Title
Exploring Three Membered Rings: Synthesis, Opening, Rearrangements and Progress Towards the Synthesis of Morphine

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Exploring Three Membered Rings: Synthesis, Opening, Rearrangements and Progress Towards the Synthesis of Morphine

A dissertation submitted in partial satisfaction of the
requirements for the degree of Doctor of Philosophy
in Chemistry

by

Daniel Lui Sun

2016

ABSTRACT OF THE DISSERTATION

Exploring Three Membered Rings: Synthesis, Opening, Rearrangements

and

Progress Towards the Synthesis of Morphine

by

Daniel Lui Sun
Doctor of Philosophy in Chemistry
University of California, Los Angeles
2016

Professor Michael E. Jung, Chair

Potential strategies toward the synthesis of rifampicin were investigated. Previous studies in the laboratory of Yamamoto described the rearrangement of terminal epoxy alcohols to yield silyl protected aldol products. The stereospecific synthesis of aldol products begin with the Horner-Wadsworth-Emmons olefination of an aldehyde followed by DIBAL reduction. The allylic alcohol was subjected to a Sharpless asymmetric epoxidation reaction. The epoxyalcohol was subjected to a Payne rearrangement followed by trapping with an aryl selenide. Using our

developed methodology, we were able to synthesize a library of aryl selenyl diols. The addition of Meerwein salt to aryl selenides followed by base mediated cyclization provided epoxides for the Yamamoto rearrangement. The Yamamoto rearrangement provided aldol products in modest yield and may be used in the future for the synthesis of rifampicin.

Chapter 2

Progress towards the synthesis of morphine is described via cyclopropyl ketone based intermediates. From simple lactones we were able to easily synthesize the starting material, aroyloxy arylketones in two to four steps. The ketones were then subjected to either Tsuji-Trost π-allyl chemistry followed base mediated cyclopropanation or simple base-mediated cyclopropanation, the former providing better yields. Upon addition of base, the starting aroyloxy arylketones exchange their aryl groups and generally provide two different cyclopropyl aryl ketones.

The dissertation of Daniel Lui Sun is approved.

Anna Wu Work

Neil Kamal Garg

Michael E. Jung, Committee Chair

University of California, Los Angeles

2016

In memory of my loving mother,

who always believed in me.

Yu Juei Sun

(November 19, 1954 – August 13, 2001)

FOREVER LOVED

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Vita

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PUBLICATIONS AND PRESENTATIONS

Jung, M. E.; Sun, D. L. "Trapping of Payne rearrangement intermediates with arylselenide anions" *Tetrahedron Lett.* **2015,** *56,* 3082-3085.

Jung, M. E.; Sun, D. L.; Dwight. T. A.; Yu. P.; Li, W.; Houk. K. N. "Synthesis of 2-Ethenylcyclopropyl Aryl Ketones Via Intramolecular SN2-like Displacement of an Ester" *Manuscript in preparation.*

"Trapping of Payne Rearrangement Intermediates with Arylselenide Anions" (Poster) Sun, D. L.; Jung, M. E. 250th ACS Fall National Meeting, **2015**, Boston, MA, USA.

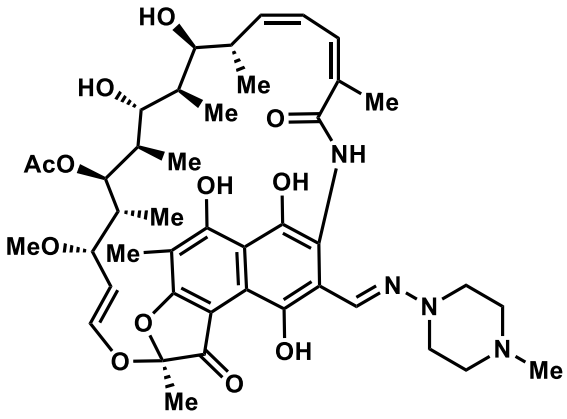
"Base Mediated Cyclopropanation Reactions of Ketone Enolates" (Poster) Sun, D. L.; Dwight. T. A.; Jung, M. E. 252th ACS Fall National Meeting, **2016**, Philadelphia, PA, USA.

Chapter 1

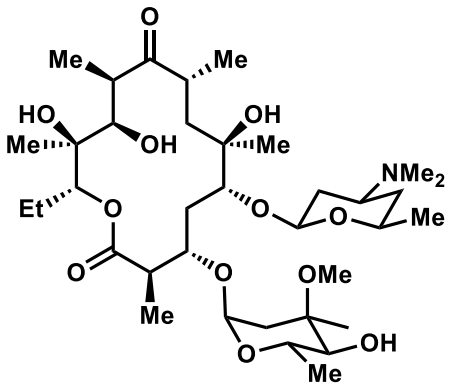
Exploring Three Membered Rings: Synthesis, Opening, Rearrangements

Introduction

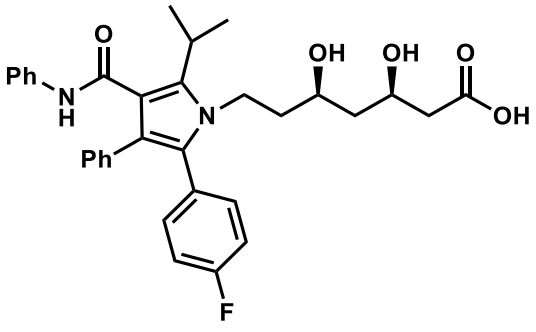
Polyketides are ubiquitous components of natural products and commercially available drugs. These structural motifs play an important role as pharmacophores in numerous antibiotics, statins, and therapeutics.[1] Despite being studied since near the birth of organic chemistry, polyketides have been a long-standing synthetic challenge due to a diverse number of possible stereoisomers. Antibiotic-resistant bacteria have become more prevalent in recent years, and the development of new effective antibiotics has been an object of interest to the scientific community.[2]



Rifampicin, 1
(antibiotic)



Erythromycin, 2
(antibiotic)



Lipitor, 3
(statin)

Scheme 1. Prominent polyketide-derived drugs.

Rifampicin (Rif) **1** (Scheme 1) is an antibiotic used as a first line drug for the treatment of tuberculosis. Rif is currently on the World Health Organization's List of Essential Medicines which highlights the importance of this effective tuberculosis (TB) drug.[3] The first production of Rif as a drug was in 1959 and then in 1971 Rif became widely used as a medication.[4] The antibacterial properties of Rif allow the drug to treat multiple diseases such as those caused by mycobacterium and gram-positive bacteria. Rif is a potent bactericidal drug which requires a dose of approximately 0.01-2.0 μg/ml (50% effective dose). Bacterial RNA polymerase is inactivated by Rif for many bacterial organisms including Mycobacterium tuberculosis, M. leprae, staphylococci, streptococci, and pneumococci. The bactericidal properties of Rif are attributed to its ability to form a stable enzyme-drug complex with bacterial RNA polymerase. The stable enzyme-drug complex impedes the initiation of bacterial RNA chain formation. Mammalian RNA is unlike bacterial RNA and is unaffected at low Rif concentrations.[5]

According to the CDC a total of 9.6 million new cases of TB were reported along with 1.5 million deaths in 2014 worldwide.[6] Four-fifths of the worlds' active TB cases are reportedly in 22 low-income and middle-income countries. Most cases of active TB lie in sub-Saharan Africa, eastern Europe, and Asia disproportionally compared to the rest of the world. The top five countries with the most TB incidence include India, China, South Africa, Nigeria, and Indonesia in 2009. The likelihood of acquiring a TB infection increases significantly on external immunosuppressive factors such as alcoholism, smoking, and other diseases. Individuals infected with HIV are 20 times more likely to contract a TB infection than people not infected with HIV. HIV-related tuberculosis has fueled the revival of TB into new strains of more robust and virulent forms of the mycobacterium.[7]

Deadly forms of TB such as multidrug-resistant tuberculosis (MDR TB) and extensively drug-resistant tuberculosis (XDR TB) are forms of TB resistant to current drug regimens. MDR TB is a form of TB resistant to two of the first-line TB drugs, isoniazid (INH) and rifampicin (RMP), regularly used in TB treatment. XDR TB is a more advanced form of MDR TB and is resistant to the most powerful first-line and second-line drugs used for TB.[6]

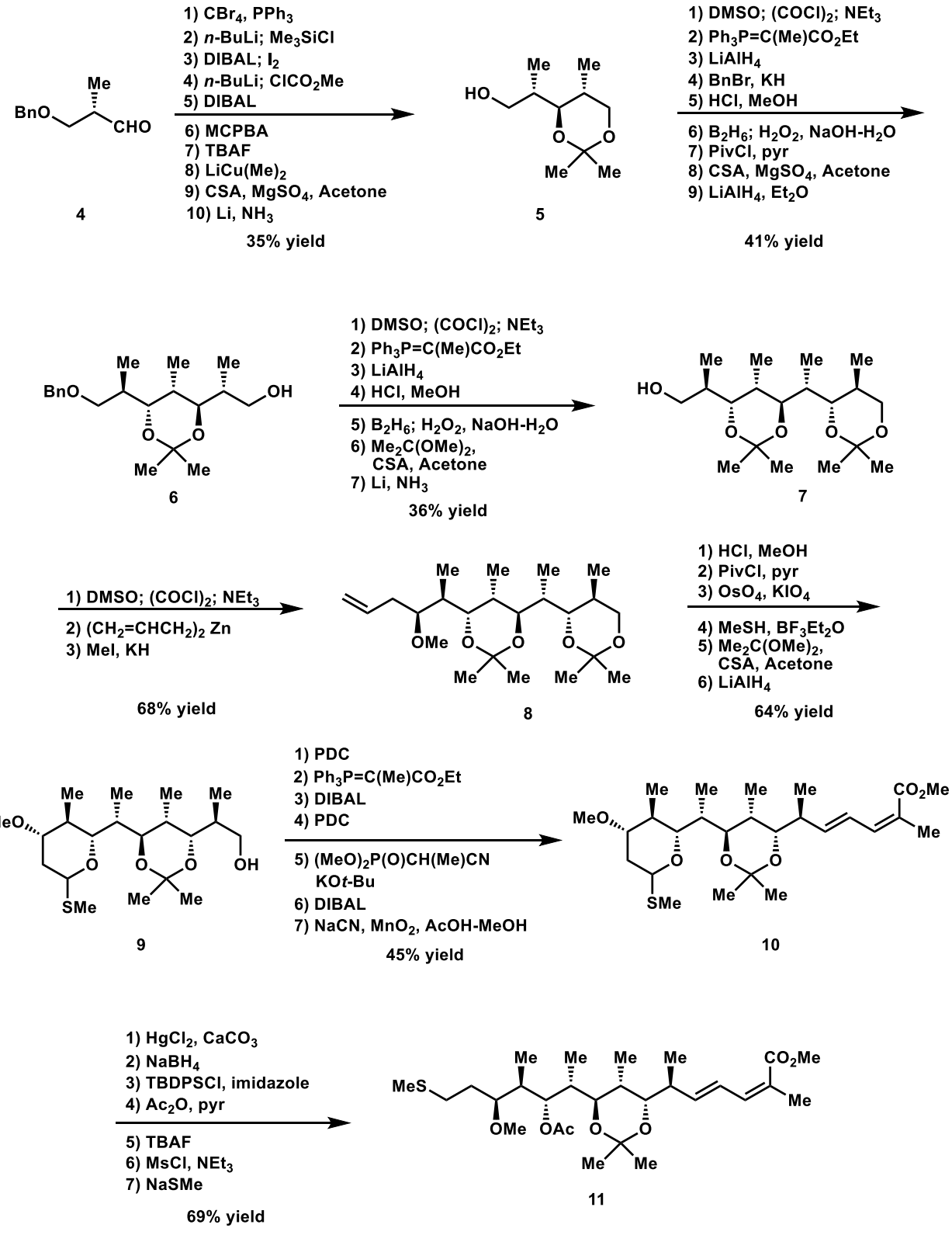
TB is inherently a deadly disease based on its resistance to drugs and its mode of infection. TB is an intracellular pathogen that thrives in areas with high oxygen content such as the lungs of its hosts. TB is an acid-fast bacterium with a capacity to evade therapeutic drugs due to several reasons, one being its ability to shelter itself inside host cells. Another reason is that TB carries a difficult to penetrate physically thick lipid-rich mycolic acid cell wall.[7]

Kishi Rifamycin S Polyketide Synthesis

Structurally Rif is a complex molecule consisting of a polyketide backbone containing eight contiguous stereogenic centers and a heavily substituted fused phenyl benzofuranone heterocyclic core. The rifamycin series show structural similarity to rifampicin and many of its members show activity against tuberculosis. The first commercial synthesis of rifampicin relied on starting from the natural product intermediate rifamycin S. A number of rifamycin S total syntheses have been accomplished but one of the first and most notable linear syntheses was accomplished by Kishi (Scheme 2).[8] The chiral aldehyde **4** was subjected to the Appel reaction forming a vinyl dibromide. Next lithiation and silylation formed a vinyl trimethylsilane which was then iodinated with DIBAL and iodide. Lithiation followed with esterification by methyl chloroformate produced a methyl ester intermediate for DIBAL reduction. Epoxidation of the allylic alcohol with mCPBA and silyl deprotection allowed for a chelation controlled methyl cuprate addition. Diol protection and debenzylation afforded the acetonide **5** in 35% yield over

10 steps. Formation of the benzyl ether **6** was accomplished through Swern oxidation, Wittig olefination, $LiAlH_4$ reduction, benzyl protection, acetonide deprotection, hydroboration-oxidation, pivaloylation, acetonide protection, and finally $LiAlH_4$ deprotection of the pivaloyl group. The 9 step sequence to synthesize the 5 contiguous stereocenters of benzyl ether **6** from acetonide **5** was accomplished in 41% yield. The next sequence mirrored the previous set of reactions up to the acetonide step, with the exception that the benzylation and pivaloylation step were removed. The debenzylation in the final step of the sequence produced the diacetonide **7** in 36% yield over 7 steps. Swern oxidation, zinc chelation controlled allyl addition, and methylation afforded the desired allylic methyl ether **8**. Methyl ether **8** was cyclized to pyran **9** through deprotection, pivaloylation, oxidative cleavage, thiolation, acetonide protection, and $LiAlH_4$ reduction in 64% yield over 6 steps. The following sequence strategy with pyran **9** involved a PDC oxidation, Wittig olefination, DIBAL reduction, reoxidation with PDC, Horner-Wadsworth-Emmons (HWE) olefination; DIBAL reduction, and esterification to give the diene **10** in 45% yield over 7 steps. The synthesis was completed with the dethiolation of diene **10**, $NaBH_4$ reduction, silyl protection, acetylation, silyl deprotection, mesylation, and finally rethiolation to form the polyketide **11** in 69% yield for the last 7 steps. The overall yield for the 49 step sequence to synthesize the polyketide **11** from the aldehyde **4** was 0.7% yield.

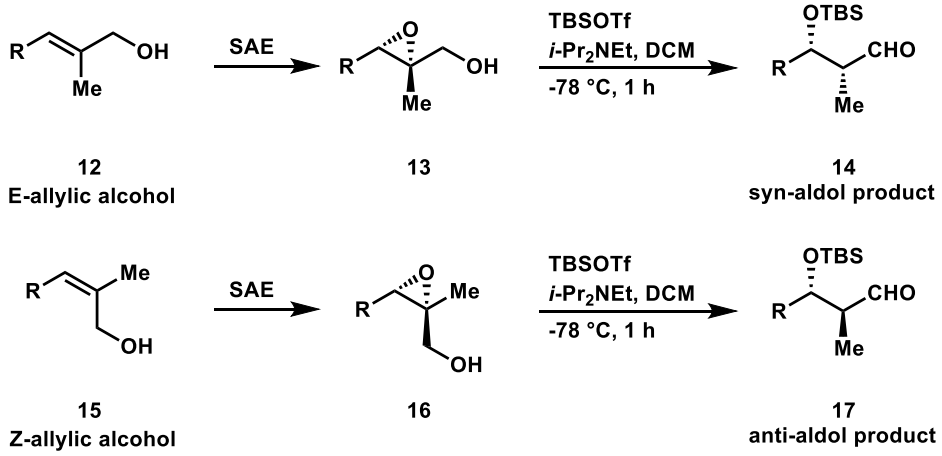
In the early 80's the Kishi synthesis was a respectable model to follow, starting from fairly easy to attain chiral starting material to furnish stereoselectively the polyketide **11**. The Kishi synthesis has several disadvantages, the major one being the fact that the synthesis is low yielding and produces 28 carbons in 49 steps just for the polyketide backbone. We envisioned a more efficient synthesis using modern non-aldol aldol chemistry and epoxide rearrangements to



Scheme 2. Kishi synthesis of rifamycin S polyketide backbone.

accomplish the same feat. Although the synthesis would not reduce the step count considerably, the synthesis would be new and use novel chemistry.

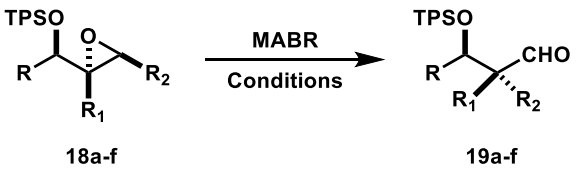
Previously our lab discovered the Jung non-aldol aldol reaction as a method to synthesize polyketides stereospecifically (Scheme 3).[9] The sequence started with the synthesis of an E-allylic alcohol **12**; subsequently a Sharpless asymmetric epoxidation forms the optically active trans-epoxy alcohol **13**. The conversion of the epoxy alcohol **13** to the silyl protected aldol product **14** is mediated through the addition of TBSOTf and Hunig's base. The same sequence of TBSOTf and Hunig's base could be duplicated starting from the Z-allylic alcohol **15** to synthesize the anti-aldol product **17**. Unfortunately, one of the shortcomings of the non-aldol aldol reaction was the ability to synthesize sterically hindered anti-aldol products. To overcome this synthetic challenge, we proposed a new but longer synthetic route.

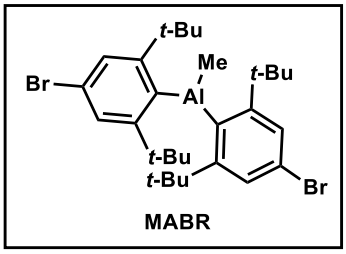


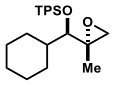
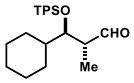
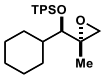
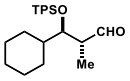
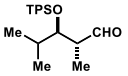
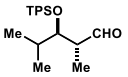
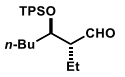
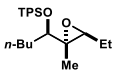
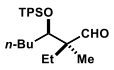
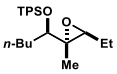
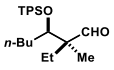
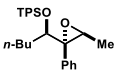
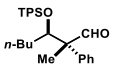
Scheme 3. The Jung non-aldol aldol reaction.

Yamamoto and coworkers have reported a Lewis acid assisted S_N2-type epoxide rearrangement of triphenylsilyl protected epoxy alcohols to give the corresponding polyketides (Table 1).[10] The Lewis acid Yamamoto and coworkers discovered, methylaluminum bis(4-bromo-2,6-

Table 1. The Yamamoto epoxide rearrangement.



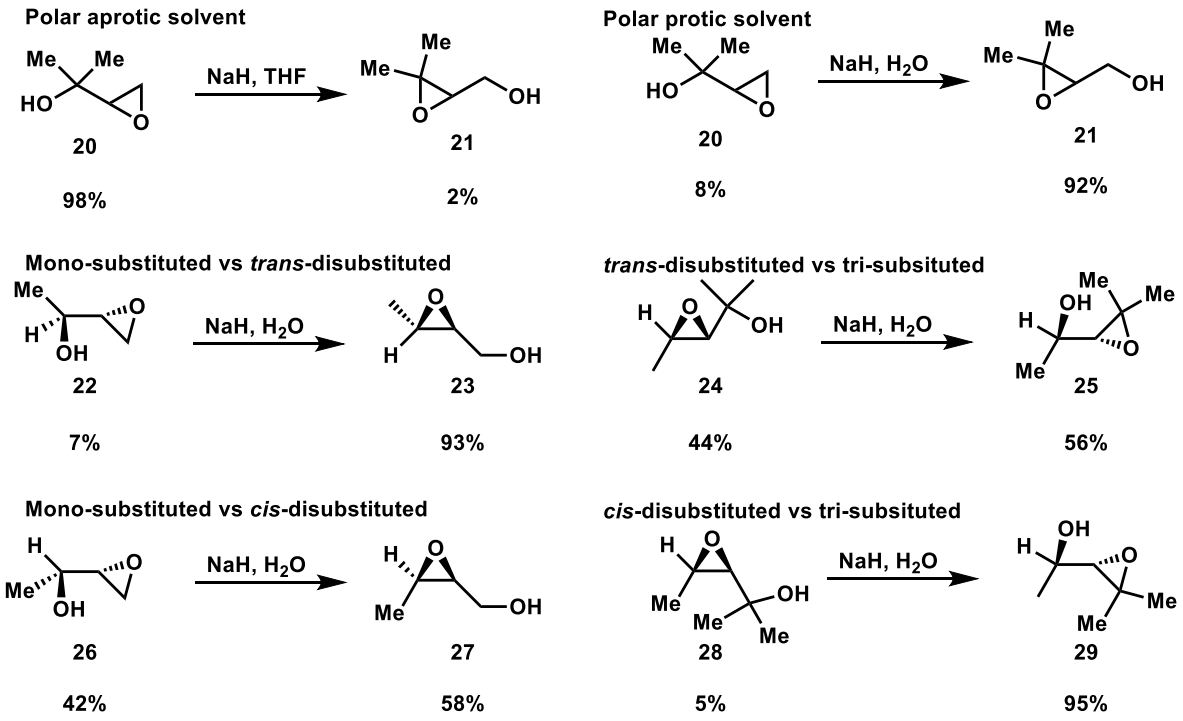


Entry	Substrate	Conditions	Major isomer	Yield % (erythro/threo)
1	 18a	dichloromethane, –78 °C, 1 h; –40 °C, 1.5 h	 19a	92 % (1:6)
2	 18a	PhMe, –78 °C, 1 h; –40 °C, 2 h	 19a	88 % (1:100)
3	 18b	dichloromethane, –78 °C, 1 h; –40 °C, 0.5 h	 19b	86 % (1:6)
4	 18b	PhMe, –78 °C, 2 h; –20 °C, 2 h	 19b	82 % (1:30)
5	 18c	dichloromethane, –40 °C, 2 h; –20 °C, 0.5 h	 19c	67 % (1:100)
6	 18d	dichloromethane, –40 °C, 2 h; –20 °C, 2 h	 19d	47 % (4:1)
7	 18d	PhMe, –40 °C, 2 h; –20 °C, 2 h	 19d	64 % (200:1)
8	 18e	dichloromethane, –78 °C, 0.5 h	 19e	83 % (0:1)
9	 18f	PhMe, –40 °C, 2 h; –20 °C, 2 h	 19f	85 % (1:0)

di-*tert*-butylphenoxide) (MABR) is a sterically hindered Lewis acid with the propensity to force a syn hydride or alkyl migration of an epoxy silyl ether to yield a silyl protected aldol product. The stereoselective reaction mainly produces the S_N2 rearranged silyl protected aldol product, but in some cases an S_N1 rearrangement can also occur to produce the other diastereomer. The solvent effect in entries 2 and 4, compared to entries 1 and 3, indicates the necessity for an aryl non-polar solvent to produce the desired threo (anti-aldol) product for a secondary R group. Although lower yielding, entry 5 retains stereoinversion to afford almost exclusively the threo product. Exemplifying that erythro products could also be obtained in this case by a syn ethyl shift, entries 6 and 7 yield the desired erythro quaternary centers. Both entries 8 and 9 produce exclusively the desired stereoinverted products through an alkyl shift.

The Payne rearrangement (Scheme 4) is a complex reaction that relies on a number of factors such as solvent, nucleophile, mixing time, and temperature.[11] Payne explains his rearrangement as the equilibrium between epoxy alcohols to favor the thermodynamic product under basic conditions. Under polar aprotic solvents such as THF, the epoxy alcohol **20** converts to the epoxy alcohol **21** in poor conversion which illustrated the need for a different solvent system. When the solvent is changed to a polar protic solvent, such as water, the epoxy alcohol **20** is converted to the epoxy alcohol **21** in excellent yield. Payne also demonstrated how both the Thorpe-Ingold effect and Zaitsev's rule (most substituted epoxide) can predict the most stable epoxy alcohol. When comparing the mono-substituted epoxy alcohol **22** vs the *trans*-epoxy alcohol **23**, the *trans*-epoxy alcohol **23** is much more thermodynamically favored as a 93:7 mixture. The equilibrium between the *trans*-epoxy alcohol **24** and tri-substituted epoxy alcohol **25** only slightly favors the more substituted epoxide, presumably due to strain relief as the *trans*-epoxy alcohol **24**. Comparing the mono-substituted epoxy alcohol **26** and the hindered *cis*-epoxy

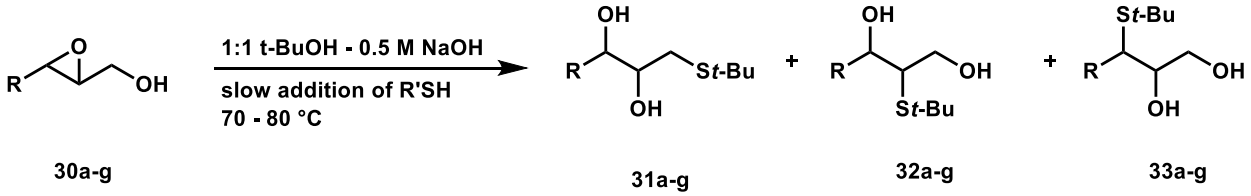
alcohol **27**, the equilibrium still shifts towards the more substituted epoxy alcohol **27**, but less so when compared to the equilibrium between the epoxy alcohols **22** and **23**. Lastly when comparing the very hindered *cis*-epoxy alcohol **28** with the trisubsituted epoxy alcohol **29**, the trisubsituted epoxy alcohol is much more thermodynamically favored.[11]

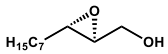
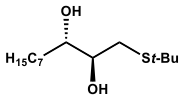
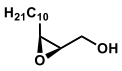
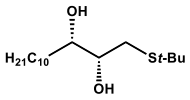
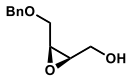
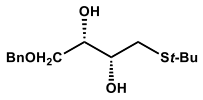
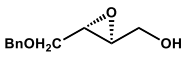
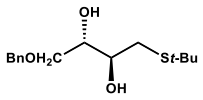
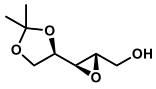
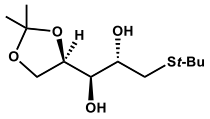
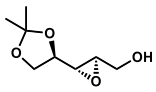
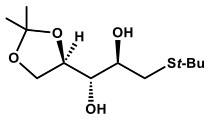
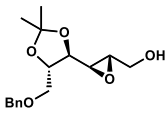
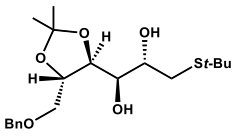


Scheme 4. The Payne rearrangement.

Sharpless and coworkers have extensively studied the reactivity of chiral epoxy alcohols under Payne rearrangement conditions. In one of the most significant studies, Sharpless probed the addition of sodium *t*-butylthiolate to 2,3-epoxy alcohols to access the latent C1 position (Table 2).[12] The regioselectivity for the simple trans alkyl substrate **30a** was poor with only a 1.4:1 selectivity for **31a** vs. the other regioisomers. The cis alkyl substrate **30b** performed very poorly, giving low yields and a mixture of regioisomers likely due to reduced

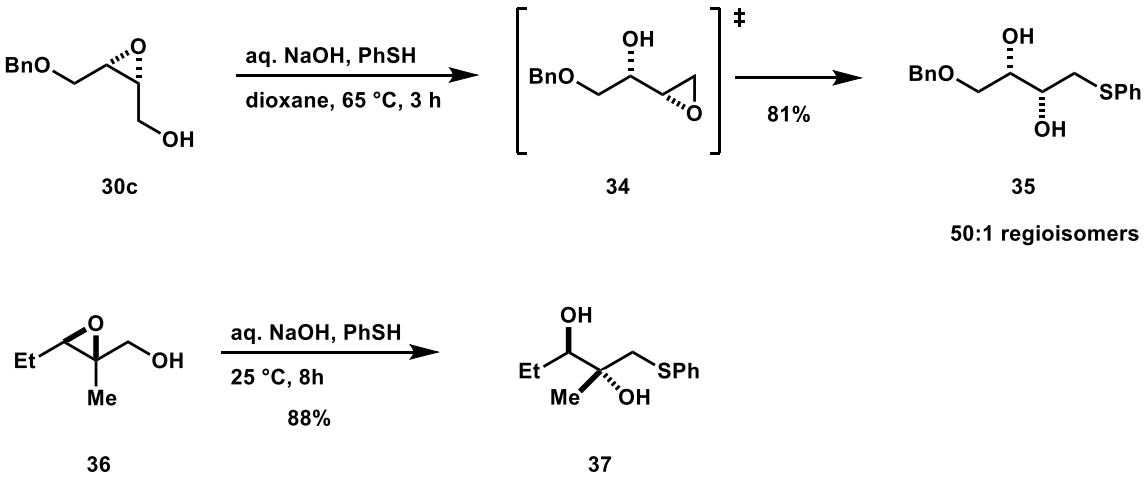
Table 2. C1 addition of *t*-BuSNa.



Entry	Substrate	Major isomer	Regioselectivity (31: 32 + 33)	Yield %
1	 30a	 31a	(1.4:1)	80
2	 30b	 31b	(2:1)	65
3	 30c	 31c	(20:1)	81
4	 30d	 31d	(20:1)	85
5	 30e	 31e	(20:1)	88
6	 30f	 31f	(20:1)	84
7	 30g	 31g	(15:1)	75

steric hindrance on one face of the molecule. Interestingly, the benzyloxy substrates **30c** and **30d** functioned well giving good yields and, in both cases, a 20:1 ratio of desired to undesired regioisomers. The results for the acetals **30e-g** were in line with expectations where a large R group would steer nucleophilic addition to the C1 position. The experiments that Sharpless executed paved the way for 2,3-epoxy alcohol chemistry for numerous sub-divisions of epoxy alcohol chemistry.[12]

In an approach to synthesize alditol products, Sharpless reported under Payne rearrangement conditions that the epoxy alcohol **30c** can equilibrate to the less hindered epoxy alcohol **34** (Scheme 5).[12] The epoxy alcohol **34** can then be trapped with a thiol nucleophile to produce thioether **35** almost exclusively, in a greater than 50:1 ratio of regioisomers in 81% yield. In a similar process, Boeckman demonstrated that under a different set of Payne rearrangement conditions, the methyl epoxy alcohol **36** could be trapped in the C1 position to give the diol **37** for the synthesis of (-)-kromycin.[13]

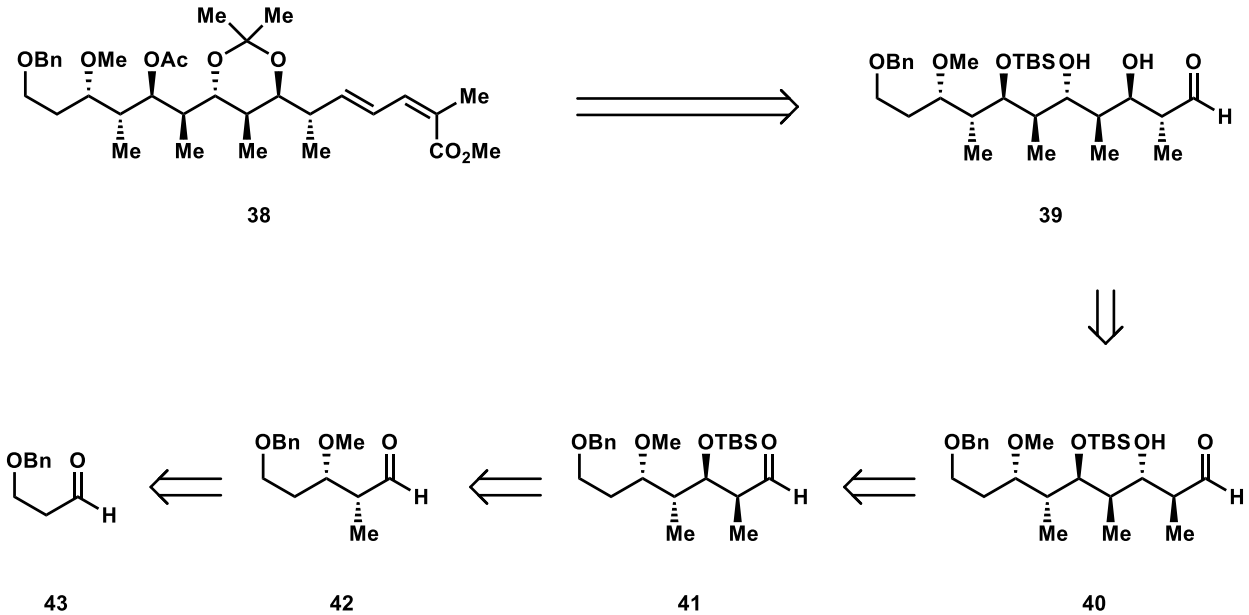


Scheme 5. Selective trapping of the Payne rearrangement intermediates.

Our synthetic approach towards the synthesis of the Rifampicin polyketide backbone relied on the reported Sharpless epoxidation, Payne rearrangement, protection, activation, cyclization, the Yamamoto rearrangement, and our groups' previous findings on the Jung non-aldol aldol rearrangement. We will now describe our efforts for the synthesis of the polyketide backbone of Rifampicin.

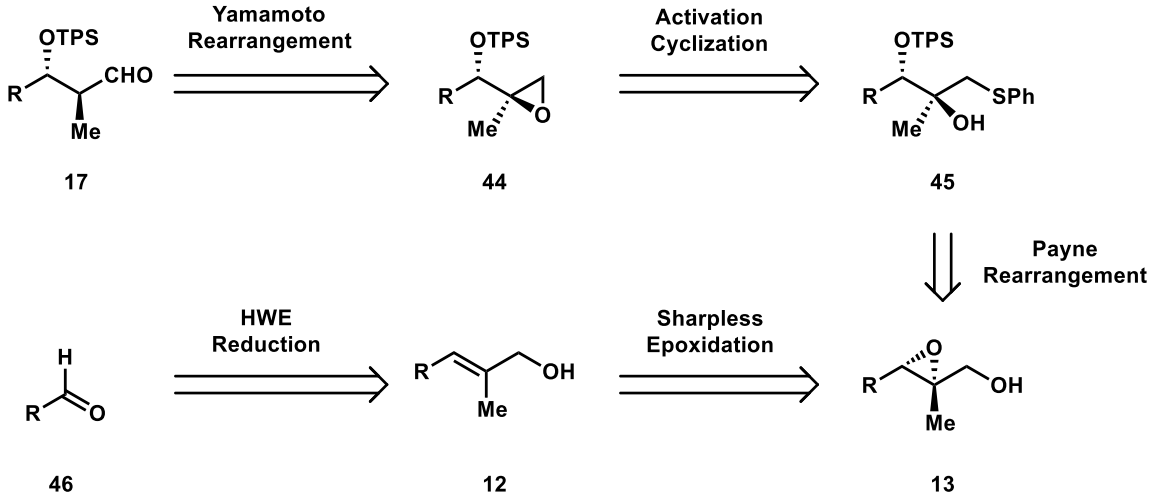
Results and Discussion

We proposed a partial synthesis of the polyketide segment of Rifampicin (Rif) **1**, which could be further functionalized through the Kishi synthesis to yield Rif **1**. Our original retrosynthetic analysis of the polyketide segment of Rif **1** is shown in Scheme 6. The retrosynthesis starts with the synthesis of the diene **38** from the polyketide **39** through a series of Wittig reactions and Horner-Wadsworth-Emmons (HWE) olefinations. The polyketide **39** would be synthesized from aldehydes **40** and **41** through two sequential Yamamoto rearrangement disconnections forming the right half of the polyketide. Following the Yamamoto rearrangement disconnections, the left half of the polyketide can be synthesized by two sequential Jung non-aldol aldol rearrangements from the simple aldehyde **43** and from its derived more complex aldehyde **42**.



Scheme 6. Retrosynthetic analysis of Kishi polyketide.

We envisioned a double inversion cyclization reaction and epoxide rearrangement to synthesize anti-aldol products for the Yamamoto retrosynthetic fragments (Scheme 7). Retrosynthetically starting from epoxide **44**, a Yamamoto rearrangement can afford the anti-aldol product **17**. Activation of the thioether **45** using Meerwein salt followed by base mediated cyclization gives epoxide **44**. The key Payne rearrangement trapping of epoxy alcohol **13**, and subsequent silyl protection, provides the thioether **45**. The Sharpless asymmetric epoxidation of allylic alcohol **12** sets the stereochemistry of the epoxy alcohol **13**. Lastly allylic alcohol **12** can be derived from the aldehyde **46** from a one-pot HWE reaction and DIBAL reduction.

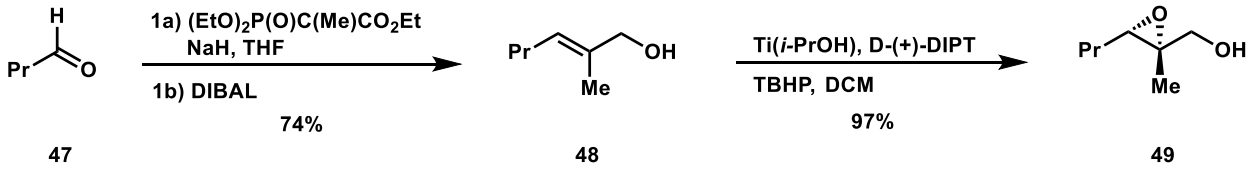


17 **44** **45**

46 **12** **13**

Scheme 7. The Jung non-aldol aldol reaction.

Our forward synthesis launched with testing our hypothesis about the Payne rearrangement (Scheme 8). We started our synthesis from butyraldehyde **47** with a one-pot HWE olefination and DIBAL reduction to generate the allylic alcohol **48,** a modification of a procedure previously established in the Jung lab.[9] Chirality was induced through a Sharpless asymmetric epoxidation to form the optically active epoxy alcohol **48** from the allylic alcohol **49**. This epoxy alcohol was a central test substrate for our epoxide studies.



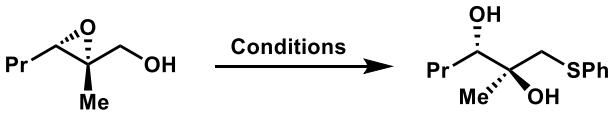
47 48 49

Scheme 8. The synthesis of epoxy alcohol **49**.

The epoxy alcohol **49** was subjected to the Payne rearrangement followed by trapping with thiols similar to the Sharpless and Boeckman methods using thiol nucleophiles. Attempts at thiophenolate addition are given in Table 3. Through the basic biphasic mixture of tert-butanol and water, we were able to trap at the C1 position in modest yield, the highest being 54% yield (entry 1). Although the reaction of sodium thiophenolate at 100 °C provided low yields of the desired product, the reaction at lower temperature and longer time provided higher yields of the product (entry 3). Solvents such as tBuOH or 1,4-dioxane (entries 4 and 5) provided either low yields or no reaction presumably due to lessened ability of the base to deprotonate in these solvents.

According to Sharpless, poor nucleophiles, such as sterically hindered thiols or trialkylamines, are prone to C1 addition.[12] Although the yields were low (Table 4, entries 1 and 2), the results with sodium *tert*-butylthiolate were promising. Nucleophilic addition at the C1 carbon increased as the temperature was reduced (entry 4) although the product was formed in only modest yield (58%).

Table 3. Trapping of Payne rearrangement intermediates using thiophenolate.

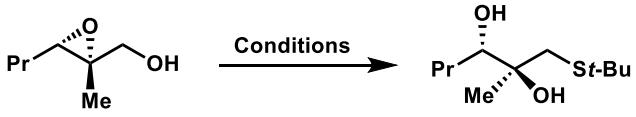


49 50

Entry	Conditions	Solvent	Time	Results	Nucleophile
1	Reflux	2:3 tBuOH:H_2O	2.5 h	54%	*t*-BuSH
2	100 °C	1:1 tBuOH:H_2O	2.0 h	1%	*t*-BuNa
3	55 °C	1:1 tBuOH:H_2O	Overnight	33%	*t*-BuNa
4	80 °C	tBuOH	Overnight	2%	*t*-BuNa
5	22 °C	1,4-Dioxane	Overnight	SM Rec	*t*-BuNa

Thiol nucleophile was added over 0.5 h.

Table 4. Trapping of Payne rearrangement intermediates using *t*-BuSH.



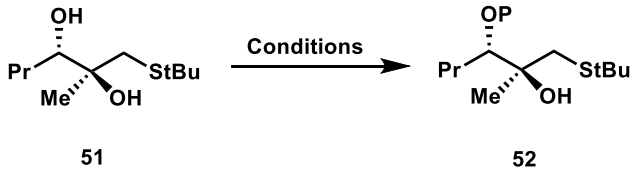
49 51

Entry	Conditions	Solvent	Time	Results	Nucleophile
1	85 °C	1:1 tBuOH:H_2O	Overnight	24%	*t*-BuSH
2	85 °C	1:1 tBuOH:H_2O	7.0 h	27%	*t*-BuNa
3	85 °C	1:2 tBuOH:H_2O	1.0 h	45%	*t*-BuSH
4	55 °C	1:1 tBuOH:H_2O	2.0 h	58%	*t*-BuSH

Thiol nucleophile was added over 0.5 h.

Treatment of the thioether **51** with either imidazole or sodium hydride and triphenyl silyl chloride (TPSCl) gave no reaction (Table 5, entries 1 and 2). The reaction using imidazole and TIPSCl was repeated to probe the reactivity of the substrate as a control reaction; in this case there was no reaction (entry 3). We decided to use a more reactive form of the silylating reagent, namely the triflate TPSOTf, which provided the modest yield of 67% of the triphenylsilyl ether **52** (entry 4). A slight modification using diisopropylethylamine (DIEA) and a shorter reaction time afforded the desired triphenylsilyl ether **52** in 74% yield.[14] With these satisfactory yields achieved we decided to test the activation cyclization step.

Table 5. Silyl protection of thioether **51**.



51 **52**

Entry	Conditions	Solvent	Time	Temp.	Results
1	Imidazole, TPSCl	DMF	Overnight	22 °C	No Rxn
2	NaH, TPSCl	THF	Overnight	22 °C	No Rxn
3	Imidazole, TIPSCl	dichloromethane	Overnight	22 °C	No Rxn
4	AgOTf, TPSCl	6:1 dichloromethane:Pyr	Overnight	22 °C	67%
5	AgOTf, TPSCl, diisopropylethylamine	6:1 dichloromethane:Pyr	0.5 h	22 °C	74%

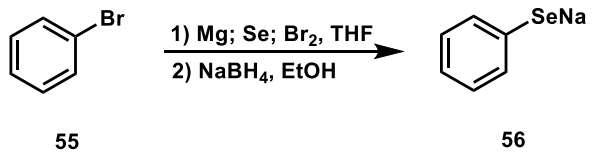
A number of conditions were attempted to synthesize the silyloxy epoxide **54** (Table 6).[12] Methylation of the thioether, to form a sulfonium salt, followed by base facilitated cyclization should produce the silyloxy epoxide **54**, following Sharpless' work.[14] Subjection of the compounds to Meerwein salt and then sodium hydride addition afforded the silyloxy epoxide **54** in 35% yield (entry 1). Methylation by methyl iodide and sodium hydride provided only the *O*-methylation product (entry 2). The addition of methyl triflate and subsequent addition of sodium hydride yielded 23% of the desired silyloxy epoxide **54** (entry 3).

Table 6. Activation-cyclization of thioether **54**.

53 **54**

Entry	Conditions	Solvent	Time	Temp.	Results
1	Me_3OBF_4, NaH	dichloromethane	2.0 h	22 °C	35%
2	MeI, NaH	dichloromethane	1.0 h	22 °C	Methylation
3	MeOTf, NaH	dichloromethane	Overnight	22 °C	23%

We turned our attention to a different set of nucleophiles containing selenium, a nucleophile similar to sulfur but more nucleophilic and when activated a better leaving group. We synthesized diphenyl diselenide and obtained sodium phenylselenide after sodium borohydride reduction (Scheme 9).[15] Addition of sodium phenylselenide to our test substrate **49** provided valuable material for our anti-aldol synthesis. After screening solvent conditions, we

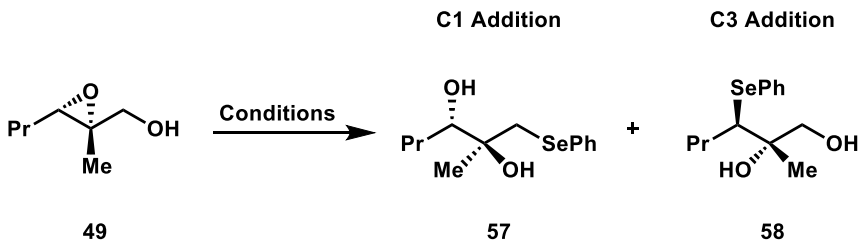


Scheme 9. Synthesis of sodium phenyl selenide **56**.

observed that the biphasic mixture of *t*-BuOH:H_2O performed poorly, providing an overall 50% yield of an approximately 1:1.8 ratio of C1 to C3 addition product (Table 7, entry 1). Since the Sharpless biphasic reaction did not proceed well, even with the addition of phase transfer reagents, we chose to pursue non-biphasic reactions for our studies. Using methanol as a solvent, we observed competition between sodium methoxide and the phenylselenide nucleophiles and obtained poor yields of our desired C1 addition product namely 24% yield (entry 3). The optimal solvent was found to be ethanol which provided a 44% yield of the desired C1 addition product and an overall yield of 80% of both regioisomers (entry 4). A peculiar finding showed that in isopropanol the phenylselenide adds primarily at the C3 position and not at the C1 position in a 5.6:1 ratio (entry 5). Phenylselenide did not add to the epoxy alcohol **49** in *t*-BuOH as the solvent, possibly due to the hydrophobicity of the solvent inhibiting the free anion from forming.

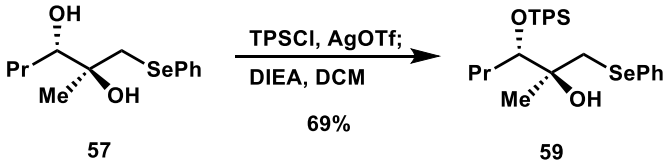
The secondary alcohol of the phenylseleno ether **57** was selectively protected using TPSOTf and diisopropylethylamine to afford the mono-silyl protected triphenylsilyl ether **59** in 69% yield (Scheme 10). The yield for the silylation of the seleno ether **57** was slightly lower compared to the TPS protection of the thioether **51** due to partial decomposition of the product.

Table 7. Trapping of Payne rearrangement intermediates using phenyl selenide.



Entry	Conditions	Solvent	Time	Temp	Results C1:C3 addition
1	NaSePh	2:1 *t*-BuOH:H_2O	4.0 h	0 °C	18%:32%
2	NaSePh, Bu_4NOH	2:1 *t*-BuOH:H_2O	Overnight	22 °C	Low C1 yields
3	NaSePh	MeOH	Overnight	22 °C	24%:40%
4	NaSePh	EtOH	Overnight	22 °C	44%:36%
5	NaSePh	iPrOH	Overnight	22 °C	12%:67%
6	NaSePh	*t*-BuOH	Overnight	22 °C	SM recovered

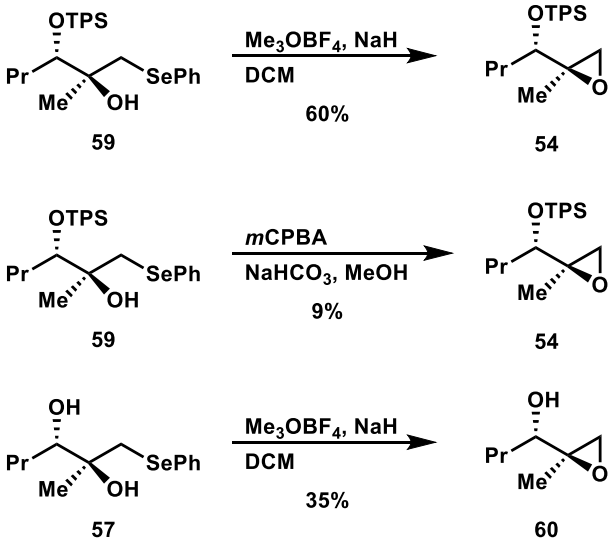
Selenide nucleophile was added over 2 h.



Scheme 10. Synthesis of triphenylsilyl ether **46**.

The triphenylsilyl ether **59** was activated by methylation of the selenophenyl unit to give the selenium salt, and then base mediated cyclization produced the epoxide **54** in 60% yield. Arylselenium groups are known to be converted into good leaving groups via an oxidation to the selenone. There is little literature precedence of their activation with an alkylating agent. Using

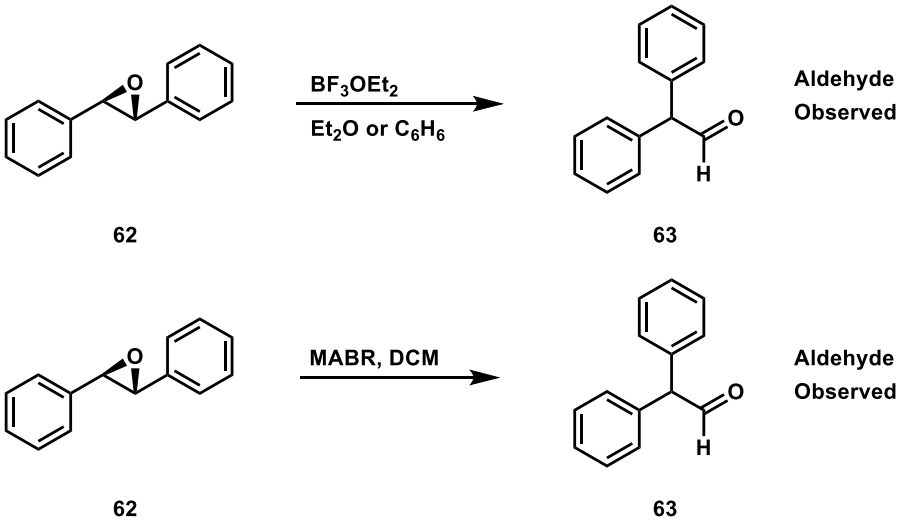
*m*CPBA and mild basic conditions, we were able to form the epoxide **54** in a very clean reaction but in regrettably very low yields.[16] We attempted the cyclization of the phenylseleno ether **57** directly to the epoxy alcohol **60** without protection of the secondary alcohol; although successful, the yields were somewhat low. Compound **60** was unstable, as described by Sharpless, and decomposes when purified by flash column chromatography.



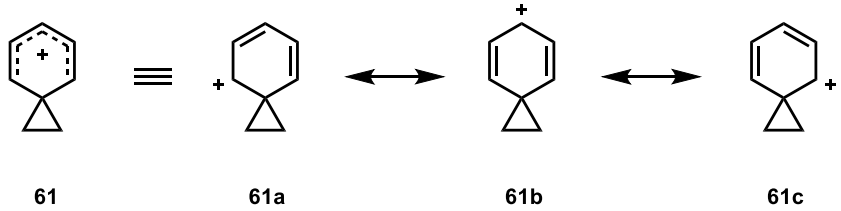
Scheme 11. Synthesis of epoxide**s 54** and **60**.

Before attempting the reaction on the valuable epoxide **54**, we decided to test the Yamamoto rearrangement on the test substrate, *trans*-stilbene oxide **66** (Scheme 12). While hydrogen has a great aptitude for migration in the case of epoxide rearrangements, phenyl groups have the highest propensity for migration partially due to its ability to stabilize unstable intermediates. The phenonium ion was postulated by Donald Cram at UCLA. He proposed that a phenonium ion such as the spirocyclic phenonium ion **61**, is an overall resonance form of the three resonance structures **61a-c** (Scheme 13).[17] The resonance structures help stabilize the phenonium ion allowing phenyl groups to migrate more efficiently compared to non-stabilized groups. Synthesis of the *trans*-stilbene oxide **63** was carried out by the epoxidation of *trans*-

stilbene **62** with the addition of peracetic acid and a buffered mixture of sodium acetate and acetic acid. As a positive control, we decided to attempt the rearrangement using the BF_3OEt_2, a Lewis acid well-known for the rearrangement of *trans*-stilbene oxide **62** to the aldehyde **63**. The rearrangement of *trans*-stilbene oxide **62** to aldehyde **63** proceeded in diethyl ether as a solvent and provided the aldehyde **63** since a carbonyl was observed in the crude NMR. The same rearrangement was also observed using a non-polar benzene solvent. Subjecting the *trans*-stilbene oxide **62** to MABR was also successful, since an aldehyde peak was observed in the proton NMR.

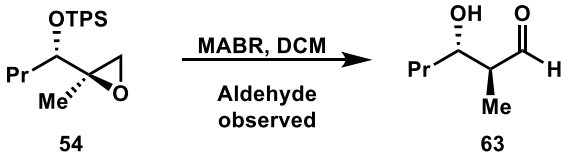


Scheme 12. Phenyl migration of *trans*-stilbene oxide **62**.



Scheme 13. Cram Phenonium resonance structures.

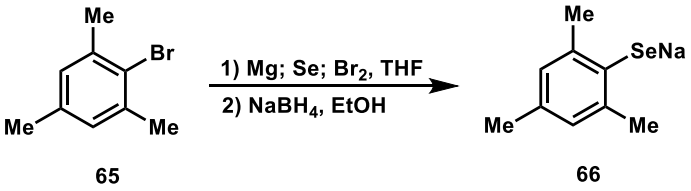
Our first attempt at the Yamamoto rearrangement of our epoxide **54** used the bulky MABR reagent (Scheme 14). The product of the reaction seemed to be a deprotected aldehyde of some sort, possibly aldehyde **63**. Formation of a baseline spot was also observed, but the product appeared to be a complex mixture. While yields were low for this reaction, we viewed it as an exciting result.



Scheme 14. Synthesis of aldol product **64** using MABR.

We decided to synthesize the much more sterically hindered mesityl selenide **66** to try to steer nucleophilic addition away from the more hindered C3 position. The mesityl selenide **66** was prepared as shown in Scheme 15, namely by making the diselenide from mesityl bromide **65** and subsequent reduction of the diselenide. We first used **66** for a temperature study on the rearrangement-trapping of the epoxy alcohol **49** (Table 8).[18] Since the Payne rearrangement requires a polar protic solvent, we decided to focus our solvent scope on alcohols. We observed that iPrOH and aq. *t*-BuOH provided poor overall yields of addition for both seleno ethers **67** and **68** (entries 6 and 7). The C1 addition of thiols to the equilibriating epoxy alcohol as described by Sharpless and coworkers requires that the nucleophile be added slowly over 30 min to allow full equilibriation of the system. Curiously we observe the best yield when we add our nucleophile to the substrate right away (entry 5). Also, as the temperature increases, the yield of our desired C-1 addition product increases with our best result being at 85 °C (Table 8, entry 4). Our temperature studies correlated very closely with the temperatures Sharpless employed for his thiol additions.

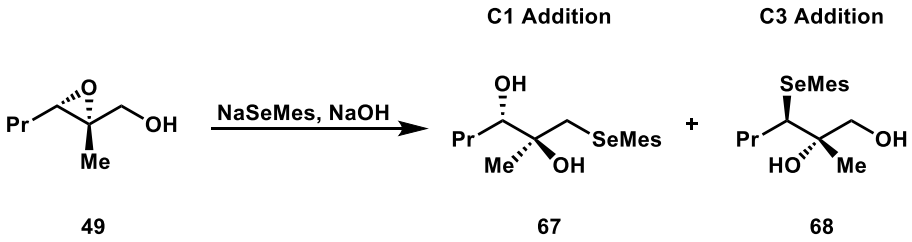
The boiling point of our solution was 85 °C and so we needed to explore methods of adding more energy to our reaction flask and decided to test using microwave energy to heat our reaction.



65 66

Scheme 15. Synthesis of sodium mesityl selenide **66**.

Table 8. Trapping of Payne rearrangement intermediates using mesityl selenide.



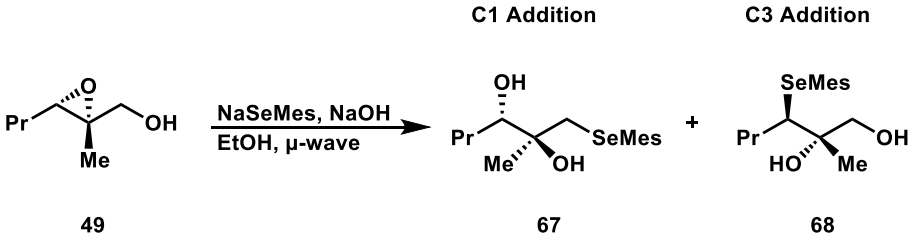
49 67 68

Entry	Temp (°C)	Solvent	**67** (%)	**68** (%)	Overall yield (%)
1	0	EtOH	13	45	58
2	22	EtOH	31	53	84
3	45	EtOH	40	23	63
4	85	EtOH	48	34	82
5[a]	22	EtOH	44	35	79
6[b]	100	iPrOH	30	13	43
7[b]	100	aq. *t*-BuOH	10	10	20

Thiol nucleophiles were added over 2 h unless noted otherwise. a) Added all at once. B) 0.5 M NaOH was used.

Subjecting our reaction to microwave conditions (Table 9), we were able to improve our yields. Heating at 100 °C for 48 h seemed to give slightly lower yield than for 12 h. Our results seemed to indicate there was a possible conversion of the seleno ether **67** to its isomer **68** (Table 9, entries 1 and 2). A similar effect was also observed at 85 °C for reactions at 48 h and 12 h (entries 3 and 4). Microwaving at higher temperatures for 12 h gave reduced yields of the desired C1 addition (entry 2 vs. entry 4). We also subjected the mesityl selenide **66** and epoxy alcohol **49** to a sealed tube reaction over 60 h, which was effective providing a 56% yield of our desired product **67** and complete consumption of starting materials.

Table 9. Trapping of Payne rearrangement intermediates using mesityl selenide under microwave conditions.

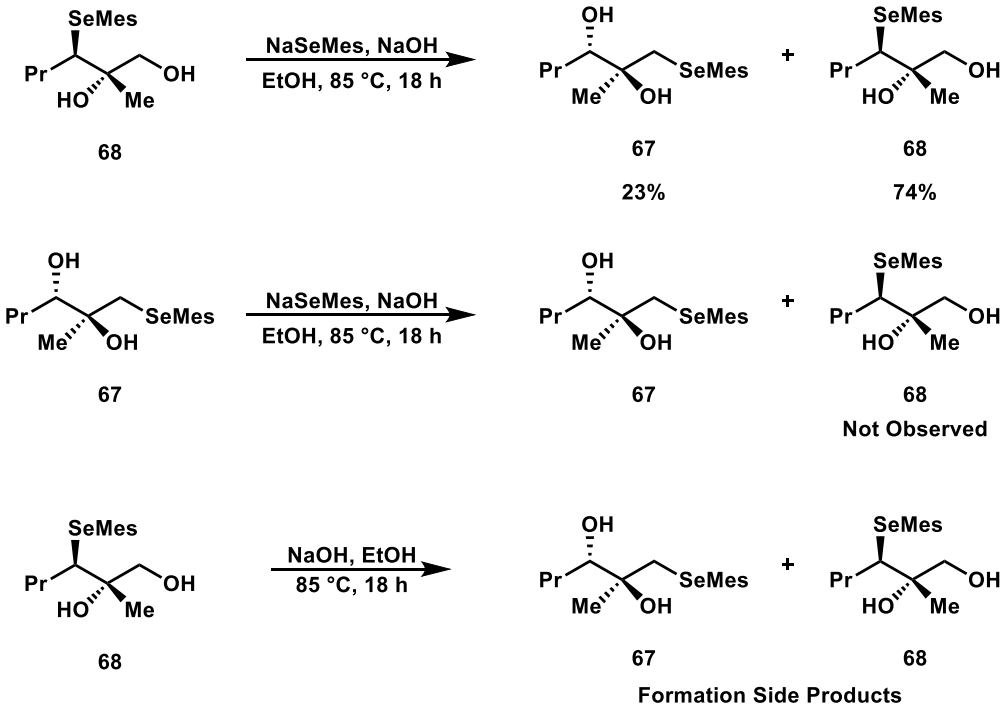


49 67 68

Entry	Time (h)	Temp (°C)	**67** (%)	**68** (%)	Overall yield (%)
1	48	100	51	10	61
2	12	100	46	23	69
3	48	85	41	0	41
4	12	85	60	17	77
5[a]	60	80	56	0	56

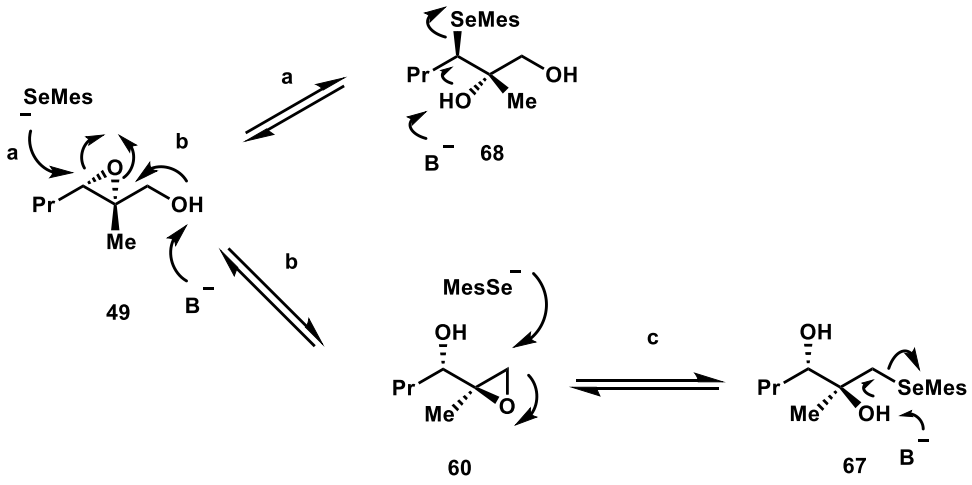
a) Not microwave; sealed tube.

We observed that longer reaction times seemed to provide higher yields of the desired C1 addition product with respect to the C3 addition product; we postulated that formation of the seleno ethers might be a reversible reaction. To probe this hypothesis, we microwaved the seleno ether **68** at 85 °C for 18 h in the presence of base and to our delight, our hypothesis was shown to be correct. We observed the formation of the seleno ether **67** in 23% yield while we recovered 74% of the starting seleno ether **68**. We also subjected the primary seleno ether **67** to sodium mesityl selenide at 85 °C over 18 h, but we were unable to detect the formation of the seleno ether **68**. Finally we reacted the seleno ether **68** in a basic ethanol solution and we observe some formation of the seleno ether **67** but mostly side products, which presumably arises by addition of ethoxide to the epoxy alcohols.



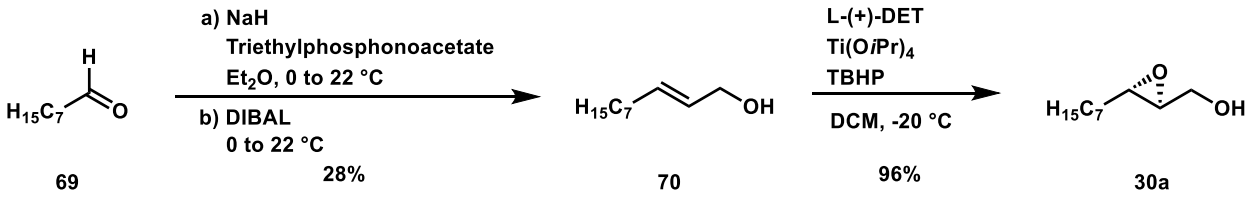
Scheme 16. Equilibrium conversion of seleno ethers **67** and **68**.

Our proposed mechanism for this rearrangement starts from the epoxy alcohol **49** (Scheme 17). Starting from **49** via path a, the selenide attacks the C3 position in the most prevalent form of equilibrating epoxy alcohol **49** to produce the seleno ether **68**. The seleno ether **68** can eject the mesityl selenide via the reverse of path a to reform the epoxy alcohol **49**. The epoxy alcohol **49** has another option to deprotonate and equilibrate, to give the epoxy alcohol **60**, namely the less sterically hindered epoxy alcohol. The selenide cannot attack the C2 tertiary epoxide center of either epoxy alcohols **49** or **60**, but the primary epoxide center has no steric hindrance and is attacked by the selenide via path c to form the seleno ether **67**. Although there is an equilibrium between the epoxy alcohol **60** and seleno ether **67**, via the inverse of path c, we believe the equilibrium lies far to the right.



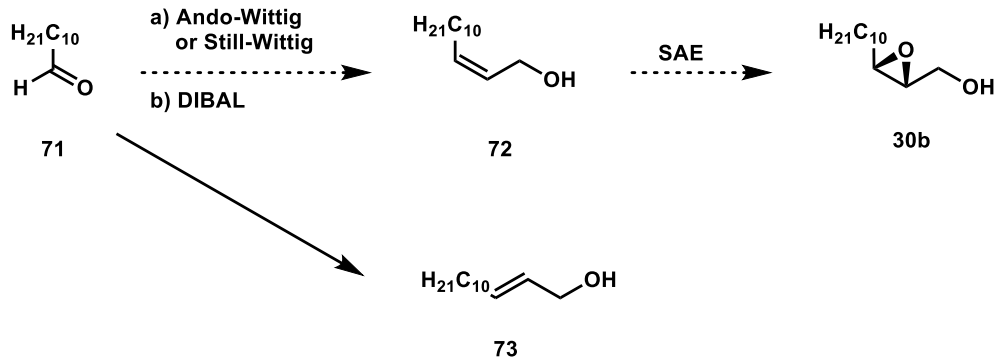
Scheme 17. Equilibrium mechanism of seleno ether **68** and **67**.

To compare the reactivity of selenium nucleophiles and thiol nucleophiles, we decided to synthesize Sharpless' disubstituted epoxy alcohol. The synthesis of the epoxy alcohol **30a** was fairly routine starting from the aldehyde **69** via a one-pot HWE reaction and DIBAL reduction to give the allylic alcohol **70**. A Sharpless asymmetric epoxidation yielded the epoxy alcohol **30a**.



Scheme 18. Synthesis of epoxy alcohol **30a**.

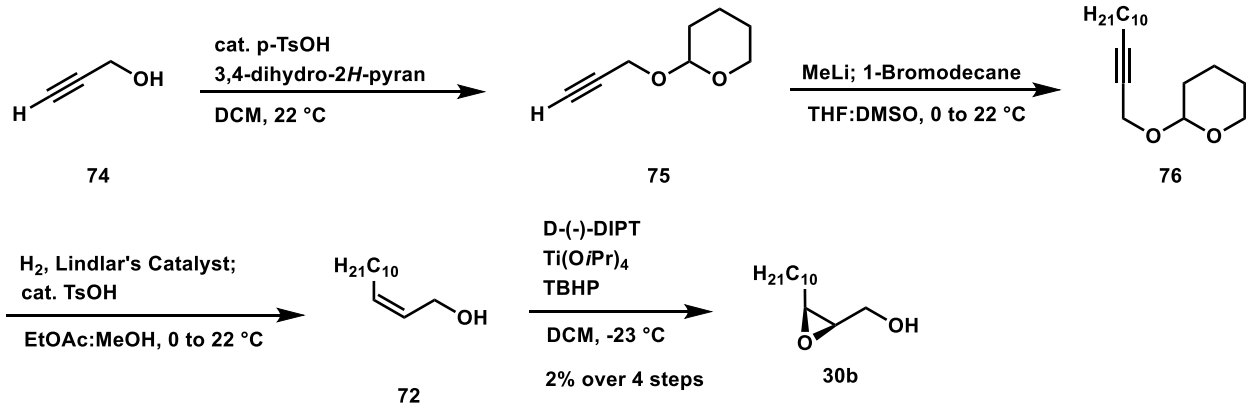
The synthesis of alkyl cis-epoxy alcohol **30b** was somewhat of a challenge. We attempted using the Ando-Wittig modification followed by DIBAL reduction but were unable to obtain any of the cis-allylic alcohol **72**. Unexpectedly we obtained the *trans*-allylic alcohol **73**.[19] In another attempt, we used the Still modification of the Wittig reaction but unfortunately we were still unable to attain our desired *cis*-allylic alcohol **72**.[20]



Scheme 19. Failed synthesis of epoxy alcohol **30b**.

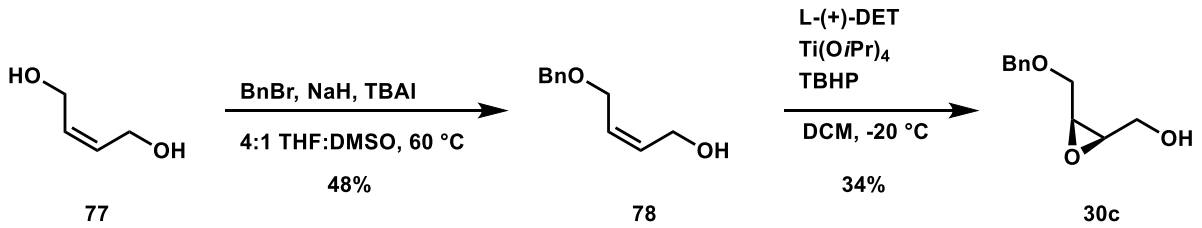
We designed a longer but better known route to establish the cis stereochemistry in the allylic alcohol **72**. Starting from propargyl alcohol **74**, THP protection using DHP and catalytic acid proceeded smoothly, producing a mixture of products that were subjected to the next two following reactions. Deprotonation of the alkyne **75** by methyllithium and nucleophilic addition to bromodecane afforded the disubstituted alkyne **76** as a mixture of protected propargyl alcohols.[21] The cis-stereochemistry of allylic alcohol **72** was established using reduction over

Lindlar's catalyst. Acidic workup of the crude product deprotected the THP ether and yielded the single product **72** from the previous mixture of starting materials.[22] Lastly a Sharpless asymmetric epoxidation of the cis-allylic alcohol **72** yielded the cis-epoxy alcohol **30b**.



Scheme 20. Synthesis of epoxy alcohol **30b**.

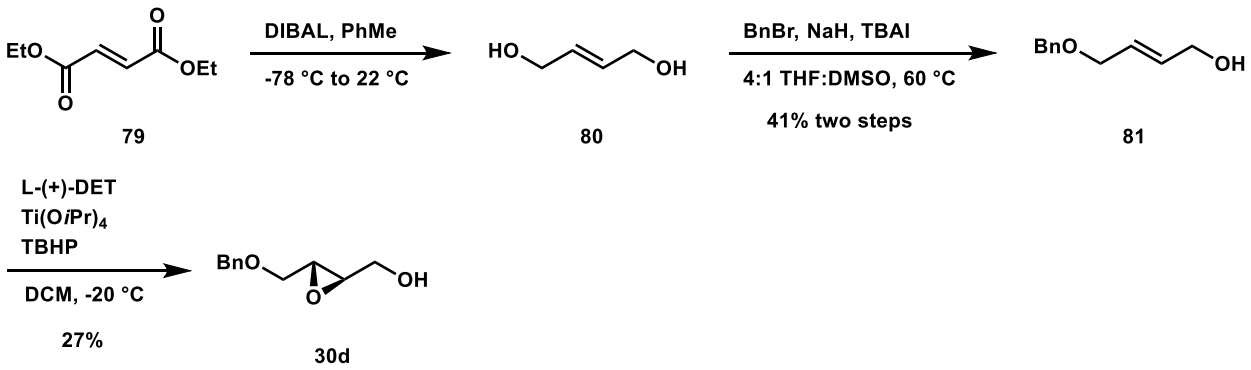
Selective mono-benzyl protection of *cis*-butene-1,4-diol **77** proved to be a reliable method to synthesize the *cis*-allylic alcohol **78**, which we utilized for subsequent epoxidation reactions. Asymmetric epoxidation of the cis-allylic alcohol **78** furnished the cis-epoxy alcohol **30c**.[21, 23]



Scheme 21. Synthesis of epoxy alcohol **30c**.

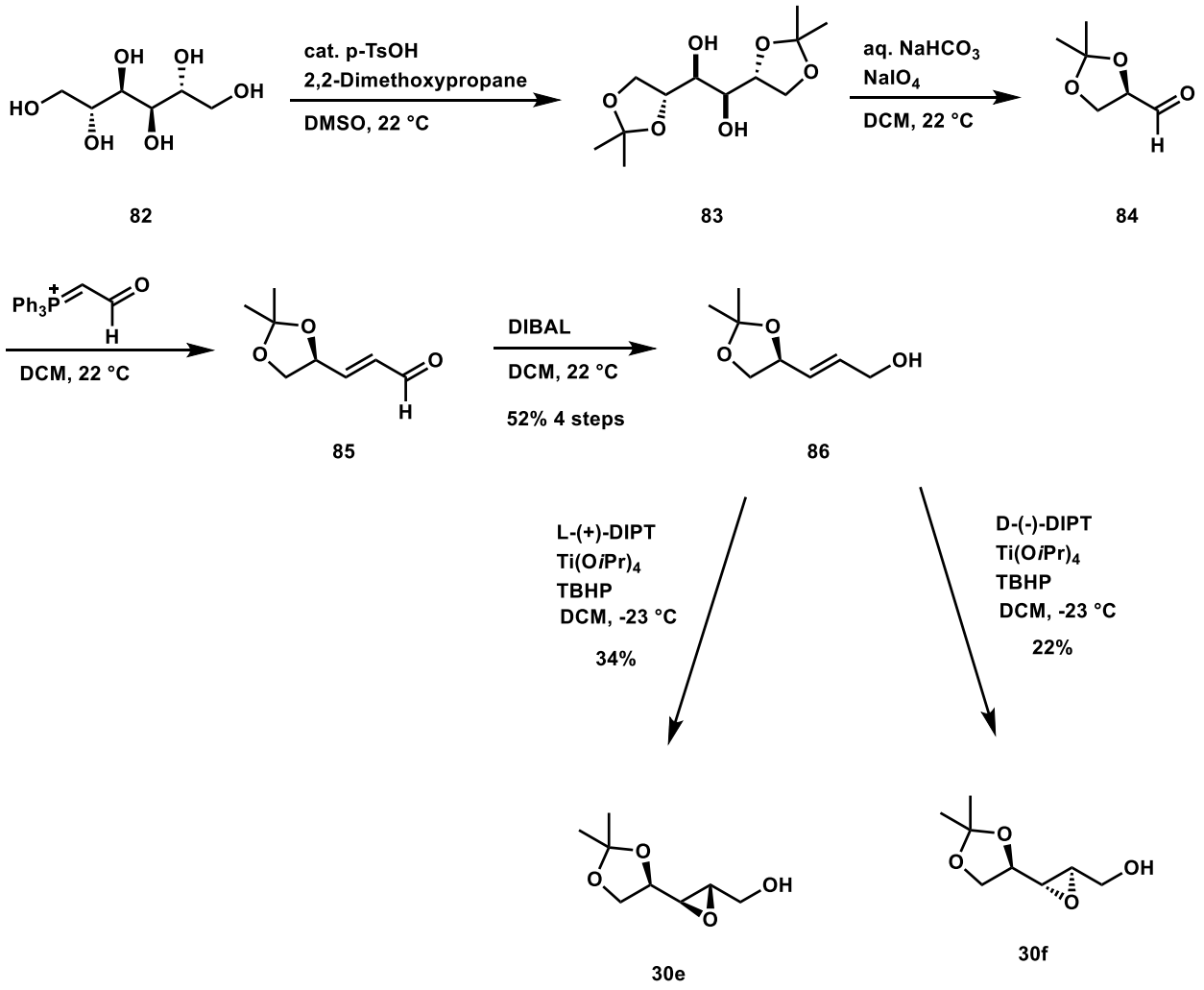
Following the previous procedure to synthesize the cis-epoxy alcohol **30c**, we were able to synthesize the trans-epoxy alcohol **30d** from diethyl fumarate **79** (Scheme 22).[23] DIBAL reduction of diethyl fumarate **79** formed trans-2-butene-1,4-diol **80**. The benzylation of the *trans*-

butenediol **80** by benzyl bromide and base afforded the *trans*-allylic alcohol **81**. The epoxidation of the *trans*-allylic alcohol **81** was the same as in the previous synthesis of the cis-epoxy alcohol **30c**, in this case to form the trans-epoxy alcohol **30d**.



Scheme 22. Synthesis of epoxy alcohol **30d**.

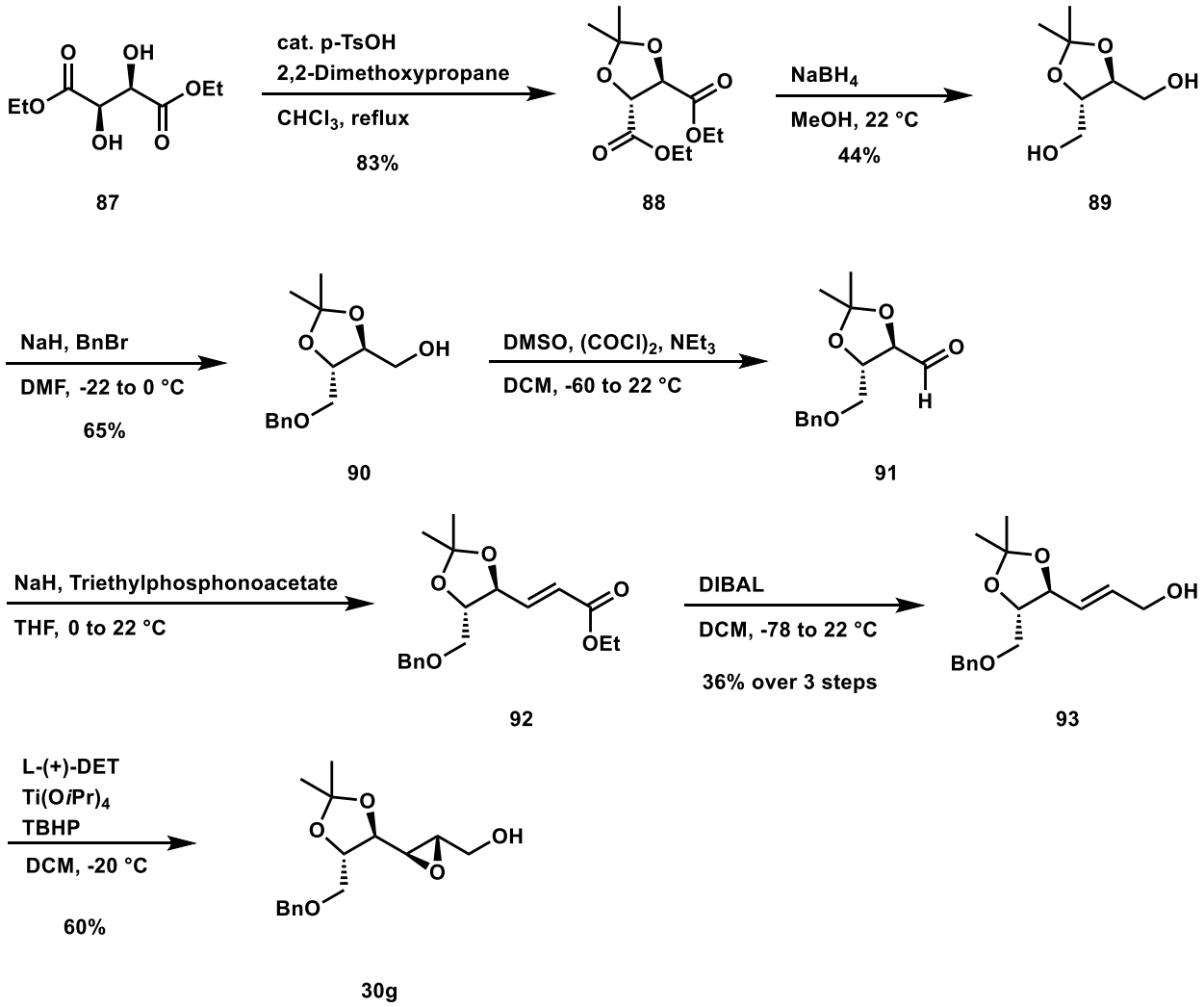
The more complex epoxy alcohols **30e** and **30f** were assembled from the intermediate allylic alcohol **86**, which originates from D-mannitol **82**. Formation of the diacetal **83** was achieved through addition of 2,2-dimethoxypropane and catalytic tosic acid to D-mannitol **82** (Scheme 23). The oxidative cleavage of the diacetal **83** with sodium bicarbonate and sodium periodate afforded the aldehyde **84** with retention of chirality as shown after the epoxidation step.[24] Wittig olefination of aldehyde **84** formed the trans-enal **85** and subsequent DIBAL reduction yielded the allylic alcohol **86** in 54% yield over 4 steps.[12] From the allylic alcohol **86**, two different products were prepared through the Sharpless epoxidation using D-DIPT and L-DIPT to form the epoxides **30e** and **30f**.



Scheme 23. Synthesis of epoxy alcohols **91** and **92**.

The final substrate we prepared to test the selenide nucleophilic addition was the epoxy alcohol **30g** (Scheme 24). L-Diethyl tartrate was efficiently protected using dimethoxypropane in refluxing chloroform to give the acetonide **88** in 83% yield. Both esters of the acetonide **88** were reduced with sodium borohydride to give the diol **89**. The C_2 symmetric alcohol **89** can be selectively mono-benzylated to produce the alcohol **90**.[18] Oxidation of the alcohol **90** under Swern conditions afforded the aldehyde **91**. HWE reaction of **91** furnished the ester **92** again without epimerization. A smooth DIBAL reduction of the ester **92** produced the allylic alcohol

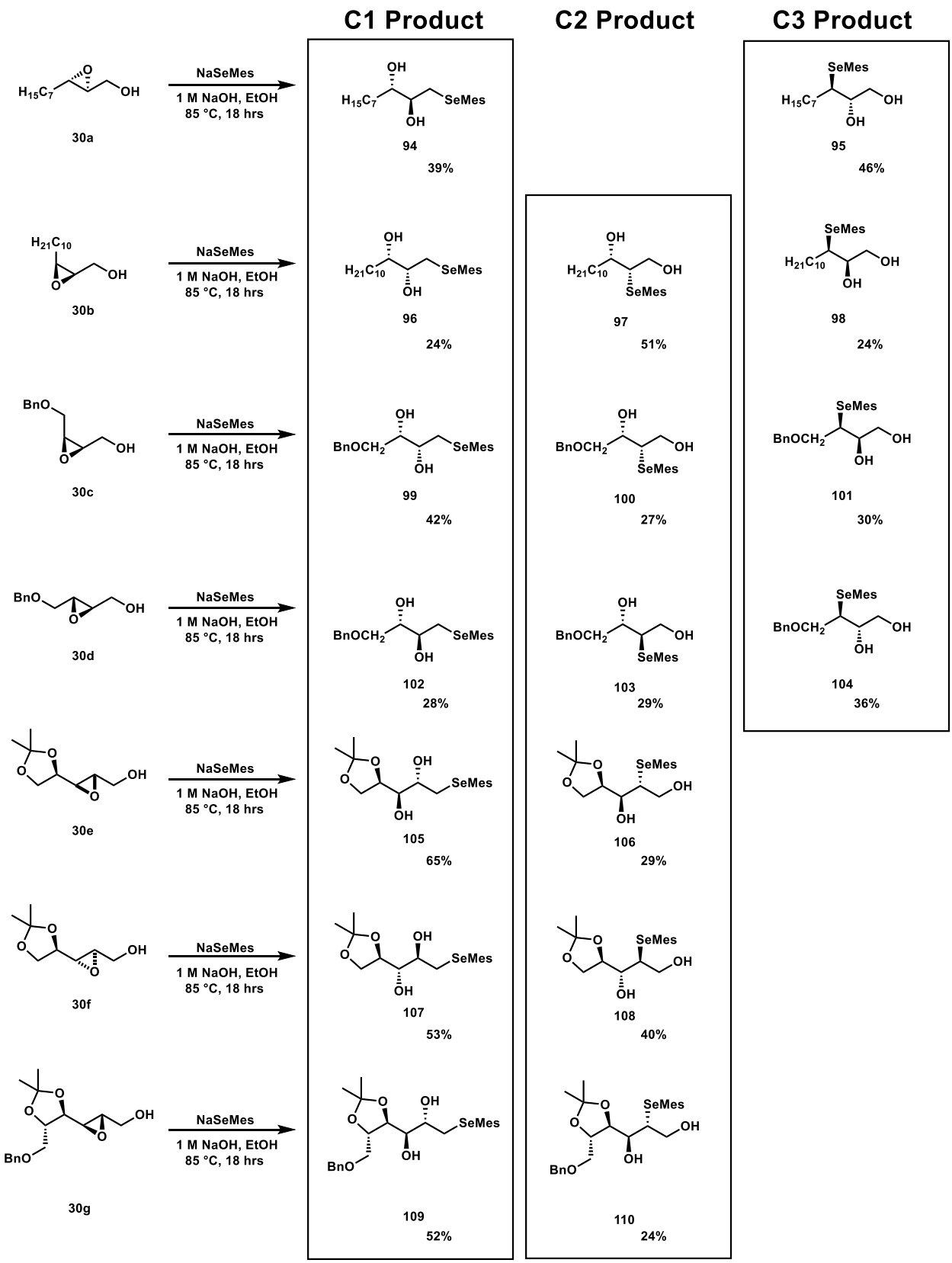
93 in 36% yield over four steps. Finally asymmetric epoxidation of the allylic alcohol **93** furnished our desired benzyl epoxy alcohol **30g** in 60% yield.



Scheme 24. Synthesis of epoxy alcohol **100**.

In our attempt to validate aryl selenides as nucleophiles for the trapping of Payne rearrangement intermediates, we tested mesityl selenide on this series of epoxy alcohols (Scheme 25).[18] We demonstrated that epoxide opening occurs in both E and Z epoxy alcohols. Mesityl selenide addition to the simple trans-epoxy alcohol **30a** provided the least complex mixture among the alkyl epoxy alcohols. The C1 addition product, the trans-epoxy alcohol **30a**, was

isolated in 39% yield as the minor product where the major product, the C3 addition product seleno ether **95**, was isolated in 46% yield. The results from the mesityl selenide addition to the *trans*-epoxy alcohol **30a** were expected since our test substrate epoxy alcohol **49** was more sterically hindered towards the C3 position and so it is not surprising that this case provided a ratio comparable with our previous results. For the *cis*-epoxy alcohols **30b** and **30c**, we observed a mixture of all three stereoisomers when we added mesityl selenide to the system. The regioselectivity of this reaction with the cis-epoxy alcohols seems somewhat unpredictable since the *cis*-alkyl epoxy alcohol **30b** provides the C2 addition seleno ether **97**, while the *cis*-benzyloxy epoxy alcohol **30c** affords the major product as the C1 addition seleno ether **99**. The unpredictable reactivity of the cis-epoxy alcohol substrates are likely due to the uncontrollable reactivity and stability of the equilibrating epoxy alcohols. Surprisingly the *trans*-benzyloxy epoxy alcohol **30d** had no regioselective similarity with the trans-alkyl epoxy alcohol **30a** in this reaction. The trans-benzyloxy epoxy alcohol **30d** delivered a fairly even distribution of C1, C2, and C3 addition regioproducts. This may be attributed to the benzyloxy group participating in a 5 or 6 membered cyclic transition state. Once the R group is sufficiently large, addition to the C3 position does not occur and regioselectivity shifts towards the C1 addition products. Thus in the case of epoxy alcohols **30e**, **30f**, and **30g**, which all contain acetonides, we observe the C1 addition products as the major regioisomeric product in all three cases. The addition to the C3 position in epoxy alcohols **30e**, **30f**, and **30g** is quite hindered and nucleophilic addition towards C1 and C2 sites are kinetically favorable. The latent C1 position is the least hindered site for the epoxy alcohols **30e**, **30f**, and **30g**, where we find the primary mesityl selenide preferentially attacks. Sterics seem to play a vital role in nucleophilic attack opening epoxides in the C1, C2, and C3 positions. Substrates containing acetonide functionality fared well and provided



Scheme 25. Epoxy alcohol substrate scope.

reasonable yields of the 1-seleno products.

Conclusion

In conclusion, we have shown that selenium nucleophiles prefer C1 addition to sterically hindered 2,3-epoxy alcohols. A variety of cis and trans epoxy alcohols were studied where cis epoxy alcohols seem to have more promiscuous reactivity. The seleno ethers could be further derived into terminal epoxy silyl ethers for the Yamamoto rearrangement. Many of these results have been published recently.[18]

Experimental

Materials and Methods

All NMR spectra were recorded on Bruker spectrometers at 400 or 500 MHz for proton and 100 or 125 MHz for carbon. High resolution mass spectra were obtained from the UCLA Molecular Instrumentation Center. Reagents were purchased through Fischer Scientific, Sigma-Aldrich, or Oakwood Chemicals. ACS grade solvents were purchased from Fischer Scientific. Toluene, benzene, THF, and diethyl ether solvents were dried prior to use by distilling over sodium metal and benzophenone. Dichloromethane was distilled over calcium hydride. Methanol was distilled over magnesium turnings. Ethanol (190 proof) was purchased from Fischer Scientific and was used without further drying. Silica gel P60 was purchased from Silicycle. All oxygen or moisture sensitive reactions were performed under an inert argon atmosphere unless otherwise noted.

Experimental Procedures

(*E*)-2-Methylhex-2-en-1-ol, 48.

Method 1

To a suspension of 60% sodium hydride in mineral oil (3.06 g, 75.6 mmol) (washed three times with hexanes) in benzene (40 mL) was added triethyl 2-phosphonopropionate (10.74 g, 44.2 mmol) dropwise. Butanal was added to the solution dropwise at 0 °C and it was stirred for 5 h. The reaction solvent was concentrated *in vacuo*, and then filtered through Celite. The gummy layer was dissolved in water then extracted with dichloromethane (3 X 20 mL) and the combined

organic extracts were washed with water (5 mL), then brine (5 mL), dried with $MgSO_4$, and filtered. The dried organic extract was then concentrated *in vacuo* and the crude oil was taken directly to the next reaction. The crude oil was dissolved in dichloromethane (50 mL) and DIBAL (1.0 M in dichloromethane, 130 mL, 130.0 mmol) was added dropwise at -78 °C. The solution was allowed to warm to 22 °C and continued to stir overnight. The solution was slowly quenched with a mixture of MeOH (165 mL) and Rochelle's salt solution (165 mL) at 0 °C. The layers were separated and then the aqueous solution was extracted with dichloromethane (5 X 130 mL). The combined organic layers were dried with $MgSO_4$, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (2:3 Et_2O:hexanes). The allylic alcohol **48** was obtained as a colorless oil (3.75 g, 32.8 mmol) in 74% yield.

Method 2

To a suspension of 60% sodium hydride in mineral oil (6.17 g, 154 mmol) (washed three times with hexanes) in THF (500 mL) was added triethyl 2-phosphonopropionate (10.74 g, 44.2 mmol) dropwise at 0 °C. Butanal was added to the solution dropwise at 0 °C and it was stirred at 22 °C for 2 h. DIBAL (1.0 M in Et_2O, 250 mL, 250.0 mmol) was added dropwise at -78 °C. The solution was allowed to warm to 22 °C and continued to stir overnight. The solution was slowly quenched with MeOH (10 mL) at 0 °C followed by an aqueous solution of KOH (50 mL) at 0 °C. The layers were separated and then the aqueous solution was extracted with dichloromethane (3 X 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica

gel (2:3 Et_2O:hexanes). The allylic alcohol **48** was obtained as a colorless oil (4.29 g, 37.6 mmol) in 36% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

5.41 (tq, *J* = 7.2, 1.2 Hz, 1H)

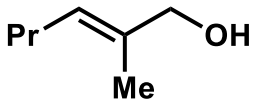
4.00 (s, 2H)

2.03-1.98 (m, 2H)

1.66 (s, 3H)

1.41-1.33 (m, 2H)

0.90 (t, *J* = 7.4 Hz, 3H).



48

^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.9, 126.5, 69.2, 29.8, 22.8, 14.0, 13.8.

((2*S*,3*S*)-2-(Methyl-3-propyloxiran-2-yl)methanol, 49.

To a solution of D-(-)-DIPT (0.46 mL, 2.2 mmol) and 4Å molecular sieves (150 mg) in dichloromethane (30 mL) was added Ti(O*i*Pr)$_4$ (0.6005g, 2.12 mmol) and *t*BuOOH (5 M in decane, 3.5 mL, 17.5 mmol) dropwise at -10 °C. The solution was stirred for 10 min at -10 °C and then cooled to -30 °C. The allylic alcohol **49** (0.8345 g, 7.31 mmol) in dichloromethane (10 mL) was added dropwise to the previous solution over 20 min. The reaction was stirred for 3 h until the reaction was complete, and then the reaction was filtered through Celite. A buffer solution (18 mL, 7.0 pH) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 X 30 mL), dried with $MgSO_4$, then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (1:1

EtOAc:pentane). The epoxy alcohol **49** was obtained as a colorless oil (0.9213 g, 7.08 mmol) in 97% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

3.66 (dd, *J* = 12.1, 4.4 Hz, 1H)

3.54 (d, *J* = 12.1, 8.8 Hz, 1H)

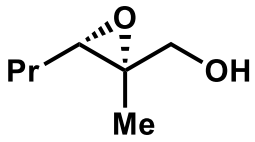
3.02 (t, *J* = 5.3 Hz, 1H)

2.06 (dd, *J* = 8.3, 4.8 Hz, 1H)

1.60–1.43 (m, 4H)

1.26 (s, 3H)

0.96 (t, *J* = 7.1 Hz, 3H).



49

^{13}C NMR (100 MHz, $CDCl_3$) δ: 65.4, 60.8, 60.0, 30.1, 19.7, 14.2, 13.9.

General procedure for the formation of thioethers.

Formation of (2*S*,3*S*)-2-methyl-1-thiophenylhexane-2,3-diol, 50.

To a refluxing solution of the epoxy alcohol **49** (29.2 g, 0.224 mmol) in a 1:1 mixture of aqueous NaOH (0.5M, 1.5 mL) and *t*BuOH (1.5 mL) was added benzenethiol (0.5 mL, 0.49 mmol) in *t*BuOH (0.3 mL) dropwise over 30 min. The reaction was refluxed for another 2 h and then the reaction was cooled to 22 °C and the layers were separated. The aqueous layer was extracted with dichloromethane (3 X 2 mL), the combined organic layers were dried over $MgSO_4$, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (2:1 EtOAc:hexanes). The thioether **50** was obtained as a yellow oil (0.0287 g, 0.12 mmol) in 54% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.43-7.40 (m, 2H)

7.30-7.26 (m, 2H)

7.22-7.17 (m, 1H)

3.57 (d, *J* = 9.2 Hz, 1H)

3.36 (d, *J* = 13.1 Hz, 1H)

3.08 (d, *J* = 13.1 Hz, 1H)

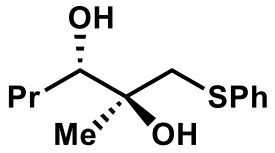
2.70 (s, 1H)

2.26 (s, 1H)

1.66-1.35 (m, 4H)

1.21 (s, 3H)

0.95 (t, *J* = 6.4 Hz, 3H).



50

^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.68, 129.63, 129.07, 126.44, 77.12, 74.39, 42.46, 33.14, 23.61, 20.00, 14.02.

(2*S*,3*S*)-1-(*tert*-Butylthio)-2-methylhexane-2,3-diol, 51.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

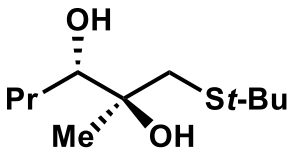
3.53-3.50 (m, 1H)

3.00 (s, 1H)

2.86 (d, *J* = 12.4 Hz, 1H)

2.63 (d, *J* = 12.4 Hz, 1H)

2.52 (br d, *J* = 3.6 Hz, 1H)



51

1.66-1.57 (m, 1H)

1.46-1.34 (m, 3H)

1.31 (s, 9H)

1.15 (s, 3H)

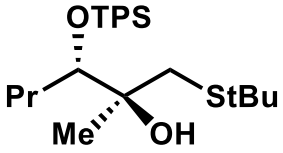
0.94 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 77.3, 73.3, 42.6, 36.0, 33.1, 31.0, 24.1, 20.2, 14.2.

(2*S*,3*S*)-1-(*tert*-Butylthio)-2-methyl-3-((triphenylsilyl)oxy)hexan-2-ol, 53.

To the thioether **51** (116.4 mg, 0.528 mmol) was added a premixed solution of triphenylsilyl chloride (TPSCl, 194.3 mg, 0.634 mmol) and AgOTf (162.5 mg, 0.634 mmol) in dichloromethane (6 mL) at -78 °C followed by addition of pyridine (1.1 mL). The reaction was stirred overnight and then concentrated directly *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (5% Et_2O:pentane). The thioether **53** was obtained as a yellow oil (158.9 g, 0.354 mmol) in 67% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ:



53

7.67-7.65 (m, 6H)

7.44-7.36 (m, 9H)

3.63 (dd, *J* = 8.0, 2.9 Hz, 1H)

2.76 (d, *J* = 12.1 Hz, 1H)

2.68 (d, *J* = 12.1 Hz, 1H)

2.43 (s, 1H)

1.63-1.52 (m, 2H)

1.41-1.25 (m, 1H)

1.22 (s, 3H)

1.21 (s, 9H)

1.12-0.97 (m, 1H)

0.64 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 134.8, 130.0, 128.0, 80.4, 73.9, 42.0, 38.1, 35.0, 31.0, 22.7, 20.3, 14.1.

General procedure for the formation of terminal epoxides.

Formation of (2*R*)-(1*S*-triphenylsilyoxylbutyl)-2-methyloxirane.

To a solution of the thioether **53** (11.3 mg, 0.0252 mmol) in dichloromethane (5 mL) was added trimethyloxonium tetrafluoroborate (4.4 mg, 0.0279 mmol). After the reaction stirred for 2 h, 60% sodium hydride in mineral oil (3.5 mg, 0.0875 mmol) was added and the reaction was stirred overnight. The reaction was quenched with water (1 mL), the layers were separated, and the aqueous layer was extracted with dichloromethane (3 X 5 mL). The combined organic layers were washed with brine (1 mL) and then dried with Na_2SO_4, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (gradient: 2%-40% Et_2O:hexanes). The epoxide **54** was obtained as a colorless oil (3.2 mg, 0.00893 mmol) in 35% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.62 (dd, *J* = 8.0, 1.5 Hz, 6H)

7.45-7.36 (m, 9H)

3.35 (dd, *J* = 7.8, 4.5 Hz, 1H)

2.34 (d, *J* = 4.9 Hz, 1H)

2.20 (d, *J* = 4.9 Hz, 1H)

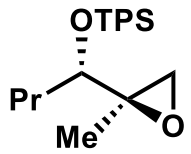
1.74-1.57 (m, 2H)

1.45-1.38 (m, 1H)

1.36 (s, 3H)

1.25-1.16 (m, 1H)

0.77 (t, *J* = 7.4 Hz, 3H).



54

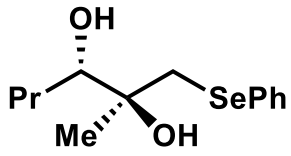
^{13}C NMR (125 MHz, $CDCl_3$) δ: 135.6, 134.7, 130.2, 128.0, 77.0, 58.4, 54.4, 36.3, 18.8, 15.9, 14.2.

General procedure for the formation of seleno ethers.

Formation of (2*S*,3*S*)-2-methyl-1-(phenylselanyl)hexane-2,3-diol, 57.

To a solution of the epoxy alcohol **49** (99.5 mg, 0.76 mmol) in EtOH (1 M NaOH, 4 mL) was added a premixed solution of diphenyl diselenide (179.3 mg, 0.57 mmol) and sodium borohydride in 12 M aqueous NaOH (4.35 M, 0.27 mL, 1.2 mmol) in EtOH (1 M NaOH, 1 mL) to the reaction at -30 °C. The reaction was allowed to warm to 22 °C overnight and then the reaction was quenched with a saturated aqueous solution of NH_4Cl (1 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 X 3 mL). The combined organic layers were dried with $MgSO_4$, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (gradient: 10%-33% Et_2O:hexanes). The seleno ether **57** was obtained as a yellow oil (95.8 mg, 0.334 mmol) in 44% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ:



57

7.57-7.55 (m, 2H)

7.28-7.23 (m, 3H)

3.57 (dd, *J* = 10.2, 2.2 Hz, 1H)

3.39 (d, *J* = 12.6 Hz, 1H)

3.07 (d, *J* = 12.6 Hz, 1H)

2.74 (s, 1H)

2.34 (s, 1H)

1.67-1.24 (m, 4H)

1.22 (s, 3H)

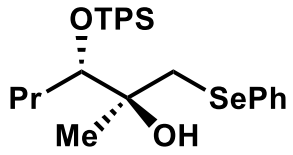
0.95 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 132.7, 130.8, 129.3, 127.3, 77.3, 74.2, 38.4, 33.4, 24.3, 20.1, 14.2.

(2*S*,3*S*)-2-Methyl-1-(phenylselanyl)-3-((triphenylsilyl)oxy)hexan-2-ol, 59.

To the seleno ether **57** (363.7 mg, 1.27 mmol) was added a premixed solution of TPSCl (357.8 mg, 1.39 mmol) and AgOTf (427.8 mg, 1.39 mmol) in dichloromethane (10 mL) at -78 °C followed by addition of (diisopropylethylamine, 0.66 mL). The reaction was stirred overnight and then the reaction was quenched with water (1 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 X 10 mL). The combined organic layers were dried with Na_2SO_4, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (gradient: 3%-15% Et_2O:hexanes). The triphenylsilyl ether **59** was obtained as a yellow oil (476.6 mg, 0.873 mmol) in 69% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ:



59

7.68 (m, 8H)

7.43 (t, *J* = 7.4 Hz, 4H)

7.40-7.36 (m, 5H)

7.22-7.18 (m, 3H)

3.70 (dd, *J* = 8.1, 2.9 Hz, 1H)

3.39 (d, *J* = 12.2 Hz, 1H)

3.08 (d, *J* = 12.1 Hz, 1H)

2.39 (s, 1H)

1.63-1.26 (m, 2H)

1.23 (s, 3H)

1.01-0.84 (m, 2H)

0.62 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 135.8, 134.5, 132.7, 130.2, 129.2, 128.1, 126.9, 80.6, 74.8, 39.5, 35.4, 23.5, 20.2, 14.0.

Preparation of sodium mesitylselenolate in EtOH: To a solution of dimesityl diselenide (3.98 g, 10.0 mmol) in 50 mL of 1.0 M NaOH in 95% EtOH was added sodium borohydride (0.7864 g, 20.0 mmol) and the reaction was refluxed at 85 °C for 2 h until the reaction turned translucent forming a 0.4 M solution of sodium mesitylselenolate.

Preparation of sodium mesitylselenolate in iPrOH: To a solution of dimesityl diselenide (3.98 g, 10.0 mmol) in 50 mL of 0.5 M NaOH in iPrOH was added sodium borohydride (0.7864 g,

20.0 mmol) and the reaction was refluxed at 100 °C for 2 h until the reaction turned translucent forming a 0.4 M solution of sodium mesitylselenolate.

Preparation of sodium mesitylselenolate in *t*BuOH:H_2O mixture: To a solution of dimesityl diselenide (3.98 g, 10.0 mmol) in 50 mL of 0.5 M NaOH in 1:1 mixture of *t*BuOH:H_2O was added sodium borohydride (0.7864 g, 20.0 mmol) and the reaction was refluxed at 100 °C for 2 h until the reaction turned translucent forming a 0.4 M solution of sodium mesitylselenolate.

Temperature Study on Epoxide Opening Reactions.

General Procedure 1.

A solution of the epoxy alcohol **49** (99.0 mg, 0.760 mmol) was pre-stirred for 1 h in 7.6 mL of 1.0 M NaOH in 95% EtOH. To this was added sodium mesitylselenolate in EtOH (3.04 mmol, 7.6 mL, 4.0 equiv) over 2 h at 85 °C and the reaction mixture stirred for 18 h. It was quenched with 5 mL of brine and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried with $MgSO_4$. After the removal of solvent *in vacuo*, purification by silica gel column chromatography using EtOAc:hexanes (1:20 to 1:5) afforded the seleno ether **66** (120.0 mg, 0.365 mmol) 48% in yield and the seleno ether **67** (85.0 mg, 0.258) in 34% yield.

General Procedure 2.

To a solution of the epoxy alcohol **49** (99.0 mg, 0.760 mmol) in 7.6 mL of 1.0 M NaOH in 95% EtOH was added sodium mesitylselenolate in EtOH (3.04 mmol, 7.6 mL, 4.0 equiv) in one portion at 85 °C and the reaction mixture was stirred for 18 h. It was quenched with 5 mL of brine and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 20 mL) and

the combined organic layers were dried with $MgSO_4$. After the removal of the solvent *in vacuo*, purification by silica gel column chromatography using EtOAc:hexanes (1:20 to 1:5) afforded the seleno ether **66** (110.0 mg, 0.334 mmol) in 44% yield and the seleno ether **67** (85.9 mg, 0.258) in 34% yield.

General Procedure 3.

A solution of the epoxy alcohol **49** (99.0 mg, 0.760 mmol) was pre-stirred for 1 h in 7.6 mL of 0.5 M NaOH in iPrOH. To this solution was added sodium mesitylselenolate in iPrOH (3.04 mmol, 7.6 mL, 4.0 equiv) over 2 h at 100 °C and the reaction mixture was stirred for 18 h. The reaction mixture was quenched with 5 mL of brine and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried with $MgSO_4$. After the removal of the solvent *in vacuo*, purification by silica gel column chromatography using EtOAc:hexanes (1:20 to 1:5) afforded the seleno ether **66** (75.9 mg, 0.228 mmol) 30% in yield and the seleno ether **67** (85.0 mg, 0.0988) in 15% yield.

General Procedure 4.

To a solution of the epoxy alcohol **49** (33.0 mg, 0.253 mmol) in 2.5 mL of 1.0 M NaOH in 95% EtOH was added sodium mesitylselenolate in EtOH (1.00 mmol, 2.5 mL, 4.0 equiv) in one portion and the reaction mixture was microwaved at 85 °C with stirring for 12 h. The reaction mixture was quenched with 2 mL of brine and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers were dried with $MgSO_4$. After the removal of the solvent *in vacuo*, purification by silica gel column chromatography using

EtOAc:hexanes (1:20 to 1:5) afforded the seleno ether **66** (150.2 mg, 0.152 mmol) 60% in yield and the seleno ether **67** (42.5 mg, 0.0430) in 17% yield.

(2*S*,3*S*)-1-(Mesitylselanyl)-2-methylhexane-2,3-diol, 67.

^{1}H NMR (400 MHz, $CDCl_3$) δ

6.92 (s, 2H)

3.50-3.54 (m, 1H)

3.09 (d, *J* = 12.0 Hz, 1H)

2.79 (d, *J* = 12.0 Hz, 1H)

2.75 (s, 1H)

2.56 (s, 6H)

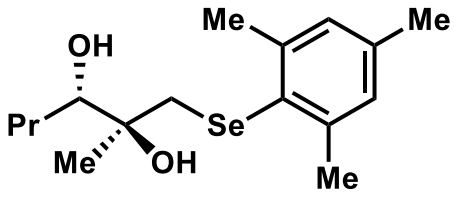
2.26 (s, 3H)

2.21 (d, *J* = 3.6 Hz, 1H)

1.26-1.63 (m, 4H)

1.30 (s, 3H)

0.93 (t, *J* = 7.0 Hz, 3H).



67

^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.6, 138.4, 128.8, 128.0, 77.3, 74.1, 38.1, 33.3, 24.4, 23.9, 20.9, 20.0, 14.0.

(EI) *m/z*: [M]+ Calcd. For $C_{16}H_{26}O_2Se$ 330.1093; found: 330.1081.

(2*S*,3*R*)-3-(Mesitylselanyl)-2-methylhexane-1,2-diol, 68.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

6.93 (s, 2H)

3.53 (d, *J* = 11.2 Hz, 1H)

3.29 (d, *J* = 11.2 Hz, 1H)

3.25 (dd, *J* = 9.4, 2.6 Hz, 1H)

2.55 (s, 6H)

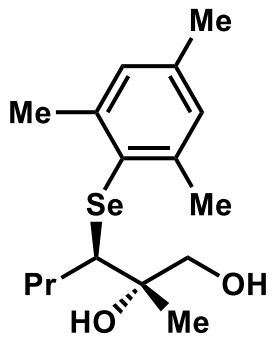
2.45 (br s, 1H)

2.24 (s, 3H)

1.39-1.97 (m, 5H)

1.24 (s, 3H)

0.91 (t, *J* = 6.8 Hz, 3H).



68

^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.4, 138.3, 129.1, 128.4, 68.9, 52.1, 33.6, 24.6, 24.5, 22.3, 20.9, 20.0, 14.2.

(EI) *m/z*: [M]+ Calcd. For $C_{16}H_{26}O_2Se$ 330.1093; found: 330.1082.

(2*S*,3*S*)-(3-Heptyloxiran-2-yl)methanol, 30a.

To a suspension of 60% sodium hydride in mineral oil (1.17 g, 29.3 mmol) (washed three times with hexanes) in Et_2O (12 mL) was added triethyl phosphonoacetate (3.2625 g, 25.2 mmol) dropwise at 0 °C and the solution was stirred for 30 min. Octanal was added to the solution dropwise at 0 °C and the mixture was stirred at 0 °C for 1 h. DIBAL (1.0 M in THF, 60.5 mL, 60.5 mmol) was added dropwise at 0 °C and the mixture was stirred for 1 h. The solution was slowly quenched with MeOH (3 mL) at 0 °C followed by a saturated Rochelle's salt solution (100 mL) at 0 °C. The layers were separated then the aqueous solution was extracted with EtOAc (3 X 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica

gel (5%-20% EtOAc:hexanes). The allylic alcohol **70** was obtained as a 1:1 mixture with the cis-allylic alcohol and was taken as such into the next reaction. To a solution of L-(+)-DIPT (0.2290 g, 1.1 mmol) and 4Å molecular sieves (195 mg) in dichloromethane (19.5 mL) was added $Ti(OiPr)_4$ (0.1992 g, 0.701 mmol) and *t*BuOOH (5 M in decane, 1.7 mL, 8.5 mmol) dropwise at 0 °C. The solution was stirred for 20 min at -20 °C then cooled to -25 °C for the following addition. The allylic alcohol mixture in dichloromethane (10 mL) was added dropwise to the previous solution over 30 min at -25 °C. The reaction mixture was stirred for 26 h until the reaction was complete. Then the reaction was quenched with water (20 mL) and 30% NaOH brine solution (6 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (4 X 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (gradient: 2%-10% Et_2O:hexanes). The epoxy alcohol **30a** was obtained as a white solid, which was recrystallized from petroleum ether to yield white crystals (688.5 mg, 4.00 mmol) in 16% yield.

^1H NMR (400 MHz, $CDCl_3$) δ:

3.90 (ddd, *J* = 12.6, 5.2, 2.6 Hz, 1H)

3.62 (ddd, *J* = 12.1, 6.7, 4.3 Hz, 1H)

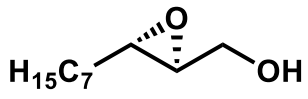
2.95 (m, 1H)

2.91 (m, 1H)

1.78-1.88 (m, 1H)

1.70-1.18 (m, 12H)

0.88 (t, *J* = 6.9 Hz, 3H).



30a

^{13}C NMR (100 MHz, $CDCl_3$) δ 61.9, 58.6, 56.2, 31.9, 31.7, 29.5, 29.3, 26.1, 22.8, 14.2.

(2*R*,3*S*)-(3-Decyloxiran-2-yl)methanol, 30b.

To a solution of propargyl alcohol **74** (8.86 mL, 150 mmol) in dichloromethane (300 mL) was added TsOH·H_2O (300.0 mg, 1.5 mmol) and 3,4-dihydro-2*H*-pyran at 0 °C. The reaction was stirred at 22 °C for 1 h and then the reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The layers were separated and the aqueous layer was extracted with dichloromethane (3 X 100 mL), dried with $MgSO_4$, filtered, and then concentrated *in vacuo* yielding the crude alkyne product **77**. To a solution of crude alkyne product **77** in THF (65 mL) was added methyllithium in Et_2O (1.6 M, 81.5 mL, 130 mmol) was added at 0 °C and the reaction was stirred for 15 min at 0 °C. A solution of 1-bromodecane (28.75g, 130 mmol) in DMSO (300 mL) was added to the previous solution at 0 °C. The reaction was warmed to 22 °C and stirred for 3 h, at which point the reaction was quenched with water (300 mL) and diluted with Et_2O (300 mL). The layers were separated, then the organic layer was washed with brine (4 X 100 mL), dried over $MgSO_4$, then concentrated in vacuo. The crude residue was purified by passing it through a pad of silica gel (20:1 petroleum ether:Et_2O) yielding a crude yellow oil. To a solution of this crude yellow oil and Lindlar's catalyst (317.3 mg) in EtOAc (60 mL) and MeOH (10 mL) was added two balloons of hydrogen. The reaction was kept for 23 h and then the reaction was filtered through a pad of silica gel eluting with EtOAc and the solution was concentrated *in vacuo*. The crude mixture was then diluted with MeOH (120 mL) and TsOH·H_2O (1.60 g, 42.0 mmol) was added and stirred for 4 h. The reaction was concentrated *in vacuo* and the crude residue was purified by flash column chromatography on silica gel (gradient: 2%-10% Et_2O:hexanes). The allylic alcohol **72** was obtained as a white solid (8.36 g, 42.1 mmol) in 28%

yield. To a solution of D-(-)-DIPT (1.86 mL, 9.22 mmol) and 4Å molecular sieves (7.4 g) in dichloromethane (110 mL) was added Ti(O*i*Pr)$_4$ (4.00 mL, 6.66 mmol) and *t*BuOOH (5 M in decane, 6.66 mL, 33.3 mmol) dropwise at -23 °C and the reaction was stirred for an additional hour. The allylic alcohol **72** in dichloromethane (15 mL) was added dropwise to the previous solution over 1 h at -23 °C. The reaction was stirred for 12 h until the reaction was complete. Then the reaction was quenched with water (40 mL) and 30% NaOH brine solution (12 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (4 X 100 mL), the organic layers were combined, dried over $MgSO_4$, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (gradient: 2%-10% EtOAc:hexanes). The epoxy alcohol **30b** was isolated as a white solid (771.6 mg, 3.60 mmol) in 2% yield over 4 steps.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

3.85 (dd, *J* = 12.2, 4.0 Hz, 1H)

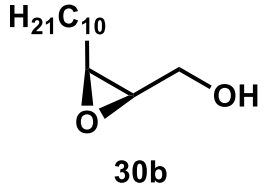
3.67 (dd, *J* = 12.1, 6.9 Hz, 1H)

3.15 (ddd, *J* = 6.9, 4.2, 4.2 Hz, 1H)

3.03 (ddd, *J* = 6.8, 5.5, 4.3 Hz, 1H)

1.71-1.26 (m, 18H)

0.88 (t, *J* = 6.9 Hz, 3H).



30b

^{13}C NMR (100 MHz, $CDCl_3$) δ: 61.1, 57.5, 56.9, 32.0, 29.7, 29.7, 29.7, 29.6, 29.5, 28.1, 26.8, 22.8, 14.3.

(*Z*)-4-(Phenylmethoxy)but-2-en-1-ol, 78.

To a suspension of 60% sodium hydride in mineral oil (4.40 g, 110 mmol) (washed three times with pentane) in THF (400 mL) and DMSO (100 mL) was added *Z*-butene-1,4-diol **77** (9.26 g, 100 mmol) in THF (250 mL). The reaction was stirred for 30 min and a solution of benzyl bromide (18.9 g, 110 mmol) in THF (250 mL) was added dropwise followed by the addition of tetrabutylammonium iodide (TBAI, 18.9 g, 50 mmol). The reaction was stirred overnight at 60 °C. The reaction was quenched with water (1 L), the layers were separated, and the aqueous layer was extracted with Et_2O (3 X 200 mL). The combined organic layers were then washed with brine (10 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (25% EtOAc:hexanes). The allylic alcohol **78** was obtained as a yellow oil (8.4754 g, 47.6 mmol) in 48% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.38-7.27 (m, 5H)

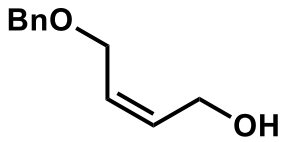
5.85-5.70 (m, 2H)

4.52 (s, 2H)

4.17-4.15 (m, 2H)

4.10-4.08 (m, 2H)

2.32 (s, 1H).



78

^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.9, 132.5, 128.6, 128.3, 128.0, 127.9, 72.6, 65.8, 58.7.

General Procedure for 30% NaOH brine solution.

NaOH (30 g) was dissolved into a solution of brine (100 mL).

(2*R*,3*S*)-3-(((Phenylmethoxy)methyl)oxiran-2-yl)methanol, 30c.

To a solution of L-(+)-DET (20 μL, 0.116 mmol) and 4Å molecular sieves (100 mg) in dichloromethane (6 mL) was added Ti(O*i*Pr)$_4$ (25 μL, 0.116 mmol) and *t*BuOOH (5 M in decane, 0.5 mL, 2.5 mmol) dropwise at -23 °C and stirred for an additional hour. The allylic alcohol **78** (152.4 mg, 0.855 mmol) in dichloromethane (2 mL) was added dropwise to the previous solution over 1 h at -23 °C. The reaction was stirred for 12 h until the reaction was complete. Then the reaction was quenched with 30% NaOH brine solution (40 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 X 6 mL), the organic layers were combined, dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (gradient: 5%-20% EtOAc:hexanes). The epoxy alcohol **30c** was isolated as a colorless oil (45.9 mg, 0.236 mmol) in 27% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.39-7.29 (m, 5H)

4.62 (d, *J* = 11.8 Hz, 1H)

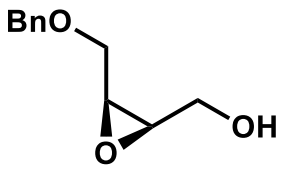
4.53 (d, *J* = 11.8 Hz, 1H)

3.80-3.71 (m, 3H)

3.66 (dd, *J* = 11.0, 5.0 Hz, 1H)

3.32-3.21 (m, 2H)

1.93 (br s, 1H).



30c

^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.5, 128.8, 128.2, 128.0, 73.7, 68.3, 60.9, 55.7, 54.9.

(*E*)-4-(Phenylmethoxy)but-2-en-1-ol, 81.

To a solution of dimethyl fumarate **79** (3.7018 g, 31.5 mmol) in toluene (21.7 mL) was added DIBAL in toluene (1.5M, 109.5 mL, 164.5 mmol) at -78 °C. The reaction was stirred overnight and then quenched with an aqueous solution of 30% NaOH (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 X 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (1:1 Et_2O:hexanes). The (*E*)-but-2-ene-1,4-diol **80** was used directly in the next reaction. To a suspension of 60% sodium hydride in mineral oil (1.15 g, 38.0 mmol) (washed three times with pentane) in THF (160 mL) and DMSO (40 mL) was added the butenediol **80** (2.77 g, 31.46 mmol) in THF (85 mL). The reaction was stirred for 30 min and a solution of benzyl bromide (6.48 g, 38 mmol) in THF (85 mL) was added dropwise followed by the addition of TBAI (5.78 g, 15.2 mmol). The reaction was stirred overnight at 60 °C. It was then quenched with water (330 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (3 X 68 mL). The combined organic layers were then washed with brine (10 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (25% EtOAc:hexanes). The allylic alcohol **81** was obtained as a yellow oil (2.51 g, 14.1 mmol) in 41% yield.

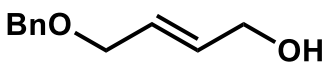
^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.35-7.27 (m, 5H)

5.95-5.81 (m, 2H)

4.53 (s, 2H)

4.16 (dq, *J* = 4.8, 1.2 Hz, 2H)



81

4.04 (d, *J* = 5.2, 1.1 Hz, 2H)

1.74 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.3, 132.3, 128.5, 127.9, 127.9, 127.8, 72.4, 70.2, 63.1.

(2*R*,3*S*)-3-(((Phenylmethoxy)methyl)oxiran-2-yl)methanol, 30d.

To a solution of L-(+)-DET (20 μL, 0.116 mmol) and 4Å molecular sieves (100 mg) in dichloromethane (6 mL) was added Ti(O*i*Pr)$_4$ (25 μL, 0.116 mmol) and *t*BuOOH (5 M in decane, 0.5 mL, 2.5 mmol) dropwise at -23 °C and the reaction was stirred for an additional hour. The allylic alcohol **80** (150.1 mg, 0.842 mmol) in dichloromethane (2 mL) was added dropwise to the previous solution over 1 h at -23 °C. The reaction was stirred for 12 h until the reaction was complete, and then the reaction was quenched with 30% NaOH brine solution (40 μL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 X 6 mL), the organic layers were combined, dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (gradient: 5%-20% EtOAc:hexanes). The epoxy alcohol **30d** was isolated as a colorless oil (110.4 mg, 0.568 mmol) in 68% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.38-7.27 (m, 5H)

4.60 (d, *J* = 12.0 Hz, 1H)

4.56 (d, *J* = 11.9 Hz, 1H)

3.94 (dd, *J* = 12.7, 2.5 Hz, 1H)

3.77 (dd, *J* = 11.5, 3.1 Hz, 1H)

30d

3.65 (dd, *J* = 12.7, 4.1 Hz, 1H)

3.53 (dd, *J* = 11.6, 5.5 Hz, 1H)

3.24 (ddd, *J* = 5.5, 2.7, 2.7 Hz, 1H)

3.10 (ddd, *J* = 4.1, 2.4, 2.4 Hz, 1H)

1.70 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.9, 128.6, 128.0, 128.0, 73.5, 69.8, 61.3, 55.8, 54.4.

(*S*,*E*)-3-(2,2-Dimethyl-1,3-dioxolan-4-(*S*)-yl)prop-2-en-1-ol, 87.

To a solution of D-mannitol **82** (36.43 g, 200 mmol) in DMSO (100 mL) was added 1,1-dimethoxyacetone (62.0 mL, 500 mmol) and TsOH (0.57 g, 3.0 mmol). The reaction was stirred for 48 h and quenched with a solution of saturated aqueous sodium bicarbonate (200 mL). The layers were separated and then the aqueous layer was extracted with EtOAc (3 X 300 mL). The combined organic layers were washed with brine (20 mL), dried with Na_2SO_4, filtered, and then concentrated *in vacuo*. The crude diacetal **83** was isolated as a white solid (42.62 g, 160 mmol) in 81% yield and was used directly in the next reaction. To a solution of the crude diacetal **83** (6.56 g, 25.0 mmol) in dichloromethane (50 mL) was added a solution of saturated aqueous sodium bicarbonate (3 mL) and $NaIO_4$ (8.02 g, 37.5 mmol). The solution was stirred vigorously for 2 h then quenched with $MgSO_4$, filtered, and then the solvent was concentrated *in vacuo*. The crude aldehyde **84** was used directly in the next reaction without further purification. To a solution of the aldehyde **84** in toluene (250 mL) was added (triphenylphosphoranylidene)acetaldehyde (15.85 g, 60 mmol) at 0 °C. The solution was filtered and then the filtrate was concentrated *in vacuo*. The crude enal **85** was used directly in the next reaction. To a solution of the enal **85** in dichloromethane (250 mL) was added DIBAL in

hexanes (1 M, 37.5 mL, 37.5 mmol) at 0 °C. The reaction was stirred at 0 °C for 5 h and quenched with MeOH (10 mL) followed by a saturated Rochelle's salt solution (50 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 X 100 mL). The organic layers were combined, dried over Na_2SO_4, filtered, then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (gradient: 10%-40% EtOAc:hexanes). The allylic alcohol **86** was isolated as a yellow oil (2.54 g, 16.0 mmol) in 52% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

5.94 (dt, *J* = 15.5, 5.1 Hz, 1H)

5.70 (ddd, *J* = 15.5, 7.5, 1.5 Hz, 1H)

4.52 (ddd, *J* = 7.2, 7.2, 7.2 Hz, 1H)

4.14 (d, *J* = 5.1 Hz, 2H)

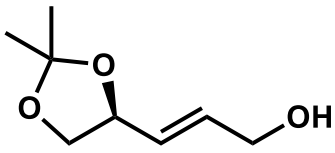
4.08 (dd, *J* = 8.2, 6.2 Hz, 1H)

3.58 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H)

2.05 (br s, 1H)

1.41 (s, 3H)

1.37 (s, 3H).



87

^{13}C NMR (100 MHz, $CDCl_3$) δ: 133.6, 128.5, 109.5, 76.6, 69.5, 62.7, 26.8, 26.0.

(2*S*,3*R*)-3-(((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)oxiran-2-yl)methanol, 30e.

To a solution of L-(+)-DET (96 μL, 0.565 mmol) and 4Å molecular sieves (425 mg) in dichloromethane (25.5 mL) was added Ti(O*i*Pr)$_4$ (100 μL, 0.404 mmol) and *t*BuOOH (5 M in

decane, 1.21 mL, 6.05 mmol) dropwise at -23 °C and stirred for an additional hour. The allylic alcohol **86** (638.8 mg, 4.04 mmol) in dichloromethane (8 mL) was added dropwise to the previous solution over 1 h at -23 °C. The reaction was stirred for 12 h until the reaction was complete. Then the reaction was quenched with 30% NaOH brine solution (40 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 X 25 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (gradient: 5%-20% EtOAc:hexanes). The epoxy alcohol **30e** was isolated as a yellow oil (239.1 mg, 1.37 mmol) in 34% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

4.12-4.07 (m, 2H)

3.95 (br d, *J* = 11.6 Hz, 1H)

3.85 (ddd, *J* = 10.6, 7.0, 1.4 Hz, 1H)

3.68 (d, *J* = 12.4 Hz, 1H)

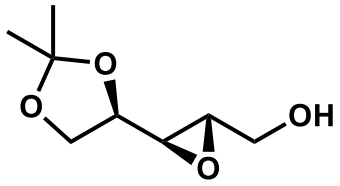
3.14-3.16 (m, 1H)

3.11-3.09 (m, 1H)

1.78 (br s, 1H)

1.42 (s, 3H)

1.36 (s, 3H).



30e

^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.1, 75.1, 66.0, 60.8, 55.3, 55.0, 26.3, 25.6.

(2*R*,3*S*)-3-(((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)oxiran-2-yl)methanol, 30f.

To a solution of D-(-)-DET (96 μL, 0.565 mmol) and 4Å molecular sieves (425 mg) in dichloromethane (25.5 mL) was added Ti(O*i*Pr)$_4$ (100 μL, 0.404 mmol) and *t*BuOOH (5 M in decane, 1.21 mL, 6.05 mmol) dropwise at -23 °C and stirred for an additional hour. The allylic alcohol **86** (638.8 mg, 4.04 mmol) in dichloromethane (8 mL) was added dropwise to the previous solution over 1 h at -23 °C. The reaction was stirred for 12 h until the reaction was complete. Then it was quenched with 30% NaOH brine solution (40 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 X 25 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (gradient: 5%-20% EtOAc:hexanes). The epoxy alcohol **30f** was isolated as a yellow oil (151.8 mg, 0.872 mmol) in 22% yield.

^{1}H NMR (400 MHz , $CDCl_3$) δ:

4.13 (dd, *J* = 8.0, 6.0 Hz, 1H)

3.89-4.00 (m, 3H)

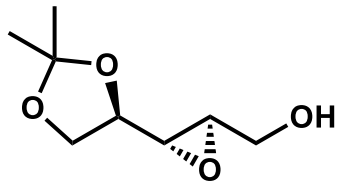
3.69 (ddd, *J* = 11.6, 7.6, 4.0 Hz, 1H)

3.08-3.12 (m, 2H)

1.65 (dd, *J* = 5.6, 7.6 Hz, 1H)

1.45 (s, 3H)

1.37 (s, 3H).



30f

^{13}C NMR (100 MHz, $CDCl_3$) δ: 109.9, 75.3, 66.9, 61.0, 57.1, 55.2, 26.5, 25.3.

(4*S*,5*S*)-(2,2-Dimethyl-1,3-dioxolane-4,5-diyl)dimethanol, 89.

To a solution of L-(+)-DET (88.35 g, 428.0 mmol) in chloroform (400 mL) was added 2,2-dimethoxyacetone (44.99 g, 480.0 mmol) and TsOH (0.4 g, 2.10 mmol). The reaction was stirred for 24 h and then quenched with a saturated aqueous solution of sodium carbonate (25 mL), filtered, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was vacuum distilled at 1 torr and 135 °C yielding a crude yellow oil of the acetonide **88**. To a solution of the crude acetonide **88** (63.90 g, 292.7 mmol) in MeOH (1 L) was slowly added $NaBH_4$ (22.60 g, 585.4 mmol). The reaction was stirred overnight and then quenched with water (50 mL) at 0 °C. The solution was concentrated *in vacuo* and filtered through Celite with EtOAc. The resulting solution was concentrated *in vacuo* yielding diol **89** (20.67 g, 127.5 mmol) in 44% yield.

^{1}H NMR (400 MHz , $CDCl_3$) δ:

4.03-3.99 (m, 2H)

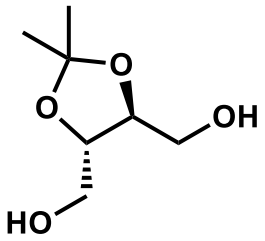
3.80 (ddd, *J* = 11.9, 2.5, 1.3 Hz, 2H)

3.69 (ddd, *J* = 11.9, 2.5, 1.3 Hz, 2H)

2.17-2.08 (m, 2H)

1.43 (s, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 109.4, 78.0, 62.1, 27.2.



89

(4*S*,5*S*)-5-(((Phenylmethoxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol, 90.

To a solution of the diol **89** (12.47 g, 76.9 mmol) in DMF (250 mL) was added 60% sodium hydride in mineral oil (6.61 g, 80.75 mmol). The solution was cooled to -22 °C and then benzyl bromide was added. The reaction was then stirred at 0 °C for 2 h and then the reaction was quenched with brine (200 mL). The layers were separated and the aqueous layer was extracted

with dichloromethane (4 X 200 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (30% EtOAc:hexanes). The alcohol **90** was isolated as a yellow oil (12.58 g, 49.8 mmol) in 65% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.34-7.27 (m, 5H)

4.58 (s, 2H)

4.05 (dt, *J* = 8.2, 5.4 Hz, 1H)

3.94 (dt, *J* = 8.4, 4.4 Hz, 1H)

3.76 (dd, *J* = 11.7, 4.4 Hz, 1H)

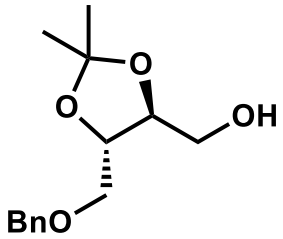
3.69-3.66 (m, 2H)

3.56 (dd, *J* = 9.9, 5.7 Hz, 1H)

2.34 (br s, 1H)

1.41 (s, 3H)

1.41 (s, 3H).



90

^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.7, 128.6, 128.0, 127.9, 109.5, 79.8, 76.7, 73.8, 70.5, 62.5, 27.10, 27.07.

(*E*)-3-(4*S*,5*S*)-5-(((Phenylmethoxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol, 93.

To a solution of oxalyl chloride (1.5 mL, 17.1 mmol) in dichloromethane (50 mL) was added DMSO (2.67 mL, 34.2 mmol) in dichloromethane (20 mL) dropwise at -60 °C. The reaction was stirred for 15 min and the alcohol **90** (2.88 g, 11.4 mmol) in dichloromethane (30 mL) was added

dropwise at -60 °C. The reaction was stirred for 1 h and triethylamine (11 mL) was added. The reaction was then warmed to 22 °C over 30 min and quenched with wet Et_2O (100 mL). The reaction was washed with brine (2 X 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was passed through a pad of silica gel (1:1 EtOAc:hexanes). The resulting solution was concentrated *in vacuo* and the resulting crude mixture was used directly in the next reaction. To a solution of triethyl phosphonoacetate (2.56g, 11.4 mmol) in THF (16.3 mL) was added 60% sodium hydride in mineral oil (0.46g, 11.4 mmol) at 0 °C. After stirring for 30 min the crude mixture of the aldehyde in THF (8 mL) was added dropwise. The reaction was stirred for 5 h and then it was filtered and concentrated in vacuo. The residue was diluted with water (15 mL) and hexanes (15 mL), the layers were separated, and the aqueous layer was extracted with hexanes (3 X 15 mL). The combined organic layers were washed with water (1 mL) and then brine (1 mL), dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The crude was diluted with dichloromethane (60 mL) and DIBAL in dichloromethane (1M, 27.3 mL, 27.3 mmol) was added at -78 °C. The reaction was warmed to 22 °C and stirred for 1 h. Then the reaction was quenched with MeOH (1 mL) and a saturated aqueous solution of Rochelle's salt (10 mL) at 0 °C. The layers were separated and the aqueous layer was extracted with dichloromethane (3 X 50 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (gradient: 10%-30% EtOAc:hexanes). The alcohol **93** was isolated as a yellow oil (1.14 g, 4.11 mmol) in 36% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.36-7.27 (m, 5H)

5.93 (dtd, J = 15.5, 5.1, 0.9 Hz, 1H)

5.72 (ddt, *J* = 15.5, 7.5, 1.7 Hz, 1H)

4.60 (d, *J* = 9.6 Hz, 1H)

4.59 (d, *J* = 9.6 Hz, 1H)

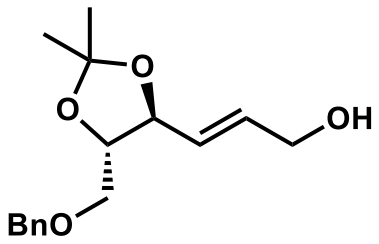
4.27 (dd, *J* = 7.9, 7.9 Hz, 1H)

4.15 (dd, *J* = 5.1, 1.0 Hz, 2H)

3.92 (ddd, *J* = 8.7, 5.4, 3.6 Hz, 1H)

3.63-3.56 (m, 2H)

1.44 (s, 6H).



93

^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.1, 135.3, 128.5, 127.9, 127.8, 127.8, 109.6, 80.2, 78.6, 73.7, 69.5, 62.8, 27.1, 27.1.

(2*S*,3*S*)-1-(Mesitylselanyl)decane-2,3-diol, 94.

Prepared according to general procedure 1 starting with the epoxy alcohol **30a**, purified by flash column chromatography (gradient: 3%-9% EtOAc:hexanes). The seleno ether **94** was isolated as a white solid (108.9 mg, 0.293 mmol) in 39% yield and the seleno ether **95** was isolated as a white solid (130.6 mg, 0.351 mmol) in 46% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ

6.93 (s, 2H)

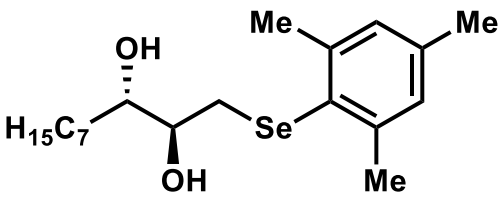
3.64-3.67 (m, 1H)

3.46 (ddd, *J* = 9.7, 9.7, 3.6 Hz, 1H)

2.89 (dd, *J* = 12.6, 3.0 Hz, 1H)

2.78 (dd, *J* = 12.8, 9.6 Hz, 1H)

2.54 (s, 6H)



94

2.26 (s, 3H)

1.91 (br s, 1H)

1.18-1.47 (m, 13H)

0.87 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.8, 138.4, 128.7, 126.5, 73.5, 72.9, 32.0, 31.7, 31.4, 29.4, 29.1, 25.7, 24.3, 22.5, 20.8, 13.9.

HRMS (EI) *m/z*: [M]+ Calcd. For $C_{19}H_{32}O_2Se$ 372.1562; found: 372.1549.

(2*S*,3*R*)-3-(Mesitylselanyl)decane-1,2-diol, 95.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

6.93 (s, 2H)

3.57-3.68 (m, 3H)

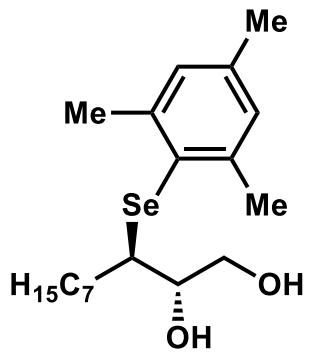
3.13-3.17 (m, 1H)

2.54 (s, 6H)

2.26 (s, 3H)

1.20-1.74 (m, 14H)

0.88 (t, *J* = 6.8 Hz, 3H).



95

^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.9, 138.4, 128.8, 126.8, 73.5, 64.5, 49.4, 31.7, 30.3, 29.5, 29.0, 28.1, 24.4, 22.5, 20.8, 14.0.

HRMS (EI) *m/z*: [M]+ Calcd. For $C_{19}H_{32}O_2Se$ 372.1562; found: 372.1551.

(2*R*,3*S*)-1-(Mesitylselanyl)tridecane-2,3-diol, 96.

Prepared according to general procedure 1 starting with the epoxy alcohol **30b**, purified by flash column chromatography (gradient: 2%-9% EtOAc:hexanes). The seleno ether **96** was isolated as a white solid (74.7 mg, 0.180 mmol) in 24% yield, the seleno ether **97** was isolated as a white solid (158.7 mg, 0.384 mmol) in 51% yield, and the seleno ether **97** was isolated as a white solid (76.8 mg, 0.186 mmol) in 24% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

6.93 (s, 2H)

3.46-3.52 (m, 1H)

3.44-3.38 (m, 1H)

2.87 (dd, *J* = 12.4, 4.4 Hz, 1H)

2.80 (dd, *J* = 12.4, 4.0 Hz, 1H)

2.59 (d, *J* = 4.0 Hz, 1H)

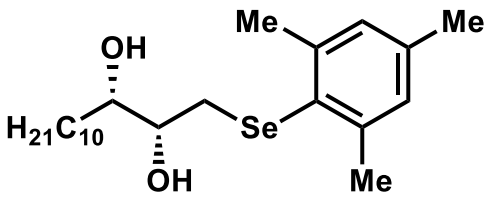
2.54 (s, 6H)

2.26 (s, 3H)

2.05 (d, *J* = 6.0 Hz, 1H)

1.18-1.48 (m, 18H)

0.88 (t, *J* = 6.8 Hz, 3H).



96

^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.9, 138.5, 128.8, 126.9, 73.6, 73.0, 33.9, 33.1, 31.9, 29.65, 29.62, 29.60, 29.58, 29.3, 25.6, 24.5, 22.7, 20.9, 14.1.

HRMS (EI) *m/z*: [M]+ Calcd. For $C_{22}H_{38}O_2Se$ 414.2032; found: 414.2019.

(2*S*,3*S*)-2-(Mesitylselanyl)tridecane-1,3-diol, 97.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

6.93 (s, 2H)

3.75 (ddd, *J* = 7.9, 3.9, 3.9 Hz, 1H)

3.61 (dd, *J* = 11.2, 4.0 Hz, 1H)

3.54 (dd, *J* = 11.2, 3.6 Hz, 1H)

3.20 (ddd, *J* = 6.4, 4.4, 4.4 Hz, 1H)

2.54 (s, 6H)

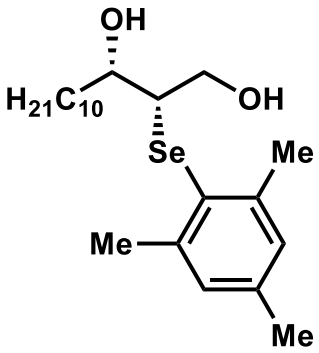
2.26 (s, 3H)

1.96 (br s, 1H)

1.73-1.82 (m, 1H)

1.20-1.60 (m, 18H)

0.88 (t, *J* = 6.7 Hz, 3H).



97

^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.9, 138.4, 128.9, 127.1, 74.0, 64.8, 49.4, 32.2, 31.9, 29.60, 29.58, 29.5, 29.3, 27.8, 24.6 (C2), 22.7, 20.9, 14.1.

HRMS (EI) *m/z*: [M]+ Calcd. For $C_{22}H_{38}O_2Se$ 414.2032; found: 414.2016.

(2*R*,3*R*)-3-(Mesitylselanyl)tridecane-1,2-diol , 98.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

6.93 (s, 2H)

3.92-3.97 (m, 1H)

3.81-3.78 (m, 2H)

3.16 (ddd, *J* = 4.8, 2.7, 2.7 Hz, 1H)

2.59 (d, *J* = 5.2 Hz, 1H)

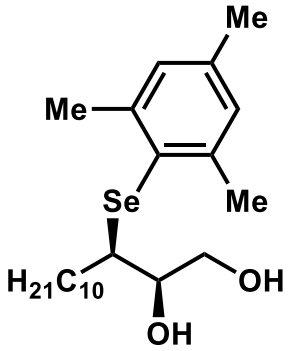
2.55 (s, 6H)

2.43 (dd, *J* = 6.0, 6.0 Hz, 1H)

2.26 (s, 3H)

1.17-1.76 (m, 18H)

0.88 (t, *J* = 6.8 Hz, 3H).



98

^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.3, 138.5, 128.8, 126.2, 74.3, 65.1, 53.9, 35.3, 31.9, 29.62, 29.61, 29.59, 29.56, 29.4, 26.2, 24.6, 22.7, 20.9, 14.1.

HRMS (EI) *m/z*: [M]+ Calcd. For $C_{22}H_{38}O_2Se$ 414.2032; found: 414.2019.

(2*S*,3*R*)-1-(Phenylmethoxy)-4-(mesitylselanyl)butane-2,3-diol, 99.

Prepared according to general procedure 1 starting with the epoxy alcohol **30c**, purified by flash column chromatography (gradient: 10%-33% EtOAc:hexanes). The seleno ether **99** was isolated as a colorless oil (126.4 mg, 0.321 mmol) in 42% yield, the seleno ether **100** was isolated as a colorless oil (80.4 mg, 0.204 mmol) in 27% yield, and the seleno ether **101** was isolated as a colorless oil (89.5 mg, 0.228 mmol) in 30% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

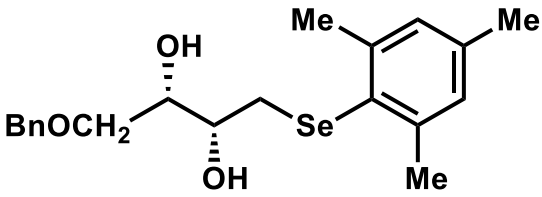
7.27-7.36 (m, 5H)

6.92 (s, 2H)

4.54 (d, *J* = 12.0 Hz, 1H)

4.50 (d, *J* = 11.8 Hz, 1H)

3.84-3.80 (m, 1H)



99

3.69-3.63 (m, 1H)

3.60-3.53 (m, *J* = 1.2 Hz, 2H)

2.84 (d, *J* = 6.4 Hz, 2H)

2.77 (d, *J* = 4.4 Hz, 1H)

2.52 (s, 6H)

2.50 (s, 1H)

2.26 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.0, 138.4, 137.6, 128.7, 128.5, 127.9, 127.8, 127.1, 73.6, 72.5, 71.5, 71.4, 32.1, 24.5, 20.9.

HRMS (EI) *m/z*: [M]+ Calcd. For $C_{20}H_{26}O_3Se$ 394.1042; found: 394.1029.

(2*S*,3*S*)-4-(Phenylmethoxy)-2-(mesitylselanyl)butane-1,3-diol, 100.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.28-7.38 (m, 5H)

6.92 (s, 2H)

4.52 (s, 2H)

4.16-4.21 (m, 1H)

3.76-3.81 (m, 3H)

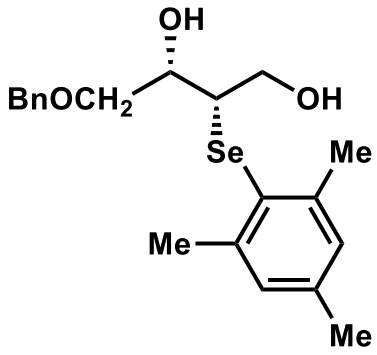
3.67 (dd, *J* = 9.2, 5.2 Hz, 1H)

3.27 (ddd, *J* = 5.2, 4.4, 3.2 Hz, 1H)

2.89 (d, *J* = 4.0 Hz, 1H)

2.51-2.56 (m, 7H)

2.26 (s, 3H).



100

^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.3, 138.6, 137.7, 128.8, 128.5, 127.9, 127.8, 126.2, 73.6, 72.4, 72.3, 64.3, 50.4, 24.6, 20.9.

HRMS (EI) *m/z*: [M]+ Calcd. For $C_{20}H_{26}O_3Se$ 394.1042; found: 394.1027.

(2*R*,3*R*)-4-(Phenylmethoxy)-3-(mesitylselanyl)butane-1,2-diol, 101.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.27-7.36 (m, 5H)

6.93 (s, 2H)

4.50 (d, *J* = 12.0 Hz, 1H)

4.47 (d, *J* = 12.0 Hz, 1H)

3.96-4.01 (m, 1H)

3.87-3.92 (m, 1H)

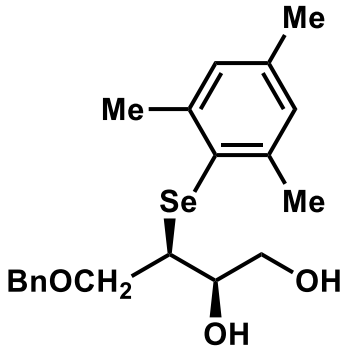
3.70-3.76 (m, 3H)

3.22 (td, *J* = 6.8, 4.0 Hz, 1H)

3.14 (d, *J* = 4.8 Hz, 1H)

2.52 (s, 7H)

2.27 (s, 3H).



101

^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.3, 138.6, 137.3, 128.8, 128.6, 128.0, 127.9, 126.6, 73.5, 73.3, 71.1, 64.5, 47.2, 24.6, 21.0.

HRMS (EI) *m/z*: [M]+ Calcd. For $C_{20}H_{26}O_3Se$ 394.1042; found: 394.1028.

(2*S*,3*S*)-1-(Phenylmethoxy)-4-(mesitylselanyl)butane-2,3-diol, 102.

Prepared according to general procedure 1 starting with the epoxy alcohol **30d**, purified by flash column chromatography (gradient: 10%-33% EtOAc:hexanes). The seleno ether **102** was isolated as a colorless oil (84.3 mg, 0.214 mmol) in 28% yield, the seleno ether **103** was isolated as a colorless oil (85.9 mg, 0.218 mmol) in 29% yield, and the seleno ether **104** was isolated as a colorless oil (106.8 mg, 0.271 mmol) in 36% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ

7.28-7.37 (m, 5H)

6.92 (s, 2H)

4.52 (s, 2H)

3.66-3.75 (m, 1H)

3.66-3.61 (m, 2H)

3.57 (dd, *J* = 9.8, 6.2 Hz, 1H)

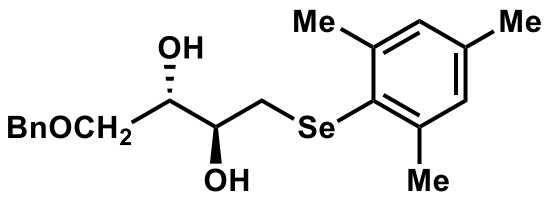
2.95 (dd, *J* = 12.4, 4.0 Hz, 1H)

2.82 (dd, *J* = 12.6, 8.6 Hz, 1H)

2.71 (d, *J* = 4.8 Hz, 1H)

2.54 (s, 7H)

2.26 (s, 3H).



102

^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.9, 138.5, 137.7, 128.7, 128.5, 127.9, 127.8, 126.8, 73.6, 72.3, 71.7, 71.2, 32.7, 24.5, 20.9.

HRMS (EI) *m/z*: [M]+ Calcd. For $C_{20}H_{26}O_3Se$ 394.1042; found: 394.1028.

(2*R*,3*S*)-4-(Phenylmethoxy)-2-(mesitylselanyl)butane-1,3-diol, 103.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.29-7.38 (m, 5H)

6.93 (s, 2H)

4.53 (s, 2H)

4.03-4.08 (m, 1H)

3.75-3.80 (m, 3H)

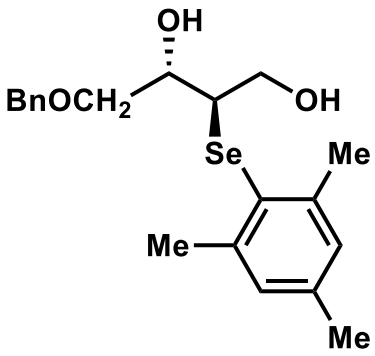
3.64 (dd, *J* = 9.6, 6.0 Hz, 1H)

3.20 (ddd, *J* = 7.2, 6.0, 4.0 Hz, 1H)

2.98 (br s, 2H)

2.52 (s, 6H)

2.26 (s, 3H).



103

^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.3, 138.7, 137.5, 128.9, 128.5, 128.0, 127.9, 126.1, 73.6, 73.2, 72.6, 63.8, 48.2, 24.6, 20.9.

HRMS (EI) *m/z*: [M]+ Calcd. For $C_{20}H_{26}O_3Se$ 394.1042; found: 394.1027.

(2*S*,3*R*)-4-(Phenylmethoxy)-3-(mesitylselanyl)butane-1,2-diol, 104.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.23-7.35 (m, 5H)

6.93 (s, 2H)

4.47 (d, *J* = 11.5 Hz, 1H)

4.44 (d, *J* = 11.5 Hz, 1H)

3.92-3.97 (m, 1H)

3.81 (dd, *J* = 10.0, 8.2 Hz, 1H)

3.70-3.77 (m, 2H)

3.66 (dd, *J* = 9.8, 3.4 Hz, 1H)

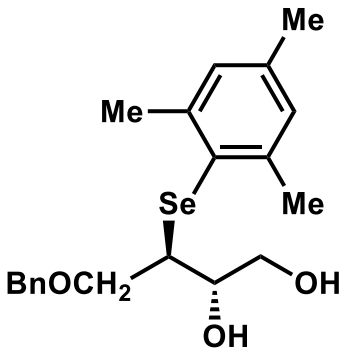
3.37 (d, *J* = 4.8 Hz, 1H)

3.26 (ddd, *J* = 8.6, 6.0, 3.6 Hz, 1H)

2.52 (s, 6H)

2.44 (br s, 1H)

2.27 (s, 3H).



104

^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.4, 138.7, 137.1, 128.8, 128.6, 128.1, 127.9, 126.4, 73.9, 73.4, 71.1, 65.1, 45.4, 24.6, 21.0.

HRMS (EI) *m/z*: [M]+ Calcd. For $C_{20}H_{26}O_3Se$ 394.1042; found: 394.1026.

(1*R*,2*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-(mesitylselanyl)propane-1,2-diol, 105.

Prepared according to general procedure 1 starting with the epoxy alcohol **30e**, purified by flash column chromatography (gradient: 10%-33% EtOAc:hexanes). The seleno ether **105** was isolated as a colorless oil (184.8 mg, 0.495 mmol) in 65% yield, and seleno ether **106** was isolated as a colorless oil (80.8 mg, 0.216 mmol) in 29% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

6.93 (s, 2H)

4.24 (ddd, *J* = 6.8, 4.4, 4.4 Hz, 1H)

4.01 (dd, *J* = 8.4, 6.4 1H)

3.86 (dd, *J* = 8.4, 7.2 Hz, 1H)

3.50-3.46 (m, 1H)

3.44-3.39 (m, 1H)

3.09 (dd, *J* = 12.6, 3.8 Hz, 1H)

2.84 (dd, *J* = 12.4, 8.4 Hz, 1H)

2.71 (br s, 1H)

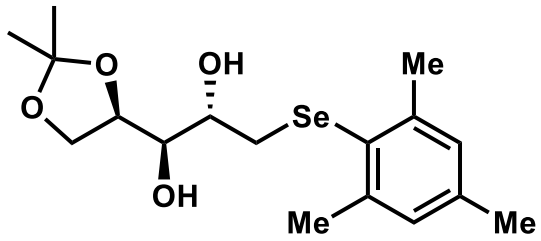
2.55 (s, 6H)

2.46 (br s, 1H)

2.26 (s, 3H)

1.40 (s, 3H)

1.36 (s, 3H).



105

^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.9, 138.5, 128.8, 126.8, 109.3, 75.9, 73.2, 72.1, 66.4, 33.6, 26.4, 25.3, 24.5, 20.9.

HRMS (EI) *m/z*: [M]+ Calcd. For $C_{17}H_{26}O_4Se$ 374.0991; found: 374.0978.

(1*S*,2*R*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(mesitylselanyl)propane-1,3-diol, 106.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

6.94 (s, 2H)

4.46 (ddd, *J* = 6.8, 2.8, 2.8 Hz, 1H)

4.07 (dd, *J* = 8.2, 6.8 Hz, 1H)

3.78-3.87 (m, 4H)

3.12-3.16 (m, 1H)

2.95 (br s, 1H)

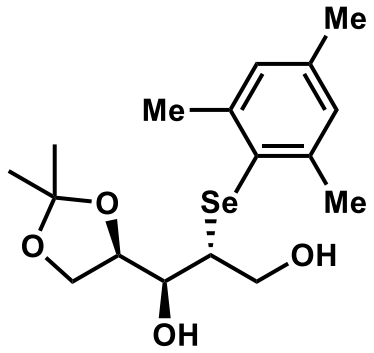
2.73 (br s, 1H)

2.54 (s, 6H)

2.26 (s, 3H)

1.44 (s, 3H)

1.35 (s, 3H).



106

^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.3, 138.8, 128.9, 126.2, 109.8, 76.8, 72.8, 66.5, 63.1, 49.8, 26.3, 25.2, 24.6, 20.9.

HRMS (EI) *m/z*: [M]+ Calcd. For $C_{17}H_{26}O_4Se$ 374.0991; found: 374.0975.

(1*S*,2*R*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-(mesitylselanyl)propane-1,2-diol, 107 and (1*R*,2*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(mesitylselanyl)propane-1,3-diol, 108.

Prepared according to general procedure 1 starting with the epoxy alcohol **30f**, purified by flash column chromatography (gradient: 10%-33% EtOAc:hexanes). The seleno ethers **107** and **108** were isolated as an inseparable colorless oil (265.0 mg, 0.710 mmol in total, 53% yield of **107**, 40% yield of **108**).

(1*S*,2*R*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3-(mesitylselanyl)propane-1,2-diol, 107

^{1}H NMR (400 MHz, $CDCl_3$) δ:

6.93 (s, 2H)

4.17 (ddd, *J* = 6.3, 6.3, 6.3 Hz, 1H)

4.02-4.06 (m, 2H)

3.92-3.86 (m, 1H)

3.72 (t, *J* = 5.8 Hz, 1H)

3.61-3.65 (m, 1H)

3.07-3.01 (m, 1H)

2.86-2.81 (m, 1H)

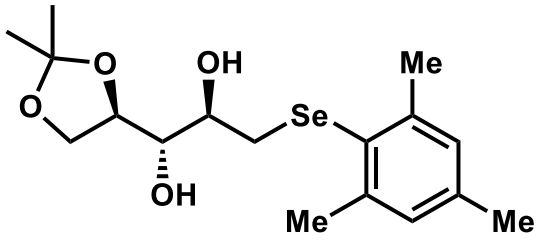
2.55 (s, 6H)

2.39-2.35 (m, 1H)

2.26 (s, 3H)

1.38 (s, 3H)

1.33 (s, 3H)



107

^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.8, 138.4, 128.7, 126.6, 109.4, 75.9, 73.2, 71.4, 66.4, 32.3, 26.4, 25.1, 24.5, 24.4 (C2), 20.8.

HRMS (EI) *m/z*: [M]+ Calcd. For $C_{17}H_{26}O_4Se$ 374.0991; found: 374.0978.

(1*R*,2*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(mesitylselanyl)propane-1,3-diol, 108.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

6.94 (s, 2H)

4.26 (ddd, *J* = 6.3, 6.3, 6.3 Hz, 1H)

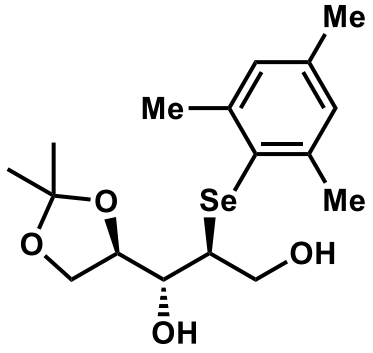
4.02-4.06 (m, 2H)

3.90 (dd, *J* = 6.8, 8.4 Hz, 1H)

3.85 (brs, 1H)

3.81 (dd, *J* = 5.2, 12.0 Hz, 1H)

3.61-3.65 (m, 1H)



108

3.23 (td, *J* = 3.2, 5.2 Hz, 1H)

3.04 (dd, *J* = 3.2, 12.4 Hz, 1H)

2.84 (dd, *J* = 8.8, 12.4 Hz, 2H)

2.53 (s, 7H)

2.36 (brs, 1H)

2.26 (s, 3H)

1.33 (s, 3H)

1.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.1, 138.7, 128.8, 125.9, 109.0, 76.5, 75.2, 65.8, 63.1, 48.5, 26.5, 25.1, 25.0, 24.4 (C2), 20.8 (C2).

HRMS (EI) *m/z*: [M]+ Calcd. For $C_{17}H_{26}O_4Se$ 374.0991; found: 374.0978.

(1*R*,2*S*)-1-((4*S*,5*S*)-5-((Phenylmethoxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(mesitylselanyl)propane-1,2-diol, 109.

Prepared according to general procedure 1 starting with the epoxy alcohol **30g**, purified by flash column chromatography (gradient: 10%-33% EtOAc:hexanes). The seleno ether **109** was isolated as a colorless oil (196.4 mg, 0.398 mmol) in 52% yield, and the seleno ether **110** was isolated as a colorless oil (90.5 mg, 0.183 mmol) in 24% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.27-7.36 (m, 5H)

6.92 (s, 2H)

4.57 (s, 2H)

4.26 (ddd, *J* = 8.4, 8.4, 5.2 Hz, 1H)

4.07 (dd, *J* = 8.2, 2.0 Hz, 1H)

3.58-3.65 (m, 2H)

3.54 (dd, *J* = 10.4, 4.8 Hz, 1H)

3.49-3.45 (m, 1H)

3.05 (dd, *J* = 12.6, 4.2 Hz, 1H)

2.86 (dd, *J* = 12.4, 8.0 Hz, 1H)

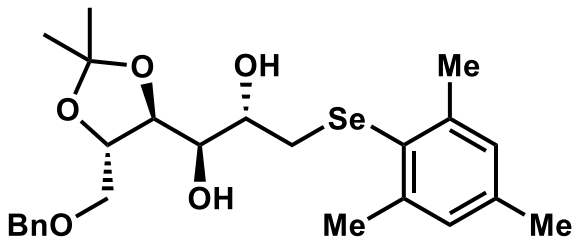
2.74 (br s, 1H)

2.54 (s, 6H)

2.41 (br s, 1H)

2.26 (s, 3H)

1.41 (s, 6H).



109

^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.8, 138.3, 137.7, 128.6, 128.3, 127.62, 127.60, 126.9, 109.6, 78.0, 76.0, 73.5, 72.4, 71.3, 70.1, 33.2, 27.1, 26.8, 24.4, 20.8.

HRMS (EI) *m/z*: [M]+ Calcd. For $C_{25}H_{34}O_5Se$ 494.1566; found: 494.1549.

(1*S*,2*R*)-1-((4*S*,5*S*)-5-((Phenylmethoxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(mesitylselanyl)propane-1,3-diol

^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.27-7.37 (m, 5H)

6.92 (s, 2H)

4.57 (s, 2H)

4.25 (dd, *J* = 8.2, 1.4 Hz, 1H)

4.17-4.22 (m, 1H)

3.82-3.87 (m, 2H)

3.78 (dd, *J* = 12.0, 6.8 Hz, 1H)

3.64 (dd, *J* = 10.0, 4.8 Hz, 1H)

3.56 (dd, *J* = 10.2, 5.0 Hz, 1H)

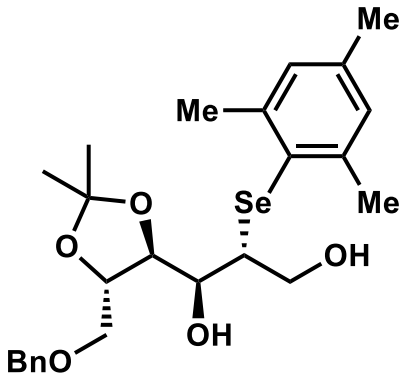
3.19 (ddd, *J* = 6.8, 6.8, 3.3 Hz, 1H)

2.52 (s, 6H)

2.25 (s, 3H)

1.43 (s, 3H)

1.36 (s, 3H).



110

^{13}C NMR (100 MHz, CDCl3) δ: 143.2, 138.6, 137.7, 128.7, 128.3, 127.7, 127.6, 126.4, 109.7, 79.5, 75.9, 73.5, 71.2, 70.1, 63.1, 50.2, 26.9, 26.7, 24.4, 20.8.

HRMS (EI) *m/z*: [M]+ Calcd; For $C_{25}H_{34}O_5Se$ 494.1566; found: 494.1547.

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Chapter 2

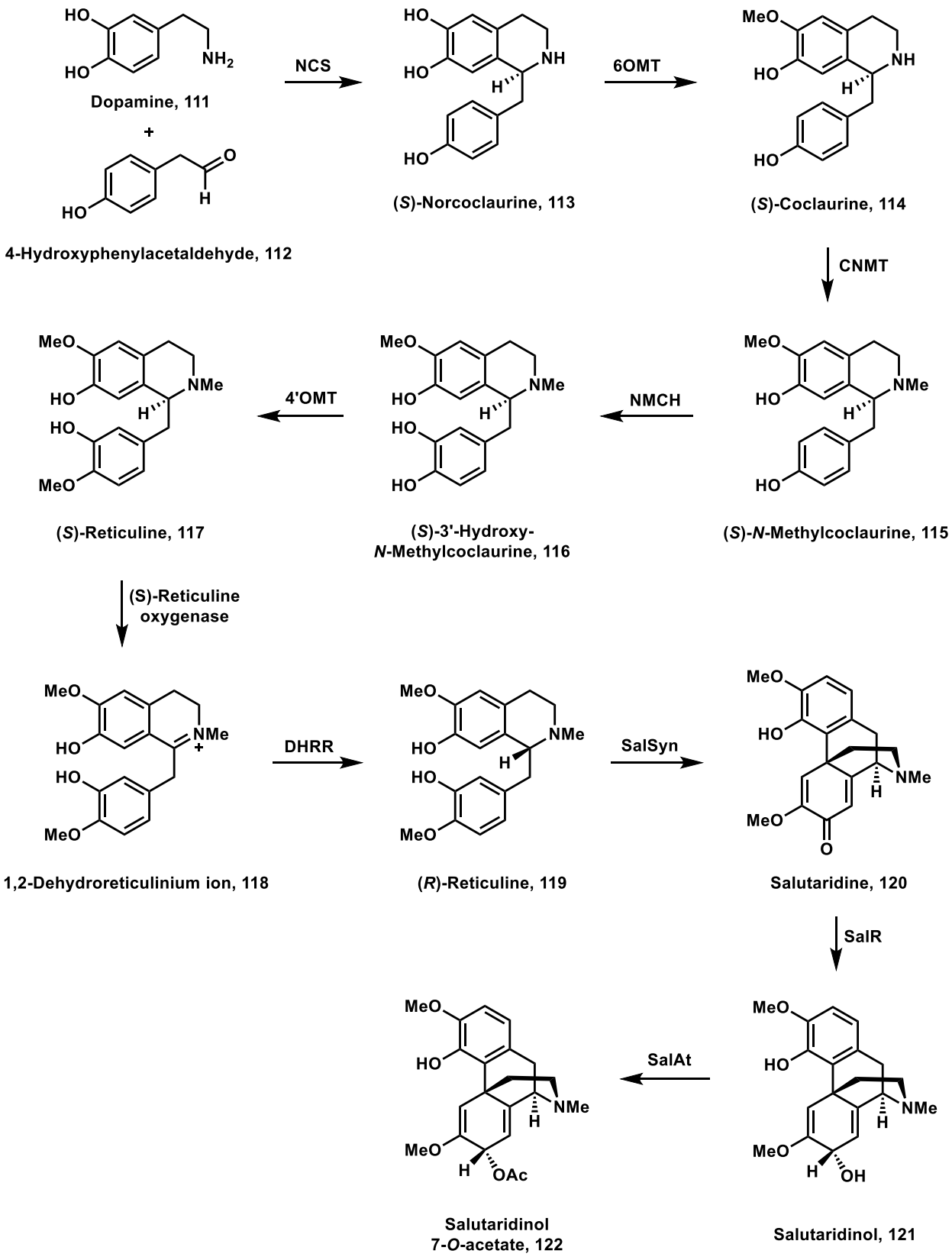
Progress Towards the Synthesis of Morphine

Introduction

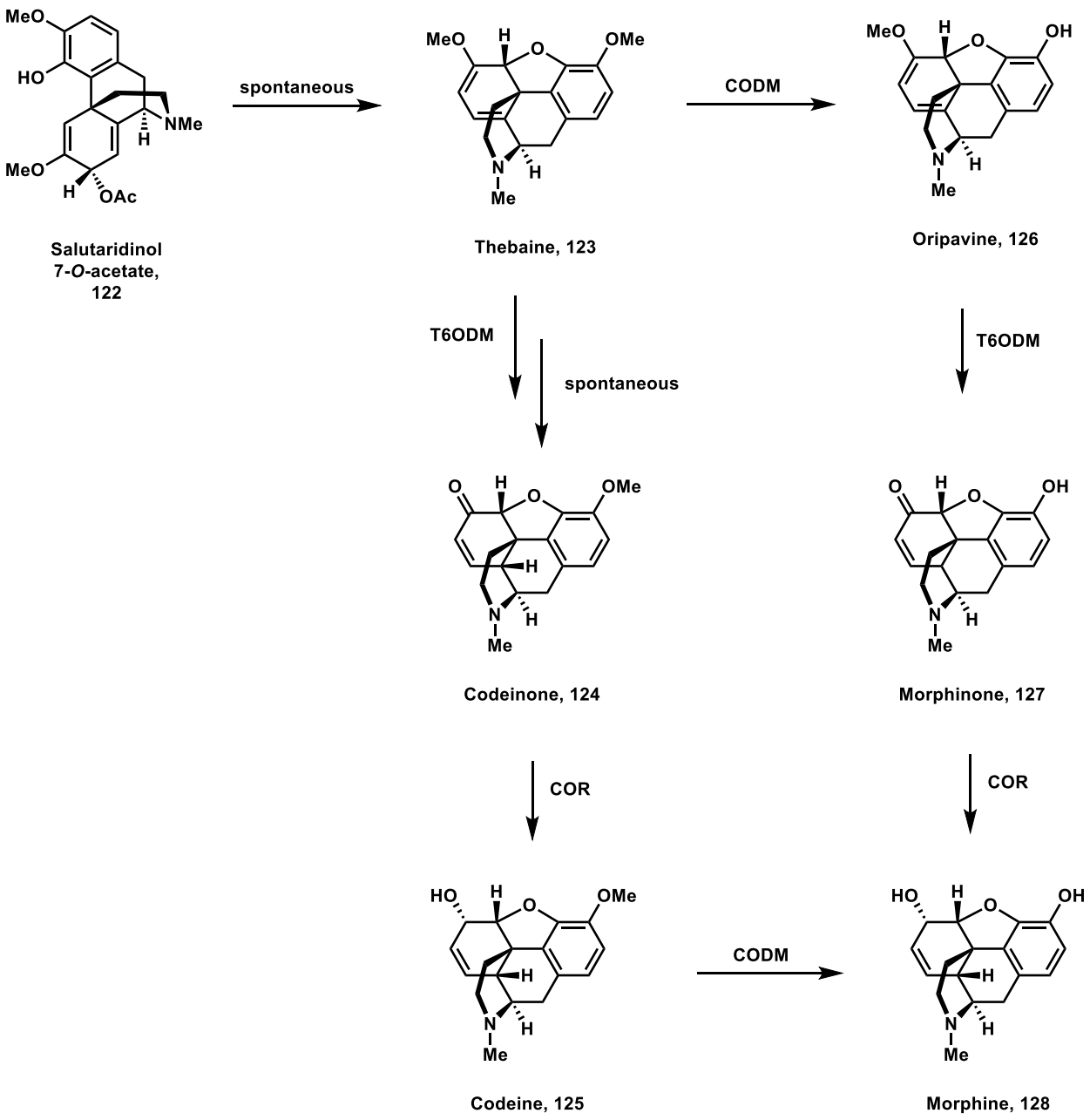
Morphine is a potent μ-opioid receptor agonist and has been used for its analgesic and sleep-inducing properties throughout human history. The primary source of morphine is from the opium poppy *Papaver somniferum* which also contains large opium content of codeine as well as of thebaine.[1] First isolated by Friederich Serturner in 1804, morphine was named after the god of dreams, Morpheus, for its sleep inducing properties.[2] The most common use for morphine is as a pain medication but it is also commonly used as an illicit drug. The structure of natural (-)-morphine was elucidated based on the Gates total synthesis in 1952 as well as X-ray diffraction data by Mackay and Hodgkin in 1955.[3,4,5]

The demand of opiates for therapeutic purposes has increased significantly over the years. The production for morphine alone has more than doubled from 247.1 tons in 1994 to 522.6 tons in 2013.[6] To supply the world demand for opiates, raw opiate materials are extracted from opium, poppy straw, and concentrate of poppy straw. These raw opiate materials are then purified and often semi-synthetically converted into other opiates. Opiates extracted from these raw materials are fairly high-yielding, producing approximately 9.5-12.0% morphine, 2.5% codeine, and 1.0-1.5% thebaine by weight.[7]

The convergent biosynthesis of morphine is known for two separate pathways both starting from dopamine **111** and 4-hydroxyphenylacetaldehyde **112** (Scheme 26 and 27).[6,8,9] The L-tyrosine derived dopamine **111** and 4-hydroxyphenylacetaldehyde **112** form (*S*)-Norcoclaurine **113**; through the enzyme norcoclaurine synthase (NCS) a Pictet-Spengler reaction occurs to close the tetrahydroisoquinoline ring of (*S*)-Norcoclaurine **113**. A series of methylation and oxidation reactions occur through the enzymes 6-O-methyltransferase (6OMT), (*S*)-coclaurine *N*-methyltransferase (CNMT), *N*-methylcoclaurine 3'-hydroxylase (NMCH), and 3'-hydroxy *N*-



Scheme 26. Biosynthesis of morphine intermediate salutaridinol-7-*O*-acetate.

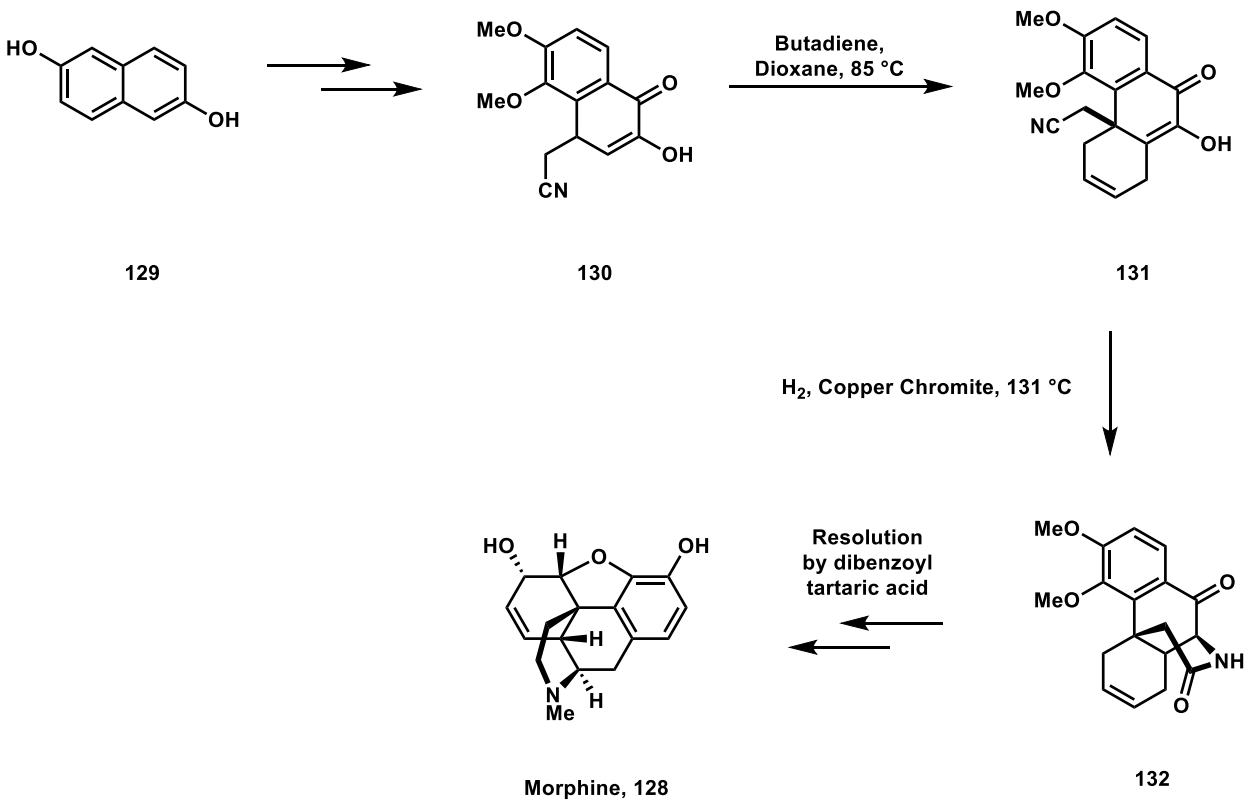


Scheme 27. Biosynthesis of morphine from salutaridinol-7-*O*-acetate.

methylcoclaurine 4'-*O*-methyltransferase (4'OMT) to provide (*S*)-Reticuline **117**. Epimerization occurs at the stereogenic carbon of (*S*)-Reticuline **117** inverting the S enantiomer to the (*R*)-Reticuline **119** enantiomer. The cytochrome p450 enzyme saltaridine synthase (SalSyn) cyclizes (*R*)-Reticuline **119** to the morphinan pentacyclic core of salutaridine **120** by a diradical type

mechanism.[10,11] Reduction and acylation proceed through the enzymes salutaridine reductase (SalR) and salutaridinol 7-*O*-acetyltransferase (SalAt) to provide Salutaridinol 7-O-acetate **122** which spontaneously attacks the cyclohexadiene in an S_N2'-like manner to form thebaine **123**. The biosynthetic paths fork at thebaine **123** which can be demethylated by either 6-*O*-demethylase (T6ODM) to spontaneously enolize to codeinone **124**, or it can be demethylated via codeine-*O*-demethylase (CODM) to provide oripavine **126**. From codeinone **124**, the NADPH-dependant codeinone reductase (COR) reduces codeinone **124** to codeine **125**, which undergoes demethylation by codeine-O-demethylase (CODM) to yield morphine **128**. On the other side of the fork, oripavine **126** undergoes the skipped set of reactions being demethylated first by T6ODM giving morphinone **127** then reduction by COR converts morphinone **127** to morphine **128**. Understanding the biosynthetic pathway is an opportunity for synthetic organic chemists to extract useful transformations for the synthesis of morphine often which is fairly convergent.

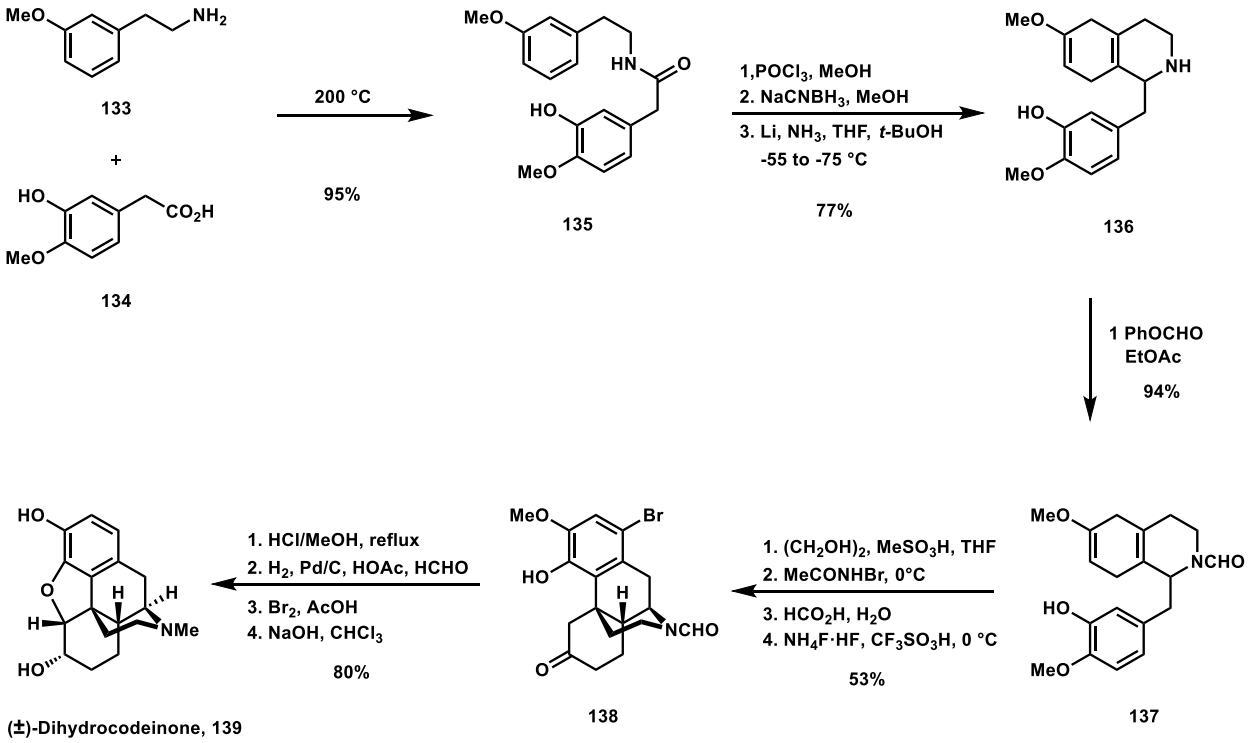
The Gates synthesis is one of the most noteworthy syntheses of morphine **128** as it was important to elucidate the structure of the molecule (Scheme 28).[3,4,5] The synthesis commences with 2,6-dihydroxynaphthalene and the nitrile intermediate **130** is synthesized through a series of redox reactions. The C-ring of morphine **128** is formed through a Diels-Alder reaction with butadiene to give the nitrile **131**. Under rigorous pressure, the nitrile **131** undergoes amidation with hydrogen and copper chromite to stitch the D-ring of morphine yielding the amide **132**. Morphine **128** is ultimately synthesized and resolved using dibenzoyl tartaric acid. The Gates synthesis provided morphine in 0.6% over 31 steps as the first total synthesis of morphine **128**.[11] Although the Gates synthesis was low yielding, it was a tremendous advancement for the bridge between chemistry and biology.



Scheme 28. Gates synthesis of (-)-morphine.

The synthesis of morphine **128** or its immediate precursors have been successfully accomplished more than 26 times over half a century.[12] The highest yielding formal synthesis to date is the Rice synthesis of racemic dihydrocodeinone in 30% yield over 13 steps (Scheme 29).[13] The synthesis begins with the formation of the amide between the amine **133** and the carboxylic acid **134** at 200 °C, a process which afforded the amide **135** in 95% yield. The following steps resemble the biosynthetic pathway, starting with a Bischler-Napieralski reaction to produce a dihydroisoquinoline intermediate which can be further reduced to a tetrahydroisoquinoline with sodium cyanoborohydride. Subjecting the crude tetrahydroisoquinoline to Birch reduction conditions afforded the amine **136** as an essentially pure material in 77% yield over 3 steps. Refluxing the amine **136** with PhOCHO displaces the

phenol allowing the formation of the formamide **137** in excellent yield (94%). The demethylation of the formamide **137** ensued under acidic acetal protection conditions. The para-bromination of the phenolic functionality was carefully selected to induce higher selectivity for the following Grewe cyclization. Acidic deprotection of the acetal and Grewe cyclization elegantly afforded the quaternary center in the intermediate ketone **138**. The methanolic HCl deformylation of formamide **138** was followed by a palladium catalyzed reductive amination to reduce both the bromine and the iminium salt. The cyclization to (±)-dihydrocodeinone **139** was simple through α-bromination of the ketone and treatment with base to give the desired cyclization. The synthesis is the most efficient racemic synthesis so far.

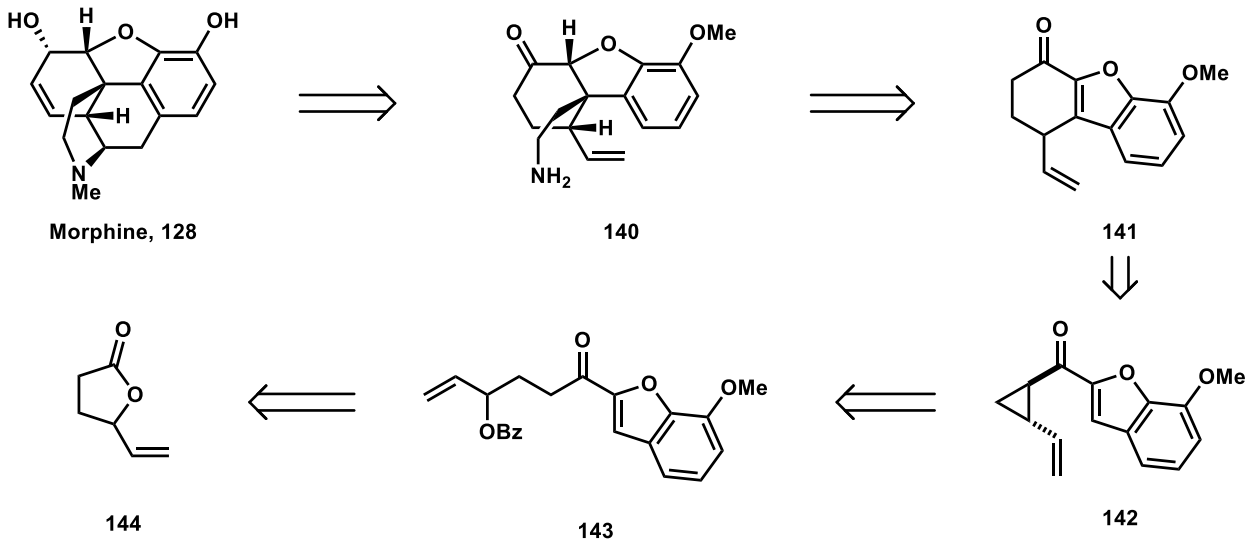


Scheme 29. Rice formal synthesis of morphine.

We envisioned a synthetic approach towards morphine which would proceed through the rearrangement of a cyclopropane intermediate to form the C-ring of morphine followed by the tandem formation of the B- and D-rings of morphine **128** via a metal-mediated aza-Heck reaction. The synthesis of the cyclopropane intermediate was done previously by Timothy Dwight of the Jung group. We will now describe our efforts for the synthesis of morphine **128** through novel cyclopropanation chemistry.

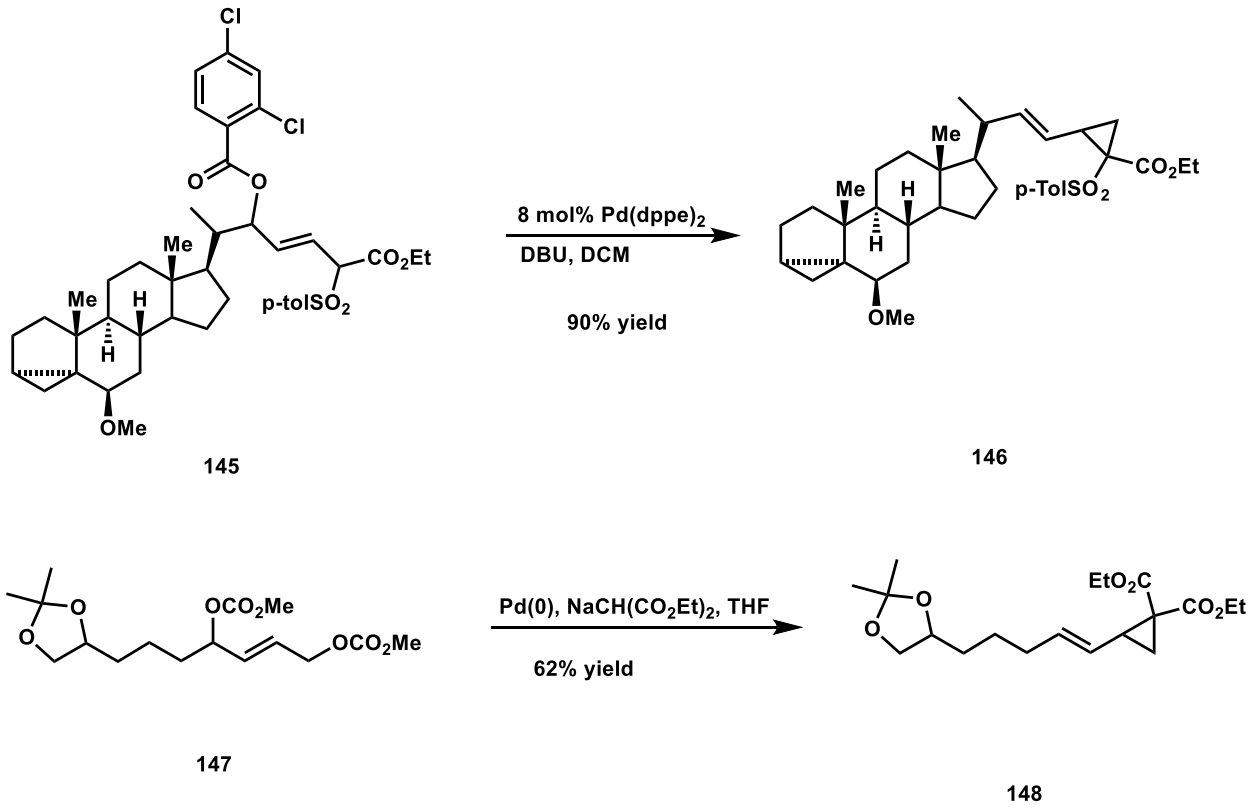
Results and Discussion

Our original retrosynthetic analysis of morphine **128** focused on the formation of C ring (Scheme 30). Morphine could be synthesized from the amine **140** through either a transition metal catalyzed cross-coupling/amination sequence or through an oxidative cyclization. Amine **140** could arise from the tricycle **141** through the 1,4-addition of methyl cyanoacetate followed by decarboxylation and reduction. A homo-Nazarov cyclization of the cyclopropane **142** could produce the tricycle **141** upon treatment with Lewis or Bronsted acid. A curious reaction arises when benzofuryl ketone **143** is treated with base and palladium to produce the benzofuryl cyclopropyl ketone **142**. This reaction was the key component of our studies towards the synthesis of morphine **128**. Addition of 2-lithiobenzofuran to the lactone **144** and subsequent benzoylation would give the ketone **143**.



Scheme 30. Initial retrosynthetic analysis of morphine.

Initially we envisioned that the Tsuji-Trost reaction could be used to synthesize the benzofuryl cyclopropyl ketone **142**, a process Timothy Dwight found during his work towards the synthesis of morphine **128** (Scheme 31). The Tsuji-Trost reaction is formally an allylation method that generally utilizes catalytic palladium and an allylic leaving group. Intramolecular Tsuji-Trost cyclopropanation reactions are well-established reactions, known for several decades involving malonic ester type bis electron-withdrawing groups. The electron-withdrawing functionalities can range from esters to nitriles to sulfones, where oxygen containing functionalities can potentially cyclize via oxygen. The S_N2' like reactions of benzoates and carbonates have previously been observed using sulfonyl ester **145** and carbonate **147**.[14,15] The stability of the enolate is likely a critical factor in the formation of the cyclopropane species.



145 146

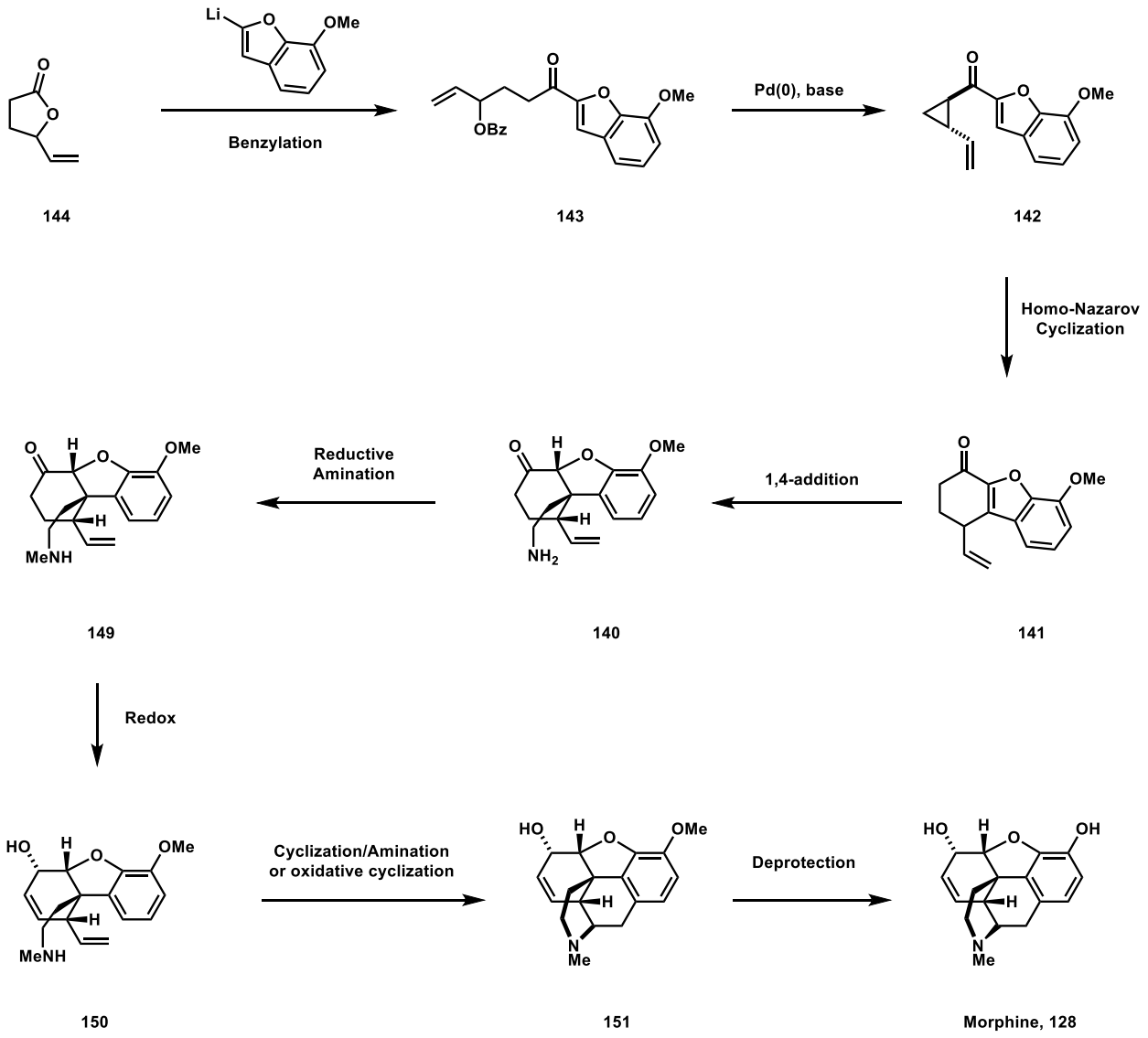
147 148

Scheme 31. Palladium catalyzed base mediated cyclopropanations.

Forward Synthesis

The proposed forward synthesis of morphine involves the addition of 2-lithio-7-methoxybenzofuran to the lactone **144** to give an allylic alcohol, which can be benzoylated to give the aroyloxy ketone **143** (Scheme 32). As mentioned earlier, Timothy Dwight discovered the cyclization of the ketone **143** to give the cyclopropane **142** using palladium(0) and base. We envisioned this discovery could help us in the synthesis of morphine by using a subsequent homo-Nazarov cyclization reaction to form the tricycle **141** and thereby the C-ring of morphine. We proposed that resolution of enantiomers followed by a nucleophilic 1,4-addition of an ethyl

amine could give the amine **140** with the formation of cis 5-6 ring juncture. The last steps to finish the

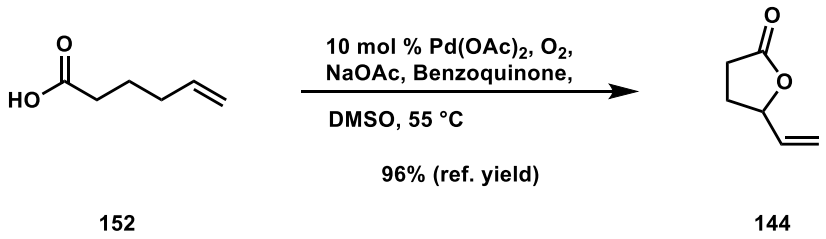


Scheme 32. Forward synthesis of morphine.

synthesis of morphine **128** would involve reductive amination, followed by redox chemistry to install the allylic alcohol forming alcohol **150**. The transition metal catalyzed cross-coupling/amination sequence or an oxidative cyclization of the amine **150** would produce the B

and D-rings of codeine **151**. Finally *O*-demethylation would complete the total synthesis of morphine **128**.

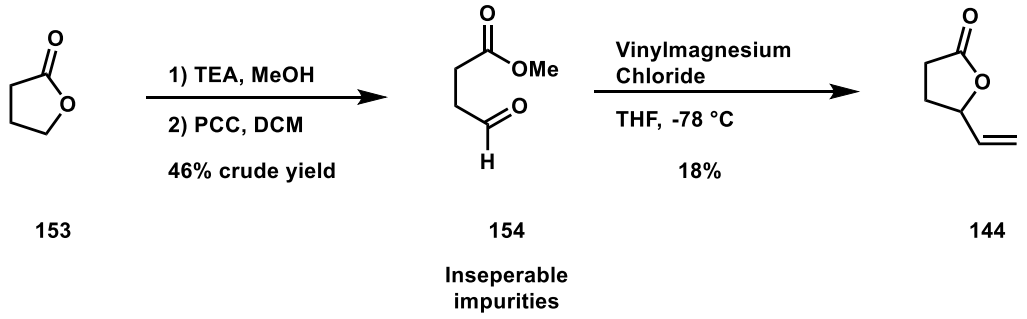
The synthesis of the lactone **144** has previously been established starting from 5-hexenoic acid **152**. An oxidative cyclization can occur in the presence of palladium(II) and oxygen to form the lactone **144** (Scheme 33).[16] This process is high yielding, with the yield of 96% reported in the literature. But the reaction itself is extremely costly. Since 5-hexenoic acid **152** costs approximately $60/g this cost and the fact that palladium was required made this route unfavorable.[17] We searched for alternative methods to make the starting lactone **144** without the need for palladium catalysis.



Scheme 33. Literature synthesis of lactone **144**.

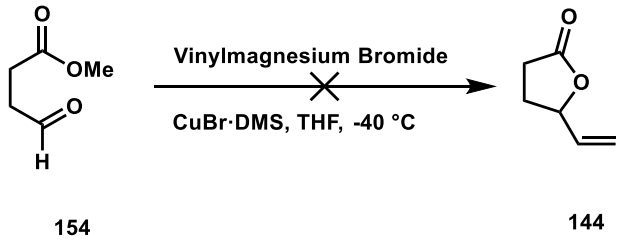
One of the most common and inexpensive syntheses of lactone **144** relied on the addition of vinylmagnesium chloride or bromide to the aldehyde **154**.[18] We attempted the synthesis of lactone **144** with commercially available lactone **153**. The addition of triethylamine (TEA) and MeOH provided the methyl ester as well as the starting material due to equilibrating relactonization (Scheme 144). The primary alcohol was then oxidized with PCC to form the ester aldehyde **154** in 46% crude yield. The ester was then subjected to the literature organometallic addition conditions at 0 °C, but failed to produce lactone **144**. However, when the reaction was repeated at -78 °C, to our delight, the lactone **144** was isolated in 18% yield. Although some

lactone **144** was isolated, the yields were poor and the synthesis of lactone **144** was difficult to reproduce by this route.



Scheme 34. Initial attempts to synthesize lactone.

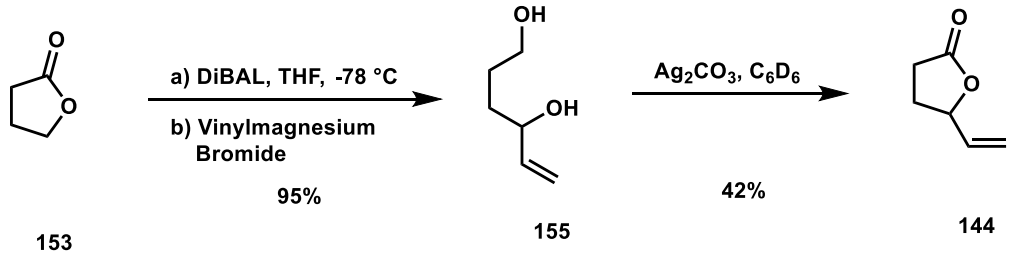
We set our sights on a slight modification using a Gilman-like reagent to synthesize lactone **144** from the ester aldehyde **154** (Scheme 35). Addition of the vinyl cuprate to the ester aldehyde **154** did not provide the desired lactone **144**, but instead seemed to add twice. Other vinyl metal reagents seemed to react violently with simple substrates such as ester **154**, providing a myriad of undesired side products. This disappointing result caused us to look at simpler methods for the synthesis of lactone **144.**



Scheme 35. Gilman vinyl cuprate addition.

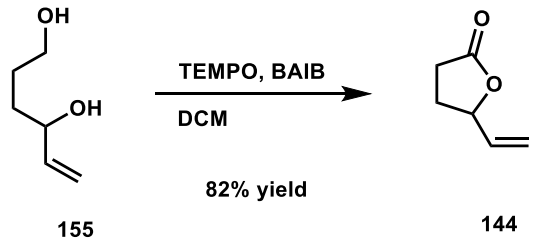
The lactonization of 1,4-diols is well known and has been used for numerous total synthesis such as the total synthesis of the anti-inflammatory (±)-bukittinggine and the antibiotic

(±)-macbecin I.[19,20] The synthesis of the diol **155** was known in the literature. The addition of DIBAL to the lactone **153** at –78 °C followed by vinylmagnesium bromide provided the diol **155** in an excellent yield of 95% (Scheme 36).[21] Although silver carbonate is a relatively expensive reagent, we decided to test it for the lactonization of diol **155** to lactone **144**. The lactonization of diol **155** afforded the lactone **144** in 42% yield at room temperature, which was a good result compared to our previous findings. The same reaction at refluxing temperatures provided mostly decomposition product, during which silver is clearly consumed because a silver mirror coating forms on the reaction vessel. The results for silver carbonate lactonization surpassed our expectations at first glance but the yields were only modest and the costly silver reagent had to be used in excess, so again we looked for a reaction that would provide the lactone **144** in a cost-effective manner.



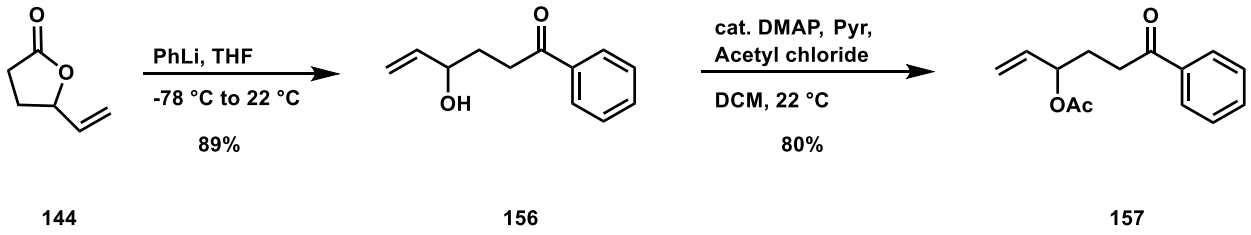
Scheme 36. Silver carbonate lactonization of diol.

Focusing on reactions that are relatively mild and economical, we looked into TEMPO reactions with diacetoxyiodobenzene (BAIB) as the ultimate oxidant (Scheme 37).[22] Employing catalytic TEMPO with BAIB we were able to synthesize lactone **144** in an excellent yield of 82% from diol **155** in not only a cost-effective manner, but also in a rapid process. With these results in hand we moved forward with our synthesis of cyclopropanes.



Scheme 37. TEMPO mediated lactonization of diol.

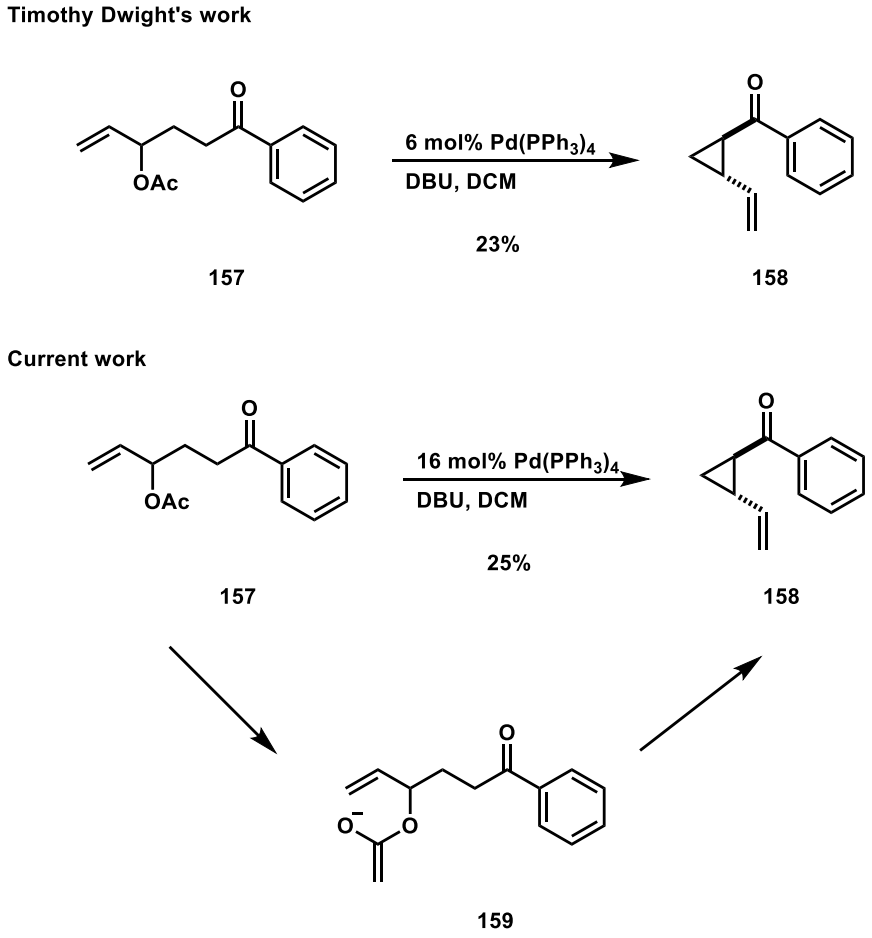
The synthesis of our desired starting ketone followed the route of aryllithium addition, ring opening, and subsequent acylation (Scheme 38). Treatment of the lactone **144** with phenyllithium provided excellent yields of the allylic alcohol **156** with a minor side product, namely the double phenyl addition to the lactone. Acylation of allylic alcohol **156** was performed using acetyl chloride which afforded the ketoester **157** in 80% yield.



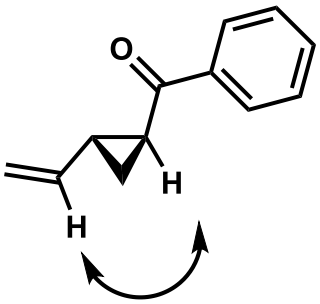
Scheme 38. Synthesis of acylated starting ketone.

As a positive control we repeated Timothy Dwight's previous work on the cyclopropanation of the phenyl ketone **157** (Scheme 39). With higher palladium loading, we were able to repeat the experiment in virtually the same low yields. The phenyl cyclopropyl ketone **158** isolated was solely the trans-isomer which was demonstrated by comparison to literature spectra from multiple sources.[23,24] In addition, we performed a NOESY experiment to

confirm the trans stereochemistry (Scheme 40).[26] We found a NOE correlation between the proton α to the ketone and the 2-vinyl proton, as shown. We believed that the acetate was participating as a proton source for the base, causing side reactions to occur. One of the main side products of concern was enolate **159**, since the acetate is incapable of leaving for any cyclopropanation to proceed.



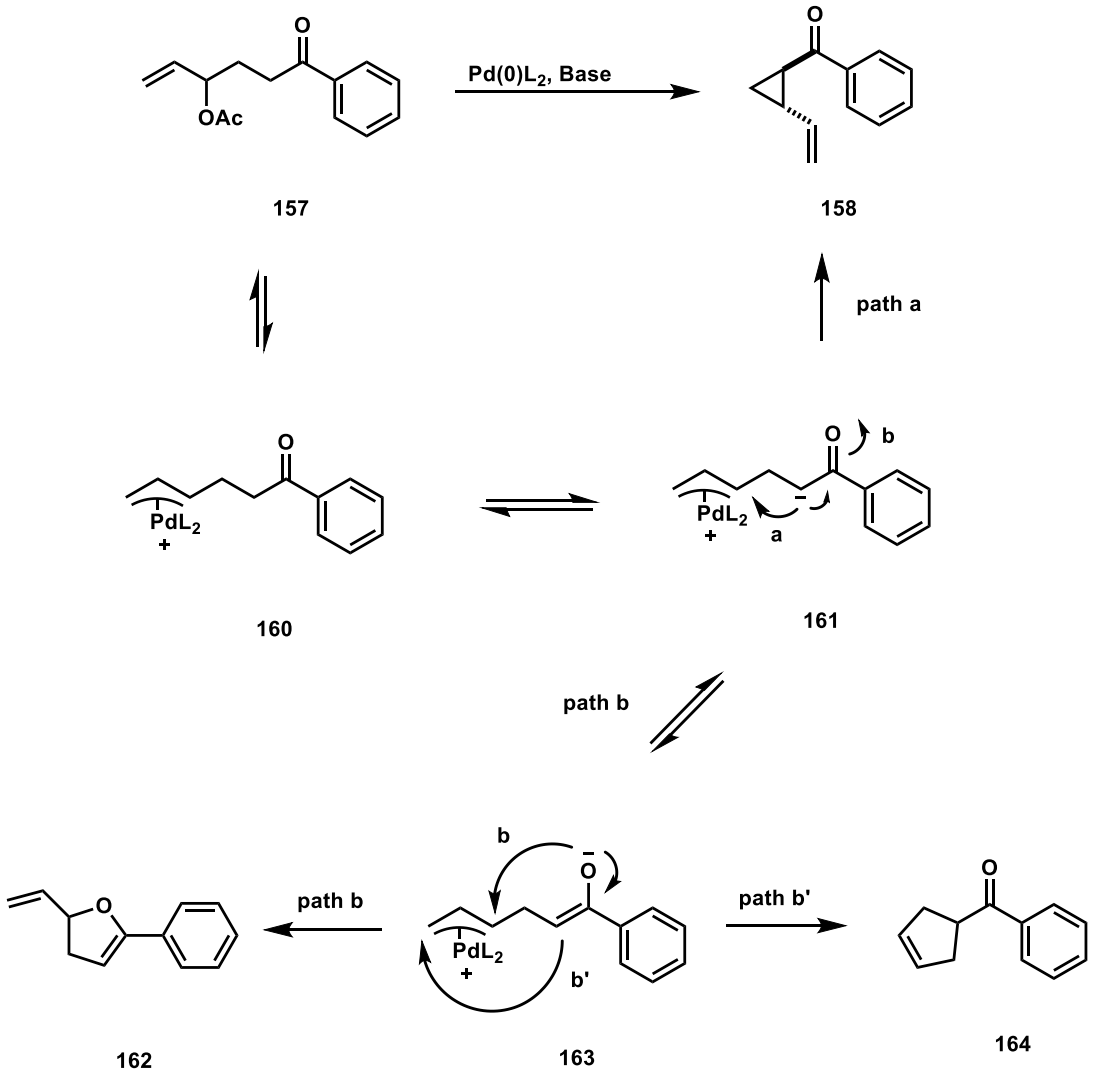
Scheme 39. Palladium catalyzed cyclopropanation reactions.



158

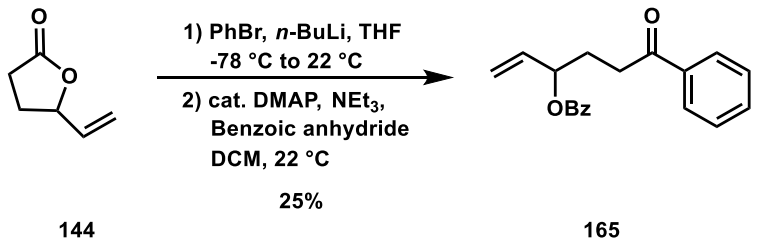
Scheme 40. NOESY proton correlations of proton α to the ketone with 2-vinyl proton.

Understanding the mechanism of this reaction was a vital part of selecting the optimal conditions and substrate for the cyclopropanation reaction. The addition of palladium to the phenyl ketone **157** would allow for the palladium π-allyl species **160** to exist transiently (Scheme 41).[27] The deprotonation of the proton α to the ketone would form the intermediate ketone enolate **161**, which can follow one of three paths. The intramolecular cyclopropanation event could occur via path a forming our desired cyclopropane **158**. Alternatively the enolate **161** could react via path b, where the oxygen of the enolate would attack and cyclize to the dihydrofuran **162**. Path c is the least likely event to occur since the palladium π-allyl species **163** is linear; the alpha carbon cannot approach the terminal end of the π-allyl species and therefore should not form the cyclopentenyl ketone **164**.



Scheme 41. Plausable palladium catalysis mechanism.

By replacing the acetate with a benzoate group, we were able to reduce the complexity of the reaction by eliminating the additional acidic proton of the acetate. The addition of phenyllithium to the lactone **144** allowed us to form the previous allylic alcohol **156** this time as a crude oil (Scheme 42). Benzoylation of the allylic alcohol **156** afforded the phenyl ketone **165** in 25% yield over two steps. We decided next to screen various bases and palladium species for optimal reaction conditions.

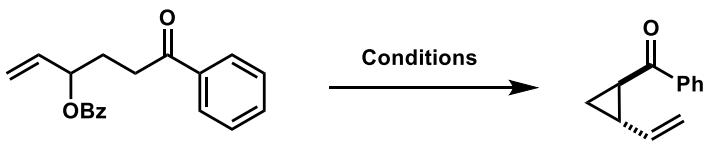


144 165

Scheme 42. Esterification of phenyl ketone.

We looked at both inorganic and organic bases with the palladium guanidine catalysts. The palladium guanidine complexes were thought to serve a dual purpose, where the tetramethyl guanidine could act as both a ligand for palladium and potentially a base for deprotonation (Table 10). Suprisingly our first attempt (entry 1) showed a trace amount of the phenyl cyclopropyl ketone **158** even though the conditions caused mostly simple benzoate cleavage. Changing the solvent to acetonitrile caused the reaction to stall altogether and no reaction was observed (entry 2). Using conditions similar to the original cyclopropanation reaction, we substituted $Pd(PPh_3)_4$ with the palladium guanidine complex, but only a trace amount of phenyl cyclopropyl ketone **158** was detected (entry 3). The palladium tetramethylguanidine complex seemed to inhibit the reaction. Dissatisfied with these results, we decided to revisit DBU as the base.

Table 10. Palladium and tetramethylguanidine catalyzed cyclopropanations.

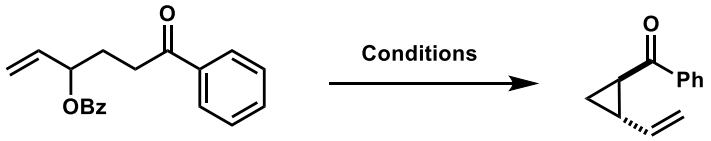


165 158

Entry	Base	Catalyst	Solvent	Time	Temp.	Results
1	K_2CO_3	10 mol % $Pd(OAc)_2$, Tetramethylguanidine	H2O/EtOH	2h	80 °C	Trace
2	K_2CO_3	10 mol % $Pd(OAc)_2$, Tetramethylguanidine	Acetonitrile	2h	80 °C	No Rxn
3	DBU	10 mol % $Pd(OAc)_2$, Tetramethylguanidine	dichloromethane	Overnight	22 °C	Trace

Using $Pd(dppf)Cl_2$ as the catalyst, we explored both DBU and TEA as bases (Table 11). With DBU alone, there was no reaction (entry 1). The addition of TEA was essential for the reaction to proceed. As the amount of TEA was increased, the yield clearly increased (entries 2 and 3) up to a maximum of 53% yield (entry 4). The unfortunate decrease in yield for entry 5 was probably due to an acidic workup, where 30% of the debenzylated starting material was recovered. With these promising results in hand, we revisited the mechanism of this process.

Table 11. $Pd(dppf)Cl_2$ catalyzed cyclopropanation reactions.

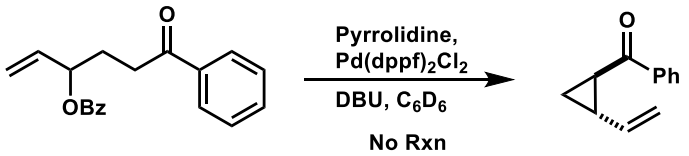


165 158

Entry	Base	Catalyst	Solvent	Time	Temp.	Results
1	DBU	10 mol % $Pd(dppf)Cl_2$	dichloromethane	12h	22 °C	No Rxn
2	1.2 eq. TEA	10 mol % $Pd(dppf)Cl_2$	1:10 DBU: dichloromethane	2h	22 °C	18% yield
3	2.4 eq. TEA	10 mol % $Pd(dppf)Cl_2$	1:10 DBU: dichloromethane	2h	22 °C	40% yield
4	3.6 eq. TEA	10 mol % $Pd(dppf)Cl_2$	1:10 DBU: dichloromethane	2h	22 °C	53% yield
5*	20 eq. TEA	10 mol % $Pd(dppf)Cl_2$	1:10 DBU: dichloromethane	2h	22 °C	27% yield

* Acidic workup.

We questioned whether the nucleophlilicity of the phenyl ketone **165** could be elevated to eject the benzoate leaving group (Scheme 43). The additive of choice was pyrrolidine, which we hoped would form an enamine for nucleophilic attack on the benzoate carbon.[28] No reaction was observed and only starting material was recovered during this reaction. We learned that basicity was a key component of the reaction over nucleophilicity.

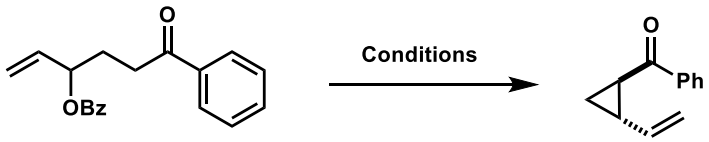


165 158

Scheme 43. Pyrrolidine mediated cyclopropanation reaction.

Next we explained 1,2-bis(diphenylphosphino)ethane (dppe) as a ligand for palladium and LiHMDS as the base (Table 12).[14,15] We were able to synthesize our desired phenyl cyclopropyl ketone **158** in a very good yield of 84% under these new conditions (entry 1). In the absence of palladium catalyst, the reaction seemed to stall under these conditions but some product was formed (entry 2). The reaction worked fairly well with $Pd(dppf)Cl_2$ with the highest yield being 54% (entry 4).

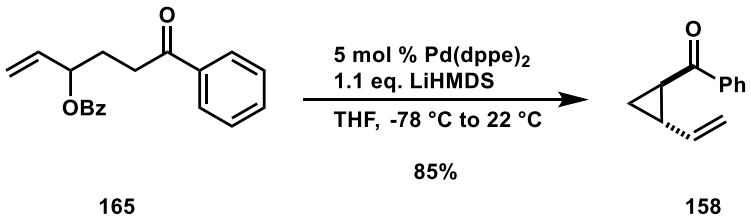
Table 12. Palladium screening reactions for the synthesis of cyclopropyl ketones.



165 158

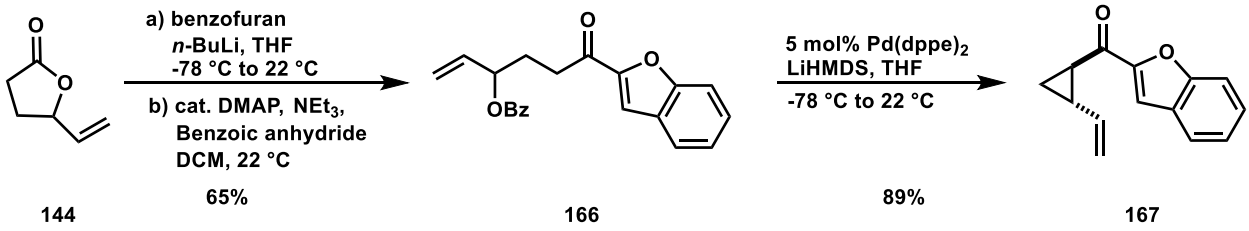
Entry	Base	Catalyst	Solvent	Time	Temp.	Results
1	2.2 eq. LiHMDS	5 mol % $Pd_2(dba)_3$, 2 eq. dppe	THF	24h	-78 to 50 °C	84% yield
2	2.2 eq. LiHMDS	No Catalyst	THF	24h	-78 to 50 °C	25% yield
3	2.2 eq. LiHMDS	5 mol % $Pd(dppf)Cl_2$	THF	24h	-78 to 50 °C	18% yield
4	2.2 eq. LiHMDS	5 mol % $Pd(dppf)Cl_2$, 1 eq. dppe	THF	1h	-78 to 50 °C	52% yield
5*	2.2 eq. LiHMDS	5 mol % $Pd(dppf)Cl_2$, 2 eq. dppe	THF	1h	-78 to 50 °C	37% yield

Our rational for the next experiment was simple, we decided to use $Pd(dppe)_2$ directly which should simplify the reaction. We were able to synthesize the target phenyl cyclopropyl ketone **158** in a very good yield of 85% (Scheme 44). Satisfied with this result, we continued to look at various substrates for this newly found cyclopropanation reaction.



Scheme 44. $Pd(dppe)_2$ catalyzed cyclopropanation reaction.

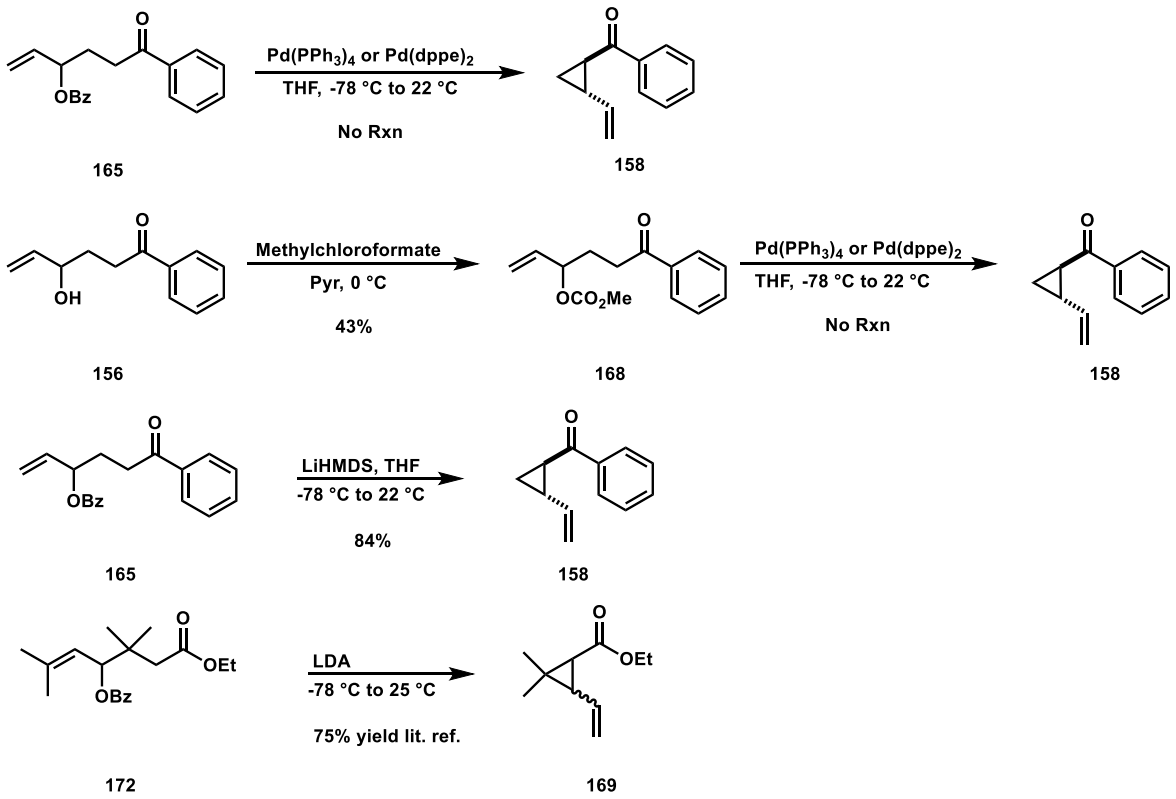
The synthesis of the benzofuryl ketone **166** followed the earlier method developed for the synthesis of the phenyl ketone **165**. The benzofuryl ketone **166** performed exceptionally well under these conditions affording the benzofuryl cyclopropyl ketone **167** in 89% yield (Scheme 45).



Scheme 45. Synthesis of benzofuryl cyclopropyl ketone.

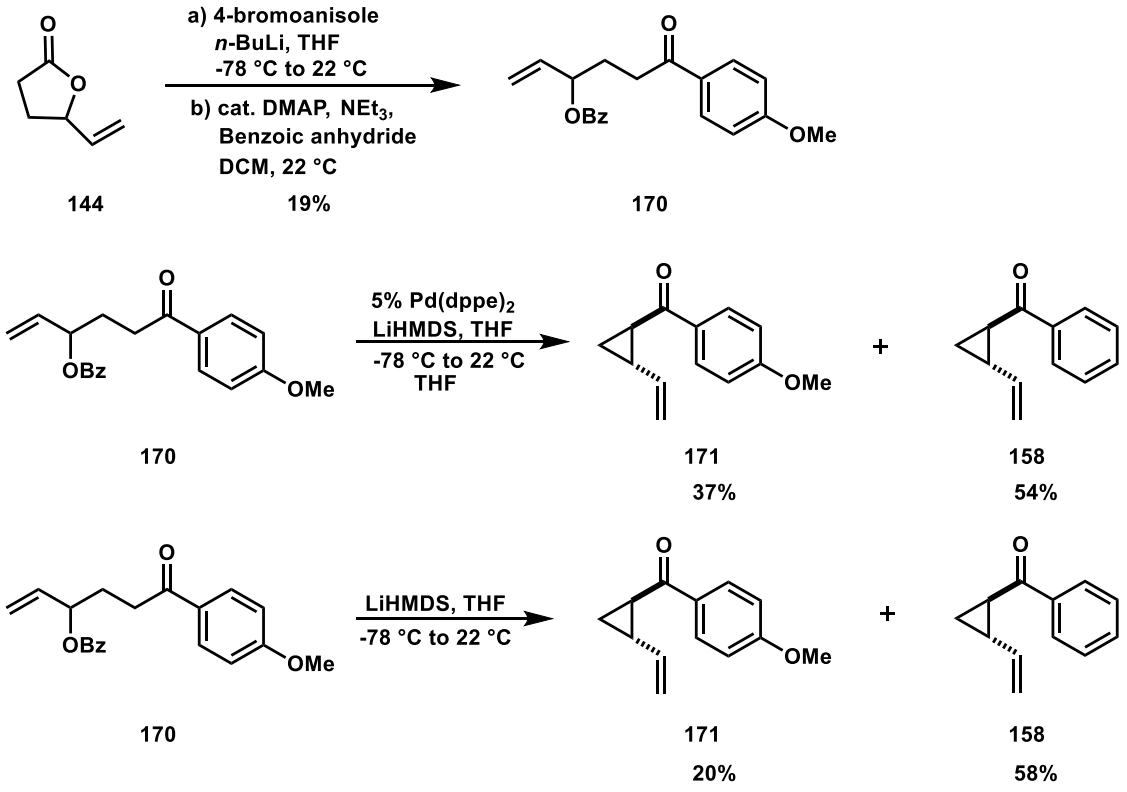
We wondered whether the selection of base or palladium was playing a larger role in our experiments (Scheme 46). Stirring the phenyl ketone **165** with $Pd(PPh_3)_4$ or $Pd(dppe)_2$, we

observed no reaction in either case, showing that the base was an essential part of the reaction. The carbonate species **168** was synthesized from the alcohol **156** because it could act as both a leaving group for the Tsuji-Trost reaction as well as generating a strong base. Subjecting carbonate **168** to the palladium conditions unfortunately generated no product, thereby putting the necessity of palladium into question. Palladium was eliminated in the following reaction and to our amazement the reaction proceeded in a very good yield of 84%. The implications of our findings were significant, since typically a benzoate leaving group would require addition of an activator to induce its latent leaving group ability. Although there are examples in the literature of using benzoate leaving groups for the synthesis of chrysanthemic acid, the nucleophilic component was an ester and so to our knowledge no aryl ketone nucleophiles have been examined.[25]



Scheme 46. Control reactions of cyclopropanation studies.

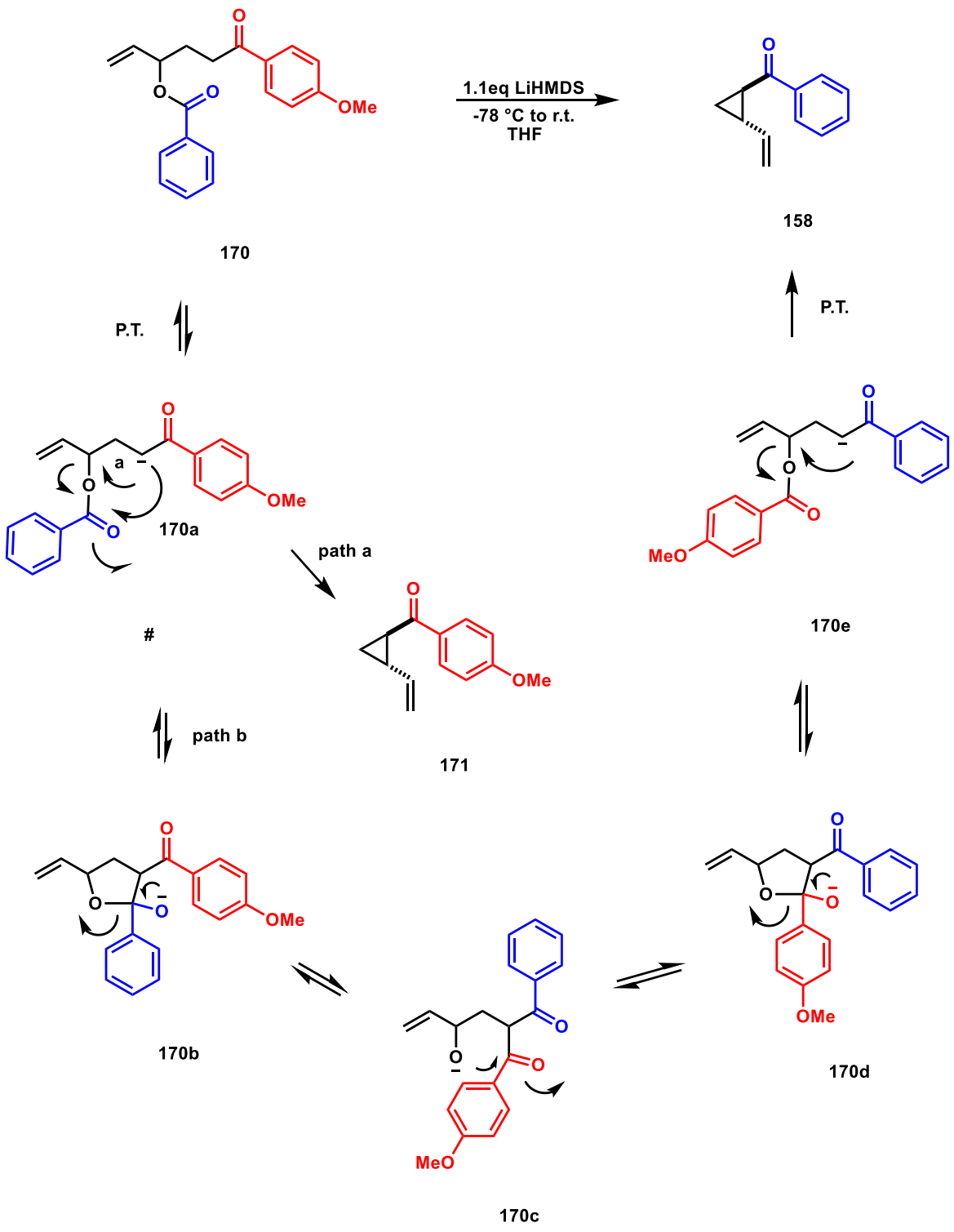
To confirm these observations, we sought another substrate to test. We synthesized the p-anisoyl ketone **170** with an anisole group by the standard procedure from lactone **144** (Scheme 47). Treating the anisoyl ketone **170** with $Pd(dppe)_2$ and LiHMDS afforded a mixture of the cyclopropanes, the expected anisoyl cyclopropyl ketone **171** (37% yield) as well as the phenyl cyclopropyl ketone **158** (54% yield). Once more we subjected the anisoyl ketone **170** to LiHMDS with a fresh reaction vessel and stir bar that had never seen palladium. The reaction outcome was fairly similar to the palladium catalyzed reaction where the anisoyl cyclopropyl ketone **171** was isolated in 20% yield and the phenyl cyclopropyl ketone **158** was obtained in 58% yield.



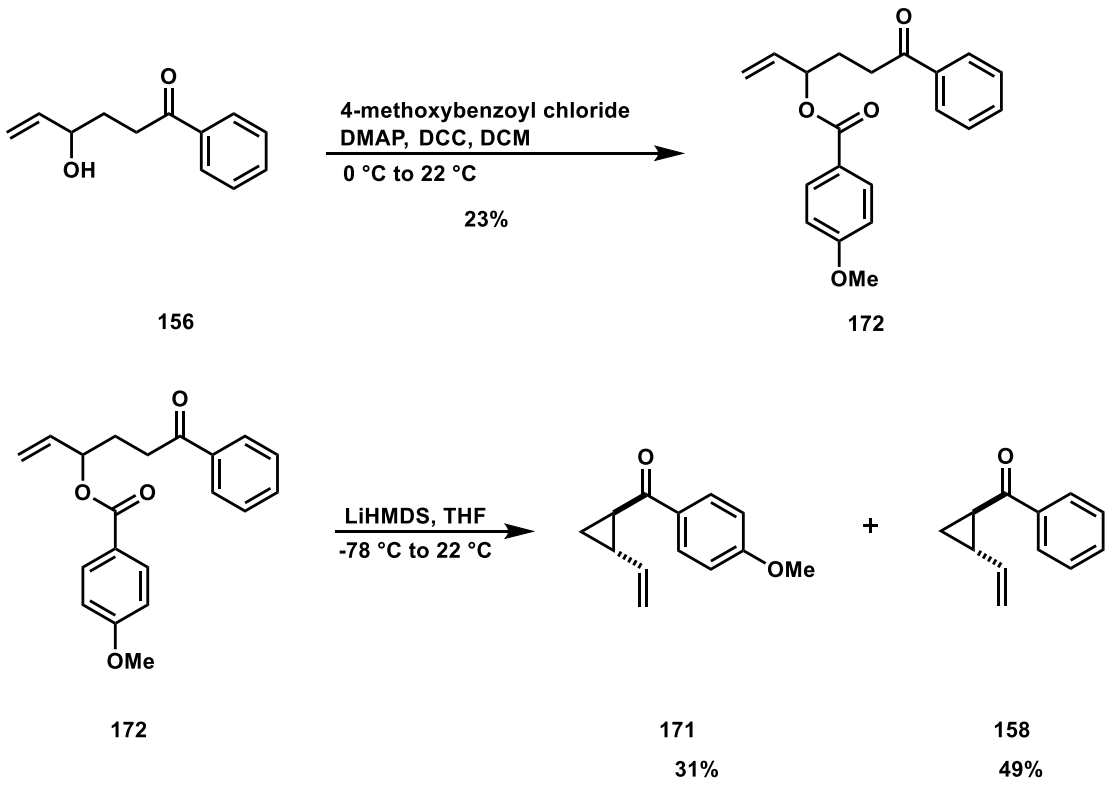
Scheme 47. Control reactions of cyclopropanation studies.

The found that a mixture of cyclopropyl ketone products was formed in this reaction had to be confronted at this point. We proposed the following mechanism (Scheme 48). Starting from the anisoyl ketone **170**, the addition of LiHMDS would deprotonate the ketone, to form the enolate **170a**. The enolate **170a** can also react via path a affording the expected anisoyl cyclopropyl ketone **171**. However the enolate **170a** can react via path b forming the hemi-acetal anion **170b**. Ejection of the alkoxide from **170b** would produce the β-diketone alkoxide **170c**. The pseudosymmetrical alkoxide from the β-diketone **170c** can revert back to the original ketone (reverse of the forward reaction) or it could choose to attack the other ketone. If the latter event occurs, the rearranged hemi-acetal **170d** would form. The overall process up to this point is the exchange of the carbonyl and ester groups. Under these conditions, the new enolate can eject the *p*-methoxybenzoate leaving group and form the phenyl cyclopropyl ketone **158**.

To test our mechanistic hypothesis we used a DCC coupling to synthesize the opposite keto ester (Scheme 49). Addition of LiHMDS to the phenyl ketone **172** gave a mixure of products like that of the previous experiment. In this case, the anisoyl cyclopropyl ketone **171** was isolated in 31% yield and the phenyl cyclopropyl ketone **158** was obtained in 49% yield.[23]



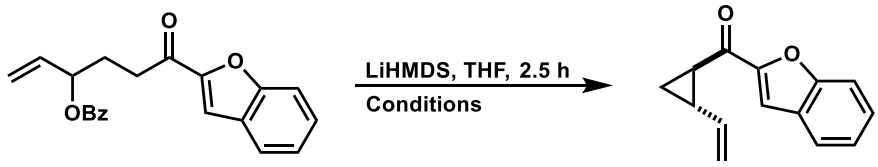
Scheme 48. Carbonyl ester exchange mechanism.



Scheme 49. Cyclization experiments.

We decided to perform a few more control studies to better understand which conditions were optimal for this reaction before we started with a substrate scope. The temperature control study in Table 13 illustrates both the suboptimal and optimal temperatures for our cyclopropanation reaction. At temperatures below 0 °C, no reaction was observed while at 0 °C we observed a small conversion of starting material to product. The best results occurred at 22 °C with complete conversion of starting material and an isolated yield of 80% of the benzofuryl cyclopropyl ketone **167**. At higher temperatures, the yields of the benzofuryl cyclopropyl ketone **167** were reduced and a small amount of the side product the phenyl cyclopropyl ketone **158** appeared.

Table 13. Temperature studies of cyclopropanation reaction.

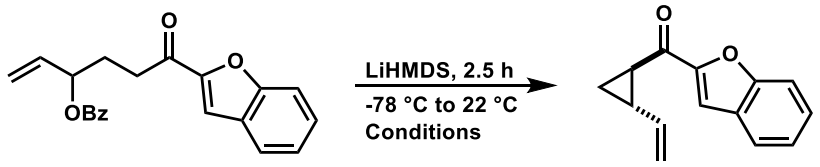


166 167

Entry	Starting Temp. (°C)	Rxn Temp. (°C)	Product yield (%)	Rearranged product yield (%)	RSM yield (%)
1	-78	-78	0	0	95
2	-78	-40	0	0	95
3	-78	0	34	0	60
4	-78	22	80	0	0
5	-78	50	74	2	0

Next we carried out solvent studies (Table 14). Non-polar solvents performed very poorly, in general affording single digit yields of product (entries 1 and 2). As the solvent became increasingly polar, the yields rose to a maxiumum in THF of 80%. Clearly a polar solvent is essential for the reaction to proceed well.

Table 14. Solvent studies of cyclopropanation reaction.

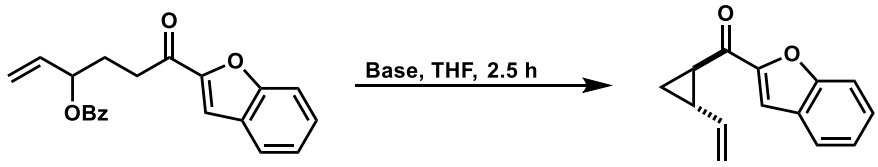


166 167

Entry	Solvent	Product yield (%)	RSM yield (%)
1	hexanes	3	89
2	benzene	8	86
3	diethyl ether	17	65
4	dichloromethane	29	71
5	THF	80	0

Finally we tested various bases to see which worked best (Table 15). We chose LDA, being similar to LiHMDS, but oddly that base gave poor yields of only 20%. LDA seemed to produce the product of benzoate cleavage and therefore was probably too nucleophilic for this reaction. Potassium *tert*-butoxide was unexpectedly good, giving 68% yield of desired product. Finally the sodium hexamethyldisilamide gave similar yields to our original base.

Table 15. Base studies of cyclopropanation reaction.



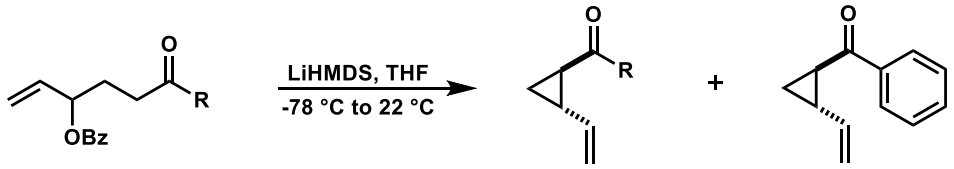
166 167

Entry	Base	R Product yield (%)	RSM yield (%)
1	LDA	20	17
2	NaH	15	49
3	*t*-BuOK	68	5
4	NaHMDS	78	8
5	LiHMDS	80	0

The substrates for this reaction were synthesized using the standard procedure of aryllithium addition to the lactone **144** followed by benzoylation. The substrate scope is summarized below for substrates containing amide, ester, alkyl, and aryl carbonyl functionality (Table 16). The Weinreb amide **173** was made for the purpose of a potential divergent synthesis, since the Weinreb amide **173** can theoretically be converted into many different carbonyl functionalities. The Weinreb amide **173** was either unreactive to LiHMDS or, if deprotonated, the anion of the Weinreb amide did not cyclize. The choice of the ester **175** followed the same logic as the Weinreb amide since esters can also be converted into a series of carbonyl derivatives. Since the Weinreb amide failed to react, we were hopeful that ester **175** might produce the cyclopropane but that did not occur. Instead the ester produced a complex mixture of products the structures of which we were unable to elucidate. The methyl ketone substrate **177** produced a complex mixture of polymeric material and various cyclized products that could not

be isolated cleanly. In an attempt to block the acidic protons on the methyl substrate we tried to synthesize the *tert*-butyl substrate but we were unsuccessful in forming the *tert*-butyl ketone cleanly by either addition of *tert*-butylmagnesium chloride or *tert*-butyllithium to the lactone. As shown before, the phenyl ketone **158** performed well with no rearrangement products because the phenyl group is the same on both the ketone and ester. The benzofuryl ketone **166** gave only the expected cyclopropyl ketone product, a preference that will be discussed later. The main compound of interest was the 7-methoxybenzofuranyl substrate, the benzofuryl ketone **143**, for progress towards the total synthesis of morphine **128**. The cyclopropanation of this morphine intermediate went well and 75% of benzofuryl cyclopropyl ketone **142** was isolated without any isolation of the side product, the phenyl cyclopropyl ketone **158**. Exposing the furyl ketone **179** to LiHMDS provided the expected furyl cyclopropyl ketone **180** in 70% yield as the major product and the unexpected phenyl cyclopropyl ketone **158** in 13% yield. The reactions of the tolyl, fluoro, and aniline substrates performed very well, with yields of 85 to 95% total yield, generally as a 1:1 mixture of expected and rearranged cyclopropanation products. As substitution changed from the para and ortho positions in entries 10 and 11 to the meta position in entry 12, the tendency for the rearranged product diminished possibly due to steric hindrance. Strangely enough the anisole substrate in entry 13 gave more of the rearranged aryl product than the expected anisoyl cyclopropyl ketone **171**, 58% to 20%.

Table 16. Substrate scope for cyclopropanation reactions.

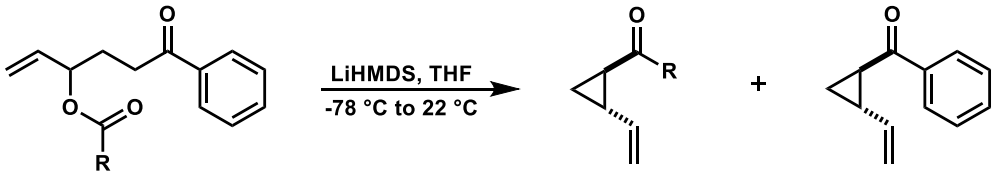


Substrate **R Product** **158**

Entry	Substrate	R	R Product	R Product yield (%)	Cyclopropane yield (%)	Time (h)
1	173	N(Me)OMe	174	0	0	24
2	175	OEt	176	0	0	24
3	177	Me	178	0	0	24
4	156	Ph	158	84	0	1.5
5	166	benzofuryl	167	80	0	2.5
6	143	7-(OMe)benzofuryl	142	75	0	5.0
7	179	furyl	180	70	13	2.0
8	181	4-$CH_3C_6H_4$	182	49	46	3.0
9	183	4-FC_6H_4	184	47	43	1.0
10	185	4-$CF_3C_6H_4$	186	60	20	1.75
11	187	3-$CF_3C_6H_4$	188	60	23	1.5
12	189	2-$CF_3C_6H_4$	190	70	5	1.5
13	170	4-$MeOC_6H_4$	171	20	58	2.5
14	191	4-$Me_2NC_6H_4$	192	43	42	3.5

We looked at a series of aryl ester substrates and, found that the anisoyloxy phenyl ketone **172** favored the benzofuryl cyclopropyl ketone product **167** (Table 17). Interestingly, the *p*-trifluoromethyl substrate afforded a nearly 1:1 mixture of the trifluoromethyl cyclopropyl ketone **186** and the expected phenyl cyclopropyl ketone **158** product. The keto substrate with the benzofuryl ester **193** gave mostly the expected product **167** (73%) with only a small amount of the rearranged product **158** (11%).

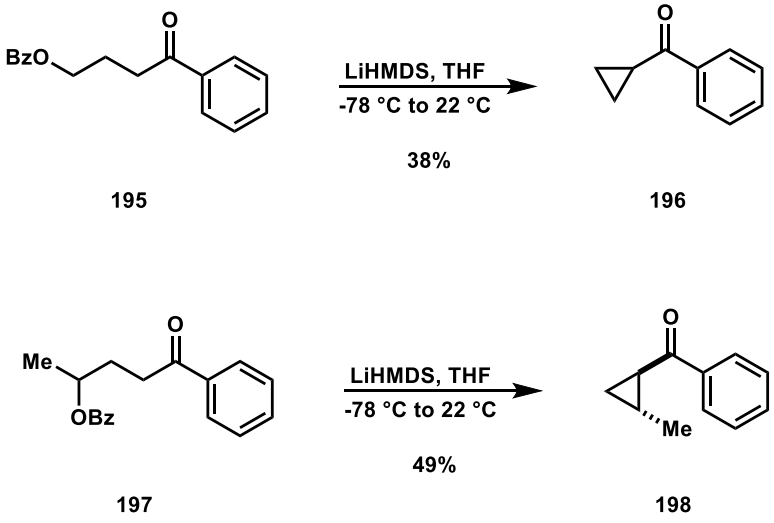
Table 17. Cyclopropanation reactions of the aroyloxy ketones.



Substrate R Product 158

Entry	Substrate	R	R Product	R Product yield (%)	Cyclopropane yield (%)	Time (h)
1	193	benzofuryl	167	73	11	3.0
2	172	4-$MeOC_6H_4$	171	31	49	2.5
3	194	4-$CF_3C_6H_4$	186	49	43	2.5

To expand our substrate scope, the vinyl substitution was replaced for hydrogen and methyl. Treatment of the simple phenyl ketone **195** afforded the simple cyclopropyl ketone **196** in 38% yield. The phenyl ketone **197** furnished the cyclopropyl ketone **198** in 49% yield. The trans-stereochemistry of **198** was determined by comparing the proton NMR data with that reported in the literature.[24,25]



Scheme 50. Cyclopropanation reactions of simple phenyl ketone substrates.

In order to understand the energetics and the mechanism of this rearrangement-cyclization manifold, the Houk group performed density functional theory (DFT) calculations at the SMD^{THF}/B3LYP-D3/6-31+G(d) level of theory using the Gaussian09 program.[30] The free energy diagram for the reaction of benzofuryl ketone **166** is shown in Figure 1. Deprotonation of benzofuryl ketone **166** forms the enolate **199** (the relative energy of which is set as 0.0), which can either undergo an intramolecular S_N2-like reaction to generate the benzofuryl cyclopropyl ketone **167** or attack the ester. Attack of the enolate **199** the ester forms the cyclic hemiacetal **200** and after the alkoxide ejects the allylic alkoxide the diketo alkoxide can form. The intermediate diketone is relatively high in energy at 15.8 kcal/mol and is 1.7 kcal/mol higher in energy than the **TS-1** barrier. From the diketone, the allylic alkoxide can attack the other carbonyl forming the rearranged cyclic acetal **201**. From the cyclic acetal **201**, ejection of the enolate gives the enolate **202** which can cyclize and generate the rearranged phenyl cyclopropyl ketone **158**. The transition state barrier for **TS-4** is 17.1 kcal/mol much higher than the **TS-1** of 14.1 kcal/mol. This larger energy difference – 3 kcal/mol - explains why no rearranged phenyl cyclopropyl ketone **158** is observed.

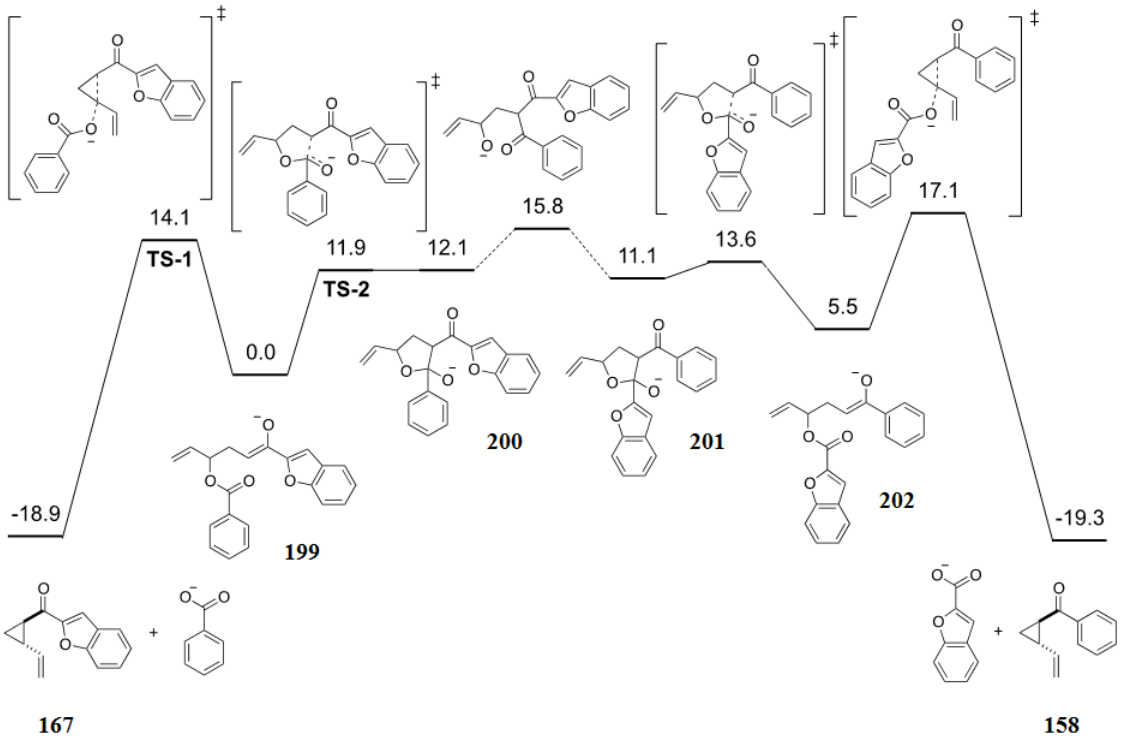
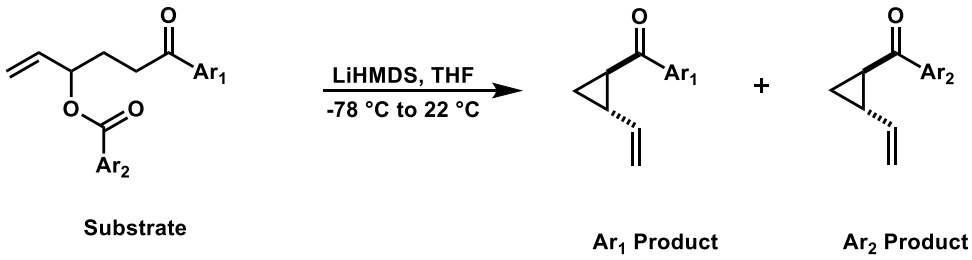


Figure 1. Free energy profile for the reaction of benzofuryl ketone **166**. Energies are in kcal/mol.

The predicted ratios of the normal to the rearranged cyclopropane products are very similar to the experimental ratios (Table 18). Comparing the related anisoyl ketone **170** the **TS-1** is 0.5 kcal/mol higher in energy than of **TS-4**. The energy difference corresponds to a 1:2 ratio of the anisole to phenyl aryl product and correlates closely with the 1:3 experimental ratio. Starting from the opposite ketone ester **172** the ratio is predicted to be 2:1, phenyl ketone to anisole ketone product, which is what we observe. For the ketone containing 4-trifluoromethylphenyl, the diketone intermediate is higher in energy than **TS-1** or **TS-4** by 0.9 and 0.3 kcal/mol respectively. In entry 5, the trifluoromethylphenyl substitution is predicted to be the major product by a 5:1 ratio and experimentally the ratio was found to be 3:1. The opposite

trifluoromethylphenyl substitution was expected to predominately give the phenyl substitution in a 2:1 ratio, but experimentally we observed a 1:1 ratio of products.

Table 18. Comparison of computational and experimental data.



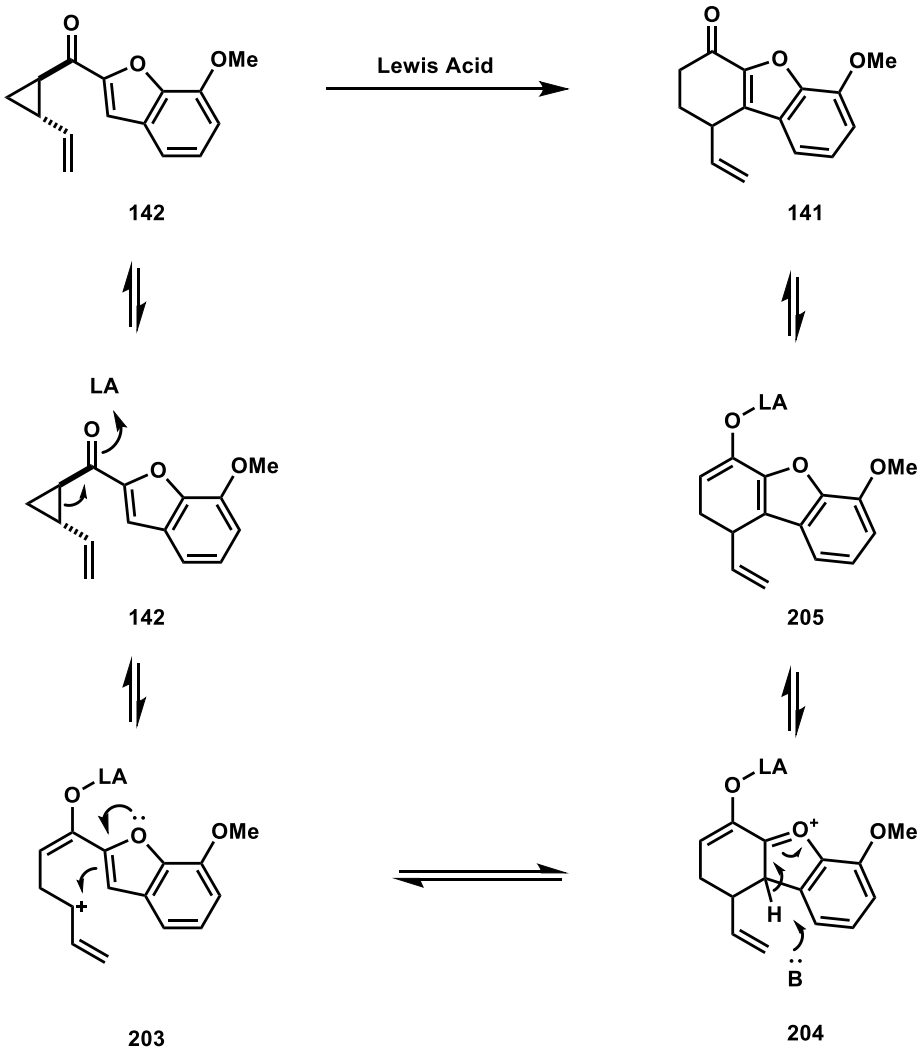
Entry	Substrate	Ar_1	Ar_2	Predicted ratio (Ar_1: Ar_2)	Experimental ratio (Ar_1: Ar_2)
1	166	benzofuryl	Ph	159:1	>20:1
2	193	Ph	benzofuryl	1:9	1:7
3	170	4-$MeOC_6H_4$	Ph	1:2	1:3
4	172	Ph	4-$MeOC_6H_4$	2:1	2:1
5	185	4-$CF_3OC_6H_4$	Ph	5:1	3:1
6	194	Ph	4-$CF_3OC_6H_4$	2:1	1:1

As indicated in Figure 1, the reaction is a complex equilibrating mixture of enolates, hemiacetals, and diketone species. The relative ratio of product may not be based on Curtin-Hammett conditions depending on the intermediate energies relative to **TS-1** or **TS-4**, since an intermediate was higher in energy than **TS-1** or **TS-4**, then the reaction would be influenced by the reactant identity. Computational and experimental data are in good agreement in our studies as shown in Table 18.

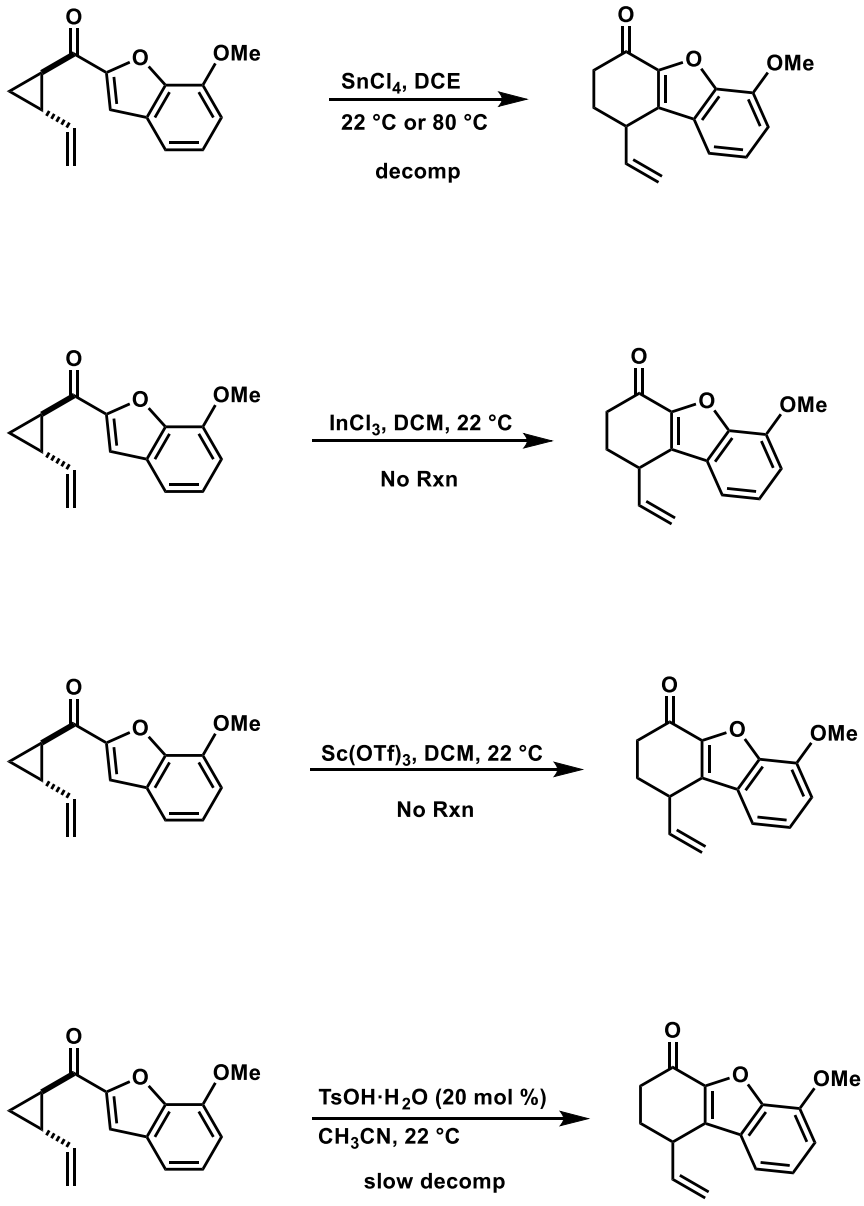
With the benzofuryl cyclopropyl ketone **142** intermediate in hand, we proceeded to the next step in our forward synthesis, the homo-Nazarov cyclization. Homo-Nazarov cyclizations

are well-known cationic rearrangement reactions that require resonance or electron-donating functionalities to stabilize the cationic intermediates.[31] The proposed mechanism for the homo-Nazarov cyclization of the benzofuryl cyclopropyl ketone **142** is illustrated below (Scheme 51). The Lewis acid would coordinate to the carbonyl oxygen, and facilitate opening of the cyclopropane to give the allyic cation intermediate **203**. The benzofuran could attack the allylic carbocation at C3 and possibly form a 6-membered ring **205** via the intermediate **204**. Rearomatization of the benzofuran would occur and tautomerization would give the desired tricycle **141**.

Attempts were made to transform the benzofuryl cyclopropyl ketone **142** to the tricycle **141** through the originally proposed homo-Nazarov reaction (Scheme 52). Addition of tin(IV) chloride to the benzofuryl cyclopropyl ketone **142** caused decomposition of the substrate at both ambient and elevated temperatures. The reactions with indium(III) chloride and scandium(III) triflate led to recovery of starting materials. Catalytic tosic acid was also too reactive for the benzofuryl cyclopropyl ketone **142** and decomposed the substrate. The cyclopropane vinyl moiety may be incompatible with the reaction conditions since it could potentially polymerize under the acidic conditions.



Scheme 51. Mechanism of homo-Nazarov cyclization of benzofuryl cyclopropyl ketone **142**.



Scheme 52. Homo-Nazarov cyclization of benzofuryl cyclopropyl ketone **142**.

After the completion of this work, we became aware of the work of Yates, who reported a related S_N2-like displacement of an ester and subsequent 1,5-acyl shift.[31] The Baran group reported the synthesis of (+)-phorbol with an intermediate Lewis acid assisted cyclopropanation step.[32] Others have also reported S_N2-like displacements of ester leaving groups to furnish cyclopropane products.[33]

Conclusion

In conclusion, we have shown that cyclopropanes reactions can be formed from a series of ketones with an appended benzoate unit. Carbonyl exchange is a common side product in this series of reactions, in some cases the exchanged product is the major product. Computational studies have given us a better understanding of this reaction where Curtin-Hammett conditions may not apply in some cases. In our attempts to synthesize morphine, we have achieved the synthesis of the intermediate benzofuryl cyclopropyl ketone **142**. The homo-Nazarov cyclization reaction failed to produce the expectedtricycle **141**, but may still be a plausible method using the appropriate Lewis acid or Bronsted for the transformation.

Experimental

Materials and Methods

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of argon using anhydrous solvents (freshly distilled). All commercially isolated reagents were used as received unless otherwise specified. Lithium bis(trimethylsilyl)amide (1 M in THF/ethylbenzene) and benzoic anhydride were purchased from Acros Organics. 4-Dimethylaminopyridine (DMAP) and (diacetoxyiodo)benzene (BAIB) were purchased from Oakwood Chemical. 2,2,6,6-Tetramethylpiperidine 1-oxyl (TEMPO) and *n*-butyllithium (2.5 M in hexanes) were purchased from Sigma-Aldrich. Reaction temperatures were controlled using an IKAmag temperature modulator. Silicycle Siliaflash P60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on Bruker spectrometers at 500 MHz and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Bruker spectrometers at 125 MHz and are reported relative to deuterated solvent signals. Data for ^{13}C NMR spectra are reported in terms of chemical shift and, when necessary, multiplicity, and coupling constant (Hz). For mixtures of regioisomers, the major regioisomer is reported with the minor regioisomer for both ^{1}H NMR and ^{13}C NMR spectra. High-resolution mass spectra were obtained on Thermo Scientific™ Exactive Mass Spectrometers with DART ID-CUBE.

A. Synthesis of Ester Precursors

5-Ethenyldihydrofuran-2(3*H*)-one, 144.

This compound was prepared following a modified procedure starting from hex-5-ene-1,4-diol.[22] To a solution of hex-5-ene-1,4-diol[21] (8.46 g, 72.8 mmol, 1.0 equiv) and (diacetoxyiodo)benzene (BAIB, 75.0 g, 233.0 mmol, 3.2 equiv) in dry dichloromethane (250 mL), 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 2.27 g, 14.6 mmol, 0.2 equiv) was added at 22 °C. The reaction was exothermic and it was stirred for 2 h at which point starting material was consumed. The reaction was quenched with 1 L of a 1:1 of a saturated aqueous solution of sodium thiosulfate and Et_2O solution. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 250 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (15 mL) and then water (15 mL). The organic layers were dried with Na_2SO_4, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (gradient, 10–30% EtOAc:hexanes) to give the lactone **144** as a pale yellow oil (6.68 g, 59.6 mmol, 82%).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

5.88 (ddd, *J* = 16.9, 10.5, 6.0 Hz, 1H)

5.37 (d, *J* = 17.1 Hz, 1H)

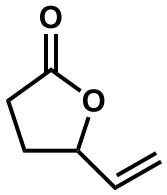
5.26 (d, *J* = 10.5 Hz, 1H)

4.96-4.92 (m, 1H)

2.59-2.50 (m, 2H)

2.44-2.38 (m, 1H)

2.04-1.97 (m, 1H).



144

^{13}C NMR (125 MHz, $CDCl_3$) δ: 177.1, 135.7, 117.6, 80.6, 28.43, 28.40.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_6H_9O_2$, 113.0597; found 113.05954. Spectroscopic data for **144** match those previously reported in the literature.[34]

4-Hydroxy-1-phenylhex-5-en-1-one, 156.

To a solution of the lactone **144** (1.7362 g, 15.5 mmol, 1.0 equiv) in dry THF (50 mL), was added phenyllithium in dibutyl ether (1.9 M, 9.4 mL, 17.9 mmol, 1.15 equiv) dropwise at –78 °C. After stirring for 1 h at –78 °C, the reaction was warmed to 22 °C and stirred for 1 h. The reaction was quenched with an aqueous solution of NaOH (1 M, 10 mL) and the layers were separated. The aqueous solution was extracted with Et_2O (3 × 50 mL) and the combined organic layers were dried with $MgSO_4$, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (gradient, 10–25% EtOAc:hexanes) to give the allylic alcohol **156** as a pale yellow oil (2.6221 g, 13.8 mmol, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.98 (dd, *J* = 8.4, 1.4 Hz, 2H)

7.56 (t, *J* = 7.4 Hz, 1H)

7.46 (t, *J* = 7.7 Hz, 2H)

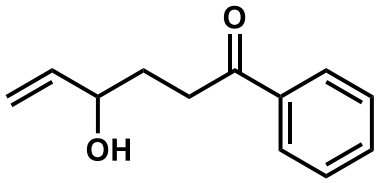
5.91 (ddd, *J* = 17.1, 10.4, 6.0 Hz, 1H)

5.28 (dt, *J* = 17.2, 1.4 Hz, 1H)

5.15 (dt, *J* = 10.4, 1.2 Hz, 1H)

4.27-4.24 (m, 1H)

3.14 (t, *J* = 7.02 Hz, 2H)



156

2.10-1.92 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 200.6, 140.8, 137.0, 133.3, 128.7 (2 C), 128.2 (2 C), 115.1, 72.4, 34.5, 31.0.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{14}O_2$, 191.1067; found 191.1063. Spectroscopic data for **156** match those previously reported in the literature.[36]

B. Synthesis of Aryl Keto Esters

6-(Benzofuran-2-yl)-6-oxohex-1-en-3-yl benzoate, 157.

To a solution of the allylic alcohol **156** (316.0 mg, 1.66 mmol, 1.0 equiv) and pyridine (0.40 mL, 4.97 mmol, 3.0 equiv), in 6 mL of dichloromethane was added acetyl chloride (0.17 mL, 2.32 mmol) dropwise. The solution was stirred for 1 h before being quenched with a saturated aqueous solution of $NaHCO_3$ (1 mL). The organic layer was removed and the aqueous layer was further extracted with dichloromethane (5 × 6 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (20% EtOAc:hexanes). The phenyl ketone **157** was isolated as a colorless oil (309.0 mg, 1.33 mmol, 80% yield).

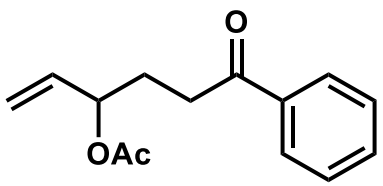
^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.94 (dd, *J* = 8.2, 1.4 Hz, 2H)

7.56 (t, *J* = 7.4 Hz, 1H)

7.46 (t, *J* = 7.7 Hz, 2H)

5.81 (ddd, *J* = 17.1, 10.6, 6.2 Hz, 1H)



157

5.36 (ddd, *J* = 6.2, 6.2, 6.2 Hz, 1H)

5.28 (d, *J* = 17.3 Hz, 1H)

5.21 (d, *J* = 10.6 Hz, 1H)

3.02 (t, *J* = 7.5 Hz, 2H)

2.18-2.06 (m, 2H)

2.05 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 199.2, 170.4, 136.9, 136.1, 133.2, 128.7 (2 C), 128.1 (2 C), 117.3, 74.1, 34.1, 28.5, 21.3.

General Procedure 1 for the synthesis of Aryl Keto Esters.

6-Oxo-6-phenylhex-1-en-3-yl acetate, 165.

The following general procedure is a modification of a known procedure.[37] To a solution of the lactone **144** (1.7362 g, 15.5 mmol, 1.0 equiv) in dry THF (50 mL), was added phenyllithium in dibutyl ether (1.9 M, 9.4 mL, 17.9 mmol, 1.15 equiv) dropwise at –78 °C. After stirring for 1 h at –78 °C, the reaction was warmed to 22 °C and stirred for 1 h. The reaction was quenched with an aqueous solution of NaOH (1 M, 10 mL) and the layers were separated. The aqueous solution was extracted with Et_2O (3 × 50 mL) and the combined organic layers were dried with $MgSO_4$, filtered, and then concentrated *in vacuo*. The residue was passed through a pad of silica gel eluting with 25% ethyl acetate in hexanes. The solution was concentrated *in vacuo* and the crude oil was used directly for the next reaction. To the crude oil was added DMAP (378.7 mg, 3.1 mmol, 0.2 equiv), triethylamine (2.8 mL, 20.2 mmol, 1.3 equiv) and dichloromethane (20 mL). The crude solution was cooled to 0 °C and benzoic anhydride (5.26 g, 23.3 mmol, 1.5 equiv), which was dissolved in dichloromethane (2.0 mL), was then added dropwise. The mixture was

allowed to warm to 22 °C and was stirred overnight. The solution was quenched with a saturated aqueous solution of NH_4Cl (20 mL) and then extracted with dichloromethane (3 × 20 mL). The combined organic layers were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes) to give the phenyl ketone **165** as a yellow oil (1.14 g, 3.87 mmol, 25% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

8.05 (dd, *J* = 8.4, 1.1 Hz, 2H)

7.94 (dd, *J* = 8.4, 1.3 Hz, 2H)

7.58-7.53 (m, 2H)

7.46-7.42 (m, 4H)

5.94 (ddd, *J* = 17.3, 10.6, 6.1 Hz, 1H)

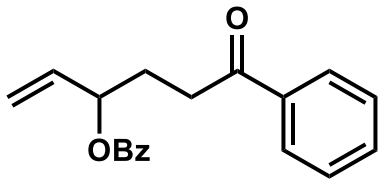
5.65-5.61 (m, 1H)

5.39 (dt, *J* = 17.2, 1.3 Hz, 1H)

5.26 (dt, *J* = 10.6, 1.2 Hz, 1H)

3.13-3.10 (m, 2H)

2.28-2.24 (m, 2H).



165

^{13}C NMR (125 MHz, $CDCl_3$) δ: 199.2, 165.9, 136.9, 136.1, 133.2, 133.1, 130.4, 129.7 (2 C), 128.7 (2 C), 128.5 (2 C), 128.1 (2 C), 117.4, 74.7, 34.2, 28.7.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{19}H_{19}O_3$, 295.1329; found 295.1326.

6-(Benzofuran-2-yl)-6-oxohex-1-en-3-yl benzoate, 166.

Prepared according to the general procedure 1, purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes), the benzofuryl ketone **166** was isolated as white crystals (485.3 mg, 1.451 mmol, 65% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

8.05-8.02 (dd, *J* = 8.3, 1.4 Hz, 2H)

7.67 (dt, *J* = 7.9, 1.0 Hz, 1H)

7.56-7.53 (m, 2H)

7.48-7.40 (m, 4H)

7.31-7.28 (m, 1H)

5.95 (ddd, *J* = 17.2, 10.6, 6.0 Hz, 1H)

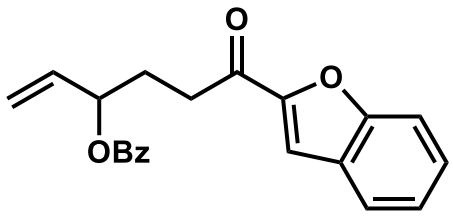
5.64 (ddd, *J* = 6.2, 6.2, 6.2 Hz, 1H)

5.40 (dt, *J* = 17.2, 1.3 Hz, 1H)

5.27 (dt, *J* = 10.6, 1.2 Hz, 1H)

3.12-3.09 (m, 2H)

2.32-2.27 (m, 2H).



166

^{13}C NMR (125 MHz, $CDCl_3$) δ: 190.4, 165.9, 155.7, 152.5, 136.0, 133.2, 130.3, 129.7 (2 C), 128.5 (2 C), 128.4, 127.1, 124.0, 123.4, 117.5, 112.9, 112.6, 74.6, 34.6, 28.6.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{21}H_{19}O_4$, 335.1278; found 335.1291.

6-(4-Methoxyphenyl)-6-oxohex-1-en-3-yl benzoate, 170.

Prepared according to the general procedure 1, purified by flash column chromatography (gradient, 3–10% EtOAc:hexanes), the 4-anisoyl ketone **170** was isolated as a yellow oil (139.1 mg, 0.429 mmol, 19% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

8.05 (dd, *J* = 8.4, 1.3 Hz, 2H)

7.92 (d, *J* = 8.9 Hz, 2H)

7.58-7.54 (m, 1H)

7.46-7.42 (m, 2H)

6.90 (d, *J* = 8.9 Hz, 2H)

5.94 (ddd, *J* = 17.2, 10.6, 6.1 Hz, 1H)

5.64-5.60 (m, 1H)

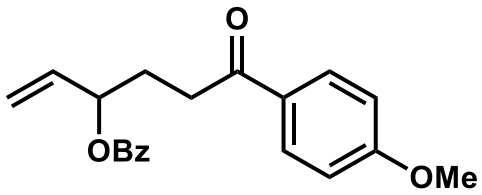
5.38 (dt, *J* = 17.2, 1.3 Hz, 1H)

5.25 (dt, *J* = 10.6, 1.2 Hz, 1H)

3.86 (s, 3H)

3.07-3.04 (m, 2H)

2.26-2.22 (m, 2H).



170

^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.8, 165.9, 163.6, 136.2, 133.1, 130.4 (3 C), 130.0, 129.8 (2 C), 128.5 (2 C), 117.3, 113.9 (2 C), 74.8, 55.6, 33.9, 28.9.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{21}O_4$, 325.1434; found 325.1426.

6-Oxo-6-phenylhex-1-en-3-yl 4-methoxybenzoate, 171.

To the allylic alcohol **156** (101.5 mg, 0.534 mmol, 1.0 equiv) was added DMAP (13.0 mg, 0.107 mmol, 0.2 equiv), triethylamine (97.2 μL, 0.694 mmol, 1.3 equiv), and dichloromethane (5.3 mL). The solution was cooled to 0 °C, and *p*-anisoyl chloride (136.5 mg, 0.800 mmol, 1.5 equiv), dissolved in dichloromethane (1.0 mL), and then dicyclohexyl carbodiimide (DCC, 121.2 mg, 0.587 mmol, 1.1 equiv), were added dropwise. The mixture was allowed to warm to 22 °C and was stirred overnight. The solution was then quenched with a saturated aqueous solution of NH_4Cl (5.3 mL) and then extracted with dichloromethane (3 × 5.3 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash column chromatography (gradient, 3–10% EtOAc:hexanes) and the phenyl ketone **171** was isolated as a colorless oil (39.1 mg, 0.121 mmol, 23% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

8.02-7.99 (m, 2H)

7.95-7.93 (m, 2H)

7.56-7.53 (m, 1H)

7.45-7.42 (m, 2H)

6.93-6.90 (m, 2H)

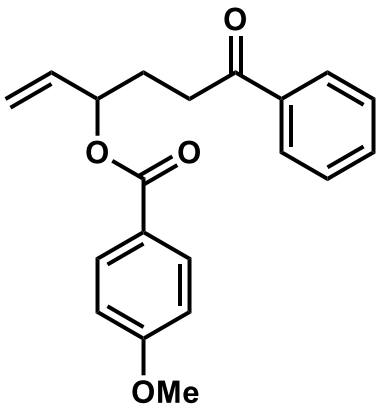
5.93 (ddd, *J* = 17.2, 10.6, 6.0 Hz, 1H)

5.62-5.58 (m, 1H)

5.36 (dt, *J* = 17.2, 1.3 Hz, 1H)

5.24 (dt, *J* = 10.6, 1.2 Hz, 1H)

3.86 (s, 3H)



171

3.12-3.08 (m, 2H)

2.26-2.21 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 199.3, 165.7, 163.6, 136.9, 136.4, 133.2, 131.8 (2 C), 128.7 (2 C), 128.2 (2 C), 122.8, 117.1, 113.8 (2 C), 74.3, 55.6, 34.3, 28.7.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{21}O_4$, 325.1434; found 325.1425.

6-(7-Methoxybenzofuran-2-yl)-6-oxohex-1-en-3-yl benzoate, 143.

Prepared according to the general procedure 1, purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes), the benzofuryl ketone **143** was isolated as white crystals (168.2 mg, 0.462 mmol, 21% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

8.04 (dd, *J* = 8.4, 1.3 Hz, 2H)

7.56-7.52 (m, 1H)

7.46 (s, 1H)

7.40-7.43 (m, 2H)

7.24 (dd, *J* = 7.9, 1.2 Hz, 1H)

7.20 (t, *J* = 7.8 Hz, 1H)

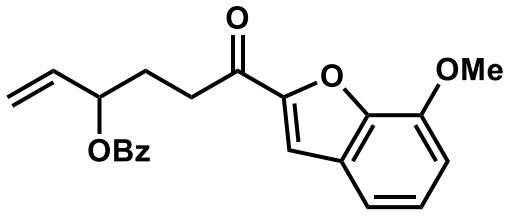
6.93 (dd, *J* = 7.6, 1.2 Hz, 1H)

5.94 (ddd, *J* = 17.2, 10.6, 6.1 Hz, 1H)

5.63 (ddd, *J* = 6.2, 6.2, 6.2 Hz, 1H)

5.39 (dt, *J* = 17.2, 1.3 Hz, 1H)

5.26 (dt, *J* = 10.5, 1.2 Hz, 1H)



143

4.00 (s, 3H)

3.16-3.12 (m, 2H)

2.29 (ddd, *J* = 7.1, 7.1, 7.1 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 190.4, 165.9, 152.9, 146.1, 145.4, 136.0, 133.1, 130.3, 129.8 (2 C), 128.8, 128.5 (2 C), 124.7, 117.5, 115.2, 112.7, 109.5, 74.6, 56.2, 34.7, 28.4.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{22}H_{21}O_5$, 365.1389; found 365.1377.

6-(Furan-2-yl)-6-oxohex-1-en-3-yl benzoate, 179.

Prepared according to the general procedure 1, purified by flash column chromatography (gradient, 3–10% EtOAc:hexanes), the furyl ketone **179** was isolated as a colorless oil (174.7 mg, 0.614 mmol, 28% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

8.04 (dd, *J* = 8.4, 1.3 Hz, 2H)

7.58-7.54 (m, 1H)

7.53 (dd, *J* = 1.7, 0.8 Hz, 1H)

7.46-7.42 (m, 2H)

7.16 (dd, *J* = 3.5, 0.8 Hz, 1H)

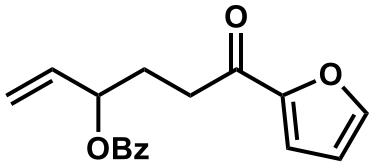
6.49 (dd, *J* = 3.6, 1.7 Hz, 1H)

5.92 (ddd, *J* = 17.3, 10.6, 6.1 Hz, 1H)

5.61-5.57 (m, 1H)

5.37 (dt, *J* = 17.2, 1.3 Hz, 1H)

5.25 (dt, *J* = 10.7, 1.2 Hz, 1H)



179

2.98-2.95 (m, 2H)

2.25-2.21 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 188.5, 165.9, 152.7, 146.4, 136.0, 133.1, 130.3, 129.8 (2 C), 128.5 (2 C), 117.4, 117.1, 112.3, 74.6, 34.1, 28.5.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{17}O_4$, 285.1121; found 285.1118.

6-Oxo-6-(4-methylphenyl)hex-1-en-3-yl benzoate, 181.

Prepared according to the general procedure 1, purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes), the 4-tolyl ketone **181** was isolated as a colorless oil (262.2 mg, 0.850 mmol, 38% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

8.05 (dd, *J* = 8.4, 1.4 Hz, 2H)

7.85-7.83 (d, *J* = 8.2 Hz, 2H)

7.58-7.55 (m, 1H)

7.46-7.42 (m, 2H)

7.23 (d, *J* = 7.8 Hz, 2H)

5.94 (ddd, *J* = 17.2, 10.5, 6.1 Hz, 1H)

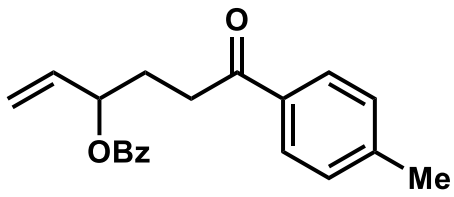
5.64-5.60 (m, 1H)

5.38 (dt, *J* = 17.3, 1.3 Hz, 1H)

5.25 (dt, *J* = 10.6, 1.2 Hz, 1H)

3.09-3.06 (m, 2H)

2.40 (s, 3H)



181

2.27-2.22 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 198.9, 165.9, 144.0, 136.2, 134.5, 133.1, 130.4, 129.8 (2 C), 129.4 (2 C), 128.5 (2 C), 128.3 (2 C), 117.3, 74.7, 34.1, 28.8, 21.8.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{21}O_3$, 309.1485; found 309.1479.

6-(4-Fluorophenyl)-6-oxohex-1-en-3-yl benzoate, 183.

Prepared according to the general procedure 1, purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes), the 4-fluorophenyl ketone **183** was isolated as a white solid (124.8 mg, 0.400 mmol, 18% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

8.04 (dd, *J* = 8.4, 1.3 Hz, 2H)

7.98-7.94 (m, 2H)

7.58-7.55 (m, 1H)

7.46-7.43 (m, 2H)

7.12-7.08 (m, 2H)

5.94 (ddd, *J* = 17.2, 10.6, 6.1 Hz, 1H)

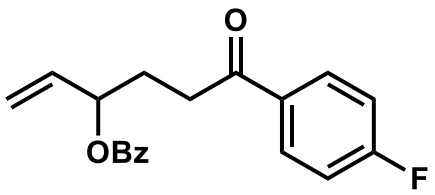
5.64-5.60 (m, 1H)

5.38 (dt, *J* = 17.2, 1.3 Hz, 1H)

5.26 (dt, *J* = 10.5, 1.2 Hz, 1H)

3.09-3.06 (m, 2H)

2.30-2.20 (m, 2H).



183

^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.6, 165.9, 165.9 (d, $^1J_{C\text{-}F}$ = 255.3 Hz), 136.1, 133.3 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 133.2, 130.8 (d, $^3J_{C\text{-}F}$ = 9.2 Hz, 2 C), 130.4, 129.8 (2 C), 128.5 (2 C), 117.4, 115.8 (d, $^2J_{C\text{-}F}$ = 21.9 Hz, 2 C), 74.6, 34.1, 28.7.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{19}H_{18}FO_3$, 313.1235; found 313.1223.

6-Oxo-6-(4-(trifluoromethyl)phenyl)hex-1-en-3-yl benzoate, 185.

Prepared according to the general procedure 1, purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes), the 4-trifluoromethylphenyl ketone **185** was isolated as a colorless oil (363.2 mg, 1.002 mmol, 45% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

8.04-8.02 (m, 4H)

7.70 (d, *J* = 8.2 Hz, 2H)

7.58-7.55 (m, 1H)

7.45-7.42 (m, 2H)

5.94 (ddd, *J* = 17.0, 10.6, 6.0 Hz, 1H)

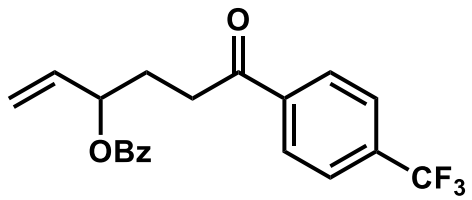
5.66-5.62 (m, 1H)

5.39 (dt, *J* = 17.2, 1.3 Hz, 1H)

5.27 (dt, *J* = 10.6, 1.3 Hz, 1H)

3.14-3.11 (m, 2H)

2.33-2.22 (m, 2H).



185

^{13}C NMR (125 MHz, $CDCl_3$) δ: 198.2, 165.9, 139.5, 136.0, 134.5 (q, $^2J_{C\text{-}F}$ = 32.6 Hz), 133.2, 130.3, 129.7 (2 C), 128.6 (2 C), 128.5 (2 C), 125.8 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, 2 C), 123.7 (q, $^1J_{C\text{-}F}$ = 272.6 Hz), 117.5, 74.4, 34.5, 28.5.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{18}F_3O_3$, 363.1203; found 363.1185.

6-Oxo-6-(3-(trifluoromethyl)phenyl)hex-1-en-3-yl benzoate, 187.

Prepared according to the general procedure 1, purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes), the 3-trifluoromethylphenyl ketone **187** was isolated as a colorless oil (475.1 mg, 1.311 mmol, 59% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

8.18 (s, 1H)

8.10 (d, *J* = 7.8 Hz, 1H)

8.05-8.03 (m, 2H)

7.79 (d, *J* = 7.8 Hz, 1H)

7.59-7.54 (m, 2H)

7.43 (m, 2H)

5.94 (ddd, *J* = 17.2, 10.6, 6.0 Hz, 1H)

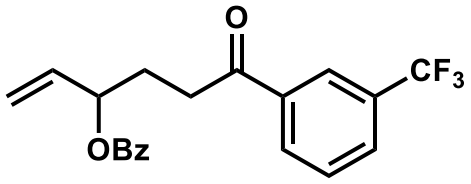
5.66-5.62 (m, 1H)

5.39 (dt, *J* = 17.2, 1.3 Hz, 1H)

5.27 (dt, *J* = 10.5, 1.2 Hz, 1H)

3.13 (t, *J* = 7.5 Hz, 2H)

2.32-2.24 (m, 2H).



187

^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.8, 165.8, 137.4, 136.0, 133.2, 131.3 (q, $^{2}J_{C\text{-}F}$ = 32.9 Hz), 131.3, 130.3, 129.7 (2 C), 129.6 (q, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 129.4, 128.5 (2 C), 124.9 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 123.8 (q, $^{1}J_{C\text{-}F}$ = 272.7 Hz), 117.5, 74.4, 34.3, 28.5.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{18}F_3O_3$, 363.1203; found 363.1195.

6-Oxo-6-(2-(trifluoromethyl)phenyl)hex-1-en-3-yl benzoate, 189.

Prepared according to the general procedure 1, purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes), the 2-trifluoromethylphenyl ketone **189** was isolated as a yellow oil (112.4 mg, 0.310 mmol, 14% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

8.05 (dd, *J* = 8.3, 1.2 Hz, 2H)

7.70 (d, *J* = 7.4 Hz, 1H)

7.59-7.52 (m, 3H)

7.45 (t, *J* = 7.7 Hz, 2H)

7.39 (d, *J* = 7.3 Hz, 1H)

5.92 (ddd, *J* = 16.9, 10.6, 6.0 Hz, 1H)

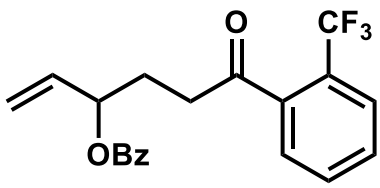
5.62-5.58 (m, 1H)

5.38 (dt, *J* = 17.3, 1.3 Hz, 1H)

5.26 (dt, *J* = 10.5, 1.2 Hz, 1H)

2.97 (t, *J* = 7.5 Hz, 2H)

2.29-2.18 (m, 2H).



189

^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.4, 165.9, 140.3 (q, $^4J_{C\text{-}F}$ = 1.8 Hz), 135.9, 133.2, 132.0, 130.3, 130.2, 129.8 (2 C), 128.6 (2 C), 127.0 (q, $^2J_{C\text{-}F}$ = 32.3 Hz), 127.0, 126.8 (q, $^3J_{C\text{-}F}$ = 5.0 Hz), 123.7 (q, $^1J_{C\text{-}F}$ = 273.9 Hz), 117.5, 74.3, 39.0 (d, *J* = 1.5 Hz), 28.2.

6-(4-(Dimethylamino)phenyl)-6-oxohex-1-en-3-yl benzoate, 191.

Prepared according to the general procedure 1, purified by flash column chromatography (gradient, 3–10% EtOAc:hexanes), the 4-dimethylaniline ketone **191** was isolated as a white solid (194.5 mg, 0.576 mmol, 26% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

8.07-8.05 (m, 2H)

7.85 (d, *J* = 9.1 Hz, 2H)

7.57-7.54 (m, 1H)

7.46-7.42 (m, 2H)

6.62 (d, *J* = 9.2 Hz, 2H)

5.94 (ddd, *J* = 17.3, 10.6, 6.1 Hz, 1H)

5.61 (ddd, *J* = 6.2, 6.2, 6.2 Hz, 1H)

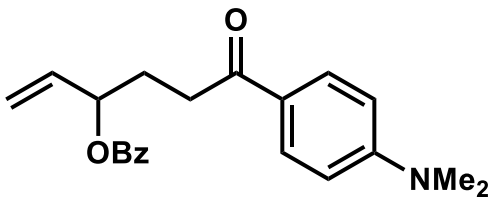
5.37 (dt, *J* = 17.2, 1.3 Hz, 1H)

5.24 (dt, *J* = 10.6, 1.2 Hz, 1H)

3.04 (s, 6H)

3.01 (td, *J* = 7.2, 2.6 Hz, 2H)

2.25-2.21 (m, 2H).



191

^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.3, 165.9, 153.5, 136.3, 133.0, 130.5, 130.3 (2C), 129.8 (2C), 128.5 (2C), 124.9, 117.2, 110.7 (2C), 75.0, 40.1 (2C), 33.4, 29.2.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{21}H_{24}NO_3$, 338.1751; found 338.1744.

6-Oxo-6-phenylhex-1-en-3-yl benzofuran-2-carboxylate, 193.

To the allylic alcohol **156** (95.1 mg, 0.500 mmol, 1.0 equiv) was added DMAP (6.0 mg, 0.050 mmol, 0.1 equiv), benzofuran-2-carboxylic acid (81.0 mg, 0.500 mmol, 1.0 equiv), and dichloromethane (10.0 mL) was added. Dicyclohexyl carbodiimide (DCC, 113.5 mg, 0.550 mmol, 1.1 equiv), dissolved in dichloromethane (1.0 mL), was then added dropwise at 0 °C. The mixture was allowed to warm to 22 °C and was stirred for 3.0 h. The solution was then quenched with a saturated aqueous solution of NH_4Cl (0.5 mL) and the layers were separated. Then the organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (0.5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified by silica gel flash column chromatography (gradient, 1–5% EtOAc:hexanes),to give the phenyl ketone **193** as a yellow oil (48 mg, 0.144 mmol, 29% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.97-7.95 (m, 2H)

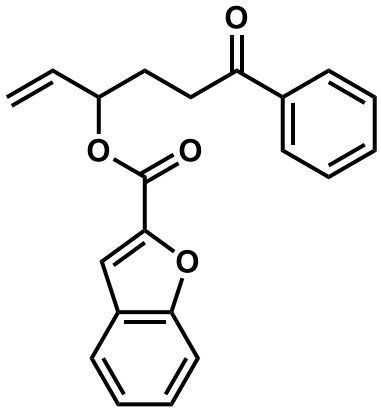
7.68 (dt, *J* = 7.9, 1.1 Hz, 1H)

7.59 (dd, *J* = 8.4, 0.9 Hz, 1H)

7.56-7.53 (m, 2H)

7.47-7.43 (m, 3H)

7.32-7.29 (m, 1H)



193

5.96 (ddd, *J* = 17.0, 10.5, 6.3 Hz, 1H)

5.69-5.65 (m, 1H)

5.43 (dt, *J* = 17.3, 1.3 Hz, 1H)

5.30 (dt, *J* = 10.5, 1.2 Hz, 1H)

3.15-3.12 (m, 2H)

2.31-2.26 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 199.0, 159.0, 155.9, 145.6, 136.9, 135.6, 133.3, 128.8 (2 C), 128.2 (2 C), 127.8, 127.1, 123.9, 123.0, 118.1, 114.2, 112.5, 75.4, 34.2, 28.6.

6-Oxo-6-phenylhex-1-en-3-yl 4-(trifluoromethyl)benzoate, 194.

To the allylic alcohol **156** (100.0 mg, 0.526 mmol, 1.0 equiv) was added DMAP (6.4 mg, 0.053 mmol, 0.1 equiv), 4-(trifluoromethyl)benzoic acid (100.0 mg, 0.526 mmol, 1.0 equiv), and dichloromethane (10.0 mL) was added. DCC (119.4, 0.579 mmol, 1.1 equiv), dissolved in dichloromethane (1.0 mL), was then added dropwise at 0 °C. The mixture was allowed to warm to 22 °C and was stirred for 3.0 h. The solution was then quenched with sat. aq. NH_4Cl (0.5 mL) and the layers were separated. Then the organic layer was washed with sat. $NaHCO_3$ (0.5 mL), dried over Na_2SO_4, filtered, then concentrated *in vacuo*. The product was purified by silica gel flash column chromatography (gradient, 1–5% EtOAc:hexanes), to give the phenyl ketone **194** as a yellow oil (65.2 mg, 0.180 mmol, 34% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

8.14 (d, *J* = 8.0 Hz, 2H)

7.93 (dd, *J* = 8.4, 1.4 Hz, 2H)

7.70 (d, *J* = 8.2 Hz, 2H)

7.57-7.53 (m, 1H)

7.44 (t, *J* = 7.8 Hz, 2H)

5.94 (ddd, *J* = 17.1, 10.6, 6.3 Hz, 1H)

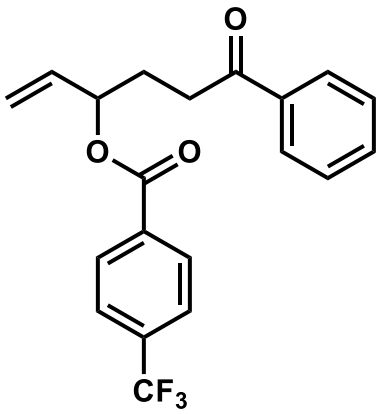
5.66-5.62 (m, 1H)

5.39 (dt, *J* = 17.2, 1.3 Hz, 1H)

5.29 (dt, *J* = 10.5, 1.2 Hz, 1H)

3.10 (t, *J* = 7.2 Hz, 2H)

2.28 (dt, *J* = 7.0, 7.0 Hz, 2H).



194

^{13}C NMR (125 MHz, $CDCl_3$) δ: 199.0, 164.7, 136.8, 135.7, 134.6 (q, $^{2}J_{C\text{-}F}$ = 32.7 Hz), 133.6, 133.3, 130.1 (2 C), 128.8 (2 C), 128.1 (2 C), 125.6 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz, 2 C), 123.8 (q, $^{1}J_{C\text{-}F}$ = 272.7 Hz), 117.9, 75.5, 34.1, 38.6.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{20}H_{18}F_3O_3$, 363.1203; found 363.1185.

4-Oxo-4-phenylbutyl benzoate, 195.

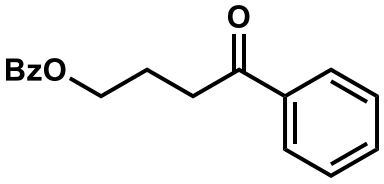
Prepared according to the general procedure 1, purified by flash column chromatography (gradient, 1–5% EtOAc:Hexanes), the phenyl ketone **195** was isolated as white crystals (40.8 mg, 0.152 mmol, 7% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

8.04-8.02 (m, 2H)

7.99-7.97 (m, 2H)

7.58-7.54 (m, 2H)



195

7.48-7.42 (m, 4H)

4.44 (t, *J* = 6.4 Hz, 2H)

3.16 (t, *J* = 7.2 Hz, 2H)

2.28-2.23 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 199.2, 166.7, 136.9, 133.3, 133.1, 130.4, 129.7 (2 C), 128.8 (2 C), 128.5 (2 C), 128.2 (2 C), 64.5, 35.1, 23.5.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{17}H_{17}O_3$, 269.1172; found 269.1164.

5-Oxo-5-phenylpentan-2-yl benzoate, 197.

Prepared according to the general procedure 1, purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes), the phenyl ketone **197** was isolated as a colorless oil (66.5 mg, 0.231 mmol, 23% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

8.04-8.02 (m, 2H)

7.95-7.93 (m, 2H)

7.57-7.52 (m, 2H)

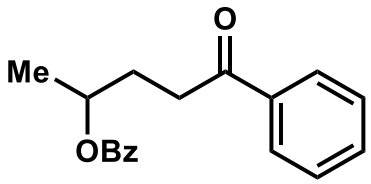
7.45-7.41 (m, 4H)

5.27 (tq, *J* = 6.4, 6.4 Hz, 1H)

3.16-3.05 (m, 2H)

2.19-2.15 (m, 2H)

1.42 (d, *J* = 6.3 Hz, 3H).



197

^{13}C NMR (125 MHz, $CDCl_3$) δ: 199.4, 166.3, 136.9, 133.2, 133.0, 130.7, 129.7 (2 C), 128.7 (2 C), 128.5 (2 C), 128.2 (2 C), 71.3, 34.8, 30.5, 20.5.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{18}H_{19}O_3$, 283.1329; found 283.1322.

C. Synthesis of Aryl Cyclopropanes

***trans* (2-Ethenylcyclopropyl)phenylmethanone, 158.**

To a solution of the phenyl ketone **165** (23.2 mg, 0.10 mmol, 1.0 equiv) and bis[1,2-bis(diphenylphosphino)ethane]palladium(0) (4.5 mg, 0.005 mmol, 0.05 equiv) in THF (4 mL) was added LiHMDS (1.0 M in THF, 110 μL, 0.11 mmol, 1.1 equiv) at –78 °C. The solution was stirred at –78 °C for 30 min, and then the reaction was gradually warmed to 22 °C over 30 min. The reaction mixture was stirred at 22 °C for 1.5 h the reaction was then quenched with brine (1 mL). The aqueous layer was separated and extracted with Et_2O (3 x 4 mL). The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded the crude product, which was further purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes) to give the cyclopropyl phenyl ketone **158** as a colorless oil (14.6 mg, 0.0848 mmol, 85% yield). The structure of **158** and the trans stereochemistry was elucidated based on previously reported spectroscopic data as well as 2D NMR results (see end of this experimental section for the 2D NMR experiments).[26]

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.99 (dd, *J* = 8.4, 1.3 Hz, 2H)

7.59-7.55 (m, 1H)

7.48 (t, *J* = 7.6 Hz, 2H)

5.55 (ddd, *J* = 17.0, 10.3, 8.5 Hz, 1H)

5.21 (ddd, *J* = 17.0, 1.4, 0.7 Hz, 1H)

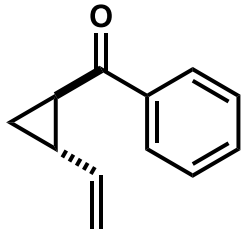
5.04 (dd, *J* = 10.3, 1.4 Hz, 1H)

2.69 (ddd, *J* = 8.0, 5.2, 3.8 Hz, 1H)

2.21 (dddd, *J* = 8.6, 8.6, 6.4, 3.8 Hz, 1H)

1.71 (ddd, *J* = 8.9, 5.2, 3.9 Hz, 1H)

1.19 (ddd, *J* = 8.0, 6.4, 3.9 Hz, 1H).



158

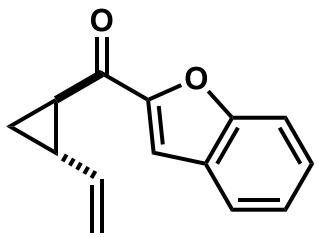
^{13}C NMR (125 MHz, $CDCl_3$) δ: 198.8, 138.6, 138.0, 133.0, 128.7 (2 C), 128.2 (2 C), 115.2, 29.6, 26.8, 18.3.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{13}O$, 173.0961; found 173.0959.

***trans* Benzofuran-2-yl(2-ethenylcyclopropyl)methanone, 167.**

To a solution of the benzofuryl ketone **166** (23.2 mg, 0.10 mmol, 1.0 equiv) and bis[1,2-bis(diphenylphosphino)ethane]palladium(0) (4.5 mg, 0.005 mmol, 0.05 equiv) in 4 mL of THF was added LiHMDS (1.0 M in THF/ethylbenzene, 110 μL, 0.11 mmol, 1.1 equiv) at –78 °C. The solution was stirred at –78 °C for 30 min and then was gradually warmed to 22 °C over 30 min. The reaction mixture was then stirred at 22 °C for 1.5 h at which time the reaction was quenched with 1 mL of brine. The aqueous layer was separated and extracted with Et_2O (3 × 4 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes) to give the cyclopropyl benzofuryl ketone **167** as a colorless oil (18.9 mg, 0.0890 mmol, 89% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:



167

7.72 (d, *J* = 7.8 Hz, 1H)

7.59 (d, *J* = 8.4 Hz, 1H)

7.55 (s, 1H)

7.49-7.46 (m, 1H)

7.32 (t, *J* = 7.5 Hz, 1H)

5.56 (ddd, *J* = 17.0, 10.3, 8.5 Hz, 1H)

5.23 (dd, *J* = 17.2, 1.4 Hz, 1H)

5.06 (dd, *J* = 10.3, 1.3 Hz, 1H)

2.78 (ddd, *J* = 8.5, 5.1, 3.8 Hz, 1H)

2.32-2.27 (m, 1H)

1.74 (ddd, *J* = 8.9, 5.1, 4.0 Hz, 1H)

1.25 (ddd, *J* = 8.1, 6.5, 4.0 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 189.4, 155.8, 153.2, 138.3, 128.2, 127.3, 124.0, 123.4, 115.4, 112.6, 112.5, 29.8, 27.2, 18.6.

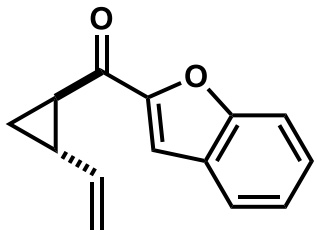
HRMS (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{13}O_2$, 213.0910; found 213.0904.

General Procedure 2 for the synthesis of cyclopropanes.

***trans* Benzofuran-2-yl(2-ethenylcyclopropyl)methanone, 167.**

To a solution of the benzofuryl ketone **166** (33.4 mg, 0.1 mmol, 1.0 equiv) in dry THF (4 mL) was added LiHMDS (1.0 M in THF, 110 μL, 0.11 mmol, 1.1 equiv) at –78 °C and after it had stirred for 30 min at –78 °C, the reaction mixture was then stirred at 22 °C for 2 h at which time

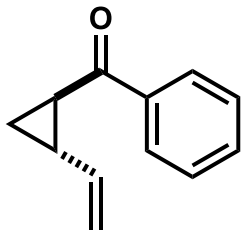
the reaction was quenched with brine (1 mL). The aqueous layer was separated and extracted with Et_2O (3 × 4 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes) to give the cyclopropyl benzofuryl ketone **167** as a colorless oil (17.0 mg, 0.0801 mmol, 80% yield).



167

***trans* Phenyl(2-ethenylcyclopropyl)methanone, 158.**

Prepared according to the general procedure 2 using the phenyl ketone **165**, after addition of LiHMDS and stirring at –78 °C for 30 min, the reaction was then stirred at 22 °C for 1 h before quenching with brine. The crude residue was purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes) to give the cyclopropyl phenyl ketone **158** as a colorless oil (14.5 mg, 0.0842 mmol, 84% yield).



158

***trans* 4-Methoxyphenyl(2-ethenylcyclopropyl)methanone, 171.**

Prepared according to the general procedure 2 using the 4-anisoyl ketone **170**, after addition of LiHMDS and stirring at –78 °C for 30 min, the reaction was then stirred at 22 °C for 2 h before quenching with brine. The crude residue was purified by flash column chromatography (gradient, 2–10% EtOAc:hexanes) to give the cyclopropyl 4-anisoyl ketone **171** as a colorless oil (4.3 mg, 0.0213 mmol, 21% yield) and the cyclopropyl phenyl ketone **158** as a colorless oil (9.9 mg, 0.0575 mmol, 58% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.93 (d, *J* = 9.0 Hz, 2H)

6.67 (d, *J* = 9.0 Hz, 2H)

5.54 (ddd, *J* = 17.0, 10.3, 8.5 Hz, 1H)

5.20 (ddd, *J* = 17.1, 1.4, 0.6 Hz, 1H)

5.02 (dd, *J* = 10.3, 1.2 Hz, 1H)

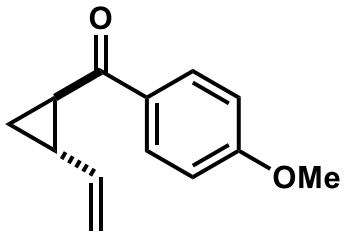
3.88 (s, 3H)

2.64 (ddd, *J* = 8.0, 5.2, 3.8 Hz, 1H)

2.17 (dddd, *J* = 8.6, 8.6, 6.3, 3.8 Hz, 1H)

1.67 (ddd, *J* = 8.9, 5.2, 3.9 Hz, 1H)

1.15 (ddd, *J* = 8.0, 6.3, 3.9 Hz, 1H).



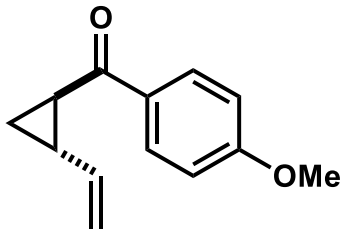
171

^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.2, 163.5, 138.9, 131.0, 130.4 (2 C), 114.9, 113.8 (2 C), 55.6, 29.1, 26.3, 17.9.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{13}H_{15}O_2$, 203.1067; found 203.1061.

***trans* 4-Methoxyphenyl(2-ethenylcyclopropyl)methanone, 171.**

Prepared according to the general procedure 2 using the phenyl ketone **172**, after addition of LiHMDS and stirring at –78 °C for 30 min, the reaction was then stirred at 22 °C for 2 h before quenching with brine. The crude residue was purified by flash column chromatography (gradient, 2–10% EtOAc:hexanes) to give the cyclopropyl 4-anisoyl ketone **172** as a colorless oil (6.2 mg, 0.0307 mmol, 31% yield) and the cyclopropyl phenyl ketone **158** as a colorless oil (8.5 mg, 0.0494 mmol, 49% yield).



171

***trans* 7-Methoxybenzofuran-2-yl(2-ethenylcyclopropyl)methanone, 142.**

Prepared according to the general procedure 2 using the benzofuryl ketone **143**, after addition of LiHMDS and stirring at –78 °C for 30 min, the reaction was then stirred at 22 °C for 4.5 h before quenching with brine. The crude residue was purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes) to give the cyclopropyl benzofuryl ketone **142** as a colorless oil (18.1 mg, 0.0750 mmol, 75% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.51 (s, 1H)

7.28 (dd, *J* = 7.9, 1.1 Hz, 1H)

7.22 (t, *J* = 7.9 Hz, 1H)

6.94 (dd, *J* = 7.8, 1.1 Hz, 1H)

5.54 (ddd, *J* = 17.1, 10.3, 8.5 Hz, 1H)

5.22 (ddd, *J* = 17.0, 1.4, 0.7 Hz, 1H)

5.04 (ddd, *J* = 10.3, 1.4, 0.5 Hz, 1H)

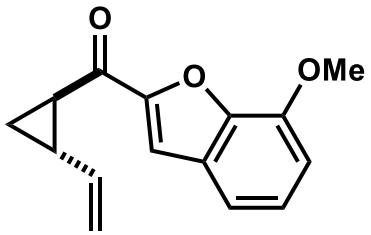
4.03 (s, 3H)

2.89 (ddd, *J* = 8.2, 5.1, 3.8 Hz, 1H)

2.33-2.28 (m, 1H)

1.71 (ddd, *J* = 9.0, 5.1, 4.0 Hz, 1H)

1.25 (ddd, *J* = 8.2, 6.5, 4.0 Hz, 1H).



142

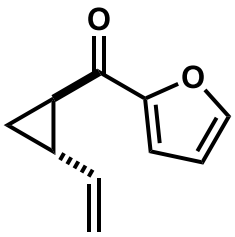
^{13}C NMR (125 MHz, $CDCl_3$) δ: 189.6, 153.5, 146.2, 145.5, 138.4, 129.0, 124.7, 115.4, 115.2, 112.2, 109.4, 56.2, 29.9, 27.0, 18.9.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{15}H_{15}O_3$, 243.1016; found 243.1000.

***trans* 2-Furanyl(2-ethenylcyclopropyl)methanone, 180.**

Prepared according to the general procedure 2 using the furyl ketone **179**, after addition of LiHMDS and stirring at –78 °C for 30 min, the reaction was then stirred at 22 °C for 1.5 h before quenching with brine. The crude residue was purified by flash column chromatography (gradient, 2–10% EtOAc:hexanes) to give the cyclopropyl furyl ketone **180** as a colorless oil (11.3 mg, 0.0697 mmol, 70% yield) and the cyclopropyl phenyl ketone **158** as a colorless oil (2.3 mg, 0.0134 mmol, 13% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:



180

7.61 (d, *J* = 1.7, 0.8 Hz, 1H)

7.22 (dd, *J* = 3.5, 0.8 Hz, 1H)

6.55 (dd, *J* = 3.6, 1.7 Hz, 1H)

5.51 (ddd, *J* = 17.0, 10.3, 8.5 Hz, 1H)

5.20 (ddd, *J* = 17.1, 1.4, 0.7 Hz, 1H)

5.03 (dd, *J* = 10.3, 1.0 Hz, 1H)

2.62 (ddd, *J* = 8.1, 5.2, 3.8 Hz, 1H)

2.24-2.19 (m, 1H)

1.66 (ddd, *J* = 8.9, 5.2, 4.0 Hz, 1H)

1.16 (ddd, *J* = 8.1, 6.4, 4.0 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 187.5, 153.4, 146.5, 138.5, 116.7, 115.2, 112.4, 29.1, 26.6, 18.0.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{10}H_{11}O_2$, 163.0754; found 163.0754.

***trans* 4-Methylphenyl(2-ethenylcyclopropyl)methanone, 182.**

Prepared according to the general procedure 2 using the 4-tolyl ketone **181**, after addition of LiHMDS and stirring at –78 °C for 30 min, the reaction was then stirred at 22 °C for 2.5 h before quenching with brine. The crude residue was purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes) to give 17.0 mg of an inseparable mixture of the cyclopropyl tolyl ketone **182** (49% yield) and the cyclopropyl phenyl ketone **158** (46% yield) as a colorless oil.

Compound 182:

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.89 (d, *J* = 8.2 Hz, 2H)

7.27 (d, *J* = 8.0 Hz, 2H)

5.58-5.50 (m, 1H)

5.20 (ddd, *J* = 17.0, 1.4, 0.7 Hz, 1H)

5.03 (dd, *J* = 10.4, 1.4 Hz, 1H)

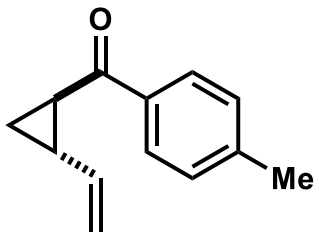
2.71-2.65 (m, 1H)

2.42 (s, 3H)

2.23-2.15 (m, 1H)

1.73-1.67 (m, 1H)

1.21-1.15 (m, 1H).



182

^{13}C NMR (125 MHz, $CDCl_3$) δ: 198.4, 143.7, 138.8, 135.5, 129.4 (2 C), 128.3 (2 C), 115.0, 29.4, 26.6, 21.8, 18.1.

HRMS of mixture (*m/z*) $[M + H]^+$ calcd for $C_{13}H_{15}O$, 187.1117; found 187.1113.

***trans* 4-Fluorophenyl(2-ethenylcyclopropyl)methanone, 184.**

Prepared according to the general procedure 2 using the 4-fluorophenyl ketone **183**, after addition of LiHMDS and stirring at –78 °C for 30 min, the reaction was then stirred at 22 °C for 30 min before quenching with brine. The crude residue was purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes) to give 16.3 mg of an inseparable mixture of the cyclopropyl 4-fluorophenyl ketone **184** (47% yield) and the cyclopropyl phenyl ketone **158** (43% yield) as a colorless oil.

Compound 184:

^{1}H NMR (500 MHz, $CDCl_3$) δ:

8.03-8.00 (m, 2H)

7.17-7.12 (m, 2H)

5.58-5.50 (m, 1H)

5.21 (d, *J* = 17.0 Hz, 2H)

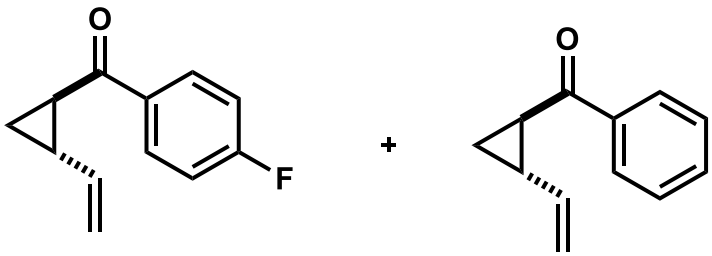
5.06-5.03 (m, 1H)

2.63 (ddd, *J* = 8.0, 5.2, 3.8 Hz, 1H)

2.23-2.17 (m, 1H)

1.73-1.68 (m, 1H)

1.21-1.17 (m, 1H).



184 **158**

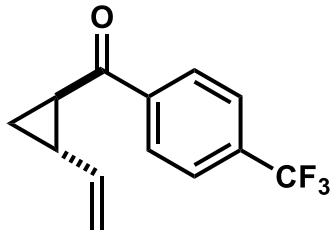
^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.2, 165.8 (d, $^{1}J_{C\text{-}F}$ = 254.2 Hz), 138.5, 134.4 (d, $^{4}J_{C\text{-}F}$ = 2.9 Hz), 130.8 (d, $^{3}J_{C\text{-}F}$ = 9.4 Hz, 2 C), 115.8 (d, $^{2}J_{C\text{-}F}$ = 21.9 Hz, 2 C), 115.3, 29.6, 26.7, 18.3.

HRMS of mixture (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{12}FO$, 191.0867; found 191.0862.

***trans* 4-Trifluorophenyl(2-ethenylcyclopropyl)methanone, 186.**

Prepared according to the general procedure 2 using the 4-trifluoromethylphenyl ketone **185**, after addition of LiHMDS and stirring at –78 °C for 30 min, the reaction was then stirred at 22 °C for 1.25 h before quenching with brine. The crude residue was purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes) to give the cyclopropyl 4-trifluoromethylphenyl ketone **186** as a colorless oil (14.5 mg, 0.0604 mmol, 60% yield) and the cyclopropyl phenyl ketone **158** as a colorless oil (3.5 mg, 0.0203 mmol, 20% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:



186

8.08 (d, *J* = 8.6 Hz, 2H)

7.74 (d, *J* = 8.2 Hz, 2H)

5.55 (ddd, *J* = 17.0, 10.3, 8.5 Hz, 1H)

5.23 (dd, *J* = 17.0, 0.6 Hz, 1H)

5.07 (dd, *J* = 10.3, 0.9 Hz, 1H)

2.67 (ddd, *J* = 8.0, 5.2, 3.7 Hz, 1H)

2.23 (dddd, *J* = 8.6, 8.6, 6.3, 3.8 Hz, 1H)

1.75 (ddd, *J* = 9.0, 5.2, 4.0 Hz, 1H)

1.25 (ddd, *J* = 8.0, 6.4, 4.0 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.9, 140.7, 138.2, 134.3 (q, $^2J_{C\text{-}F}$ = 32.5 Hz), 128.5 (2 C), 125.8 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, 2 C), 123.8 (q, $^1J_{C\text{-}F}$ = 272.7 Hz), 115.7, 30.3, 27.2, 18.7.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{13}H_{12}F_3O$, 241.0835; found 241.0828.

***trans* 3-Trifluorophenyl(2-ethenylcyclopropyl)methanone, 188.**

Prepared according to the general procedure 2 using the 3-trifluoromethylphenyl ketone **187**, after addition of LiHMDS and stirring at –78 °C for 30 min, the reaction was then stirred at 22 °C for 1 h before quenching with brine. The crude residue was purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes) to give 18.2 mg of an inseparable mixture of the cyclopropyl 3-trifluoromethylphenyl ketone **188** (60% yield) and the cyclopropyl phenyl ketone **158** (23% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ:

8.23 (s, 1H)

8.16 (d, *J* = 7.8, 1H)

7.82 (d, *J* = 7.8 Hz, 1H)

7.62 (t, *J* = 7.8 Hz, 1H)

5.59-5.51 (m, 1H)

5.24 (ddd, *J* = 17.0, 1.2, 0.7 Hz, 1H)

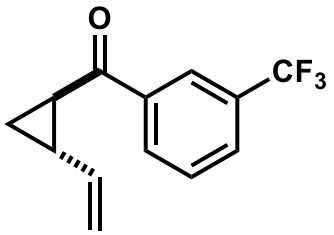
5.07 (dd, *J* = 10.3, 1.3 Hz, 1H)

2.71-2.66 (m, 1H)

2.28-2.17 (m, 1H)

1.76-1.69 (m, 1H)

1.26 (ddd, *J* = 8.0, 6.4, 4.0 Hz, 1H).



188

^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.5, 138.5, 138.2, 131.3 (q, $^{2}J_{C\text{-}F}$ = 32.9 Hz), 131.3, 129.4 (q, $^{4}J_{C\text{-}F}$ = 3.5 Hz), 129.4, 125.1 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 123.9 (q, $^{1}J_{C\text{-}F}$ = 272.6 Hz), 115.7, 30.2, 26.9, 18.8.

HRMS of mixture (*m/z*) $[M + H]^+$ calcd for $C_{13}H_{12}F_3O$, 241.0835; found 241.0833.

***trans* 2-Trifluorophenyl(2-ethenylcyclopropyl)methanone, 190.**

Prepared according to the general procedure 2 using the 2-trifluoromethylphenyl ketone **189**, after addition of LiHMDS and stirring at –78 °C for 30 min, the reaction was then stirred at 22 °C for 1 h before quenching with brine. The crude residue was purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes) to give the cyclopropyl 2-trifluoromethylphenyl ketone **190** as a colorless oil (16.8 mg, 0.0699 mmol, 70% yield) and the cyclopropyl phenyl ketone **158** as a colorless oil (0.9 mg, 0.00523 mmol, 5% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.71 (d, *J* = 7.8 Hz, 1H)

7.63-7.51 (m, 3H)

5.48 (ddd, *J* = 17.0, 10.3, 8.4 Hz, 1H)

5.23 (dd, *J* = 16.9, 0.2 Hz, 1H)

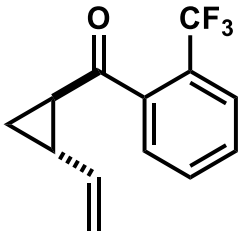
5.04 (dd, *J* = 10.2, 1.4 Hz, 1H)

2.35 (ddd, *J* = 8.0, 5.2, 3.8 Hz, 1H)

2.32-2.27 (m, 1H)

1.76 (ddd, *J* = 8.9, 5.1, 4.0 Hz, 1H)

1.26 (ddd, *J* = 7.9, 6.6, 4.0 Hz, 1H).



190

^{13}C NMR (125 MHz, $CDCl_3$) δ: 202.7, 140.8 (q, $^{4}J_{C\text{-}F}$ = 1.9 Hz), 137.9, 132.0, 130.2, 127.6, 127.1 (q, $^{2}J_{C\text{-}F}$ = 33.5 Hz), 126.7 (q, $^{3}J_{C\text{-}F}$ = 5.0 Hz), 123.7 (q, $^{1}J_{C\text{-}F}$ = 273.6 Hz), 115.6, 31.3, 31.1 (q, *J* = 2.0 Hz), 19.6.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{13}H_{12}F_3O$, 241.0835; found 241.0828.

***trans* (4-*N,N*-Dimethylaminophenyl)(2-ethenylcyclopropyl)methanone, 192.**

Prepared according to the general procedure 2 using the 4-dimethylaniline ketone **191**, after addition of LiHMDS and stirring at –78 °C for 30 min, the reaction was then stirred at 22 °C for 2 h before quenching with brine. The crude residue was purified by flash column chromatography (gradient, 2–10% EtOAc:hexanes) to give the cyclopropyl dimethylaniline ketone **192** as a colorless oil (9.2 mg, 0.427 mmol, 43% yield) and the cyclopropyl phenyl ketone **158** as a colorless oil (7.3 mg, 0.0424 mmol, 42% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.93 (d, *J* = 9.0 Hz, 2H)

6.67 (d, *J* = 9.0 Hz, 2H)

5.54 (ddd, *J* = 17.0, 10.3, 8.6 Hz, 1H)

5.18 (dd, *J* = 17.1, 0.8 Hz, 1H)

5.00 (dd, *J* = 10.2, 1.5 Hz, 1H)

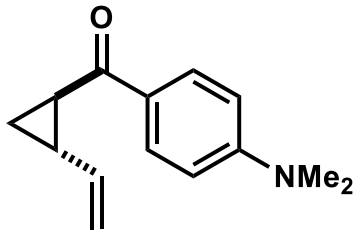
3.06 (s, 6H)

2.63 (ddd, *J* = 8.0, 5.2, 3.8 Hz, 1H)

2.14 (dddd, *J* = 8.6, 8.6, 6.2, 3.8 Hz, 1H)

1.64 (ddd, *J* = 8.8, 5.2, 3.8 Hz, 1H)

1.09 (ddd, *J* = 8.1, 6.2, 3.8 Hz, 1H).



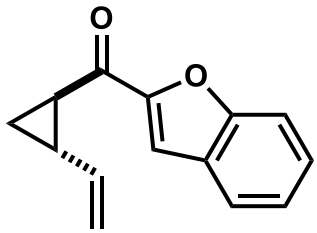
192

^{13}C NMR (125 MHz, $CDCl_3$) δ: 196.4, 153.5, 139.4, 130.4 (2 C), 125.9, 114.5, 110.8 (2 C), 40.2 (2 C), 28.5, 25.9, 17.5.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{14}H_{18}NO$, 216.1383; found 216.1378.

***trans* Benzofuran-2-yl(2-ethenylcyclopropyl)methanone, 167.**

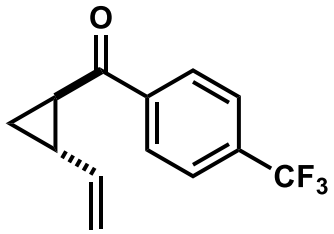
Prepared according to the general procedure 2 using the phenyl ketone **193**, after addition of LiHMDS and stirring at –78 °C for 30 min, the reaction was then stirred at 22 °C for 2.5 h before quenching with brine. The crude residue was purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes) to give the cyclopropyl benzofuryl ketone **167** as a colorless oil (15.5 mg, 0.0730 mmol, 73% yield) and the cyclopropyl phenyl ketone **158** as a colorless oil (1.9 mg, 0.0110 mmol, 11% yield).



167

***trans* 4-Trifluorophenyl(2-ethenylcyclopropyl)methanone, 186.**

Prepared according to the general procedure 2 using the phenyl ketone **194**, after addition of LiHMDS and stirring at –78 °C for 30 min, the reaction was then stirred at 22 °C for 2 h before quenching with brine. The crude residue was purified by flash column chromatography (gradient, 1–5% EtOAc:hexanes) to give the cyclopropyl 4-trifluoromethylphenyl ketone **186** as a colorless oil (10.4 mg, 0.0433 mmol, 43% yield) and the cyclopropyl phenyl ketone **158** as a colorless oil (8.4 mg, 0.488 mmol, 49% yield).



186

Phenyl(cyclopropyl)methanone, 196.

Prepared according to the general procedure 2 using the phenyl ketone **195**, after addition of LiHMDS and stirring at –78 °C for 30 min, the reaction was then stirred at 22 °C for 2 h before quenching with brine. The crude residue was purified by flash column chromatography (gradient,

1–5% EtOAc:hexanes) to give the cyclopropyl phenyl ketone **196** as a colorless oil (5.5 mg, 38% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

8.02 (d, *J* = 7.5 Hz, 2H)

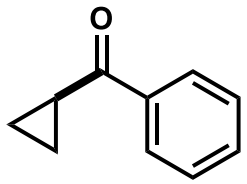
7.57 (t, *J* = 7.3 Hz, 1H)

7.48 (t, *J* = 7.6 Hz, 2H)

2.71-2.66 (m, 1H)

1.26-1.24 (m, 2H)

1.06-1.04 (m, 2H).



196

^{13}C NMR (125 MHz, $CDCl_3$) δ: 200.8, 138.2, 132.9, 128.6 (2 C), 128.2 (2 C), 17.3, 11.8 (2 C). HRMS (*m/z*) $[M + H]^+$ calcd for $C_{10}H_{11}O$, 147.08044; found 147.08022. Spectroscopic data for **196** match those previously reported in the literature.[24,25]

***trans* Phenyl(2-methylcyclopropyl)methanone, 198.**

Prepared according to the general procedure 2 using the phenyl ketone **197**, after addition of LiHMDS and stirring at –78 °C for 30 min, the reaction was then stirred at 22 °C for 2 h before quenching with brine. The crude residue was purified by flash column chromatography (gradient, 1–5% EtOAc:Hexanes) to give the cyclopropyl phenyl ketone **198** as a colorless oil (8.2 mg, 51% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ:

7.99 (d, *J* = 7.5 Hz, 2H)

7.56 (t, *J* = 7.3 Hz, 1H)

7.47 (t, *J* = 7.6 Hz, 2H)

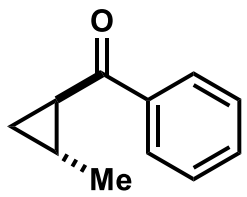
2.40 (ddd, *J* = 8.2, 4.3, 4.3 Hz, 1H)

1.63-1.58 (m, 1H)

1.51-1.47 (m, 1H)

1.23 (d, *J* = 6.0 Hz, 3H)

0.90 (ddd, *J* = 7.0, 7.0, 3.3 Hz, 1H).

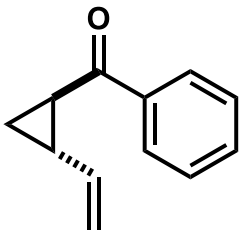


198

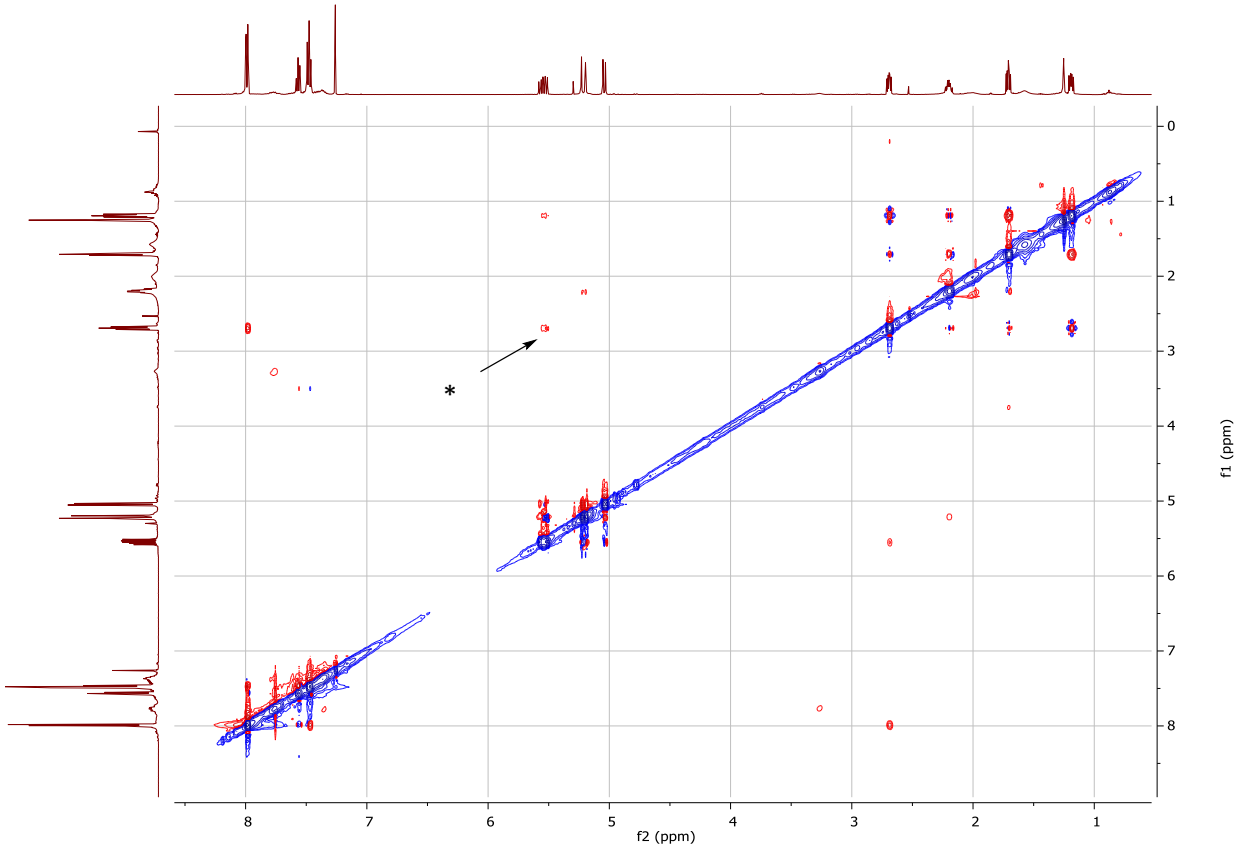
^{13}C NMR (125 MHz, $CDCl_3$) δ: 200.3, 138.3, 132.7, 128.6 (2 C), 128.1 (2 C), 26.6, 21.5, 20.3, 18.5.

HRMS (*m/z*) $[M + H]^+$ calcd for $C_{11}H_{13}O$, 161.09609; found 161.09566.

Appendix:



158



*The NOESY experiment was performed on compound **158** and showed a correlation between the proton alpha to the carbonyl and the 2-vinyl proton, designated by the arrow.

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23. We thank Professor Craig Merlic for helpful discussions on the mechanism.

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