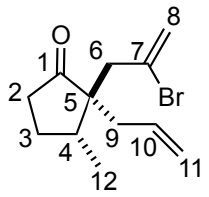


6.43

Allyl (1*R*,2*R*)-1-(2-bromoallyl)-2-methyl-5-oxocyclopentane-1-carboxylate (6.43). (JCH-V-075) A suspension of **6.27** (0.500 g, 2.74 mmol), ethyl bromoacetate (1.09 g, 7.94 mmol), and K_2CO_3 (1.51 g, 7.94 mmol) in acetone (17 mL) was heated at 55 °C for 12 h. The reaction was cooled to room temperature and partitioned between Et_2O (30 mL) and H_2O (15 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude

product was purified by column chromatography eluting with hexanes/EtOAc (20:1) on SiO_2 (120 mL) to provide 0.536 g (65%) of **6.43** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddt, J = 17.2, 10.4, 5.8 Hz, 1 H), 5.67 (t, J = 1.2 Hz, 1 H), 5.54-5.53 (m, 1 H), 5.32-5.23 (m, 2 H), 4.65-4.53 (m, 2 H), 3.28-3.23 (m, 1 H), 3.17 (d, *J* = 15.1 Hz, 1 H), 2.64-2.55 (m, 2 H), 2.36 (ddd, *J* = 19.1, 11.5, 9.1 Hz, 1 H), 2.14-2.06 (m, 1 H), 1.92-1.81 (m, 1 H), 1.05 (d, *J* = 6.9, 3 H); ^{13}C (100 MHz, $CDCl_3$) δ 215.2, 169.4, 131.2, 128.2, 122.3, 119.2, 65.9, 63.2, 41.2, 38.9, 37.4, 27.9, 15.3; IR (NaCl, film) 2961, 1752, 1730, 1624, 1224, 1164, 1117 cm^{-1}; HRMS (CI) *m/z* 301.0432 [$C_{13}H_{18}O_3Br$ (M+1) requires 301.0439].

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddt, J = 17.2, 10.4, 5.8 Hz, 1 H, C11-H), 5.67 (t, J = 1.2 Hz, 1 H, C8-H_a), 5.54-5.53 (m, 1 H, C8-H_b), 5.32-5.23 (m, 2 H, C12-H), 4.65-4.53 (m, 2 H, C10-H), 3.28-3.23 (m, 1 H, C6-H_a), 3.17 (d, J = 15.1 Hz, 1 H, C6-H_b), 2.64-2.55 (m, 2 H, C2-H), 2.36 (ddd, J = 19.1, 11.5, 9.1 Hz, 1 H, C4-H), 2.14-2.06 (m, 1 H, C3-H_a), 1.92-1.81 (m, 1 H, C3-H_b), 1.05 (d, J = 6.9, 3 H, C13-H); ^{13}C (100 MHz, $CDCl_3$) δ 215.2 (C1), 169.4 (C9), 131.2 (C7), 128.2 (C11), 122.3 (C8), 119.2 (C12), 65.9 (C5), 63.2 (C10), 41.2 (C6), 38.9 (C4), 37.4 (C2), 27.9 (C3), 15.3 (C13)



6.44

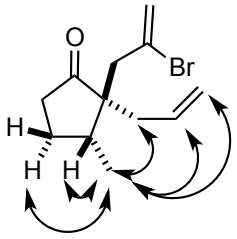
(2*S*,3*R*)-2-Allyl-2-(2-bromoallyl)-3-methylcyclopentan-1-one (6.44). (JCH-V-066) A solution of **6.43** (0.020 g, 0.70 mmol) in THF (1 mL) was added to a solution of $Pd(PPh_3)_4$ (0.008 g, 0.007 mmol) in THF (1.3 mL), and the solution was stirred for 12 h. The reaction was concentrated under reduced pressure to provide crude **6.44** as a mixture (3:1) of diastereomers. The crude product was purified via column chromatography eluting with hexanes/EtOAc (25:1) on SiO_2 (30 mL) to provide 0.013 g (67%) of **6.44** as a single diasteromer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.71-5.64 (m, 1 H), 5.55-5.49 (m, 1 H), 5.44-5.44 (m, 1 H), 5.05-5.99 (m, 2 H), 3.01 (d, *J* = 14.0 Hz, 1 H), 2.45-2.37 (m, 2 H), 2.35-2.30 (m, 1 H), 2.26-2.19 (m, 1 H), 2.13-2.10 (m, 1 H), 2.04-1.99 (m, 2 H), 1.60-1.53 (m, 1 H), 1.07 (d, *J* = 6.9 Hz, 3 H); ^{13}C (125 MHz, $CDCl_3$) δ 220.3, 133.0, 129.7, 120.9, 118.5, 54.5, 44.6, 37.6, 36.5, 35.9, 26.9, 14.2; IR (NaCl, film) 3077, 2959, 2901, 1737, 1624, 1465, 1436, 1404, 1380, 1121 cm^{-1}; HRMS (CI) *m/z* 257.0536 [$C_{12}H_{18}O_1Br$ (M+1) requires 257.0541].

NMR Assignments: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.71-5.64 (m, 1 H, C10-H), 5.55-5.49 (m, 1 H, C8-H_a), 5.44-5.44 (m, 1 H, C8-H_b), 5.05-5.99 (m, 2 H, C11-H), 3.01 (d, *J* = 14.0 Hz, 1 H, C6-H_a), 2.45-2.37 (m, 2 H, C6-H_b and C2-H_a), 2.35-2.30 (m, 1 H, C2-H_b), 2.26-2.19 (m, 1 H, C4-H), 2.13-2.10 (m, 1 H, C9-H_a), 2.04-1.99 (m, 2 H, C9-H_b and C3-H_a), 1.60-1.53 (m, 1 H, C3-H_b), 1.07 (d, 6.9 Hz, 3 H, C12-H); ^{13}C (125 MHz,

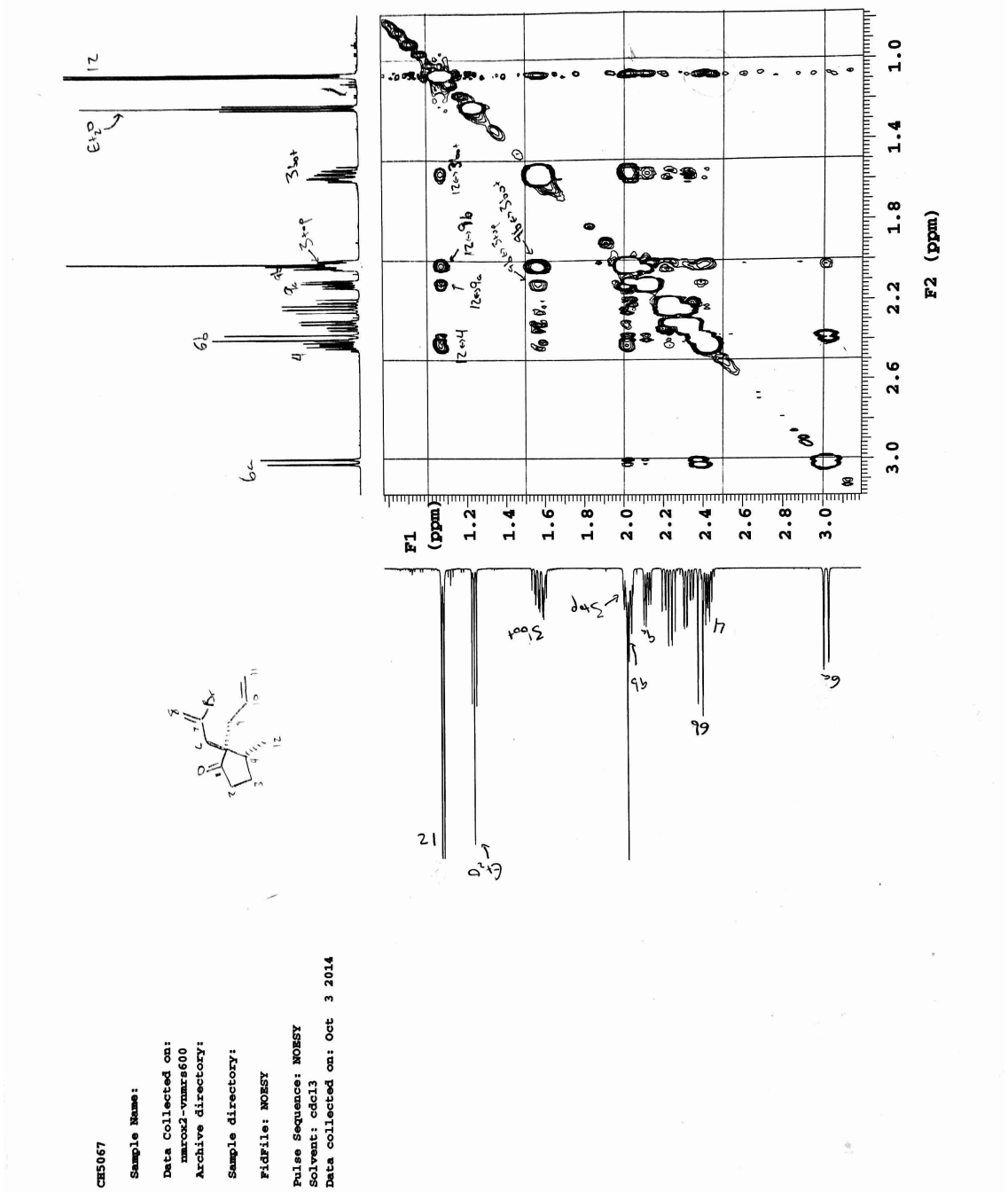
$CDCl_3$) δ 220.3 (C1), 133.0 (C10), 129.7 (C7), 120.9 (C8), 118.5 (C11), 54.5 (C5), 44.6 (C6), 37.6 (C2), 36.5 (C4), 35.9 (C9), 26.9 (C3), 14.2 (C12)

NOE Correlations:

Spectra on following page



6.44
NOE between the Me group and all positions of the allyl group
No NOE between the Me group and the bromoallyl group


CM5067
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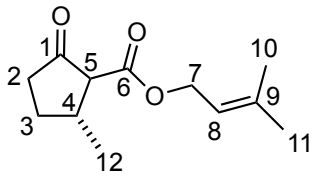
F1 (ppm)
F2 (ppm)

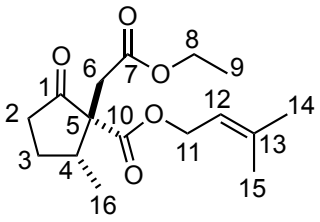


6.28

3-Methylbut-2-en-1-yl (2*R*)-2-methyl-5-oxocyclopentane-1-carboxylate (6.28). (JCH-V-062) A solution of methyl (2*R*)-2-methyl-5-oxocyclopentane-1-carboxylate (**6.24**) (0.50 g, 3.2 mmol), DMAP (0.97 g, 0.80 mmol), and prenyl alcohol (2.7 g, 32.0 mmol) in cyclohexane (7 mL) was heated at 80 °C with until methanol and cyclohexane with continuous removal of solvent (vigreux column with Claisen head) until methanol and cyclohexane were no longer condensing in the collection vessel. After removal of methanol and some cyclohexane by distillation, the temperature was raised to 105 °C and the cyclohexane and most of the crotyl alcohol was removed. The crude product was purified by column chromatography, eluting with hexanes/EtOAc (15:1) to provide 0.35 g (53%) of **6.28** as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (dddt, *J* = 7.2, 5.8, 2.8, 1.4 Hz, 1 H), 4.64 (d, *J* = 7.2 Hz, 2 H), 2.75 (dd, *J* = 11.3, 0.6 Hz, 1 H), 2.64-2.53 (m, 1 H), 2.45-2.26 (m, 2 H), 2.22-2.15 (m, 1 H), 1.75 (s, 3 H), 1.70 (s, 3 H), 1.46 (dtd, *J* = 12.6, 11.2, 8.5, 1 H), 1.18 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 163.7, 133.0, 115.3, 66.1, 62.9, 46.8, 38.7, 31.7, 31.3, 20.2, 16.9; IR (NaCl, film) cm^{-1}; HRMS (CI) *m/z* 211.1255 [$C_{12}H_{19}O_3$ (M+H) requires 211.1256].

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (dddt, *J* = 7.2, 5.8, 2.8, 1.4 Hz, 1 H, C8-H), 4.64 (d, *J* = 7.2 Hz, 2 H, C7-H), 2.75 (d, *J* = 11.3 Hz, 1 H, C5-H),

2.64-2.53 (m, 1 H, C2-H_a), 2.45-2.26 (m, 2 H, C2-H_b and C4-H), 2.22-2.15 (m, 1 H, C3-H_a), 1.75 (s, 3 H, C10-H or C11-H), 1.70 (s, 3 H, C10-H or C11-H), 1.46 (dtd, *J* = 12.6, 11.2, 8.5, 1 H, C3-H_b), 1.18 (d, *J* = 6.5 Hz, 3 H, C12-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9 (C1), 163.7 (C6), 133.0 (C9), 115.3 (C8), 66.1 (C5), 62.9 (C7), 46.8 (C2), 38.7 (C4), 31.7 (C10 or C11), 31.3 (C10 or C11), 20.2 (C3), 16.9 (C12)

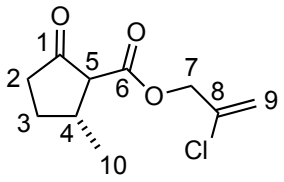


6.29

3-Methylbut-2-en-1-yl (1*R*,2*R*)-1-(2-ethoxy-2-oxoethyl)-2-methyl-5-oxocyclopentane-1-carboxylate (6.29). (JCH-V-074) A suspension of **6.28** (0.300 g, 1.43 mmol), ethyl bromoacetate (0.955 g, 5.72 mmol), and K_2CO_3 (0.394 g, 2.85 mmol) in acetone (9 mL) was heated at 55 °C for 12 h. The reaction was cooled to room temperature and partitioned between Et_2O (20 mL) and H_2O (10 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude product was purified by column chromatography, eluting with hexanes/EtOAc (12:1) on SiO_2 (70 mL) to provide 0.318 g (75%) of **6.29** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31-5.26 (m, 1 H), 4.64 (dd, *J* = 12.2, 7.2 Hz, 1 H), 4.50 (dd, *J* = 12.2, 7.2 Hz, 1 H), 4.12-4.04 (m, 2 H), 3.10 (d, *J* = 17.9 Hz, 1 H),

2.80 (d, J = 17.9 Hz, 1 H), 2.59-2.44 (m, 3 H), 2.13-2.06 (m, 1 H), 1.88-1.77 (m, 1 H), 1.74 (s, 3 H), 1.68 (s, 3 H) 1.23 (t, J = 7.2 Hz, 3 H), 1.01 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.5, 170.9, 169.6, 139.8, 117.9, 62.0, 60.73, 60.70, 39.2, 38.1, 35.9, 28.2, 25.7, 18.0, 15.3, 14.1; IR (NaCl, film) 2966, 2880, 1754, 1730, 1455, 1404, 1373, 1338, 1216, 1159, 1120, 1026 cm^{-1}; HRMS (CI) m/z 297.1699 [$C_{16}H_{26}O_5$ (M+1) requires 297.1702].

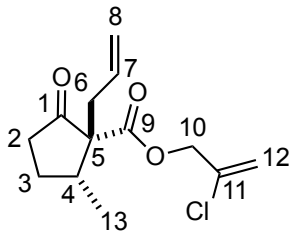
NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31-5.26 (m, 1 H, C12-H), 4.64 (dd, J = 12.2, 7.2 Hz, 1 H, C11-H_a), 4.50 (dd, J = 12.2, 7.2 Hz, 1 H, C11-H_b), 4.12-4.04 (m, 2 H, C8-H), 3.10 (d, J = 17.9 Hz, 1 H, C6-H_a), 2.80 (d, J = 17.9 Hz, 1 H, C6-H_b), 2.59-2.44 (m, 3 H, C2-H and C4-H), 2.13-2.06 (m, 1 H, C3-H_a), 1.88-1.77 (m, 1 H, C3-H_b), 1.74 (s, 3 H, C14-H or C15-H), 1.68 (s, 3 H, C14-H or C15-H) 1.23 (t, J = 7.2 Hz, 3 H, C9-H), 1.01 (d, J = 7.1 Hz, 3 H, C16-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.5 (C1), 170.9 (C10), 169.6 (C7), 139.8 (C13), 117.9 (C12), 62.0 (C5), 60.73 (C11), 60.70 (C8), 39.2 (C4), 38.1 (C6), 35.9 (C3), 28.2 (C14 or C15), 25.7 (C14 or C15), 18.0 (C2), 15.3 (C16), 14.1 (C9)



2-Chloroallyl (2*R*)-2-methyl-5-oxocyclopentane-1-carboxylate (unnumbered). (JCH-V-080) A solution of **6.24** (0.500 g, 3.20 mmol), DMAP (0.980 g, 0.800 mmol), and 2-chloro-2-propenol (2.96 g, 32.0 mmol) in cyclohexane (8 mL) was heated at 80 °C with continuous removal of solvent (vigreux column with Claisen head) until methanol and cyclohexane were no longer condensing in the collection vessel. After removal of methanol and some cyclohexane, the temperature was raised to 105 °C and the cyclohexane and most of the 2-chloro-2-propenol was removed by distillation. The crude reaction was purified by column chromatography, eluting with hexanes/EtOAc (12:1) on SiO_2 (140 mL) to provide 0.462 g (67%) of the title compound as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54-5.53 (m, 1 H), 5.41 (dt, *J* = 1.8, 0.8 Hz, 1 H), 4.77-4.68 (m, 2 H), 2.84 (d, *J* = 11.5 Hz, 1 H), 2.68-2.56 (m, 1 H), 2.48-2.29 (m, 2 H), 2.21 (dddd, *J* = 12.6, 8.4, 6.4, 2.0 Hz, 1 H), 1.50 (dtd, *J* = 12.6, 11.3, 8.5 Hz, 1 H), 1.21 (d, *J* = 6.4, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3, 168.3, 135.2, 114.9, 66.3, 62.9, 38.7, 36.5, 29.4, 19.2; IR (NaCl, film) 2961, 2875, 1757, 1733, 1639, 1458, 1404, 1381, 1331, 1284, 1227, 1187, 1125 cm^{-1}; HRMS (CI) *m/z* 217.0630 [$C_{10}H_{14}O_3Cl$ (M+1) requires 217.0631].

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54-5.53 (m, 1 H, C10-H_a), 5.41 (dt, *J* = 1.8, 0.8 Hz, 1 H, C10-H_b), 4.77-4.68 (m, 2 H, C7-H), 2.84 (d, *J* = 11.5 Hz, 1

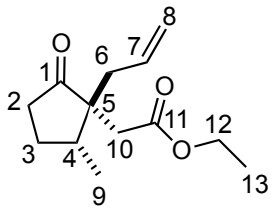
H, C5-H), 2.68-2.56 (m, 1 H, C2-H_a), 2.48-2.29 (m, 2 H, C2-H_b and C4-H), 2.21 (dddd, *J* = 12.6, 8.4, 6.4, 2.0 Hz, 1 H, C3-H_a), 1.50 (dtd, *J* = 12.6, 11.3, 8.5 Hz, 1 H, C3-H_b), 1.21 (d, *J* = 6.4, 3 H, C10-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3 (C1), 168.3 (C6), 135.2 (C8), 114.9 (C9), 66.3 (C7), 62.9 (C5), 38.7 (C2), 36.5 (C4), 29.4 (C3), 19.2 (C10).



6.45

2-Chloroallyl (1*R*,2*R*)-1-allyl-2-methyl-5-oxocyclopentane-1-carboxylate (6.45). (JCH-V-081) A suspension of 2-chloroallyl (2*R*)-2-methyl-5-oxocyclopentane-1-carboxylate (0.200 g, 0.923 mmol), allyl bromide (0.447 g, 3.69 mmol), and K_2CO_3 (0.255 g, 1.85 mmol) in acetone (6 mL) was heated at 55 °C for 12 h. The reaction was cooled to room temperature and partitioned between Et_2O (12 mL) and H_2O (6 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude product was purified by column chromatography eluting with hexanes/EtOAc (20:1) on SiO_2 (60 mL) to provide 0.170 g (72%) of **6.45** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67-5.57 (m, 1 H), 5.45-5.41 (m, 2 H), 5.14-5.09 (m, 2 H), 4.73-4.69 (m, 1 H), 4.63-4.59 (m, 1 H), 2.67 (ddt, *J* = 14.2, 6.3, 1.3 Hz, 1 H), 2.61-2.49 (m, 2 H), 2.41-2.31 (m, 1 H), 2.21-2.02 (m, 3 H), 1.94-1.83 (m, 1 H), 1.06 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.6, 169.7, 135.2, 132.8, 119.7, 116.2, 66.6, 62.9, 38.9, 38.7, 35.6, 28.1, 15.3; IR (NaCl, film) 3078, 2961, 1753, 1733, 1640, 1459, 1434, 1403, 1382, 1222, 1185, 1161, 1114 cm^{-1}; HRMS (CI) *m*/*z* 257.0867 [$C_{13}H_{18}O_3Cl$ (M+1) requires 257.0866].

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67-5.57 (m, 1 H, C7-H), 5.45-5.41 (m, 2 H, C12-H), 5.14-5.09 (m, 2 H, C8-H), 4.73-4.69 (m, 1 H, C10-H_a), 4.63-4.59 (m, 1 H, C10-H_b), 2.67 (ddt, *J* = 14.2, 6.3, 1.3 Hz, 1 H, C6-H_a), 2.61-2.49 (m, 2 H, C6-H_b and C2-H_a), 2.41-2.31 (m, 1 H, C2-H_b), 2.21-2.02 (m, 2 H, C4-H and C3-H_a), 1.94-1.83 (m, 1 H, C3-H_b), 1.06 (d, *J* = 6.9 Hz, 3 H, C13-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.6 (C1), 169.7 (C9), 135.2 (C11), 132.8 (C7), 119.7 (C12), 116.2 (C8), 66.6 (C10), 62.9 (C5), 38.9 (C6), 38.7 (C2), 35.6 (C4), 28.1 (C3), 15.3 (C13).



6.5

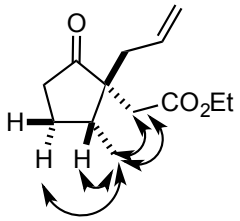
Ethyl 2-((1*R*,2*R*)-1-allyl-2-methyl-5-oxocyclopentyl)acetate (6.5). (JCH-V-249) Ligand **6.59** (0.323 g, 0.542 mmol) was dissolved in THF (55 mL) and Pd_2pmdba_3 (0.232 g, 0.210 mmol) was added. The reaction was stirred for 0.5 h, and the color progressed from dark red/purple to red/orange. A solution of β-keto ester **6.27** (1.13 g, 4.23 mmol) in THF (3 mL) was added, whereupon the solution turned green, and the reaction was stirred for 12 h. Upon completion of the reaction, the solvent was removed under reduced pressure to provide crude **6.5** as a mixture (10:1) of diastereomers. The crude reaction mixture was purified via flash column chromatography eluting with hexanes/EtOAc (4:1) on SiO_2 (100 mL) to provide 0.800 g (84%) of **6.5** as a colorless to pale yellow oil: ^{1}H

NMR (500 MHz, $CDCl_3$): δ 5.69-5.61 (m, 1 H), 5.10-5.03 (comp, 2 H), 4.13-4.04 (m, 2 H), 2.46-2.39 (comp, 3 H), 2.35-2.29 (m, 2 H), 2.23-2.15 (comp, 2 H), 2.10-2.03 (m, 1 H), 1.63-1.58 (m, 1 H), 1.24 (t, J = 7.3 Hz, 3 H), 1.00 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 220.9, 171.6, 133.2, 118.9, 60.5, 52.6, 41.0, 38.2, 37.3, 36.9, 27.5, 15.7, 14.1; IR (film, NaCl) 2961, 1731, 1639, 1463, 1443, 1407, 1372, 1325, 1288, 1201, 1170 cm^{-1}; HRMS (CI) m/z 225.1492 [$C_{13}H_{21}O_3$ (M+1) requires 225.1491].

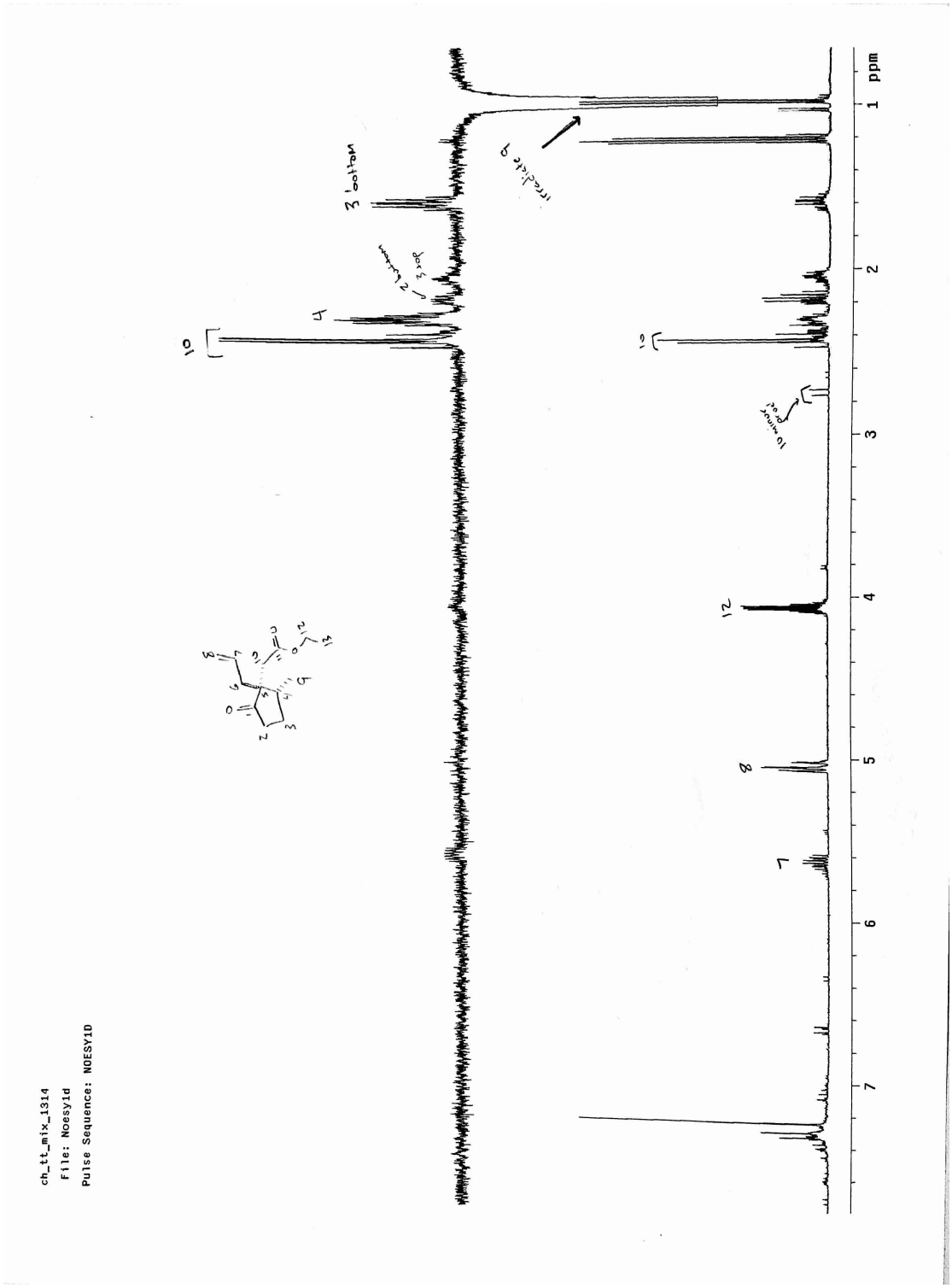
NMR Assignments: ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.69-5.61 (m, 1 H, C7-H), 5.10-5.03 (comp, 2 H, C8-H), 4.13-4.04 (m, 2 H, C12-H), 2.46-2.39 (comp, 3 H, C10-H and C6-H_a), 2.35-2.29 (m, 2 H, C6-H_a and C4-H), 2.23-2.15 (comp, 2 H, C2-H_b and C6-H_b), 2.10-2.03 (m, 1 H, C3-$H_{top\ face}$), 1.63-1.58 (m, 1 H, C3-$H_{bottom\ face}$), 1.24 (t, J = 7.3 Hz, 3 H, C13-H), 1.00 (d, J = 7.1 Hz, 3 H, C9-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 220.9 (C1), 171.6 (C11), 133.2 (C7), 118.9 (C8), 60.5 (C12), 52.6 (C5), 41.0 (C2, C6, or C10), 38.2 (C4), 37.3 (C2, C6, or C10), 36.9 (C2, C6, or C10), 27.5 (C3), 15.7 (C9), 14.1 (C13)

NOE Correlations:

Spectra on following page as a mixture (4:1) of diastereomers favoring **6.5**.



6.5
NOE between both protons of the ester and methyl
No NOE between allylic protons or vinyl protons and methyl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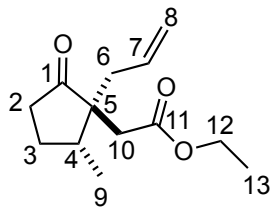
4
3 protons
2 protons
1 proton
9
12
8
7
10 protons
1 ppm



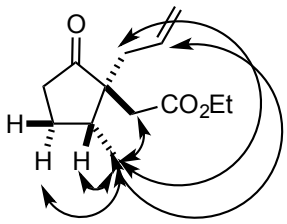
***epi*-6.5**

Ethyl 2-((1*S*,2*R*)-1-allyl-2-methyl-5-oxocyclopentyl)acetate (*epi*-6.5). (JCH-V-249). Product is the minor diastereomer from the above reaction: ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.75-5.65 (m, 1 H), 5.09-5.02 (comp, 2 H), 4.11-4.03 (m, 2 H), 2.76 (d, *J* = 16.8 Hz, 1 H), 2.47-2.30 (comp, 4 H), 2.22-2.01 (comp, 3 H), 1.63-1.54 (m, 1 H), 1.22 (t, *J* = 7.2 Hz, 3 H), 1.05 (d, *J* = 6.9 Hz, 3 H); ^{13}C (125 MHz, $CDCl_3$) 220.4, 171.5, 133.1, 118.7, 60.4, 52.1, 40.9, 38.14, 38.10, 35.1 27.2, 14.2, 14.1.

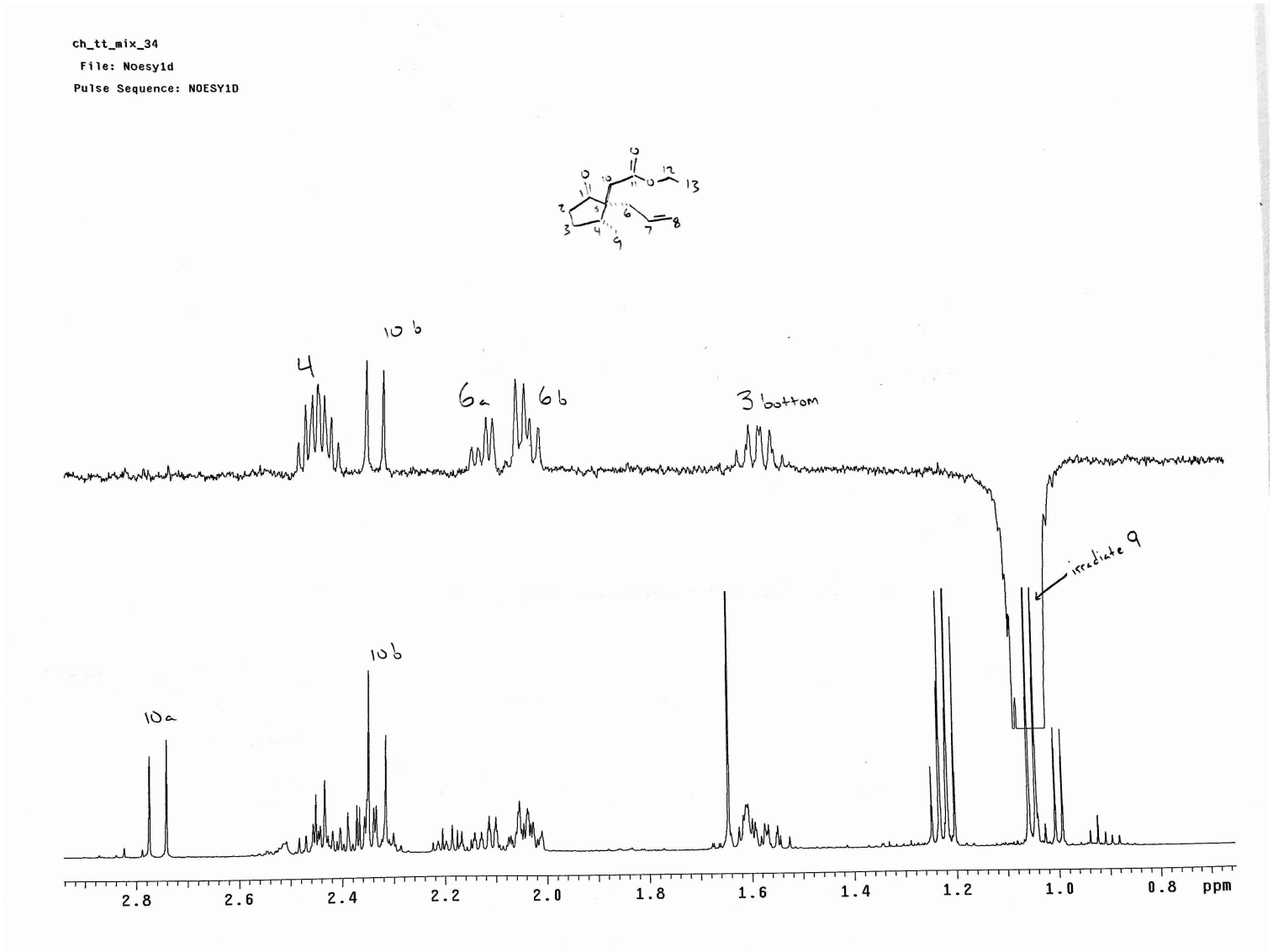
NMR Assignments: ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.75-5.65 (m, 1 H, C7-H), 5.09-5.02 (comp, 2 H, C8-H), 4.11-4.03 (m, 2 H, C12-H), 2.76 (d, *J* = 16.8 Hz, 1 H, C10-H_a), 2.47-2.30 (comp, 4 H, C4-H, C2-H, C10-H_b), 2.22-2.01 (comp, 3 H, C3-$H_{top\ face}$, C6-H), 1.63-1.54 (m, 1 H, C3-$H_{bottom\ face}$), 1.22 (t, *J* = 7.2 Hz, 3 H, C13-H), 1.05 (d, *J* = 6.9 Hz, 3 H, C9-H); ^{13}C (125 MHz, $CDCl_3$) 220.4 (C5), 171.5 (C11), 133.1 (C7), 118.7 (C8), 60.4 (C12), 52.1 (C5), 40.9 (C2), 38.14 (C10), 38.10 (C3), 35.1 (C6), 27.2 (C3), 14.2 (C9), 14.1 (C13).

NOE Correlations:

Spectra on following page as a mixture (3:1) of diastereomers favoring ***epi*-6.5**.



epi-**6.5**
NOE between both allylic protons and methyl
NOE between one vinyl proton and methyl
NOE between one ester proton and methyl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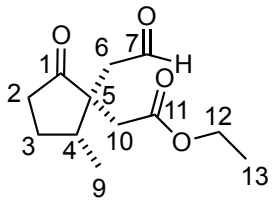
4
10b
6a
6b
3 bottom
irradiate 9
10a
10b
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
ppm

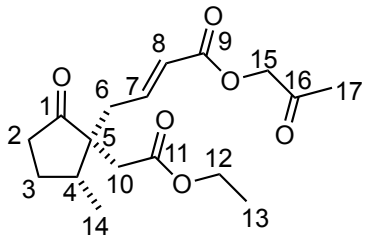


6.4

Ethyl 2-((2*R*)-2-methyl-5-oxo-1-(2-oxoethyl)cyclopentyl)acetate (6.4). (JCH-VI-137/138) Potassium osmate (VI) dihydrate (0.008 g, 0.022 mmol) was added to a solution of **6.5** (0.100 g, 0.446 mmol) and NMO (0.083 g, 0.714 mmol) in mixture (5:2) of THF/H_2O (1.3 mL). The reaction was stirred at room temperature for 15 h, whereupon saturated aqueous sodium thiosulfate (1.3 mL) was added. The mixture was extracted with EtOAc (3 x 2 mL), and the combined organic layers were washed with brine (1 x 5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude diol was dissolved in a mixture (2:1) of THF/H_2O (3.4 mL), and cooled to 0 °C, whereupon sodium periodate (0.229 g, 1.07 mmol) was added. The cooling bath was removed, and the reaction was stirred at room temperature for 1 h. The reaction was filtered through celite, washing with EtOAc (6 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with brine (1 x 8 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified via flash column chromatography eluting with CH_2Cl_2/Et_2O (20:1) to provide 0.80 g (80%) of aldehyde **6.4** as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.61 (t, *J* = 1.1 Hz, 1 H), 4.08 (q, *J* = 7.2 Hz, 2 H), 3.00 (dd, *J* = 0.9, 18.2 Hz, 1 H), 2.78 (dd, *J* = 1.5, 18.2 Hz, 1 H), 2.53-2.31 (comp, 5 H), 2.11-2.06 (m, 1 H), 1.61-1.54 (m, 1 H), 1.22 (t, *J* = 7.2 Hz, 3 H), 0.99 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ

219.7, 199.67, 170.8, 60.9, 50.6, 48.7, 38,5, 36.7, 36.4, 27.6, 14.64, 14.03; IR (film, NaCl) 2925, 2854, 2360, 1732, 1458, 1364, 1183, 1096, 1037 cm^{-1}; HRMS (ESI) *m/z* 249.1098 [$C_{12}H_{18}O_4$ (M+Na) requires 249.1097].

NMR Assignments: ^1H NMR (600 MHz, $CDCl_3$) δ 9.61 (t, *J* = 1.1 Hz, 1 H, C7-H), 4.08 (q, *J* = 7.2 Hz, 2 H, C12-H), 3.00 (dd, *J* = 0.9, 18.2 Hz, 1 H, C6-H_a), 2.78 (dd, *J* = 1.5, 18.2 Hz, 1 H, C6-H_b), 2.53-2.31 (comp, 5 H, C2-H, C4-H, C10-H), 2.11-2.06 (m, 1 H, C3-H_a), 1.61-1.54 (m, 1 H, C3-H_b), 1.22 (t, *J* = 7.2 Hz, 3 H, C13-H), 0.99 (d, *J* = 7.0 Hz, 3 H, C9-H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 219.7 (C1), 199.67 (C7), 170.8 (C11), 60.9 (C12), 50.6 (C5), 48.7 (C6), 38.5 (C10), 36.7 (C2), 36.4 (C4), 27.6 (C3), 14.64 (C9), 14.03 (C13)

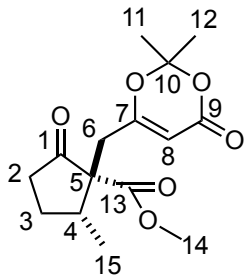


6.76

2-oxopropyl-(*E*)-4-((2*R*)-1-(2-ethoxy-2-oxoethyl)-2-methyl-5-oxocyclopentyl)but-2-enoate (6.76). (JCH-V-260) Hoveyda-Grubbs catalyst 2nd generation (0.005 g, 0.008 mmol) was added to a solution of 2-oxopropyl acrylate (**6.75**) [396] (0.020 g, 0.134 mmol) and **6.5** (0.015 g, 0.067 mmol) in CH_2Cl_2 (0.2 mL). The reaction was stirred for 12 h at 40 °C in a sealed vial, whereupon the reaction was concentrated under reduced pressure. The crude pruduct was purified via flash column chromatography, eluting with hexanes/EtOAc (2:1) on SiO_2 (10 mL) to provide 0.19 g (85%) of **6.76** as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.87 (ddd, *J* = 15.6, 8.3, 7.5 Hz, 1 H), 5.78 (dt, *J* = 15.6, 1.3 Hz, 1 H), 4.67 (s, 2 H), 4.11-4.04 (m, 2 H), 2.53-2.49 (m, 1 H), 2.47-2.38 (comp, 4 H), 2.23-2.17 (comp, 2 H), 2.15 (s, 3 H), 2.08-2.04 (m, 1 H), 1.62-1.59 (m, 1 H), 1.22 (t, *J* = 7.1 Hz, 3 H), 0.99 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.8, 201.7, 171.1, 164.9, 145,5, 123.7, 68.0, 60.8, 52.8, 38.73, 38.70, 36.9, 36.7, 27.4, 26.1 15.4, 14.0; IR (NaCl, film) 2963, 1729, 1654, 1419, 1372, 1276, 1159 cm^{-1}; HRMS (ESI) *m/z* 347.1472 [$C_{17}H_{24}O_6$ (M+Na) requires 347.1465].

NMR Assignments: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.87 (ddd, *J* = 15.6, 8.3, 7.5 Hz, 1 H, C7-H), 5.78 (dt, *J* = 15.6, 1.3 Hz, 1 H, C8-H), 4.67 (s, 2 H, C15-H), 4.11-4.04

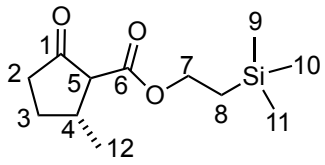
(m, 2 H, C12-H), 2.53-2.49 (m, 1 H, C6-H_a), 2.47-2.38 (comp, 4 H, C10-H, C6-H_b, C2-H_a), 2.23-2.17 (comp, 2 H, C6-H_b, C4-H), 2.15 (s, 3 H, C17-H), 2.08-2.04 (m, 1 H, C3-H_a), 1.62-1.59 (m, 1 H, C3-H_b), 1.22 (t, J = 7.1 Hz, 3 H, C13-H), 0.99 (d, J = 7.0 Hz, 3 H, C14-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.8(C1), 201.7 (C16), 171.1 (C11), 164.9 (C9), 145.5 (C7), 123.7 (C8), 68.0 (C15), 60.8 (C12), 52.8 (C5), 38.73 (C2 or C4), 38.70 (C6), 36.9 (C10), 36.7 (C2 or C4), 27.4 (C3), 26.1 (C17), 15.4 (C14), 14.0 (C13)



Methyl (1*R*,2*R*)-1-((2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)methyl)-2-methyl-5-oxocyclopentane-1-carboxylate. (JCH-VI-149) A suspension of **6.24** (0.300 g, 3.20 mmol), **6.16** (0.848 g, 34.80 mmol), sodium iodide (0.720, 4.80 mmol) and K_2CO_3 (0.885 g, 6.40 mmol) in acetone (16 mL) was heated at 55 °C for 12 h. The reaction was cooled to room temperature and partitioned between Et_2O (30 mL) and H_2O (15 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude product was purified by column chromatography eluting with hexanes/EtOAc (1.5:1) on SiO_2 (100 mL) to provide 0.300 g (30%) of the title compound as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (s, 1 H), 3.71 (s, 3 H), 3.02 (d, *J* = 15.1 Hz, 1 H), 2.76 (d, *J* = 15.1 Hz, 1 H), 2.62-2.55 (m, 1 H), 2.32-2.17 (comp, 2 H), 2.12-2.04 (m, 1 H), 1.88-1.77 (m, 1 H), 1.63 (s, 6 H), 1.03 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ213.6, 169.7, 167.3, 160.5, 106.7, 96.3, 61.7, 52.4, 38.9, 38.1, 34.9, 27.9, 25.4, 24.6, 15.4; IR (NaCl, film) 3100, 2959, 1729, 1633, 1461, 1433, 1391, 1273, 1273, 1230, 1170, 1122, 1013 cm^{-1}; HRMS (ESI) *m*/*z* 319.1162 [$C_{15}H_{20}O_6$ (M+Na) requires 319.1152].

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (s, 1 H, C8-H), 3.71 (s, 3 H, C14-H), 3.02 (d, *J* = 15.1 Hz, 1 H, C6-H_a), 2.76 (d, *J* = 15.1 Hz, 1 H, C6-H_b), 2.62-

2.55 (m, 1 H, C2-H_a), 2.32-2.17 (comp, 2 H, C2-H_b and C4-H), 2.12-2.04 (m, 1 H, C3-H_a), 1.88-1.77 (m, 1 H, C3-H_b), 1.63 (s, 6 H, C11-H and C12-H), 1.03 (d, J = 6.8 Hz, 3 H, C15-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ213.6 (C1), 169.7, 167.3, 160.5, 106.7, 96.3, 61.7, 52.4, 38.9, 38.1, 34.9, 27.9, 25.4, 24.6, 15.4 (C15)

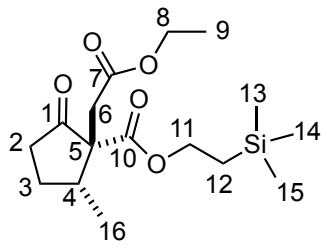


6.116

2-(Trimethylsilyl)ethyl (2*R*)-2-methyl-5-oxocyclopentane-1-carboxylate (6.116). (JCH-VI-175) A solution of **6.47** (0.953 g, 3.20 mmol), DMAP (0.186 g, 1.52 mmol), and 2-chloro-2-propenol (2.89 g, 24.4 mmol) in cyclohexane (8 mL) was with continuous removal of solvent (vigreux column with Claisen head) until methanol and cyclohexane were no longer condensing in the collection vessel. After removal of methanol and some cyclohexane, the temperature was raised to 105 °C and the cyclohexane and most of the alcohol was removed by distillation. The crude product was purified by column chromatography, eluting with hexanes/EtOAc (12:1) on SiO_2 (150 mL) to provide 1.20 g (81%) of **6.116** as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (t, J = 8.4 Hz, 2 H), 2.68 (d, J = 11.2 Hz, 1 H), 2.61-2.51 (m, 1 H), 2.41-2.22 (m, 2 H), 2.19-2.11 (m, 1 H), 1.49-1.38 (m, 1 H), 1.15-1.14 (m, 3 H), 1.01-0.96 (m, 2 H), -0.01 (bs, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 169.3, 63.6, 38.7, 36.4, 29.3, 19.2, 17.3,

14.1, -1.6; IR (NaCl, film) 2956, 2900, 1754, 1728, 1458, 1407, 1381, 1331, 1293, 1250, 1129, 1153 cm^{-1}; HRMS (ESI) *m/z* 265.1234 [$C_{12}H_{22}O_3Si$ (M+Na) requires 254.1230].

NMR Assignments: ^1H NMR (400 MHz, $CDCl_3$) δ 4.19 (t, *J* = 8.4 Hz, 2 H, C7-H), 2.68 (d, *J* = 11.2 Hz, 1 H, C5-H), 2.61-2.51 (m, 1 H, C4-H), 2.41-2.22 (m, 2 H, C2-H), 2.19-2.11 (m, 1 H, C3-H_a), 1.49-1.38 (m, 1 H, C3-H_b), 1.15-1.14 (m, 3 H, C12-H), 1.01-0.96 (m, 2 H, C8-H), -0.01 (bs, 9 H, C8-H, C9-H, and C10-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9 (C1), 169.3 (C6), 63.6 (C7), 38.7 (C5), 36.4 (C4), 29.3 (C2), 19.2 (C3), 17.3 (C12), 14.1 (C8), -1.6 (C8, C9, and C10).

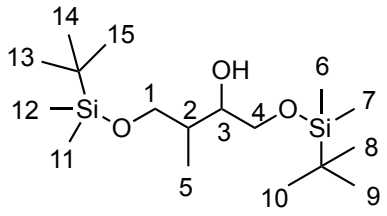


6.110

2-(Trimethylsilyl)ethyl (1*R*,2*R*)-1-(2-ethoxy-2-oxoethyl)-2-methyl-5-oxocyclopentane-1-carboxylate (6.110). (JCH-VI-176) A suspension of **6.116** (1.00 g, 4.13 mmol), ethyl bromoacetate (1.03 g, 6.20 mmol), and K_2CO_3 (1.14 g, 8.26 mmol) in acetone (20 mL) was heated at 55 °C for 12 h. The reaction was cooled to room temperature and partitioned between Et_2O (40 mL) and H_2O (20 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated under

reduced pressure. The resulting crude product was purified by column chromatography eluting with hexanes/EtOAc (20:1) on SiO_2 (100 mL) to provide 0.544 g (40%) of **6.110** as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16-4.03 (comp, 4 H), 3.07 (d, *J* = 17.8 Hz, 1 H), 2.78 (d, *J* = 17.8 Hz, 1 H), 2.61-2.45 (m, 3 H), 2.12-2.04 (m, 1 H), 1.88-1.77 (m, 1 H), 1.21 (t, *J* = 7.2 Hz, 3 H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.98-0.93 (m, 2 H), 0.0 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.5, 169.8, 167.2, 63.7, 62.3, 60.7, 39.1, 38.1, 35.9, 28.2, 25.9, 17.5, 15.4, 14.1, 13.9, -1.7; IR (NaCl, film) cm^{-1}; HRMS (ESI) *m/z* 351.1600 [$C_{16}H_{28}O_5Si$ (M+Na) requires 351.1598].

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16-4.03 (comp, 4 H, C8-H and C11-H), 3.07 (d, *J* = 17.8 Hz, 1 H, C6-H_a), 2.78 (d, *J* = 17.8 Hz, 1 H, C6-H_b), 2.61-2.45 (m, 3 H, C2-H and C4-H), 2.12-2.04 (m, 1 H, C3-H_a), 1.88-1.77 (m, 1 H, C3-H_b), 1.21 (t, *J* = 7.2 Hz, 3 H, C9-H), 1.01 (d, *J* = 6.9 Hz, 3H, C16-H), 0.98-0.93 (m, 2 H, C12-H), 0.0 (s, 9 H, C13-H, C14-H, and C15-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.5 (C1), 169.8 (C7), 167.2 (C10), 63.7 (C5), 39.1 (C8), 38.1 (C11), 35.9 (C7), 28.2 (C2), 25.9 (C4), 17.5 (C3), 15.4 (C16), 14.1 (C9), 13.9 (C12), -1.7 (C13, C14, and C15)

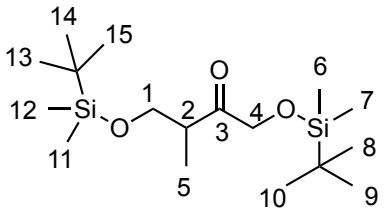


6.124

2,2,3,3,7,10,10,11,11-Nonamethyl-4,9-dioxa-3,10-disiladodecan-6-ol (6.124). (JCH-VI-184) Methylmagnesium bromide (3 mL, 3 M) and copper iodide (0.914 g, 4.8 mmol) in Et_2O (12 mL) was stirred at 0 °C for 30 min. The reaction was cooled to –78 °C, whereupon a solution of epoxide **6.123**[397] (1.00 g, 3.00 mmol) in Et_2O (4 mL) was added dropwise. The reaction was warmed to 0 °C and stirring continued for 3 h. Saturated NH_4Cl (5 mL) was added, and the cooling bath was removed. Upon reaching room temperature, the septum was removed, and the solution was stirred until a homogeneous blue solution was obtained. . The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified via column chromatography eluting with hexanes/EtOAc (20:1) on SiO_2 (100 mL) to provide 0.645 g (65%) of **6.124** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (ddd, J = 6.5, 4.8, 1.9 Hz, 1 H), 4.02 (dd, J = 5.6, 3.0 Hz, 2 H), 3.64 (dd, J = 9.9, 6.0 Hz, 1 H), 3.47 (dd, J = 9.9, 6.9 Hz, 1 H), 3.17-3.11 (m, 1 H), 2.72 (d, J = 4.7 Hz, 1 H), 0.91 (s, 9 H), 0.89 (s, 10 H), 0.87 (d, J = 8.1 Hz, 3 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 71.3, 67.6, 67.0, 40.6, 31.6, 25.8, 25.7, 22.6, 18.2,

14.1, -5.3, -5.4, -5.5; IR (NaCl, film) 3393, 2954, 2930, 2885, 2858, 1471, 1256, 1102, 1102 cm^{-1}; HRMS (ESI) *m/z* 371.2412 [$C_{17}H_{40}O_3Si_2$ (M+Na) requires 371.2408].

NMR Assignments: ^1H NMR (400 MHz, $CDCl_3$) δ 4.37 (ddd, *J* = 6.5, 4.8, 1.9 Hz, 1 H), 4.02 (dd, *J* = 5.6, 3.0 Hz, 2 H), 3.64 (dd, *J* = 9.9, 6.0 Hz, 1 H), 3.47 (dd, *J* = 9.9, 6.9 Hz, 1 H), 3.17-3.11 (m, 1 H), 2.72 (d, *J* = 4.7 Hz, 1 H), 0.91 (s, 9 H), 0.89 (s, 10 H), 0.87 (d, *J* = 8.1 Hz, 3 H), 0.10 (s, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 71.3, 67.6, 67.0, 40.6, 31.6, 25.8, 25.7, 22.6, 18.2, 14.1, -5.3, -5.4, -5.5



6.125

2,2,3,3,7,10,10,11,11-Nonamethyl-4,9-dioxa-3,10-disiladodecan-6-one (6.125). (JCH-VI-185). Dess-Martin periodinane (0.584 g, 1.38 mmol) and **6.124** (0.400 g, 1.15 mmol) in CH_2Cl_2 (25 mL) was stirred 15 h. The reaction was concentrated under reduced pressure and purified via column chromatography, eluting with hexanes/Et_2O (15:1) on SiO_2 (40 mL) to provide 0.380 g (90%) of **6.125** as a colorless oil: ^{1}H (400 MHz, $CDCl_3$) δ 4.80 (dd, *J* = 5.6, 8.9 Hz, 1 H), 4.48 (d, *J* = 17.6 Hz, 1 H), 4.27 (d, *J* = 18.6 Hz, 1 H), 4.06 (dd, *J* = 9.1, 10.4 Hz, 1 H), 3.83 (dd, *J* = 5.6, 10.4 Hz, 1 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 0.92 (s, 9 H), 0.85 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H), 0.06 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 204.3, 66.7, 64.4, 34.6, 34.5, 31.5, 25.7, 25.6, 22.6, 14.1, -5.42, -5.44, -5.5, -5.6; IR (NaCl, film) 2929, 1748, 1732, 1716, 1698, 11683, 1656, 1638, 1540, 1456 cm^{-1}; HRMS (ESI) *m/z* 369.2249 [$C_{17}H_{38}O_3Si_2$ (M+Na) requires 369.2252].

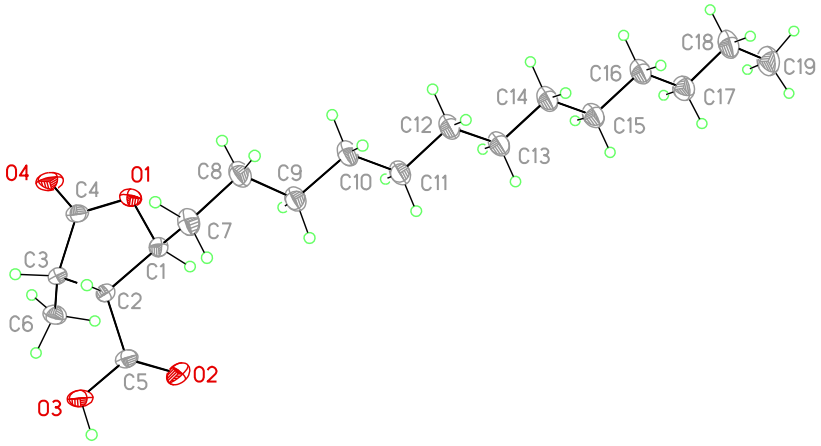
NMR Assignments: ^{1}H (400 MHz, $CDCl_3$) δ 4.80 (dd, *J* = 5.6, 8.9 Hz, 1 H, C2-H), 4.48 (d, *J* = 18.0 Hz, 1 H, C4-H_a), 4.27 (d, *J* = 18.0 Hz, 1 H, C4-H_b), 4.06 (dd, *J* = 9.1, 10.4 Hz, 1 H, C1-H_a), 3.83 (dd, *J* = 5.6, 10.4 Hz, 1 H, C1-H_b), 0.95 (d, *J* = 6.9 Hz, 3 H, C5-H), 0.92 (s, 9 H, C8-H, C9-H, and C10-H or C13-H, C14-H, and C15-H), 0.85 (s, 9 H, C8-H, C9-H, and C10-H or C13-H, C14-H, and C15-H), 0.11 (s, 3 H, C6-H, C7-H, C11-H, or C12-H), 0.09 (s, 3 H, C6-H, C7-H, C11-H, or C12-H), 0.06 (s, 3 H, C6-H, C7-

H, C11-H, or C12-H), 0.04 (s, 3 H, C6-H, C7-H, C11-H, or C12-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 204.3 (C3), 66.7 (C4), 64.4 (C1), 34.6, 34.5, 31.5, 25.7 (C8, C9, and C10 or C11, C12, and C13), 25.6 (C8, C9, and C10 or C11, C12, and C13), 22.6, 14.1 (C5), -5.42 (C6, C7, C8, or C9) , -5.44 (C6, C7, C8, or C9) , -5.5 (C6, C7, C8, or C9) , -5.6 (C6, C7, C8, or C9)

7.3 CRYSTALLOGRAPHIC DATA

Figure 7.2 Crystal structure of **2.61** showing the atom labeling scheme.

Displacement ellipsoids are scaled to the 50% probability level.



X-ray Experimental for $C_{19}H_{34}O_4$: Crystals grew as large, colorless laths by vapor diffusion of hexanes into an ethyl acetate solution containing the target molecule. The data crystal was cut from a larger crystal and had approximate dimensions; 0.61 x 0.33 x 0.15 mm. The data were collected on a Rigaku SCX-Mini diffractometer with a

Mercury CCD using a graphite monochromator with MoKa radiation (l = 0.71075Å). A total of 1440 frames of data were collected using w-scans with a scan range of 0.5° and a counting time of 20 seconds per frame. The data were collected at 153 K using a Rigaku XStream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using the Rigaku Americas Corporation's Crystal Clear version 1.40.[398] The structure was solved by direct methods using SIR97[399] and refined by full-matrix least-squares on F2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[400] Structure analysis was aided by use of the programs PLATON98[401] and WinGX.[402] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The hydrogen atom on O3 was observed in a ΔF map and refined with an isotropic displacement parameter. The absolute configuration was determined by internal comparison to the known configuration of the starting material. The function, Σw(|Fo|2 - |Fc|2)2, was minimized, where w = 1/[(s(Fo))2 + (0.0562*P)2 + (0.0427*P)] and P = (|Fo|2 + 2|Fc|2)/3. Rw(F2) refined to 0.0836, with R(F) equal to 0.0296 and a goodness of fit, S, = 1.02. Definitions used for calculating R(F), Rw(F2) and the goodness of fit, S, are given below.[403] The data were checked for secondary extinction effects but no correction was necessary. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[404] All figures were generated using SHELXTL/PC.[405] Tables of positional and thermal parameters, bond lengths and angles, torsion angles and figures are found in the proceeding sections.

Table 7.1 Crystal data and structure refinement for **2.61**.

Empirical formula	C19 H34 O4	
Formula weight	326.46	
Temperature	153(2) K	
Wavelength	0.71075 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 5.491(2) Å	α= 98.701(8)°.
	b = 5.543(2) Å	β= 95.642(9)°.
	c = 16.171(6) Å	γ = 90.291(8)°.
Volume	484.1(3) Å3	
Z	1	
Density (calculated)	1.120 Mg/m3	
Absorption coefficient	0.076 mm-1	
F(000)	180	
Crystal size	0.61 x 0.33 x 0.15 mm	
Theta range for data collection	3.72 to 27.49°.	
Index ranges	-7<=h<=7, -7<=k<=7, -20<=l<=20	
Reflections collected	6769	
Independent reflections	2196 [R(int) = 0.0267]	
Completeness to theta = 27.49°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00 and 0.783	

Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	2196 / 3 / 214
Goodness-of-fit on F2	1.017
Final R indices [I>2sigma(I)]	R1 = 0.0296, wR2 = 0.0832
R indices (all data)	R1 = 0.0300, wR2 = 0.0836
Absolute structure parameter	n/a
Largest diff. peak and hole	0.273 and -0.157 e.Å-3

Table 7.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2x10^3$) for **2.61**.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C1	1752(2)	3631(2)	5640(1)	20(1)
C2	-266(2)	3928(2)	6241(1)	19(1)
C3	948(3)	3225(2)	7072(1)	20(1)
C4	3159(3)	1832(2)	6785(1)	23(1)
C5	-1353(2)	6441(2)	6327(1)	22(1)
C6	1762(3)	5306(3)	7785(1)	27(1)
C7	827(3)	2497(3)	4753(1)	28(1)
C8	2777(3)	2066(3)	4137(1)	32(1)
C9	4021(3)	4366(3)	3950(1)	28(1)
C10	5518(3)	3787(3)	3195(1)	29(1)
C11	6941(3)	5955(3)	2993(1)	30(1)
C12	8368(3)	5263(3)	2230(1)	31(1)
C13	9864(3)	7356(3)	2014(1)	31(1)
C14	11240(3)	6641(3)	1240(1)	31(1)
C15	12776(3)	8719(3)	1030(1)	32(1)
C16	14152(3)	8013(3)	257(1)	32(1)
C17	15703(3)	10087(3)	49(1)	34(1)
C18	17156(4)	9344(3)	-703(1)	38(1)

C19	18703(4)	11407(4)	-906(1)	45(1)
O1	3520(2)	2001(2)	5995(1)	24(1)
O2	-678(2)	8086(2)	5993(1)	38(1)
O3	-3165(2)	6604(2)	6811(1)	34(1)
O4	4521(2)	685(2)	7213(1)	33(1)

Table 7.3 Bond lengths [Å] and angles [°] for **2.61**.

C1-O1	1.4643(16)	C8-H8B	0.99
C1-C7	1.5147(19)	C9-C10	1.534(2)
C1-C2	1.5375(18)	C9-H9A	0.99
C1-H1	1.00	C9-H9B	0.99
C2-C5	1.5107(18)	C10-C11	1.524(2)
C2-C3	1.5446(18)	C10-H10A	0.99
C2-H2	1.00	C10-H10B	0.99
C3-C4	1.5159(19)	C11-C12	1.528(2)
C3-C6	1.5328(19)	C11-H11A	0.99
C3-H3	1.00	C11-H11B	0.99
C4-O4	1.2162(18)	C12-C13	1.520(2)
C4-O1	1.3288(17)	C12-H12A	0.99
C5-O2	1.2017(18)	C12-H12B	0.99
C5-O3	1.3210(18)	C13-C14	1.527(2)
C6-H6A	0.98	C13-H13A	0.99
C6-H6B	0.98	C13-H13B	0.99
C6-H6C	0.98	C14-C15	1.523(2)
C7-C8	1.528(2)	C14-H14A	0.99
C7-H7A	0.99	C14-H14B	0.99
C7-H7B	0.99	C15-C16	1.525(2)
C8-C9	1.526(2)	C15-H15A	0.99
C8-H8A	0.99	C15-H15B	0.99

C16-C17	1.525(2)	C1-C2-H2	108.2
C16-H16A	0.99	C3-C2-H2	108.2
C16-H16B	0.99	C4-C3-C6	109.91(12)
C17-C18	1.524(2)	C4-C3-C2	102.10(10)
C17-H17A	0.99	C6-C3-C2	117.51(11)
C17-H17B	0.99	C4-C3-H3	109.0
C18-C19	1.515(2)	C6-C3-H3	109.0
C18-H18A	0.99	C2-C3-H3	109.0
C18-H18B	0.99	O4-C4-O1	121.64(13)
C19-H19A	0.98	O4-C4-C3	125.53(13)
C19-H19B	0.98	O1-C4-C3	112.82(12)
C19-H19C	0.98	O2-C5-O3	123.95(13)
O3-H3O	0.83(3)	O2-C5-C2	124.66(13)
O1-C1-C7	109.02(11)	O3-C5-C2	111.39(11)
O1-C1-C2	105.08(10)	C3-C6-H6A	109.5
C7-C1-C2	113.23(11)	C3-C6-H6B	109.5
O1-C1-H1	109.8	H6A-C6-H6B	109.5
C7-C1-H1	109.8	C3-C6-H6C	109.5
C2-C1-H1	109.8	H6A-C6-H6C	109.5
C5-C2-C1	112.73(10)	H6B-C6-H6C	109.5
C5-C2-C3	114.46(11)	C1-C7-C8	115.41(13)
C1-C2-C3	104.79(11)	C1-C7-H7A	108.4
C5-C2-H2	108.2	C8-C7-H7A	108.4

C1-C7-H7B	108.4	C12-C11-H11A	109.2
C8-C7-H7B	108.4	C10-C11-H11B	109.2
H7A-C7-H7B	107.5	C12-C11-H11B	109.2
C9-C8-C7	115.41(13)	H11A-C11-H11B	107.9
C9-C8-H8A	108.4	C13-C12-C11	114.12(13)
C7-C8-H8A	108.4	C13-C12-H12A	108.7
C9-C8-H8B	108.4	C11-C12-H12A	108.7
C7-C8-H8B	108.4	C13-C12-H12B	108.7
H8A-C8-H8B	107.5	C11-C12-H12B	108.7
C8-C9-C10	111.12(12)	H12A-C12-H12B	107.6
C8-C9-H9A	109.4	C12-C13-C14	113.36(13)
C10-C9-H9A	109.4	C12-C13-H13A	108.9
C8-C9-H9B	109.4	C14-C13-H13A	108.9
C10-C9-H9B	109.4	C12-C13-H13B	108.9
H9A-C9-H9B	108.0	C14-C13-H13B	108.9
C11-C10-C9	114.76(13)	H13A-C13-H13B	107.7
C11-C10-H10A	108.6	C15-C14-C13	113.60(13)
C9-C10-H10A	108.6	C15-C14-H14A	108.8
C11-C10-H10B	108.6	C13-C14-H14A	108.8
C9-C10-H10B	108.6	C15-C14-H14B	108.8
H10A-C10-H10B	107.6	C13-C14-H14B	108.8
C10-C11-C12	112.13(13)	H14A-C14-H14B	107.7
C10-C11-H11A	109.2	C14-C15-C16	113.74(13)

C14-C15-H15A	108.8	H17A-C17-H17B	107.7
C16-C15-H15A	108.8	C19-C18-C17	113.46(16)
C14-C15-H15B	108.8	C19-C18-H18A	108.9
C16-C15-H15B	108.8	C17-C18-H18A	108.9
H15A-C15-H15B	107.7	C19-C18-H18B	108.9
C17-C16-C15	113.80(14)	C17-C18-H18B	108.9
C17-C16-H16A	108.8	H18A-C18-H18B	107.7
C15-C16-H16A	108.8	C18-C19-H19A	109.5
C17-C16-H16B	108.8	C18-C19-H19B	109.5
C15-C16-H16B	108.8	H19A-C19-H19B	109.5
H16A-C16-H16B	107.7	C18-C19-H19C	109.5
C18-C17-C16	113.60(14)	H19A-C19-H19C	109.5
C18-C17-H17A	108.8	H19B-C19-H19C	109.5
C16-C17-H17A	108.8	C4-O1-C1	110.94(10)
C18-C17-H17B	108.8	C5-O3-H3O	111.3(17)
C16-C17-H17B	108.8		

Table 7.4 Anisotropic displacement parameters ($Å^2x10^3$) for **2.61**

The anisotropic displacement factor exponent takes the form: -2p2[h2 a*2U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
C1	20(1)	19(1)	23(1)	6(1)	5(1)	2(1)
C2	20(1)	15(1)	23(1)	5(1)	5(1)	2(1)
C3	24(1)	17(1)	22(1)	6(1)	6(1)	6(1)
C4	25(1)	18(1)	26(1)	1(1)	4(1)	5(1)
C5	19(1)	17(1)	28(1)	4(1)	2(1)	3(1)
C6	32(1)	26(1)	24(1)	0(1)	6(1)	7(1)
C7	30(1)	32(1)	23(1)	3(1)	4(1)	-5(1)
C8	41(1)	31(1)	23(1)	0(1)	11(1)	-3(1)
C9	32(1)	31(1)	22(1)	3(1)	7(1)	0(1)
C10	34(1)	34(1)	20(1)	3(1)	7(1)	-1(1)
C11	33(1)	33(1)	24(1)	4(1)	9(1)	0(1)
C12	35(1)	34(1)	24(1)	3(1)	10(1)	-2(1)
C13	35(1)	34(1)	26(1)	2(1)	10(1)	-2(1)
C14	36(1)	33(1)	25(1)	2(1)	10(1)	-4(1)
C15	35(1)	33(1)	28(1)	3(1)	10(1)	-4(1)
C16	37(1)	34(1)	26(1)	3(1)	9(1)	-4(1)
C17	37(1)	33(1)	32(1)	6(1)	9(1)	-3(1)

C18	47(1)	42(1)	27(1)	5(1)	10(1)	-10(1)
C19	52(1)	47(1)	40(1)	12(1)	15(1)	-9(1)
O1	23(1)	24(1)	26(1)	4(1)	7(1)	8(1)
O2	47(1)	21(1)	53(1)	16(1)	20(1)	8(1)
O3	32(1)	20(1)	55(1)	10(1)	20(1)	12(1)
O4	39(1)	29(1)	32(1)	5(1)	2(1)	18(1)

Table 7.5 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x10^3) for **2.61**.

	x	y	z	U(eq)
H1	2553	5251	5633	24
H2	-1604	2707	6014	23
H3	-177	2087	7284	24
H6A	2829	4663	8219	41
H6B	320	6027	8030	41
H6C	2657	6557	7562	41
H7A	-430	3569	4529	34
H7B	16	912	4775	34
H8A	4050	1020	4366	38
H8B	2009	1152	3600	38
H9A	5112	5096	4450	34
H9B	2763	5574	3831	34
H10A	6688	2492	3305	35
H10B	4393	3127	2694	35
H11A	8095	6607	3486	35
H11B	5785	7261	2882	35
H12A	9484	3923	2338	37
H12B	7200	4636	1737	37

H13A	11058	7963	2501	37
H13B	8756	8709	1914	37
H14A	12325	5268	1336	37
H14B	10042	6060	751	37
H15A	13975	9299	1518	38
H15B	11691	10093	934	38
H16A	15229	6632	351	38
H16B	12953	7442	-233	38
H17A	14618	11441	-69	41
H17B	16857	10704	546	41
H18A	18238	7986	-586	46
H18B	16003	8733	-1201	46
H19A	17635	12702	-1069	67
H19B	19662	10791	-1370	67
H19C	19811	12062	-409	67
H3O	-3740(50)	7990(50)	6866(15)	44(6)

Table 7.6 Torsion angles [°] for **2.61**.

O1-C1-C2-C5	145.72(11)
C7-C1-C2-C5	-95.39(14)
O1-C1-C2-C3	20.63(12)
C7-C1-C2-C3	139.52(12)
C5-C2-C3-C4	-142.04(11)
C1-C2-C3-C4	-18.04(12)
C5-C2-C3-C6	-21.76(16)
C1-C2-C3-C6	102.24(13)
C6-C3-C4-O4	63.28(18)
C2-C3-C4-O4	-171.27(13)
C6-C3-C4-O1	-115.80(13)
C2-C3-C4-O1	9.66(15)
C1-C2-C5-O2	-2.7(2)
C3-C2-C5-O2	116.90(17)
C1-C2-C5-O3	176.74(12)
C3-C2-C5-O3	-63.62(15)
O1-C1-C7-C8	-61.11(16)
C2-C1-C7-C8	-177.69(12)
C1-C7-C8-C9	-64.70(19)
C7-C8-C9-C10	-167.78(13)
C8-C9-C10-C11	-176.76(13)
C9-C10-C11-C12	-179.38(13)

C10-C11-C12-C13	-178.76(13)
C11-C12-C13-C14	-178.95(14)
C12-C13-C14-C15	-179.02(14)
C13-C14-C15-C16	-179.95(13)
C14-C15-C16-C17	-179.64(14)
C15-C16-C17-C18	177.63(15)
C16-C17-C18-C19	-179.78(16)
O4-C4-O1-C1	-175.49(13)
C3-C4-O1-C1	3.63(15)
C7-C1-O1-C4	-137.17(12)
C2-C1-O1-C4	-15.50(14

Table 7.7 Hydrogen bonds for **2.61** [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O3-H3O...O4#1	0.83(3)	1.82(3)	2.6270(18)	163(2)

Symmetry transformations used to generate equivalent atoms:

#1 x-1,y+1,z

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$R(F) = \sum(|F_o| - |F_c|)/\sum|F_o|\}$ for reflections with $F_o > 4(\sum(F_o))$.

$S = [\sum w(|F_o|^2 - |F_c|^2)^2/(n - p)]^{1/2}$, where n is the number of reflections and p is the number of refined parameters.

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Vita

John Caleb Hethcox was born on April 2, 1998 to Scott and Deb Hethcox in Montgomery, Alabama. He graduated co-valedictorian from Prattville High School in 2006. He graduated cum laude with a B.A. in chemistry from Auburn University in 2006. While at Auburn, he discovered his love for chemistry research while working under the direction of Professor Michael Squillacote on the synthesis and characterization of photodegradable polymers. He then entered graduate school at The University of Texas at Austin to continue studying organic chemistry under the supervision of Professor Stephen F. Martin with a focus on methodology development and natural product synthesis. In January 2016, he will move to Pasadena, where he has accepted a postdoctoral research position with Professor Brian Stoltz at Caltech.

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