Title
Progress Towards the Total Synthesis of Steroidal Natural Products Clionastatins A and B

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Author
Tartakoff, Samuel Steucek

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Progress Towards the Total Synthesis of Steroidal Natural Products Clionastatins A and B

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Chemistry

by

Samuel Steucek Tartakoff

Dissertation Committee:
Professor Christopher D. Vanderwal, Chair
Professor Scott D. Rychnovsky
Professor Sergey Pronin

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DEDICATION

To my wife for her patience.  
To my children for their love.  
To my labmates for their friendship. 
To my professor for his trust. 
   To my God for His help.
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LIST OF ABBREVIATIONS

Ac: acetyl
Acac: acetoacetate
AIBN: 2,2'-azabisbutyronitrile
BTT: benzenethiothiazole
nBu: n-butyl
tBu: tert-butyl
DCM: dichloromethane
Cl: chemical ionization
Cod: cyclooctadiene
COSY: correlation spectroscopy
Cy: cyclohexyl
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
DCE: 1,2-dichloroethane
DEAD: diethyl azodicarboxylate
DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD: diisopropyl azodicarboxylate
DIBAL-H: diisobutylaluminum hydride
DIPA: diisopropylamine
DMAP: 4-dimethylaminopyridine
DMDO: dimethyldioxirane
DMF: dimethylformamide
DMPU: 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO: dimethylsulfoxide
EDTA: ethylenediaminetetraacetic acid
Et: ethyl
ESI: electrospray ionization
HFIP: hexafluoroisopropanol
HMBC: heteronuclear multiple-bond correlation
HMDS: hexamethyldisilazide
HMQC: Heteronuclear multiple quantum coherence spectroscopy
HRMS: high-resolution mass spectrometry
Hz: Hertz
IBS: 2-iodoxybenzenesulfonic acid
IBX: 2-iodoxybenzoic acid
IPNBSH: N-isopropylidene-N'-2-nitrobenzenesulfonyl hydrazine
iPr: isopropyl
IR: infrared
LC50: lethal concentration, 50%
LDA: lithium diisopropylamide
LRMS: low-resolution mass spectrometry
mCPBA: meta-chloroperoxybenzoic acid
Me: methyl
Mes: mesetyl
mIBX: 3-iodoxybenzoic acid
MMC: magnesium methyl carbonate
MOM: methoxymethyl
MPO: 4-methoxypyridine N-oxide
MS: mass spectrometry
Ms: mesyl
MTBE: methyl tert-butyl ether
NBS: N-bromosuccinamide
NBSH: 2-nitrobenzenesulfonylhydrazide
NCS: N-chlorosuccinamide
NMM: N-methylmorpholine
NMR: nuclear magnetic resonance
nOe: nuclear Overhauser effect
NOESY: nuclear Overhauser enhancement spectroscopy
Ns: nosyl
Ox: oxylate
PAA: p-anisaldehyde
Ph: phenyl
Piv: pivaloyl
Pyr: pyridine
Red-Al: sodium bis(2-methoxyethoxy)aluminumhydride
TBAF: tetra-n-butylammonium fluoride
TBDPS: tert-butyldiphenylsilyl
TBS: tert-butyldimethylsilyl
TCA: trichloroacetoxy
TES: triethylsilyl
TFA: trifluoroacetic acid
Tf: triflinate
THF: tetrahydrofuran
TIPS: triisopropylsilyl
TLC: thin-layer chromatography
TMS: trimethylsilyl
Ts: tosyl
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Let me begin by saying that a public acknowledgement is not the same as a “thank-you.” There are an enormous number of people who have supported, strengthened, taught, and otherwise influenced me over the years, helping me to become who and what I am today. They are all deserving of my thanks, and I have tried to make a point of telling them that in person, rather than burying my gratitude in some dusty tome that only a handful of people (optimistically) in the world will ever read. In writing these acknowledgements, I want to recognize those people who have contributed in some direct way to bringing about the work that is discussed in this thesis, and to immortalize, in a way, their names beside that very work.

With that preface, I first need to recognize Professor Chris Vanderwal. When I was a fresh graduate student with more zeal than understanding, he took a chance on me and accepted me into his lab. In my six years here, he has mentored, coached, encouraged, and occasionally cajoled me, but never criticized or demeaned me. He has bolstered my opinion of myself when I was discouraged and given me advice on everything from how to separate compounds to how to find a work/life balance. He offered me a project that fascinated me and gave me the freedom to work at my own pace and under my own direction, while still always being accessible and offering advice freely. By his easy manner, genuine concern for his students, and his passion for science, he also fostered a tight-knit lab environment, in which it has been a pleasure to work (mostly). I have learned a lot since starting here, both good and bad, but if I had it to do over again, I would join the Vanderlab in a heartbeat.

It is also essential that I acknowledge the labmates with whom I have worked. Their ideas, support, and physical help (e.g. distilled reagents) enabled me to accomplish much more than I could otherwise have done. Specifically, Dr. Allen Hong and Sean Feng have worked closely with me on the clionastatin project and, while they are mentioned at several points in this thesis, their efforts impacted almost every facet of my research. Allen inspired me to work harder and accomplish more than I otherwise might have. Sean, although often a trial on my patience, kept me laughing through some rough times. Professor David Martin, Dr. Fiona Lin, and Borja López Perez also worked briefly on parts of this project and, while those efforts never met with much success, they influenced the directions that I chose to pursue. Dmitriy Uchenik and Brian Atwood also deserve special recognition. While they shared a workspace with me, they were willing to put up with my idiosyncrasies, they vetted nearly all of my ideas, and they made long hours in the lab more enjoyable.

I want to acknowledge Prof. Scott Rychnovsky and Prof. Sergey Pronin, both for sitting on my thesis committee and also for their advice. Scott coached me through my advancement exams in a way that left a lasting impression on me (a good one) and Sergey has given me numerous suggestions about my proposed chemistry, in addition to acting as a role-model regarding work ethic. I am also indebted to UC-Irvine for funding me through a chancellor’s fellowship and a dissertation fellowship, as well as to the NSF-GRFP for funding me for most of my graduate career.

There are several mentors in my past, without whom, I would not have come to this point. Mr. Gerald Page taught chemistry at Holliston High School with such passion and excitement that I promised myself I would someday become a chemistry teacher and return that gift to others. President Steven Smith of the Novosibirsk, Russia Mission...
convincing me to pursue an advanced degree so that I could teach at a university level. Prof. Steve Castle (BYU) hired me on as an undergraduate researcher and provided training in both the technical skills and critical thinking that I would need in order to succeed in graduate school. He also gave me a taste for the beauty and challenge of total synthesis...to this day, I am uncertain whether he did me a favor or not but either way, it helped me get to where I am.

I also must acknowledge my family. Although my wife's synthetic advice has been limited to “add more enzyme, Honey,” her unfailing support, patience, and love made long hours and repeated failures bearable. It was her encouragement that sent me back into lab the next day and her unflagging confidence in my ability that drove me to complete my Ph.D., even at times when I had little confidence in myself. My children have similarly been an aide to my research, despite taking time away from my lab work. Infant laughter is a sure cure for whatever ails you, and the unquestioning trust of a little child cannot help but make you more optimistic in other facets of your life.

Finally, I would like to acknowledge my God, who set in motion the natural laws that I have spent my Ph.D. studying. I am grateful for the mind and body He gave me to use, for the opportunities I have been granted, and for the moments of pure insight He has provided. He, alone, has understood completely all of my difficulties and joys and I am indebted to His guidance for steering me through stormy weather to where I am now.
CURRICULUM VITAE

Samuel Steucek Tartakoff

EDUCATION

Ph. D. Organic Chemistry
University of California-Irvine, Irvine, California
September 2009 – Present
Thesis: “Progress towards the total synthesis of clionastatins A and B.”
  • Advisor: Christopher D. Vanderwal

B.S. Chemistry
Brigham Young University, Provo, Utah
April 2009
  • Advisor: Steven L. Castle

TEACHING EXPERIENCE

Teaching Assistant
University of California-Irvine

  • Advanced Organic Chemistry Laboratory
    Fall 2014
    o Supervised eight hours of lab/week
    o Planned and delivered in-laboratory lectures
    o Trouble-shot laboratory experiments
    o Graded written lab reports; wrote and graded quizzes

  • Organic Chemistry I, II, & III Laboratory
    Fall – Spring 2009, Summer 2014
    o Supervised eight hours of lab/week
    o Planned and delivered in-laboratory lectures
    o Prepared review sections for written and practical exams
    o Graded oral presentations, written lab reports, and exams

  • Organic Chemistry I Lecture
    Summer 2014
    o Was head teaching assistant for lecture
    o Wrote quizzes, exams, and worksheets for 121 undergraduate students
    o Planned and taught four 1-hour discussions each week

Sunday School President
The Church of Jesus Christ of Latter-day Saints, Irvine, California
March 2011 – February 2012

  • Planned and taught weekly lessons
    o Both youth (ages 12–18, 5–10 students) and adult classes (ages 19+, 30–50 students)
  • Organized and managed Sunday school program for my congregation
    o Five different curricula, 10 teachers, over 200 church-members in attendance
  • Planned and conducted quarterly teacher development classes
    o Two-hour seminars focused on mechanics of effective teaching, lesson planning, and classroom time-management

Volunteer English Teacher
The Church of Jesus Christ of Latter-day Saints, Novosibirsk, Russia
August 2006 – August 2008

  • Taught volunteer English classes to Russian natives
    o Taught groups of 5–40 students, 1–2 times/week, ages 8–65+
    o Organized classes, planned lessons, and taught both singly and as a team
    o Tailored lessons for beginning, intermediate, and advanced students
  • Planned and co-taught personalized lessons for families and small groups
MENTORING

Fellowship Writing Mentor
University of California-Irvine
July 2010 – Present
- Mentor for the National Science Foundation-Graduate Research Fellowship (NSF-GRFP) writing workshop
  - Worked with 20–40 graduate students each year
  - Peer edited for 5–10 students each year
  - Two of my mentees received the NSF-GRFP and three received honorable mentions
- Assisted in the writing and revision of various grants and fellowships, including Undergraduate Research Opportunities Program fellowships, Summer Undergraduate Research Program fellowships, an American Heart Association fellowship, and National Institute of Health pre-doctoral and postdoctoral fellowships

Graduate and Undergraduate Mentor
University of California-Irvine
- Sean Feng (Undergraduate) January 2013 – Present
  - Trained in synthetic organic chemistry: theory, laboratory practice, and techniques
  - Developed and guided a research project on the synthesis of substituted cyclohexenones
  - Provided guidance for graduate school and fellowship applications
- Brian Atwood (Graduate student) September 2012 – Present
  - Trained in synthetic organic chemistry: theory, laboratory practice, and techniques
  - Mentored in the successful application for the NSF-GRFP
  - Provided guidance for a research project on the synthesis of chlorinated natural products

RESEARCH AND LABORATORY EXPERIENCE

National Science Foundation-Graduate Research Fellow
University of California-Irvine
July 2009 – Present
- Research advisor: Christopher D. Vanderwal
- Progress towards the synthesis of the steroidal natural products clionastatins A and B, potential anti-cancer compounds
  - Developed a 12-step route for the synthesis of the functionalized clionastatin cores and screened them for biological activity
  - Presented on research in weekly subgroup meetings and gave seminars bimonthly in larger group meetings
  - Took courses on ethical conduct of research, academic honesty, and laboratory safety

Research Assistant
Brigham Young University
May 2007 – June 2009
- Research advisor: Steven L. Castle
- Completed and published on the total synthesis of the natural alkaloid acutumine
- Proposed and worked on synthesis of deuterated octadecylsilanes for laser absorption studies

Stockroom assistant
Brigham Young University
- Prepared for chemistry laboratory sections (over 400 students)
- Distributed equipment and chemicals

HONORS AND AWARDS

- Regents’ Dissertation Fellowship Award (UCI) August 2014
- Associated Graduate Student Travel Grant (UCI) March 2014
- Department of Chemistry Travel Award (UCI) March 2014
• NSF-Graduate Research Fellowship (UCI) June 2011 – June 2014
• Chancellor’s Fellowship (UCI) September 2009 – May 2010
• Outstanding Undergraduate Student in Inorganic Chemistry (BYU) April 2009
• ACS Inorganic Chemistry Award (BYU) April 2009
• Undergraduate Research Awards for 6 semesters (BYU) June 2007 – April 2009
• Half tuition scholarship recipient for 6 semesters (BYU) June 2007 – April 2009
• Best poster presentation at the Pacific Northwest Undergraduate Research Symposium August 2008

PUBLICATIONS


PRESENTATIONS

6. “Progress towards the total synthesis of clionastatins A and B.” San Francisco, California, August 11, 2014 (248th ACS National Conference, Organic session, oral presentation.)

5. “Progress towards the total synthesis of clionastatins A and B.” Dallas, Texas, March 17, 2014 (247th ACS National Conference, Organic session, poster presentation.)


3. “Progress towards the total synthesis of clionastatins A and B.” University of California, Irvine, California, February 18, 2011 (Departmental colloquium, oral presentation.)

2. “Progress towards the total synthesis of acutumine.” Oregon State University, Corvallis, Oregon, August 11, 2008 (Pacific Northwest undergraduate research symposium, poster presentation, Best Poster Presentation award.)

1. “Progress towards the synthesis of acutumine.” Brigham Young University, Provo, Utah, March 30, 2008 (Spring research conference, oral presentation.)

PROFESSIONAL ORGANIZATIONS

• Member of the American Chemical Society September 2010 – Present

SERVICE

Laboratory Experiments and Activities in the Physical Sciences (LEAPS) University of California-Irvine

• Prepared and performed chemistry demonstrations for 5th–11th grade students
• Presented for over 100 students from underrepresented groups
• Coordinated and organized quarterly LEAPS visits to the Vanderwal laboratory

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UC Irvine Chemistry Outreach  January 2010 – Present

University of California-Irvine

- Prepared and performed chemistry demonstrations for K–12th grade an average of 3 hours each week during the school year
- Personally presented for over 3000 students total
- Developed new chemical demonstrations to illustrate additional chemical principles

Independent Community Outreach  October 2010 – Present

Irvine, California

- Co-organized and performed Halloween-themed chemistry demonstrations for over 100 cub scouts and families
- Organized and conducted several chemistry demonstrations and lab tours for home-schooled students and cub-scouts
ABSTRACT OF THE DISSERTATION

Progress Towards the Total Synthesis of Steroidal Natural Products Clionastatins A and B

By

Samuel Steucek Tartakoff

Doctor of Philosophy in Chemistry

University of California, Irvine, 2015

Professor Christopher D. Vanderwal, Chair

A total synthesis of naturally occurring polychlorinated steroids, clionastatins A and B, was undertaken. Efforts were first directed at the synthesis of a truncated tricyclic steroid core and multiple synthetic routes were developed, many of which featured a Diels–Alder reaction. Ultimately, these efforts culminated in the successful synthesis of the clionastatin core. Efforts then focused on development of a bicyclic diene that would allow us to apply the successful Diels–Alder route to the synthesis of a tetracycle, which could be elaborated into clionastatin A. While a suitable diene was made and a tetracyclic cycloadduct was synthesized, the undesired stereochemistry of that cycloadduct suggests that an alternative route to the clionastatins may be necessary.
Chapter 1: Background

1.1 Introduction

Steroids are one of the most ubiquitous, well-studied classes of natural products. They are isolated from both terrestrial and marine sources, and are produced by virtually every multi-celled, and many single-celled, organisms. Possessing a basic structure comprised of “cyclopenta[a]phenanthrene (Figure 1.1) or a skeleton derived therefrom by one or more bond scissions or ring expansions or contractions,” steroids share many structural features with each other but are responsible for a host of different biological functions, including cell signaling, the development of primary and secondary sexual characteristics, and cellular structural features. Because of their diverse biological activities and varied structures, steroids have been the targets of many synthetic efforts and both legitimate and illicit commercial enterprises. Research on steroids has spanned the gap between chemistry, biology, and medicine, and has led to 11 Nobel Prizes, ten of which were in chemistry: Heinrich Otto Wieland in 1927 for his work on the constitution of bile acids and sterols, Adolf Otto Reinhold Windaus in 1928 for his work on the constitution of sterols and their connection with vitamins, Adolf Butenandt and Leopold Ruzicka in 1939 for their isolation of, and studies on, sex hormones, Edward Calvin Kendall, Tadeus Reichstein, and Philip Hench in 1950 for their studies on the structure and effects of adrenal hormones, Robert Burns Woodward in 1965, in part, for his synthetic work on cholesterol, cortisone, and lanosterol, Derek Barton and Odd Hassel in 1969 for their studies of molecular conformation, specifically of the steroid nucleus, and Vladimir Prelog in 1975 for his work on the cholesterol biosynthesis.
1.2 Discovery of Steroids and Nomenclature

In 1769, François Poulletier de la Salle is reported to have isolated a solid, crystalline organic substance from gallstones and bile. It was not until 1815, however, when Michel Eugène Chevreul reisolated the substance, that it was named "cholesterine," and more fully characterized. Structural assignments were made by degradation studies and gravimetric analysis, as well as comparison to other known organic fragments. The name, as explained by Chevreul, was a compound of the Greek words “chole-” (bile) and “stereos-” (solid). Later, with the advent of a more formal naming system for organic molecules, the suffix “-ol” replaced “-ine” to denote the presence of an alcohol on the cholesterol molecule (Figure 1.2). Since that time, hundreds of other steroids have been isolated, identified, and characterized. Some, such as cholesterol, are found in living organisms in significant quantities and serve a structural role in biological machinery, while many others exist in minute amounts and are used as potent signaling compounds.

Because steroids are such a large, structurally distinct class of natural products, they have a nomenclature that is also distinct from other, related molecules (decalins and hydroanthracenes, for example.) Identified as steroids by their characteristic 6-6-6-5 ABCD-ring system, they are usually divided into classes by the number of carbons in their skeleton. The simplest possible steroid possesses 17 carbons, lacking the C18 and C19 angular methyl groups, and belongs to the gonane (from “gone” meaning “generation or seed”) family (Figure 1.3). In order of ascending carbon number, other classes include the estranes (from “estrus” meaning “producer of”), androstanes (from “andro” meaning
“masculine”), pregnanes (from “praegnans” meaning “before birth”), cholanes and cholestanes (from “chole” meaning “bile”). Commonly, the alkyl chain at C17 can vary significantly in both length and substitution. Ring-size and methylation at C18 and C19 can also vary somewhat, earning molecules the distinction of nor- or homosteroids (Figure 1.4). Ring-cleavage is also possible in what are known as the seco-steroids, which make up a large and varied class of natural products that will not be covered in this chapter. Stereochemistry on steroids is given the distinction of being either α (down) or β (up), as illustrated on cyclopamine (1.11), which possesses a C3 β-OH group and a C10 β-Me group.

Figure 1.3. The different classes of steroids, as characterized by number of carbon atoms in their skeleton and by the presence of C18 and C19 angular methyl groups.

Figure 1.4. A generic 19-norpregnane (1.9), a generic D-homopregnane (1.10), a naturally occurring C-nor-D-homosteroid, cyclopamine (1.11), and vitamin D₃ (1.12), a seco-steroid.
1.3 Steroid Biosynthesis

Biosynthetically, all steroids, both in plants and animals, are constructed from the triterpene squalene and are built from acetyl-CoA (1.13) subunits via the mevalonate pathway. Six separate enzymes are involved in this process of converting three subunits of 1.13 into isopentenyl pyrophosphate (IPP, 1.14), which is equilibrated into dimethylallyl pyrophosphate (DMPP, 1.15) by IPP isomerase. One unit of 1.14 and one of 1.15 are then combined by GPP synthase to form geranyl pyrophosphate (GPP, 1.16). Addition of one more unit of 1.14 results in farnesyl pyrophosphate (FPP, 1.17), which is reductively dimerized by squalene synthase and NADPH to produce squalene (1.18). Polyene 1.18 is converted into a variety of natural products. For steroid synthesis, epoxidation by squalene monooxygenase affords squalene oxide (1.19), which cyclizes in an enzymatically-guided

Scheme 1.1 Biosynthesis of Lanosterol (1.21)
cascade reaction to afford tetracycle 1.20. A series of methyl and hydride shifts, terminated by deprotonation, then affords lanosterol (1.21).

A polyene-cascade similar to this was first proposed by Robinson,15 but the correct mechanism was first postulated by Woodward16 based on isotopic 14C labeling studies, and was later confirmed by Tamelen,17 who identified the role of the lanosterol synthase enzyme in creating the observed stereochemistry and methylation pattern, as distinct from a non-enzymatic process.18 In plants and some bacteria, epoxide 1.19 cyclizes in the same fashion but a different series of methyl and hydride shifts affords cycloartenol (1.22). From these two steroidal precursors, it is suggested that all other steroids are derived. In animals, lanosterol (1.21) is converted into cholesterol (1.2) by a series oxidations, involving 14 discrete steps and seven different enzymes, ultimately leading to decarboxylative loss of the geminal methyl groups at C4.19

Cholestane 1.2 is then converted into all other animal steroids by steroidogenesis pathway,20 which differs between different species. In humans, this pathway involves mitochondrial side-chain cleavage of 1.2 to afford pregnenolone (1.23, Scheme 1.1). Oxidation of 1.23 by 17α-hydroxylase and 3β-hydroxysteroid dehydrogenase (3β-HSD) allow for formation of the other progestogens 1.24, 1.28, and 1.29. C21 oxidation of progesterone (1.24) or 17α-hydroxyprogesterone (1.29) by 21-hydroxylase gives access to the glucocorticoids and mineralocorticoids 1.25, 1.26, 1.27, 1.30, and 1.31. Alternatively, the androgens 1.32, 1.33, 1.36, 1.37, and 1.39 can be accessed from either 17α-hydroxyprogrenolone (1.28) or 17α-hydroxyprogesterone (1.29) with C–C bond cleavage mediated by 17,20-lyase, followed by further oxidation with 3β-HSD. Aromatase-mediated oxidative demethylation of either androstenedione (1.33) to estrone (1.34) or testosterone
(1.37) to estradiol (1.38) provides access to the estrogens. This seemingly inefficient, multistep synthesis from a common precursor allows for careful biological regulation of each of the individual steroids being produced, which is vital, as many of the sex hormones must be closely regulated for proper biological function.
1.4 Synthetic Approaches to Steroid Frameworks

Several years after Robinson’s proposed mechanism for steroid synthesis by squalene cyclization, but still 14 years before Woodward’s correct mechanism (Scheme 1.1) was disclosed, approaches to the steroids by chemical synthesis had already been undertaken. The first recognized steroid total synthesis was reported in 1939 by Wilds et al. with the synthesis of equilenin (1.48), although several semi-synthetic efforts towards steroids had previously been reported. This synthesis is most notable, not for the chemical reactions that were utilized, which the authors themselves described as “fairly obvious ones and the successful preparation of the hormone depended principally on developing the proper conditions for making the reactions proceed,” but rather for its pioneering nature.

Starting from Cleve’s acid (1.40), previously reported ketone 1.41 was made in 11 steps. Condensation with methyl oxalate and thermal elimination of carbon monoxide afforded keto-ester 1.42, which was subsequently methylated to give tricycle 1.43.
Nucleophilic addition of an alkylzinc reagent, elimination of the resultant tertiary alcohol, and hydrolysis of both methyl esters provided di-acid 1.44. Poorly diastereoselective reduction of the alkene using sodium amalgam, followed by methylation with diazomethane, hydrolysis of the less sterically hindered ester, and conversion of the resulting acid into the acid chloride afforded 1.46. An Arndt–Eistert reaction provided one-carbon homologated ester 1.47, which underwent clean Dieckmann cyclization and decarboxylation to afford equilenin (1.48).

While this synthesis was an incredible achievement for its time and is deserving of recognition, it demonstrated several key challenges that prompted development of methods for the synthesis of increasingly complex steroidal targets. First, starting from aniline 1.40, the final two rings were built in a very step-wise fashion, leading to a long, linear synthesis. Second, stereochemistry was left largely to chance rather than being strategically installed or directed. Of the methods that have been developed in the ensuing decades, several have stood out as the preferred strategy in which many chemists have synthesized both natural and unnatural steroids.

1.4.1 Cationic Polyene Cyclizations

Given that the biosynthesis of steroids builds all four rings in a single, elegant cascade reaction, it seems obvious that this reaction would be used synthetically. Indeed, in 1968, Johnson et al. showed this to be a viable method for the synthesis of progesterone (1.24). The requisite polyene 1.54 was constructed using a modified Wittig coupling to join furan derivative 1.50 and alkyne 1.52, followed by intramolecular aldol condensation and methylation. Ionization of the tertiary alcohol on 1.54 enabled the cationic π-cascade to proceed, setting five contiguous stereocenters in a single step from an achiral molecule.
The high yield for this transformation (72% for the conversion of \(1.54\) to \(1.56\)) and the formation of almost exclusively a single diastereomer was consistent with the Stork-Eschenmoser hypothesis,\(^{24}\) which predicted that polyenes with trans-oriented double bonds would preorganize and cyclize in a stereospecific manner to afford trans-anti-trans products. Conversion of \(1.56\) to progesterone (1.24) was fairly trivial, involving hydrolysis, ozonolysis, and aldol condensation to effect the final ring expansion.

This first example of a biomimetic, cationic \(\pi\)-cascade reaction for total synthesis using a non-biological substrate demonstrated the impressive power of this reaction for the construction of both natural steroids and unnatural, biologically active steroid analogues. Since Johnson’s pioneering work, a variety of other developments have been made to expand on this reaction, including the use of other initiating groups to form the cation (from epoxides\(^{25}\) and acetals,\(^{26}\) for example) as well as having other terminating groups, such as propargylic\(^{27}\) or allylic silanes.\(^{28}\) In the course of these studies,
investigation also uncovered some of the substitution patterns and effects that lead to cationic stabilization, including the role of vinyl fluorides in cationic π-cascades.\textsuperscript{29}

Further work has also rendered this transformation enantioselective, as demonstrated in Johnson’s synthesis of 4β-hydroxyandrostan-17-one 1.61.\textsuperscript{30} For this synthesis, fluorotriene 1.59 was made in 15\% yield over 12 steps, starting from chlorofluorocyclopropane 1.57 and propyne 1.58, using similar transformations to those employed for the construction of triene 1.54. The conversion of acyclic 1.59 into tetracycle 1.60 could be achieved by use of a number of Lewis acids, but the best results were found with SnCl\(_4\) in DCM at \(-90\) °C. It is noteworthy that the fluorine atom was essential as a cation-stabilizing group, without which bicyclic and tricyclic products predominated. The seemingly modest yield for this step is somewhat misleading, as 68\% of the crude reaction mixture was actually comprised of various tetracyclic products, including dehydrofluorination product 1.62, which further isomerized to 1.63, and product

\textbf{Figure 1.5.} Three of the tricyclic biproducts made from the polycyclization of triene 1.59.
containing a cis-fused CD-ring \((1.64)\). At higher reaction temperatures \((-40 \, ^\circ C)\), compound \(1.62\) predominated and desired \(1.60\) became the minor component (only 6% yield.) Conversion of \(1.60\) to the desired androstanone \(1.61\) involved reduction of the fluoride, oxidative cleavage of the C17 alkene, and deprotection of the C4 alcohol.

1.4.2 Radical Methods

While not a direct application of the biomimetic, cationic \(\pi\)-cascade reactions, radical polyene cyclizations have also been employed in the construction of steroid ring-systems. One good example of this is the synthesis of 5\(\alpha\)-pregnane \(1.69\) by Zoretic.\(^{31}\)

Starting from commercially available geranylacetone \(1.65\), eight steps were required to make tetraene \(1.66\), required for the radical cyclization. The yield for this transformation was modest due, in large part, to a poorly selective Horner–Wadsworth–Emmons reaction. However, under oxidative conditions, formation of a stabilized radical at C1, followed by a series of 6-endo-trig cyclizations afforded tetracycle \(1.67\) in 61% yield. Impressively, this cyclization set seven contiguous stereocenters and four rings with good stereocontrol, albeit as an inseparable mixture of alkene regioisomers. However, alkene isomerization with TFA, reduction of the C1 chloride, decarboxylation, and reduction of the C2 ketone and

---

**Scheme 1.6 Total Synthesis of 5\(\alpha\)-Pregnane 1.69**

\[
\begin{align*}
1.65 & \xrightarrow{8 \text{ steps}} 1.66 \quad \xrightarrow{9\%} \\
1.66 & \xrightarrow{4 \text{ steps}} 1.68 \quad \xrightarrow{32\%} \\
1.68 & \xrightarrow{3 \text{ steps}} 1.69 \quad \xrightarrow{61\%} \\
1.69 & \xrightarrow{\text{Mn(OAc)}_3 \cdot 2\text{H}_2\text{O}} \xrightarrow{\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}} \xrightarrow{\text{AcOH}} \xrightarrow{61\%}
\end{align*}
\]
C8 cyano group afforded tetracycle 1.68, which Johnson had shown\textsuperscript{22} could be elaborated into pregnane 1.69 in three more steps.

Radical cyclizations have also been used in non-biomimetic polyene cascades, as illustrated by Pattenden’s estrone synthesis.\textsuperscript{32} Starting from commercially available anisaldehyde derivative 1.70, cyclopropane 1.71 could be made in 12 steps. Upon treatment with AIBN in toluene at reflux, radical cyclization of 1.71 proceeded via an unusual 12-\textit{endo}-trig, 9-\textit{endo}-trig, 6-\textit{endo}-trig cascade to afford 1.75 in a modest 12\% yield, accompanied by a 52\% yield of uncyclized, de-iodinated 1.71. Despite the low yield, this still amounts to a 49\% yield per ring formed, with good diastereoselectivity in the formation of four contiguous stereocenters. Multiple analogues of substrate 1.71 were tested for this reaction in an effort to improve the yield but incorrect stereochemistry in the products and reduction of iodide without cyclization plagued all other approaches.
From tetracycle 1.75, deprotection and oxidation afforded racemic estrone 1.34 in a total of 15 steps.

1.4.3 Diels–Alder Reactions

While elegant in their construction of the complex, steroid ring-systems, all of the cascade reactions have been limited to a fairly linear approach, as the polyene precursor must be built prior to the cyclization step, followed by post-cyclization functional-group manipulations. Furthermore, the use of strong Lewis acids to trigger the cationic polynene cyclizations limits the functional-group tolerance somewhat. For those reasons, another method that has proven popular for the synthesis of steroids is the use of the Diels–Alder reaction, which forms six-membered rings readily, can set up to four stereocenters in a single step, and can be used to construct otherwise challenging all-carbon quaternary centers. Due to the vast range of substitution tolerated by the Diels–Alder reaction, it has been used in total syntheses to form the A-, B-, and C-rings of various steroids. Perhaps the pinnacle of this methodology, however, is the application of the intramolecular Diels–Alder reaction for steroid synthesis, where multiple rings are formed in a single step.

Scheme 1.8 Enantioselective Total Synthesis of Testosterone 1.37
Fukumoto was able to employ the intramolecular Diels–Alder reaction towards the synthesis of testosterone 1.37 and a formal synthesis of androsterone 1.79. Starting from the known Hajos–Parrish ketone (1.76), 13 steps were needed to build the requisite triene 1.77. This intermediate was obtained as an unknown mixture of E/Z isomers, which, upon heating in a sealed tube with a radical inhibitor, afforded a nearly quantitative yield of tetracycle 1.78. Interestingly, this Diels–Alder reaction afforded ~4:1 mixture of trans-/cis-fusion of the AB-rings, regardless of the E/Z alkene ratio of the starting material, suggesting equilibration to a thermodynamic mixture under the reaction conditions. Three steps were then needed to oxidize and deprotect 1.78, affording testosterone (1.37), which matched an authentic sample in all characteristics. Tetracycle 1.78 could also be converted into androsterone 1.79 in five steps via a known route, albeit in lower yields.

Another good illustration of the intramolecular Diels–Alder reaction in steroid synthesis is Nicolaou’s synthesis of estra-1,3,5(10)-triene-17-one (1.83), in which the B- and C-rings are both closed in a single step. In this case, the required triene was synthesized from cyclopentadione 1.80 via alkylation of a cyclic sulfone. Thermolysis of

**Scheme 1.9 Total Synthesis of Estra-1,3,5(10)-triene-17-one (1.83)**
1.81 resulted in cheletropic extrusion of $\text{SO}_2$ and in situ unveiling of the reactive $o$-quinonemethide,\textsuperscript{39} which readily underwent cycloaddition to the electronically neutral dienophile to afford target 1.83 with the desired stereochemistry in good yield in a 9:1 dr.

### 1.4.4 Other Methods for Steroid Synthesis

One of the classical methods for building steroids has been by application of the Robinson annulation,\textsuperscript{40} which allows a single ring to be appended, while leaving an enone that can be further manipulated. Indeed, the Robinson annulation still provides one of the most reliable and general methods for construction of the CD-ring fragment of the steroid cores, via the Hajos–Parrish ketone (1.76). This annulation reaction was further employed by Rychnovsky in the synthesis of ent-testosterone 1.89.\textsuperscript{41} Hydrindenone 1.84, available in two steps from ketone 1.76, could be elaborated into exocyclic enone 1.85 with magnesium methyl carbonate (MMC), followed by hydrogenation and condensation with formaldehyde. The two-step Robinson annulation was accomplished under fairly mild conditions, leaving the ketal moiety in enone 1.87 intact. Reduction of the enone with dissolving metal conditions and methylation resulted in ketone 1.88. Cleavage of the ketal and tert-butyl ether under acidic conditions resulted in formation of a dione, which

**Scheme 1.10 Total Synthesis of ent-Testosterone 1.89**

![Scheme 1.10 Total Synthesis of ent-Testosterone 1.89](image)
underwent in situ aldol condensation to afford testosterone 1.89, which was elaborated to ent-cholesterol (see 1.2) in eight additional steps.

While less general, the Torgov reaction\textsuperscript{42} has also been used widely for those steroids possessing an aromatic A-ring and remains an industrially important reaction for production of certain hormones at Schering AG. Torgov showed that when allylic alcohol 1.90 was heated with diketone 1.80 in the presence of either catalytic Triton B or pTsOH, intermediate 1.91 was formed. Upon extended heating, alkene isomerization led to tricycle 1.92, which underwent a Prins reaction to give tetracycle 1.93 as a mixture of alkene isomers. Further heating lead to dehydration and further alkene isomerization, with the isolation of diene 1.94 in 50% yield. Complete hydrogenation of this compound led to a mixture of unnatural diastereomers but stepwise reduction and deprotection afforded desired estrone 1.34, although yields were not reported for the final transformation. Further contributions by List\textsuperscript{43} showed that, with the use of chiral Brønsted acids, dione 1.91 could be converted enantioselectively into diene 1.94 in good yields.

**Scheme 1.11 Torgov Reaction in the Total Synthesis of Estrone 1.34**

\[
\begin{align*}
\text{MeO}1.90 & \xrightarrow{\text{H}^+ (\text{cat.}) 50\%} 1.91 \\
1.91 & \xrightarrow{1. \text{H}_2, \text{Pd}} 1.34
\end{align*}
\]
1.5 Discovery of Halogenated Steroids

Originally believed to be mistakenly assigned or artifacts of the isolation process, halogenated natural products have gone from being a rare curiosity to being a major class of known compounds. However, halogenated steroids continue to be relatively rare. In fact, fewer than 100 chlorinated natural steroids have been isolated to date, and only a few brominated steroids have yet been identified. Most of the chlorinated steroids contain only a single chlorine and included physalolactones (1.95) from the Solanaceae plant Physalis peruviana, blattellastanosides (1.96) from the German cockroach Blattella germanica, and kiheisterones (1.97) from the sponge Strongylacidon sp. In almost all cases, the halogen is part of a chlorohydrin group, suggesting their origin from the corresponding epoxide. This theory is supported by the fact that, in many cases, the suggested parent epoxide co-occurs with the chlorinated derivative.

Figure 1.6. Several representative naturally-occurring chlorinated steroids: physalolactone C (1.95), blattellastanoside B (1.96), and kiheisterone C (1.97).

1.6 Isolation of Clionastatins and Structural Elucidation

Previous to the isolation of the clionastatins, studies of the Cliona species had yielded linear peptides, pyrrole alkaloids, and simple sterols. Clionastatins A and B (1.98 and 1.99) were isolated from the Mediterranean burrowing sponge Cliona nigricans in the
fall of 2002, off the coast of Gallinara, Italy. After bioassay guided fractionation of the organic materials, 1.0 mg of 1.98 and 1.3 mg of 1.99 were isolated as amorphous solids. The EIMS showed the presence of three chlorine atoms for clionastatin A, and, in conjunction with 1H NMR, 13C NMR, HMQC, COSY, and HMBC, was used to assign the structure as that of a highly unsaturated androstane steroid. Fattorusso et al. next assigned the relative stereochemistry as that observed in all androstanes using ROESY correlations but was not able to obtain a crystal structure from the small amount of amorphous solid isolated. The EIMS for clionastatin B showed an additional chlorine atom, replacing the C16 proton, but otherwise showed similar spectroscopic features for the ABC-ring system to those found for clionastatin A. Given the unusual structure of the clionastatins, some concern was expressed about whether or not these compounds were artifacts of the isolation process, leading to their re-isolation in the spring of 2003 in the Gulf of Genoa, in similar quantities from a second sample of C. nigricans. Despite this evidence that these compounds are, in fact, natural products, it remains unclear whether they were produced by Cliona nigricans itself or by the zooxanthellae, with which burrowing sponges are known to maintain a symbiotic relationship.

Both new compounds were tested against three different tumor cell lines: WEHI 164 (murine fibrosarcoma), RAW 264-7 (murine macrophage), and THP-1 (human monocytes). Clionastatins A and B both exhibited moderate cytotoxicity against all three lines (expressed in µg/µL): against WEHI 164 (1.98: 0.8; 1.99: 1.1), against RAW 264-7 (1.98: 1.1; 1.99: 1.4), and against THP-1 (1.98: 1.5 and 1.99: 2.0).

The clionastatins were the first polyhalogenated steroids observed in nature, were the first halogenated androstanes, and remain the most heavily chlorinated steroids
isolated to date. In light of their fascinating structures, interesting bioactivity, and unknown biosynthesis, we were interested in engaging in synthetic studies of these molecules. Our efforts towards this goal are detailed in the following chapters.

1.7 Notes and References

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9 For a typical 68 kg adult male, the body produces approximately 1g/day of cholesterol and usually contains a total of about 35g of this steroid. See: Lecerf, J. M. and de Lorgeril, M. *Br. J. Nutr.* **2011**, *106*, 6–14.

10 Cholesterol can make up as much as 30% of the total lipids present in mammalian cell membranes. See: ref. 5.

11 Estrogen, for example, was first isolated by concentrating down hundreds of gallons of urine from pregnant women at a rate of ~8,000 “rat units” per gallon (~1.3 mg/gallon). The isolate was termed “theelin,” from the Greek word for “woman.” Estrogen exists in


For an examination of the role and rate of squalene monooxygenase, see: Sharpe, L. J. and Brown, A. *J. Biol. Chem.* **2013**, *288*, 18707–18715.

For Robinson's initial proposal, which required no methyl or hydride shifts, see: Robinson, R. *J. Soc. Chem. Ind.* **1934**, *53*, 1062.


For the original disclosure of the Diels–Alder reaction, see: Diels, O. and Alder, K. *Justus Liebig’s Annalen der Chemie* **1928**, *460*, 98–122.


For an example from the isolation and characterization of the physalolactones, see: Nittala, S. S.; Velde, V. V.; Frolov, F.; Lavie, D. *Phytochemistry* **1981**, *20*, 2547–2552.


Chapter 2: Initial Efforts Towards the Clionastatin Core

2.1 Introduction

Despite their isolation in 2004 and their fascinating structures,¹ at the outset of this project in 2009, no synthetic efforts towards clionastatins A or B (2.1 and 2.2) had been reported. Their biological activity was intriguing, and a synthetic supply² that would allow further testing, as well as enable the elucidation of mode-of-action, would be useful but was not available from natural sources. Furthermore, given their unprecedented structure and the lack of a crystal structure in the isolation paper, there was some question about the accuracy of the original structural assignment, a question that could only be answered with total synthesis.

![Image of clionastatins A and B and an energy-minimized structure of clionastatin A.](image)

**Figure 2.1.** Clionastatins A and B and an energy-minimized structure of clionastatin A.

2.2 Expected Synthetic Challenges and Proposed Model System

In spite of their well-known androstane steroidal framework, 2.1 and 2.2 have several distinctive structural features that, while making the clionastatins attractive as synthetic targets, also warranted careful consideration when planning a synthetic strategy. One of the most striking features that stands out on even a casual glance at the clionastatins is the high degree of chlorination. As the first polyhalogenated steroids found in nature and the most highly chlorinated steroids discovered to date,³ any synthetic approach needed to account for both how and when these potential leaving-groups would be installed. This issue is further complicated by the fact that the C1 and C2 chlorides are pseudoequatorial,
both in energy-minimized structures (Figure 2.1) and according to coupling constant data, and dichlorination reactions of cyclohexenes tend to favor the formation of diaxial products. \(^4\) The relative stereochemistry on the AB-ring fragment was also anticipated to be problematic, as the C19 angular chloromethyl group was expected to shield the top face of ring system, giving the undesired anti, anti configuration between C2-C1-C10, rather than the required anti, syn stereochemistry. As a final challenge related to installation of the chlorine atoms, both the C1 and C19 chlorides are neopentylic, presumably making late-stage introduction by substitution difficult.

In addition to the chlorination, the high degree of unsaturation found in the clionastatins is striking. The 3,5,8(9)-16-tetraen-7,15-dione oxidation pattern observed in the clionastatins is not found in any other natural or synthetic steroids and renders synthesis via a biomimetic \(\pi\)-cascade polycyclization impractical. Of special note is the tetrasubstituted \(\Delta^{8,9}\)-enone which, while not unknown, \(^5\) is difficult to install via standard Saegusa–Ito or other similar oxidative conditions. \(^6\) Of lesser concern to us was the formation of the desired trans-ring junction for the CD-ring system, due to the preponderance of work that has been done on that particular motif in classical steroid syntheses.

### 2.3 Unsuccessful Retrosynthetic Strategies

#### 2.3.1 Tandem Diels–Alder Approach

In light of these expected challenges, it seemed reasonable to first target a truncated, tricyclic model system (2.3). The proposed ABC-ring target has several attractive features. It contains most of the unsaturation and all of the chlorides that make 2.1 a challenging target, while removing some of the stereochemical complexity from the CD-ring junction.
that could otherwise confound NMR analysis and complicate handling of synthetic intermediates. However, all retrosynthetic approaches to tricycle 2.3 were undertaken with an eye towards making certain that they would be amenable to eventual synthesis of the fully substituted natural products.

It was initially proposed that the challenging stereochemistry on tricycle 2.3 could be set using a tandem-Diels–Alder reaction sequence, first combining diene 2.8 with a sufficiently electron deficient alkyne 2.7. The resulting bicycle (2.6) could then undergo a further [4+2] cycloaddition to afford, after enone formation and installation of the C19 chloride, tricycle 2.4. Elimination of a leaving group and electrophilic chlorination of an allylsilane would result in formation of the desired clionastatin core. This reaction sequence would allow for the rapid synthesis of both the A and B rings with a minimum of
late stage functional group manipulation, while addressing the C1 and C2 chlorination in a very reliable manner. Furthermore, all of the synthons (2.5, 2.7, and 2.8) were known or could be made rapidly (Equations 2.1–2.3). However, this route would rely on a neopentyllic chlorination at C19.

Additionally, several difficulties with this route quickly became apparent when Dr. Fiona Lin and Prof. David Martin began preliminary studies. First, it was observed that the deactivated chlorodiene 2.11, in addition to being volatile, reacted only sluggishly under thermal conditions with even very active dienophiles, including DMAD and maleic anhydride. Secondly, it was found that known alkynyl dienophile 2.14 was unreactive under thermal conditions and, under Lewis acid catalyzed conditions, reacted with diene 2.13 in a hetero-Diels–Alder reaction to give heterocycle 2.16 instead of the desired bicycle 2.15 (Equation 2.4). While this type of reactivity is not unknown with substituted propargyl aldehydes, accounts of hetero-Diels–Alder reactions are fairly rare in comparison with the desired Diels–Alder reactivity. Later attempts to utilize either iminium catalysis or ionic Diels–Alder conditions also met with failure. It was anticipated that these problems could be alleviated by the introduction of a second electron-withdrawing group on the alkynyl dienophile, making the alkyne more reactive towards diene 2.11, while making the aldehyde moiety a less attractive electrophile towards enol ether 2.13. To this end, efforts were made to obtain alkynyl sulfoxide 2.17 or

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{PhS} & \quad \text{2.14} \\
\text{2.13} & \\
\text{OTMS} & \\
\text{---} &
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{OTMS} \\
\text{PhS} & \quad \text{2.15} \\
\text{not observed} & \\
\text{---} &
\end{align*}
\]

\[
\begin{align*}
\text{PhS} & \quad \text{OTMS} \\
\text{2.16} & \\
\text{---} &
\end{align*}
\]
sulfone 2.18. However, this seemingly simple proposal proved an insurmountable challenge.

A variety of methods were examined to synthesize the requisite dienophile (Scheme 2.2). The simplest approach seemed to be oxidation of alkynyl sulfide 2.14, which we already had on hand, to the corresponding sulfoxide or sulfone. However, treatment with mCPBA resulted solely in recovered starting material, presumably because the conjugated aldehyde significantly reduced the nucleophilicity of the sulfide. Efforts were then made to protect the aldehyde as the corresponding cyanohydrin (2.19) or as an acetal (2.21), which could be unmasked after oxidation of the sulfide. While this strategy did allow us to obtain
both sulfoxide 2.22 and sulfone 2.23, deprotection\textsuperscript{13} to the aldehyde was never successful. Mild, acidic conditions (H\textsubscript{2}O/SiO\textsubscript{2} or cat. FeCl\textsubscript{3}/SiO\textsubscript{2}/H\textsubscript{2}O, rt–80 °C) returned only starting acetal, while stronger acids (TsOH in H\textsubscript{2}O/THF or aqueous HCl) led to some consumption of starting material with no observable aldehyde. Surprisingly, even very forcing conditions (50% TFA/CHCl\textsubscript{3}, 100 °C or 95% formic acid/CuSO\textsubscript{4}) returned mostly starting material, although these conditions were reported\textsuperscript{14} for the synthesis of a very similar propargyl aldehyde.

Having failed to unmask the aldehyde in the presence of the sulfoxide/sulfone, the next logical step was to obtain the aldehyde via oxidation of known\textsuperscript{15} propargylic alcohol 2.25. However, treatment with Dess–Martin periodinane, Swern conditions, or DDQ returned only starting material. Treatment with MnO\textsubscript{2} or NaIO\textsubscript{4} resulted in a complex mixture with multiple aldehyde peaks in the \textsuperscript{1}H NMR, but no desired product was ever isolated. Direct nucleophilic formylation of known\textsuperscript{16} sulfoxide 2.27 was also attempted but this reaction largely resulted in decomposition of starting material to uncharacterizable mixtures. This finding especially reinforced the growing suspicion that the desired, electron-poor alkynes were extremely unstable. Indeed, efforts directed at oxidation of the analogous thiophenyl propynoate 2.28 by the literature procedure to known\textsuperscript{17} sulfoxide 2.29 or sulfone 2.30 never provided any of the desired product. While the oxidation was successful as judged by \textsuperscript{1}H NMR, LRMS and TLC analysis, attempted isolation and/or purification of these reactions always resulted in decomposition. Convinced that the necessary dienophiles could not be obtained, this route was abandoned for a while.

At a later point, with the benefit of additional experience and understanding, several further attempts were made at finding Diels–Alder conditions that would utilize more
stable substrates (Equation 2.5). It seemed reasonable that by using the ester moiety instead of the aldehyde as an activating group for the alkyne (2.28 vs. 2.14), undesired hetero-Diels–Alder reactivity could be eliminated. However, because esters are less electron-withdrawing than the analogous aldehydes, the problem posed by the poorly reactive chlorodiene 2.11 would be exacerbated. It would then become necessary to find sufficiently forcing Diels–Alder conditions to effect the desired transformation. In this endeavor, we were encouraged by the literature precedent, although limited, that exists for the reaction of propargylic esters as dienophiles.¹⁸

Several potential dienophiles were made from ethyl propiolate using known methods¹⁹ and these alkynes were subjected to a variety of Lewis acid mediated (Et₂AlCl, MnBr₂, ZnBr₂) and thermal (60–210 °C, various solvents) Diels–Alder reaction conditions. Thiophenyl substituted 2.28 was used primarily but the other dienophiles (2.31, 2.32, and 2.33) were all tested. The conditions investigated largely returned unreacted dienophile, sometimes with deprotected siloxydiene when acid might have been generated in situ. More forcing thermal conditions led to decomposition of the dienophile, accompanied by the strong odor of thiophenol. In light of these failures, several tests (Scheme 2.3) were run to check the reactivity of both the dienophiles and the diene with known, reactive partners. Dienophiles were tested with furan²⁰ over a range of temperatures, with and without MnBr₂, but no [2.2.1]-bicycle 2.35 was ever observed. Diene 2.13, however, reacted readily
with DMAD (2.35) to give 2.37 transiently, as observed by aliquot $^1$H NMR analysis. However, even when care was taken to exclude oxygen, this product rapidly oxidized further to diester 2.38.

**Scheme 2.3 Test Reactions for Dienophiles 2.28 and 2.31–2.33 and Diene 2.13**

![Scheme 2.3](image)

**2.3.2 Anionic Oxy-Cope Rearrangement of a Bicyclo[2.2.2]octane**

With the failure to access the clionastatin core 2.3 via tandem Diels–Alder reactions, an alternate route was examined (Scheme 2.4). In a retrosynthetic sense, 2.3 could be obtained from 2.39 by late-stage dichlorination, elimination of ethanol, and oxidation to form the Δ$^{3,4}$-alkene. In the key step, tricycle 2.39 would be formed by an anionic oxy-Cope

**Scheme 2.4 Retrosynthetic Analysis Featuring an Anionic Oxy-Cope Rearrangement**

![Scheme 2.4](image)
rearrangement,\textsuperscript{21} with β-alkoxide elimination upon work-up to provide the Δ\textsuperscript{8,9}-enone. This strategy has been employed successfully in multiple syntheses\textsuperscript{22} and, most notably, had been applied independently by Paquette and Ireland to make tricyclic systems similar to the clionastatin core (Scheme 2.5).\textsuperscript{23} It is notable that this rearrangement is applicable to a wide range of ring systems, including highly oxidized bicyclo[2.2.1]heptanes (2.46), with the accompanying relief of ring-strain, and less strained, non-polar bicyclo[3.2.2]nonanes (2.48). The low yield for the conversion of 2.48 to 2.49 was not viewed as a warning, \textit{per se}, since Ireland \textit{et al.} make it clear that that particular reaction was not optimized. Similar to the tandem Diels–Alder strategy discussed in Section 2.3.1, this proposed route would be convergent, joining two pieces of similar complexity (bicyclo[2.2.2]octane 2.41 and enol ether 2.42) that could, themselves, be rapidly synthesized. As an additional feature, this route would install a Δ\textsuperscript{1,2}-alkene, which would allow for anti-dichlorination to install the C1 and C2 chlorides. Furthermore, this route would be applicable to the synthesis of the fully functionalized clionastatins A and B by employing enol ether 2.45 instead of 2.42.

\textbf{Scheme 2.5 Known Anionic Oxy-Cope Rearrangements to make Tetracycle 2.47 and Tricycle 2.49}

\begin{center}
\begin{tikzpicture}
\node[draw] (A) at (0,0) {\includegraphics[width=2cm]{Scheme25.png}};
\node[draw] (B) at (3,0) {\includegraphics[width=2cm]{Scheme25.png}};
\end{tikzpicture}
\end{center}

Bicyclo[2.2.2]octane 2.41 was readily synthesized (Equation 2.6) by conversion of vinylogous ester 2.50 into the corresponding siloxydiene, then performing a Lewis acid-mediated Diels–Alder reaction between ethyl propiolate 2.43 and siloxydiene 2.44. Vinylmetals of the type 2.42 were made in two steps from cyclohexanone, which could be α-brominated conveniently in 94% yield using Amberlyst 15 and NBS,\textsuperscript{24} after which
bromoketone 2.52 could converted into several different enol ethers. Deprotonation with KHMDS and quenching with TBSCl afforded enol ether 2.53 in 85% yield, while quenching with MOMCl afforded only a 21–39% yield of the desired 2.55, along with a significant amount of C-alkylation. However, attempts to effect Li-Br exchange, followed by addition of the presumed vinylithium species into ketone 2.41 failed in all cases.

With silyl enol ether 2.53, a 3:1 mixture of protodebrominated silyl enol ether and α-silyl ketone was observed, suggesting facile Li-Br exchange with either nBuLi or tBuLi, followed by 1,3-Brook rearrangement or simple quenching of the vinyl anion. With vinyl ether 2.55, only MOM enol ether was observed. We suspected that the vinylithium species was being quenched by the acidic α-protons on ketone 2.41 and that the resulting lithium enolate was unreactive toward excess nucleophile. This hypothesis was supported when the use of multiple equivalents of tBuLi resulted in tBu- addition into the ester, while the ketone moiety remained unaffected.

It is well known that for enolizable ketones, the use of organocerium reagents can improve nucleophilic addition over deprotonation. Organocerium reagents are kinetically much slower bases than the corresponding organolithium or organomagnesium reagents,

\[
\text{Scheme 2.6 Attempted Formation of Tricyclic 2.40}
\]
while pre-coordination to the ketone of the very oxophilic cerium reagent can lead to improved diastereoselectivity. However, attempts to lithiate 2.55 and convert it into the corresponding vinylcerium reagent also failed to give addition product 2.40 in either THF or Et$_2$O. It was postulated that the MOM enol ether might be unsuited to this type of nucleophilic chemistry, as the MOM group could coordinate to the vinyllithium or -cerium, deactivating these reagents for attack on the ketone. The corresponding methyl enol ether (2.54) would have been an ideal substrate but deprotonation of ketone 2.52 and quenching with Me$_2$SO$_4$ failed to deliver any of the desired vinyl bromide, while published methods$^{26}$ also failed to produce any product in our hands. Efforts to directly deprotonate the acidic vinyl position$^{27}$ of enol ether 2.55 also failed to give any addition products, and a control experiment showed that, upon quenching with MeOD, no deuterium incorporation was observed.

While these 1-bromo-2-alkoxycyclohexene substrates would have been the ideal nucleophiles for this chemistry, it appeared that the alkoxy group might be an unnecessary complicating factor, both chelating the organometallic and increasing the steric bulk of the nucleophile. The same basic retrosynthetic strategy could still be viable, relying on an additional oxidative enone formation step after the anionic oxy-Cope reaction. With this in mind, 4-tert-butylcyclohexanone was converted into vinyl bromide 2.57 using (PhO)$_3$P and Br$_2$ in 74% yield$^{28}$ which was isolated as a waxy solid. This vinyl bromide could be lithiated using tBuLi, then used directly or converted into a variety of other organometallic reagents (using MgBr$_2$, MnCl$_2$/LiCl, or CeCl$_3$). All of these efforts resulted predominantly in proto-demetalation. The failure of the organocerium reagent was particularly surprising, considering how successfully known alcohol$^{29}$ 2.61 was made from ketone 2.60. One
A possible explanation was that the organocerium reagent was being chelated between the ester and ethyl ether of 2.41, preventing nucleophilic addition into the desired ketone. Additionally, a careful look at the literature30 showed that vinylcerium reagents are prone to thermal decomposition above –20 °C. One remedy for these suspected problems was to pre-mix CeCl3 with the starting ketone, then add an organolithium reagent. Indeed, this resulted in up to a 15% yield of desired tricycle 2.58, but even after extensive optimization, the yield could never be increased. The small amount of tricycle thus obtained was deprotonated with KHMDS and stirred for several hours at ambient temperature but no tricycle 2.59 was observed, despite [2.2.1]-bicycle 2.45 undergoing an anionic oxy-Cope rearrangement as low as –78 °C.

Scheme 2.7 Formation of Tricyclic 2.58 and Attempted Anionic Oxy-Cope Rearrangement

![Scheme 2.7](image_url)

To see whether these low yields resulted from a general problem with bicyclic ketone 2.41, commercially available vinyl Grignard reagent was employed as a test.
nucleophile with known stability and reduced steric hindrance (Equation 2.7). By pre-mixing ketone 2.41 with 3–6 equivalents of CeCl₃ in THF, followed by addition of 3–6 equivalents of vinylmagnesium bromide, up to a 10% yield of the desired product 2.62 could be isolated as a single diastereomer. These results suggested that this method would not, ultimately, be useful for the synthesis of the clionastatin core or the natural clionastatins, as the nucleophile would eventual consist of a much bulkier, more precious hydrindane fragment.

We next turned our attention to Nozaki–Hiyama–Kishi (NHK) reactions, which generate non-basic, nucleophilic Cr species, similar in many respects to the vinylcerium reagents used previously. For this approach, cyclohexanone was converted into known vinyl triflate 2.63, which could in turn be converted into the corresponding vinyl bromide 2.64. Both of these 1-substituted cyclohexenes were somewhat volatile, which complicated handling, but they were produced in sufficient quantities to test some NHK conditions with
ketone 2.41. Starting either with CrCl₂ or reducing CrCl₃ in situ with Zn° or LiAlH₄, a catalytic amount of NiCl₂ was employed in DMF, THF, or a mixed-solvent system but no addition product 2.65 was ever observed. It is well known that the NHK reaction is selective for addition into aldehydes over ketones, but there are reports of addition of vinyl halides and triflates into ketones. However, it is also known that vinyl triflates and bromides are not ideal substrates for the NHK reaction. Given that both of our coupling partners (2.41 and 2.63/2.64) were known to be challenging, lack of reactivity was not entirely surprising. Indeed, to test standard conditions, vinyl triflate 2.63 was added into 3,5-dimethoxybenzaldehyde in 55% yield but failed to add into cyclohexanone.

With this series of failures, several other attempts were made to gauge the general reactivity of ketone 2.41 towards nucleophilic addition in aldol-type reactions (Scheme 2.9). It was reasoned that aldol reactions might occur using conditions that would not

Scheme 2.9 Aldol-type Reactions Towards the Synthesis of oxy-Cope Precursors
enolize the bicyclo[2.2.2]octanone. Mukaiyama-aldol conditions were tested with enol ether\textsuperscript{35} \textbf{2.66} using TiCl₄, ZnBr₂, and Et₂AlCl but no desired reaction was ever observed. Sulfoxide and sulfone\textsuperscript{36} \textbf{2.69} were both synthesized easily from bromocyclohexane and tested with a variety of bases (LDA, \textit{n}BuLi, \textit{t}BuLi, EtMgBr, NaHMDS). However, while sulfoxides of this type have been added to aldehydes and ketones before,\textsuperscript{37} these substrates also failed to provide any of the tricyclic \textbf{2.70}. Finally, when nitrile \textbf{2.71} was treated with LDA, then added to bicyclo[2.2.2]octane \textbf{2.41}, 23\% of desired tricycle \textbf{2.72} was observed. While promising, a ready method for conversion of this nitrile into the requisite alkene \textbf{2.65} could not be envisioned. In light of the persistently low or non-existent yields obtained from nucleophilic addition into ketone \textbf{2.41}, this retrosynthetic approach was finally abandoned in pursuit of other strategies.

\textbf{2.4 Conclusion}

Several potentially concise synthetic strategies were initially examined for the clionastatin synthesis. These routes were designed to address some of the expected challenges posed by the unique structure of the clionastatins but also sought to employ chemical reactivity, and to access chemical structures, about which we had little understanding or appreciation from the outset. These routes also approached the clionastatin core in such a way that the key transformations, which we were not able to achieve, taught us little about the reactivity of that core. Therefore, while educational for those working on the project, these routes ultimately did very little to advance the project and were abandoned in favor of slightly less ambitious but, ultimately, much more successful strategies.
2.5 Experimental Procedures

(3,3-Diethoxyprop-1-yn-1-yl)(phenyl)sulfane (2.21): A stirred solution of 3,3-diethoxyprop-1-yne (65 mg, 0.507 mmol) and LiCl (22 mg, 0.507 mmol) in THF (2 mL) under argon was cooled to −40 °C. nBuLi (0.21 mL, 2.59 M in hexanes, 0.544 mmol) was added dropwise and stirred 30 min. To this reaction was added a premixed solution of Ph₂S₂ (111 mg, 0.508 mmol) and MeI (35 µL, 0.560 mmol) in THF (0.75 mL) dropwise. The reaction mixture was warmed to rt and stirred for 90 min, quenched with saturated aqueous NH₄Cl solution (5 mL), and the organic layer was washed with saturated aqueous NaCl and H₂O (2 mL each). The combined aqueous layers were extracted with Et₂O (3 x 5 mL), the combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, 1:19 EtOAc/hexanes, Rf = 0.61 in 1:4 EtOAc/hexanes, KMnO₄) to afford 2.21 (115 mg, 81%) as an orange oil that was identical in all respects to reported spectroscopic values.

[(3,3-Diethoxyprop-1-yn-1-yl)sulfinyl]benzene (2.22): A stirred solution of thioether 2.21 (72.3 mg, 0.306 mmol) in DCM (7 mL) was cooled to 0 °C and mCPBA (62.3 mg, 0.367 mmol) was added in one portion. The reaction was allowed to stir at that temperature for 2 h and quenched with 1:1 saturated aqueous NaHCO₃/Na₂S₂O₃ solution (5 mL). The aqueous layer was extracted with DCM (3 x 3 mL) and the combined organic extracts were washed with saturated aqueous NaHCO₃ (3 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, gradient
eluent from 1:9 EtOAc/hexanes to 1:4 EtOAc/hexanes, R_f = 0.48 in 2:3 EtOAc/hexanes, KMnO_4) to afford 2.22 (59 mg, 77%). Data for 2.22: 1H NMR (500 MHz, CDCl_3) δ 7.81 (q, J = 4.9, 1.3, 2H), 7.47 (t, J = 3.3, 3H), 5.39 (s, 1H), 3.73–3.66 (m, 2H), 3.62–3.56 (m, 2H), 1.21 (t, J = 7.6, 6H); LRMS (ES+) m/z calculated for C_{13}H_{16}O_3Na [M + Na]^+ 275.07, found 275.4.

[(3,3-Diethoxyprop-1-yn-1-yl)sulfonyl]benzene (2.23): A stirred solution of thioether 2.21 (101 mg, 0.427 mmol) in DCM (8 mL) was cooled to 0 °C and mCPBA (130 mg, 0.577 mmol) was added in one portion. The reaction was allowed to stir at rt for 1 h and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 1:4 EtOAc/hexanes, R_f = 0.58 in 2:3 EtOAc/hexanes, KMnO_4) to afford 2.23 (137 mg, 65%). Data for 2.23: 1H NMR (600 MHz, CDCl_3) δ 7.44 (d, J = 7.4, 2H), 7.35 (t, J = 7.7, 2H), 7.24 (t, J = 7.5, 1H), 5.47 (s, 1H), 3.79 (m, J = 7.7, 2H), 3.65 (m, J = 7.7, 2H), 1.27 (t, J = 7.1, 6H); LRMS (Cl+) m/z calculated for C_{13}H_{17}O_4S [M + H]^+ 269.08, found 269.22.

(Ethynylsulfinyl)benzene (2.27): A stirred solution of trimethylsiylacetylene (348 mg, 3.54 mmol) in THF (4 mL) was cooled to −78 °C under argon and nBuLi (1.44 mL, 2.59 M in hexanes, 3.72 mmol) was added dropwise. The reaction was stirred for 1.5 h and Ph_2S_2 in THF (2 mL) was added slowly. The resultant slurry was stirred an additional 3 h, warming slowly to rt before being quenched with H_2O (8 mL). The aqueous phase was extracted with DCM (2 x 5 mL), the organic extracts were dried with Na_2SO_4 and concentrated in vacuo. The crude material (447 mg) was redissolved in MeOH (4 mL) and aqueous NaOH (2.7 mL, 2 N), then allowed to stir at rt for 2 h. This reaction mixture was diluted with H_2O (5 mL), extracted with DCM (3 x 5 mL), dried with Na_2SO_4 and concentrated in vacuo to afford an
orange oil (280 mg). This crude material was dissolved in DCM (20 mL), cooled to 0 °C, and treated with mCPBA (468 mg, 2.09 mmol) in several portions. After 2 h, the reaction was quenched with saturated aqueous Na₂S₂O₃ and saturated aqueous NaHCO₃ (10 mL each). The organic layer was washed again with saturated aqueous NaHCO₃, dried with Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, 3:10 EtOAc/hexanes, Rf = 0.29 in 3:10 EtOAc/hexanes, KMnO₄) to afford 2.27 (192 mg, 36%), which was identical in all respects to reported spectroscopic values.

**Dimethyl 4-hydroxy-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate (2.38):** DMAD (0.33 mL, 2.67 mmol) and diene 2.13 (350 mg, 1.78 mmol) were dissolved in dry toluene and heated by microwave irradiation to 160 °C for 3 h. The crude reaction was loaded directly onto silica and purified by column chromatography (SiO₂, gradient eluent from hexanes to 1:9 EtOAc/hexanes to 1:4 EtOAc/hexanes, Rf = 0.52 in 1:4 EtOAc/hexanes, KMnO₄) to afford 2.38 (456 mg, 97%), which was identical in all respects to reported spectroscopic values.³⁸

![Image of dimethyl 4-hydroxy-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate]

**(±)-Ethyl (1R,4S)-1-ethoxy-5-oxobicyclo[2.2.2]oct-2-ene-2-carboxylate (2.41):** Ethyl propiolate (78 mg, 0.798 mmol) in dry DCM (3 mL) were cooled to 0 °C and treated dropwise with Et₂AlCl (0.80 mL, 1.0 M in hexanes, 0.798 mmol). Known³⁹ ([5-ethoxycyclohexa-1,5-dien-1-yl]oxy)trimethylsilane (154 mg, 0.725 mmol) in DCM (1 mL)
was then added and the reaction was stirred for 15 min. The reaction was quenched with aqueous HCl (2 mL, 1 N) and the organic layer was washed with saturated aqueous NaCl (2 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, 1:4 EtOAc/hexanes, Rf = 0.13 in 1:4 EtOAc/hexanes, KMnO₄) to afford **2.41** (68 mg, 40%). Data for **2.41**: ¹H NMR (600 MHz, CDCl₃) δ 6.87 (d, J = 6.7, 1H), 4.21 (q, J = 7.1, 2H), 4.08 (q, J = 7.1, 1H), 3.55 (m, J = 7.4, 2H), 3.22 (m, 1H), 2.49 (d, J = 17.8, 1H), 2.21 (d, J = 17.8, 1H), 1.88 (m, 1H), 1.29 (t, J = 7.1, 3H), 1.22 (t, J = 6.9, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 206.7, 164.1, 141.8, 135.1, 78.8, 60.8, 60.4, 48.9, 44.9, 31.6, 30.3, 22.7, 21.7, 21.1, 15.6, 14.1.

**[(2-Bromocyclohex-1-en-1-yl)oxy]((tert-butyldimethyl)silane (2.53):** A stirred solution of ketone **2.52** (2.50 g, 14.1 mmol) in Et₂O (70 mL) under argon was cooled to −78 °C and treated with KHMDS (18.4 mL, 1.0 M in THF, 18.4 mmol). The reaction was stirred for 30 min, after which TBSCI (3.19 g, 21.2 mmol) in Et₂O (30 mL) was added and stirred an additional 4 h, warming slowly to rt. The reaction was quenched with saturated aqueous NaHCO₃ (50 mL), diluted with pentane (50 mL), and the aqueous layer was extracted with pentane (3 x 30 mL). The combined organic layers were washed with saturated aqueous NaHCO₃, H₂O, and saturated aqueous NaCl (30 mL each). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, hexanes, Rf = 0.80 in 1:4 EtOAc/hexanes, KMnO₄) to afford **2.53** (3.51 g, 85%) as a colorless oil. Data for **2.53**: ¹H NMR (600 MHz, CDCl₃) δ 2.48 (s, 2H), 2.16 (s, 2H), 1.71–1.66
(m, 4H), 0.98 (s, 9H), 0.20 (s, 6H); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 185.1, 102.1, 34.5, 31.8, 26.0, 24.6, 23.2, 18.5, −3.6.

**1-Bromo-2-(methoxymethoxy)cyclohex-1-ene (2.55):** A stirred solution of ketone 2.52 (3.69 g, 20.9 mmol) in Et$_2$O (100 mL) under argon was cooled to −78 °C and treated with KHMDS (25.0 mL, 1.0 M in THF, 25.0 mmol). The reaction was stirred for 30 min, after which MOMCl (2.37 mL, 31.2 mmol) was added and stirred an additional 1.5 h, warming slowly to 0 °C. The reaction was quenched with saturated aqueous NaHCO$_3$ (100 mL) and NaOH (10 mL, 1 N), whereupon the aqueous layer was extracted with hexanes (3 x 50 mL). The organic extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO$_2$, gradient eluent from hexanes to 1:19 EtOAc/hexanes to 1:9 EtOAc/hexanes, $R_f$ = 0.54 in 1:4 EtOAc/hexanes, KMnO$_4$) to afford 2.55 (930 mg, 21%) as a colorless oil. Data for 2.55: $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 4.94 (s, 2H), 3.49 (s, 3H), 2.49 (m, 2H), 2.28 (m, 2H), 1.76−1.67 (m, 4H); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 193.6, 56.7, 37.2, 34.6, 27.2, 24.4, 22.7.

(±)-Ethyl $^{(1R,4S,5R)-5-[4-(tert-butyl)cyclohex-1-en-1-yl]-1-ethoxy-5-hydroxybicyclo[2.2.2]oct-2-ene-2-carboxylate (2.58):}$ To carefully dried CeCl$_3$ (155 mg, 0.630 mmol) under argon was added THF (2.0 mL) and ketone 2.41 (50 mg, 0.210
mmol). This slurry was stirred for 1-2 h until all solids dissolved completely. A solution of vinyl bromide 2.57 (44 mg, 0.189 mmol) in THF (1 mL) under argon was also cooled to –78 °C, treated with tBuLi (0.22 mL, 1.7 M in pentane, 0.377 mmol), and allowed to stir 30 min. The vinyl lithium solution was added to the ketone/CeCl₃ mixture and the resulting red/orange solution was stirred for 90 min at –78 °C, then warmed to –20 °C and allowed to continue stirring overnight. The reaction was quenched with aqueous HCl (1 mL, 1 N) and the aqueous layer was extracted with EtOAc (3 x 2 mL). The organic extracts were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, gradient eluent from 1:4 EtOAc/hexanes to 1:1 EtOAc/hexanes, Rf = 0.64 in 1:1 EtOAc/hexanes, KMnO₄) to afford 2.58 (12 mg, 15%). Data for 2.58: ¹H NMR (600 MHz, CDCl₃) δ 6.95 (d, J = 6.5, 1H), 5.74–5.60 (m, 1H), 4.28 (m, 4H), 3.69–3.50 (m, 3H), 2.75–1.63 (m, 10H), 0.95–0.80 (m, 15H).

(±)-Ethyl (1R,4S,5S)-1-ethoxy-5-hydroxy-5-vinylbicyclo[2.2.2]oct-2-ene-2-carboxylate (2.62): To freshly fused LiCl (16 mg, 0.378 mmol) was added pre-dried CeCl₃ (47 mg, 0.189 mmol). These solids were placed under vacuum, further flame-dried, after which they were placed under argon and ketone 2.41 (30 mg, 0.126 mmol) in THF (1.5 mL) was added. The slurry was stirred 30 min until it became a homogeneous, pale-yellow solution. This solution was cooled to –78 °C, treated with commercial vinyl magnesium bromide (0.18 mL, 1.05 M in THF, 0.189 mmol), and allowed to stir 3 h, then warmed to 0 °C and stirred an additional 3 h. The reaction was quenched with aqueous HCl (1 mL, 1 N)
and the aqueous layer was extracted with DCM (3 x 2 mL). The organic extracts were washed with saturated aqueous NaCl, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, gradient eluent from 1:4 EtOAc/hexanes to 2:3 EtOAc/hexanes, R_f = 0.39 in 1:1 EtOAc/hexanes, KMnO₄) to afford 2.62 (3 mg, 10%). Data for 2.62: ¹H NMR (600 MHz, CDCl₃) δ 6.92 (d, J = 6.9, 1H), 5.84 (dd, J = 14.0, 10.7, 1H), 5.16 (d, J = 17.3, 1H), 5.00 (d, J = 10.7, 1H), 4.22 (q, J = 7.1, 2H), 3.55 (q, J = 7.5, 2H), 2.50 (m, 1H), 2.37 (t, J = 12.0, 1H), 2.07 (dd, J = 12.9, 3.5, 1H), 1.85 (m, 1H), 1.83 (dt, J = 10.8, 5.0, 1H), 1.68 (d, J = 12.9, 1H), 1.32 (t, J = 7.1, 3H), 1.24 (t, J = 7.0, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 165.1, 145.9, 140.9, 139.4, 111.3, 78.6, 75.7, 60.6, 60.3, 42.8, 42.6, 29.7, 20.6, 15.9, 14.4.

(±)-Ethyl (1R,4S,5R)-5-(1-cyanocyclohexyl)-1-ethoxy-5-hydroxybicyclo[2.2.2]oct-2-ene-2-carboxylate (2.72): DIPA (0.06 mL, 0.420 mmol) in THF (1 mL) was cooled to −78 °C under argon and treated with nBuLi (0.17 mL, 2.47 M in hexanes, 0.420 mmol). This solution was stirred 10 min before cyclohexanecarbonitrile (50 mg, 0.459 mmol) was added as a solution in THF (0.5 mL) and the solution was allowed to stir an additional 30 min. Ketone 2.41 (91 mg, 0.383 mmol) in THF (0.5 mL) was added and the resulting solution was stirred at −78 °C overnight. The reaction was quenched with saturated aqueous NaHCO₃ (2 mL), allowed to warm to rt, and the aqueous layer was extracted with EtOAc (3 x 2 mL). The organic extracts were washed with saturated aqueous NaCl, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column
chromatography (SiO$_2$, gradient eluent from 1:4 EtOAc/hexanes to 1:1 EtOAc/hexanes, R$_f$ = 0.13 in 1:4 EtOAc/hexanes, KMnO$_4$) to afford 2.72 (30 mg, 23%). Data for 2.72: $^1$H NMR (600 MHz, CDCl$_3$) δ 6.92 (s, 1H), 4.32–4.08 (m, 2H), 3.61–3.44 (m, 2H), 2.85–2.77 (s, 1H), 2.33–2.23 (m, 1H), 2.12–1.99 (m, 3H), 1.99–1.91 (m, 5H), 1.86–1.62 (m, 2H), 1.38–1.16 (m, 6H), 1.16–0.98 (m, 1H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 164.7, 140.6, 137.3, 122.4, 78.6, 78.3, 60.5, 60.2, 51.0, 44.5, 39.0, 31.5, 29.8, 27.5, 25.2, 23.3, 23.13, 22.7, 15.7, 14.3.

### 2.6 Notes and References


2. Fattorusso et al. (*ibid.*) report isolation of 2.2 mg of clionastatin A and 3.1 mg of clionastatin B total from over 3.5 kg (dry weight) of *Cliona nigricans*.


5. For examples from the main class of steroids (ergostanes) containing a $\Delta^{8,9}$-ene that had been reported at the start of this project, see: Tanaka, R.; Kasubuchi, K.; Kita, S.; Matsunaga, S. *Phytochemistry*. 1999, 51, 457–463.


A cursory search of the literature shows 127 regular Diels–Alder reactions with substituted propargyl aldehydes and only 4 hetero-Diels–Alder reactions.


Furan was initially used for these studies as a stable, commercial diene that could potentially provide useful products, after cleavage of the resultant ether bridge. However, due to its aromatic character, furan is known to be a poorly reactive diene and, in retrospect, should probably not have been used for these studies.


For some examples of the instability of vinylcerium reagents, see: Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763–4766. For a more comprehensive view of the limitations and mechanism for this instability, forward search this reference.


Anhydrous CeCl$_3$ was stored in a vacuum oven (pressure ~30 torr) set to 110 °C and weighed out quickly under normal atmosphere. It was then gently flame-dried on high vacuum (pressure ~0.01 torr) until no vapor further H$_2$O vapor could be driven off, then heated an additional 5–10 min. This flask was then back-filled with argon and used the same day.
Chapter 3: Successful Efforts Towards the Clionastatin Core

3.1 Introduction

While the series of unsuccessful approaches to the clionastatin core 3.1 (Chapter 2) were instructional from a training standpoint and informed later retrosynthetic analyses, all of our routes thus far had failed to achieve the primary goals of our proposed model system; namely, we had learned nothing about the stability and behavior of the ABC ring-system or the key alkyl chlorides on the A-ring. On a personal note, at this point in the project, it was also suggested by Prof. Vanderwal that my education might be better served by switching projects. In a somewhat desperate bid to hold on to clionastatin, I started targeting the simplest tricyclic core that could reasonably meet the goals outlined above, while allaying the concerns of my PI. The result was an iterative series of retrosynthetic analyses based on a similar Diels–Alder reaction, each new route addressing issues raised by the previous one. Ultimately, this process lead to the development of a diene/dienophile pair that would eventually facilitate the synthesis of tricycle 3.1.

3.2 Successful Diels–Alder Approach

3.2.1 Featuring Enal 3.8

Although several previous efforts to use Diels–Alder reactions in the construction of the clionastatin ABC system had failed (see Section 2.3.1), there remained a wealth of literature (see Section 1.4.3) suggesting that some variation of this powerful reaction could effectively form the B-ring, leading to a convergent synthesis of the clionastatins. In particular, many examples¹ show that by employing the appropriate Lewis acid for
activation of the dienophile, even otherwise sluggish dienophiles could react rapidly under mild conditions with exquisite diastereocontrol.

**Scheme 3.1 Example of Lewis Acid Catalyzed Diels–Alder Reaction with Enals**

![Scheme 3.1](image)

We envisioned that core 3.1 could be formed from enone 3.5 by late-stage dehydrogenation or other oxidation. Trichloride 3.5 could be formed by dichlorination of the Δ1,2-alkene and attack of nucleophilic chloride at C19. This substrate would, in turn, come from enol ether 3.7 via oxidative enone formation and reduction of a C19 aldehyde, while 3.7 is the product of the key Diels–Alder reaction between known 2 enal 3.8 and diene 3.9, which had been employed by us previously (Section 2.3.1).

**Scheme 3.2 Retrosynthetic Analysis Featuring Diels–Alder Reaction Between Enal 3.8 and diene 3.9**

![Scheme 3.2](image)

Several mild Lewis acids were tested based on their use with similar enal dienophiles1,3 before desired Diels–Alder reaction was observed (Table 3.1), but it was gratifying to note that the undesired hetero-Diels–Alder reactivity observed by us with alkynyl systems (Section 2.3.1) was not a competing reaction in the case of this cyclic dienophile. Ultimately, the best results were obtained by employing carefully dried ZnI₂ in
toluene at room temperature to afford tricycle 3.7 as an inseparable mixture of endo- and exo-adducts. It should be mentioned here that several attempts were made to use chlorinated dienophile 3.10 (the product of selective dichlorination on the less electron-poor olefin of diene 3.8) in a Diels–Alder reaction with diene 3.9. These reactions were plagued by low conversion (≤25%) of enal 3.10 and complex diastereomeric mixtures of products. As this approach offered no obvious advantage over the reaction between 3.8 and 3.9, it was not investigated further.

Reduction of aldehyde 3.7 to alcohol 3.11 proceeded in moderate yields, as competitive hydrolysis of the silyl enol ether was always observed. Treatment of alcohol 3.11 under Appel conditions, which are known to halogenate sterically congested neopentylic alcohols, resulted in the formation of what appeared to be tetracycle 3.12, with recovery of a single diastereomer of 3.11. This suggests that the C19 alcohol was, in fact,
activated by the Ph₃P but intramolecular nucleophilic attack outcompeted Sₙ2 displacement by chloride.

Due to the reactive nature of the enol ether moiety and the undesired cyclobutane formation during attempted chlorination, efforts were made to convert the enoxysilane into the desired Δ⁸⁻⁹-enone before attempting any further manipulations on the ABC ring system. Unfortunately, treatment of silyl enol ether 3.7 under Saegusa–Ito conditions or with DDQ or IBX afforded desired enone 3.13 in only low to moderate yields (10–40%). While multiple solvents, oxidants, and temperatures were examined, the best conditions required 1.5–2.0 equivalents of Pd(OAc)₂ and hydrolysis product 3.14 was always the major component. There were several factors that led to these unsatisfactory yields. It appeared that use of a bulky TBS group, while increasing the stability of the enol ether, was retarding oxidative addition to form the requisite palladium enolate intermediate.

**Scheme 3.4 a) Saegusa–Ito Oxidation of Enol Ether 3.7 and b) Conformational Rational for Observed Reactivity**

![Scheme 3.4](image)

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3.16/3.17, allowing for adventitious acid to competitively protodesilylate enol ether 3.7. Although Saegusa–Ito reactions on TBS enol ethers are known,\(^5\) such reactions are likely uncommon in the literature for precisely this reason.\(^6\) Additionally, it was observed that when starting tricycle 3.7 was re-isolated from the reaction mixture, only the minor diastereomer had been consumed. It seemed consistent that the Pd-enolate forms exclusively on the convex face of tricycle 3.7 to form intermediates 3.16 and 3.17, at which point only the minor diastereomer from the Diels–Alder reaction can undergo syn \(\beta\)-hydride elimination to form desired enone 3.13. Based on this model, it can be inferred that the major diastereomer formed in the Diels–Alder reaction was the expected endo-adduct, although no satisfactory NOE data was ever obtained for these compounds. It is also worth noting that undesired elimination product 3.15 was never observed, presumably because the conformation of the C14 methylene makes protodepalladation more favorable than \(\beta\)-hydride elimination.

Because oxidative conditions to form the \(\Delta^{8,9}\)-enone suffered from multiple problems, we next considered that enone 3.13 could be formed directly from a Diels–Alder reaction using a 1,3-diketone derived diene (Scheme 3.5), where acidic work-up of enol ether 3.20 would result in spontaneous elimination of the \(\beta\)-silyloxy or alkoxy group. The desired dienes 3.18 and 3.19 were obtained in good yield and acceptable purity following standard procedures.\(^7\) However, because these dienes were so electron-rich, they proved
incredibly unstable to even pH-neutral protic conditions and purification proved impossible. Because of this instability, all reactions using these dienes contained several decomposition byproducts, complicating NMR spectra and TLC analyses. To compensate for the decomposition, multiple equivalents of the both dienes were always used and proton scavengers, such as 2,6-lutidine, were added to the reactions. Despite precautions, these Diels–Alder reactions all failed to produce any tricycle 3.13, either with thermal or microwave heating up to 200 °C, or with the use of catalytic or stoichiometric amounts of various Lewis acids. It is possible that while dienes 3.18 and 3.19 are significantly more electron rich than diene 3.9, they are also sterically hindered enough to preclude the required s-cis diene conformation needed for a concerted Diels–Alder reaction to occur.

While very electron-rich dienes were being investigated as an alternative to oxidative enone formation, the possibility of using a pyrone-Diels–Alder was also examined. This proposed cycloaddition between 3.21 and 3.9 would afford a cycloadduct which, after thermal extrusion of CO₂ via a retro-Diels–Alder reaction, would also afford the desired enone 3.13 directly. This strategy had the added bonus of not requiring the very labile enoxysilane moiety that led to reduced yields in previous synthetic routes. However, while pyrone-Diels–Alder reactions are not uncommon in the literature,⁸ they generally occur between electron-rich dienophiles in an inverse-demand sense.⁹

![Scheme 3.6 Proposed Pyrone Diels–Alder Sequence](image-url)
There were major practical problems with this route from the outset. While pyrone 3.21 is a known compound, the synthesis using enol ether 3.21 and malonyl chloride is plagued by competitive formation of the known bicyclo[3.3.1]nonane 3.24. Yields for this reaction varied widely and removal of 3.24 was challenging. The stepwise approach, using a morpholine-derived enamine and methyl malonyl chloride, followed by warming to reflux with DBU, was moderately successful but the desired product proved difficult to handle. Being very polar and fairly water-soluble, it was difficult to isolate, purify, or, indeed, to dissolve in suitable non-polar solvents for the desired Diels–Alder reaction. Laborious effort resulted in a 24% yield of a material that, while not pure, was used in the Diels–Alder reaction (dissolved in a mixture of toluene/DMSO.) The crude $^1$H NMR for the attempted formation of cycloadduct 3.22 was extremely messy and efforts to isolate any new, identifiable compound were unsuccessful. Weighing all of the above-mentioned challenges, this route was set aside in favor of a more manageable, equally promising synthetic route.

3.2.2 Using Enone 3.33
The preceding synthetic efforts highlighted several important lessons and warnings:
1) electron-deficient cyclohexenyl dienophiles are satisfactory partners for construction of the clionastatin ABC carbon skeleton, 2) converting a C19 neopentyl alcohol would likely result in competing side reactions or in no reaction at all, and 3) while less stable, a TMS enol ether would be more readily convertible into the necessary Δ^{8,9}-enone than the corresponding TBS analogue.

With these lessons in mind, we were particularly encouraged by the model study for Corey’s nicandrenone synthesis, which utilized the same diene (3.9) that we had previously employed and a cyclohexenone-derived dienophile (3.2) to make tricycle 3.27 (Scheme 3.8).

Inspired by Corey’s work, we redesigned our retrosynthetic strategy, envisioning that 3.1 could be formed from 3.28 after sulfoxide elimination and B-ring oxidation. 3.28 could be formed by diastereoselective dichlorination of 3.29, relying on the sterics of the
sulfoxide to help block the α-face. 3.29 would, in turn, be formed by 1,2-reduction of the A-ring enone on 3.30, followed by sulfinate ester formation and Mislow–Evans rearrangement.\textsuperscript{12} Tricycle 3.30 would be the product of extensive oxidation of enol ether 3.32, which would be the cycloadduct formed by reaction of known\textsuperscript{13} dienophile 3.33 and silyloxy diene\textsuperscript{14} 3.34.

The Diels–Alder reaction worked readily using either of two aluminum Lewis acids, and tricycle 3.32 was obtained in 1:1 dr, albeit in moderate yields, accompanied by significant quantities of desilylated starting material and products. Due to the sensitive, acid-labile nature of the resultant enoxysilane,\textsuperscript{15} immediate oxidation to the desired B-ring $\Delta^{8,9}$-enone was attempted. While conversion of enol ethers to enones can be accomplished under a variety of oxidative conditions,\textsuperscript{16} many of these methods fail to give desired product when β-branching is present. Specific to forming $\Delta^{8,9}$-enones on steroid cores, almost no direct oxidative conditions exist, relying instead on the elimination of a β-leaving

![Chemical Reaction](image)

**Table 3.2.** Conditions tested for the oxidation of enol ether 3.32.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl\textsubscript{2}</td>
<td>DMF</td>
<td>room temperature</td>
<td>complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>CuCl\textsubscript{2}</td>
<td>DMF</td>
<td>60 °C</td>
<td>mostly 3.35</td>
</tr>
<tr>
<td>3</td>
<td>IBX</td>
<td>DMSO</td>
<td>80 °C</td>
<td>complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>DMSO</td>
<td>room temperature</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>DMSO</td>
<td>60 °C</td>
<td>hydrolysis</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>CH\textsubscript{2}CN</td>
<td>room temperature</td>
<td>no reaction</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>CH\textsubscript{2}CN</td>
<td>60 °C</td>
<td>hydrolysis</td>
</tr>
<tr>
<td>8</td>
<td>Et\textsubscript{4}NCl\textsubscript{3}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>0 °C</td>
<td>mostly 3.35</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)\textsubscript{2}/DDQ</td>
<td>CH\textsubscript{2}CN</td>
<td>0 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)\textsubscript{2}/DDQ</td>
<td>CH\textsubscript{2}CN</td>
<td>60 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>11</td>
<td>1: NBS</td>
<td>THF</td>
<td>1: 0 °C</td>
<td>80% of 3.31</td>
</tr>
<tr>
<td>12</td>
<td>2: Li\textsubscript{2}CO\textsubscript{3}/LiCl</td>
<td>DMF</td>
<td>2: 120 °C</td>
<td></td>
</tr>
</tbody>
</table>
Several conditions were investigated for the conversion of cycloadduct 3.32 to enone 3.31 (Table 3.2) and, while some product was observed with transition metal-mediated oxidation conditions, those reactions suffered from the same limitations previously observed with the attempted oxidation of tricycle 3.7.

Ultimately, a two-step procedure, featuring a completely diastereoselective bromination on the β-face, followed by elimination of HBr, proved effective. It should be noted that these are a modification of the standard conditions, as use of LiBr instead of LiCl resulted in some amount of S2N bromination at C19. As with previous oxidations on tricycle 3.7, it is not clear why no enone 3.35 was observed under these conditions, especially in light of the fact that only the exo-Diels–Alder adduct possesses an α-C9 proton that is antiperiplanar to the β-bromide. No satisfactory explanation for this outcome has yet been found.

It was originally anticipated that after formation of the Δ8,9-alkene, the Δ2- and Δ5-alkenes could be installed relatively easily. This assumption was based, in part, on the supposition that several of the failed attempts to form the Δ8,9-alkene were complicated by formation of these other enones. However, attempts to form either dienone 3.32 or 3.33 were unsuccessful (Table 3.3), starting either with ketone 3.31 or by first pretreating 3.31 with TMSOTf and Et3N to make the corresponding bis-enol ether. The results using catalytic Ph2Se2 are particularly surprising (entries 12–14), given the seemingly analogous example from Barton, in which both an enone and dienone were installed on the A- and C-rings of a steroid in a single step in good yield (Scheme 3.10). The fact that similar reaction conditions failed to oxidize ketone 3.31 highlights the subtle stereoelectronic differences caused by changing the oxidation pattern on the ABC ring system. Presumably, alignment
of the α-protons with the carbonyl π-systems make enolization slow relative to nucleophilic attack on the ketones, resulting in formation of Baeyer–Villiger type byproducts, which are known to form in significant quantities in elevated-temperature selenium reactions.

![Diagram](image)

**Table 3.3.** Attempted oxidative enone formation on tricycle 3.31.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IBX</td>
<td>DMSO, 65 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>IBX</td>
<td>DMSO, 80 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>IBX</td>
<td>DMSO, 110 °C</td>
<td>IBX decomposed</td>
</tr>
<tr>
<td>4</td>
<td>LDA/NBS</td>
<td>THF, –78 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>CuBr₂/LiBr</td>
<td>EtOAc, 80 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>CuBr₂/LiBr</td>
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</tr>
<tr>
<td>7</td>
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<td>EtOAc, HCl then H₂O₂</td>
<td>no reaction</td>
</tr>
<tr>
<td>8</td>
<td>PhSeCl</td>
<td>benzene, Et₃N then mCPBA</td>
<td>decomposition</td>
</tr>
<tr>
<td>9</td>
<td>PhSeCl</td>
<td>benzene, benzoic acid then mCPBA</td>
<td>decomposition</td>
</tr>
<tr>
<td>10</td>
<td>PhSeCl</td>
<td>benzene, then mCPBA</td>
<td>no reaction</td>
</tr>
<tr>
<td>11</td>
<td>PhSeCl</td>
<td>toluene, 100 °C</td>
<td>no reaction</td>
</tr>
<tr>
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<td>decomposition</td>
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<td>no reaction</td>
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<td>cat. Ph₂Se₂/mlBX</td>
<td>benzene, HCl, 115 °C</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

**Scheme 3.10** Example of Selenium-Mediated Installation of Multiple Enones On a Steroid System

![Scheme](image)

3.37: 67%  
3.38: trace  
3.39: trace  
3.40: trace
Recognizing the challenges involved in late-stage enone formation, we considered that the desired oxidation state would better be installed before the Diels-Alder reaction. However, the ideal dienophile would be, in reality, a tautomer of a phenol (Figure 3.2), which could hardly be expected to react as such. To circumvent this problem, the Ogasawara-Takano cyclohexenone\textsuperscript{20} (3.43) was employed, which utilizes cyclopentadiene as a protecting group for an enone.

![Figure 3.2](image)

Following the published procedure, the Diels-Alder reaction between cyclopentadiene and benzoquinone proceeded cleanly within an hour. 1,2-Reduction under Luche conditions afforded diol 3.46, which was enzymatically mono-protected as the corresponding acetate 3.47. Under the reported conditions, this reaction proceeded sluggishly, taking several days to give even 15\% conversion to product, a problem which has been noted in the literature.\textsuperscript{21} Varying solvents and concentrations gave modest improvements but it was pointed out (A. Myers and D. Kummar, personal communication, June 2012) that the immobilized PS Amano lipase dramatically outperforms non-immobilized lipase. Indeed, this proved true and 90\% yield was obtained in 2 days. The immobilized PS Amano could then be washed and reused without significant loss of activity. Redox-neutral Pd-mediated chemistry afforded enantioenriched enone 3.43, which participated in a Morita-Baylis-Hillman reaction with CH\textsubscript{3}O to give alcohol 3.48. Unfortunately, conditions could not be found to convert the alcohol into the desired
chloride 3.49. Using various combinations of Et₃N, pyridine, or collidine and MsCl, with and without the addition of NEt₄Cl or LiCl, decomposition was always observed. With MsCl and collidine in DCM, a 30% yield of a promising white solid could be obtained, but this solid rapidly decomposed almost immediately upon standing and this route was abandoned.

Failure to access the desired Mislow–Evans precursor, while disappointing, was by no means fatal for the synthesis of tricyclic core 3.1. In fact, selective reduction of ketone 3.31, formal dehydration of alcohol 3.50 via the intermediate triflate, then dichlorination afforded trichloride 3.52 as a 1:1.2 mixture of diastereomers. The diastereoselectivity of this first attempt was very encouraging, as it showed that substrate-control did not preclude the desired C1-C10 syn configuration.
While it is not unreasonable to imagine that conditions could be found to oxidize dichloride 3.52 to core 3.1, in light of my earlier failed attempts at enone formation on similar systems, it was a daunting prospect. Furthermore, any route that successfully yielded the model core would ultimately be applied to a much more precious CD-ring diene and, in the interest of a more convergent synthesis, a higher oxidation state would preferably be installed on the A-ring prior to the Diels–Alder reaction. With attention to these details, two new approaches were decided upon.

3.3 Efforts to Install Additional Oxidation on the Dienophile

3.3.1 Benzoquinone Diels–Alder Approach

A common theme with the approaches outlined in Sections 3.2.1 and 3.2.2 was an effort to combine, in a convergent manner, substrates with lower oxidation states than the functionality found in the final clionastatin core. This approach would require late-stage oxidative installation of unsaturation. An alternative strategy, investigated by Dr. Allen Hong, would employ highly oxidized starting materials, with reliance on late-stage, selective reductions (Scheme 3.13). This synthetic route lacked a clear retrosynthetic strategy but focused more on pure exploratory chemistry, designed to probe the general reactivity of a heavily oxidized ABC-system.

Using diene 3.34 and known22 quinone 3.53, the thermal Diels–Alder reaction proceeded rapidly at 0 °C to give tricycle 3.54. However, the resulting enol ether was too labile to survive any subsequent transformations and the A-ring was undifferentiated, making selective reductions challenging. Replacing 3.34 with TBDPS-protected diene 3.56 and starting with mono-ketal23 3.55 afforded a much more appealing cycloadduct 3.57. Hydrogenation of the enone in the presence of the enol ether proceeded readily, and
treatment with Red-Al resulted in exclusive hydride delivery from the β-face to give alcohol 3.58, contaminated with a small amount of material that was epimeric at C9; a result of exo-Diels–Alder reaction. Elimination to provide the Δ1,2-alkene was achieved by treatment with Tf₂O in pyridine, giving a 57% yield of olefin 3.59.

This material was, in theory, only 5–6 steps from the desired clionastatin core. However, efforts to oxidize either the enol ether in the presence of the A-ring alkene, or to chlorinate the A-ring olefin resulted in destruction of the ketal and further decomposition. Several attempts were made to deprotect the ketal, revealing either a skipped enone or the Δ²,³-enone but these reactions were accompanied by decomposition of the B-ring enol ether. At this point, ongoing efforts towards a second route proved successful and this route was not investigated further.
3.3.2 Alternative 4-Substituted Cyclohexenone Derivatives

Between under-oxidized dienophile 3.33 and over-oxidized quinone 3.55, there was a wide range of chemical space that could be explored when selecting a new dienophile. There were also several limitations that would have to be considered when designing that dienophile. All functional groups on the new dienophile would still have to be compatible with the key Diels–Alder reaction conditions (Scheme 3.14) and the new functionality would have to have orthogonal reactivity to the existing functionality found on enone 3.31. Additionally, the leaving group would have to be stable enough to survive the reaction conditions for the majority of the synthetic route but labile enough to be readily eliminated late stage (conversion of 3.62 into 3.1). From a casual perusal of the periodic table and the body of chemical literature, there were several functional groups that could fulfill all of those requirements.

Scheme 3.14 Retrosynthetic Approach Featuring 4-Substituted Cyclohexenones as Dienophiles

The first class of dienophiles that we endeavored to make were a series of 4-halo-, thio-, and selenenylicyclohexenones (Scheme 3.15). However, despite literature procedures for the synthesis of these substrates, efforts to brominate cyclohexenone via a radical mechanism resulted almost exclusively in phenol formation. This competitive phenol
formation became a major challenge with many of the later efforts to access 4-substituted cyclohexenones, as the thermodynamic driving force for aromatization often precluded the use of harsh or equilibrating conditions.

An additional challenge was recognized when attempts were made to obtain iodinated or selenylated analogues 3.71. These efforts resulted not in the desired compound but almost exclusively in regioisomeric 3.72 instead. Upon closer examination of the literature, it has been observed on multiple occasions that the thermodynamically preferred enolate of unsubstituted cyclohexenone is the cross conjugated structure 3.70, not the through-conjugated structure 3.69. Under carefully controlled conditions, a 2:1 ratio (still favoring cross-conjugated 3.70) could be formed by kinetic deprotonation but results were inconsistent between runs, depending heavily upon concentration, and often afforded exclusively 3.70. As a more practical method, skipped diene 3.73 (the commercial
product of Birch reduction on anisole) could be readily converted into silyloxydiene 3.69 in two steps.\textsuperscript{27} Treatment of diene 3.69 with PhSCl, formed \textit{in situ} from NCS and PhSH, resulted in γ-thiolation to afford known\textsuperscript{28} 3.74 in good yields. Unfortunately, repeated attempts to elaborate enone 3.74 under Morita–Baylis–Hillman reaction conditions resulted in intractable mixtures of solid, polymeric compounds or phenol. γ-Selenenylation 3.71, obtained in the same manner as 3.74 using PhSeBr in place of PhSCl, reacted similarly under Morita–Baylis–Hillman conditions. γ-Thiolation of 3.69 with EtSH and NCS afforded 3.75 in modest yields but seemed like a possible solution to undesired phenol formation, as ethane thiol is \~100 times less acidic than benzene thiol, making it a much worse leaving group. However, alkyl thioethers also air-oxidize much more readily and the resultant sulfoxide (3.76) unselectively introduced an additional stereocenter, confounding analysis of the already messy Morita–Baylis–Hillman reaction.

In the face of these failures, we next turned our attention to making 4-silyloxydienophile 3.78. While the 4-halogenated, thiolated, or selenylated compounds previously discussed would have made late-stage elimination trivial, the oxygenated analogues could still be eliminated under a variety of dehydrating conditions, would be more stable through intermediate synthetic manipulations, and were more widely known in the literature.\textsuperscript{29} One of the disappointing features about the 4-silyloxy cyclohexenone substrates was the number of steps usually required to access them (Scheme 3.16).\textsuperscript{30}
It was with this in mind that we endeavored to make a more expedient route to the desired enone 3.78, starting from cheap, readily available cyclohexane-1,4-diol. Silyl protection under standard conditions afforded a nearly statistical mixture of mono-protected 3.79, di-protected, and unprotected diol, which could be taken on as a mixture and purified at a later point. Given the low cost of the starting materials and the watersoluble nature of the diol, it was generally simpler to use an excess of the diol relative to TBSCI and purify by successive aqueous washes.

There are several literature methods for converting an alcohol directly to an enone and these were examined for this application (Table 3.4). Mechanistically, these methods rely first on oxidation of the alcohol to the ketone, followed by acid- or base-mediated enolization, which enables the formation of some activated enolate species. β-hydride elimination or β-hydrogen atom abstraction then yields the desired enone. Unfortunately, the same conditions that enable enolization of the ketone can also facilitate

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Conditions</th>
<th>3.79 : 3.80 : 3.78 : 3.68 : 3.81</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBX (2.5 equiv)</td>
<td>DMSO, 65 °C</td>
<td>0 : 70 : 20 : 0 : 10</td>
</tr>
<tr>
<td>IBX (1.5 equiv) starting from 3.80</td>
<td>DMSO, 65 °C</td>
<td>0 : 60 : 30 : 0 : 10</td>
</tr>
<tr>
<td>IBX-MPO (2.0 equiv) starting from 3.80</td>
<td>DMSO, 65 °C</td>
<td>0 : 50 : 50 : 0 : 0</td>
</tr>
<tr>
<td>Pd(OAc)$_2$ starting from 3.80</td>
<td>DMSO/AcOH, 80 °C</td>
<td>0 : 85 : 15 : 0 : 0</td>
</tr>
<tr>
<td>Pd(OAc)$_2$, O$_2$ balloon</td>
<td>DMSO/AcOH, O$_2$ balloon, 80 °C</td>
<td>85 : 3 : 12 : 0 : 0</td>
</tr>
<tr>
<td>Pd(OAc)$_2$</td>
<td>DMSO/AcOH/H$_2$O, 80 °C</td>
<td>90 : 2 : 8 : 0 : 0</td>
</tr>
<tr>
<td>Pd(OAc)$_2$</td>
<td>DMSO/AcOH (dilute), 80 °C</td>
<td>80 : 5 : 15 : 0 : 0</td>
</tr>
<tr>
<td>cat. IBS/oxone</td>
<td>DMSO, 70 °C</td>
<td>0 : 0 : 0 : 100 : 0</td>
</tr>
<tr>
<td>cat. IBS/oxone</td>
<td>MeNO$_2$, 5 hr, 70 °C</td>
<td>0 : 50 : 50 : 0 : 0</td>
</tr>
<tr>
<td>cat. IBS/oxone</td>
<td>MeNO$_2$, 10 hr, 70 °C</td>
<td>0 : 0 : 60 : 0 : 40</td>
</tr>
<tr>
<td>cat. IBS/oxone/Na$_2$SO$_4$</td>
<td>MeNO$_2$, 10 hr, 70 °C</td>
<td>0 : 0 : 0 : 100 : 0</td>
</tr>
</tbody>
</table>
enolization of the carbonyl of enone 3.78, resulting in further oxidation to the dienone, which can aromatize via tautomerization to form hydroquinone. Alternately, the enolic tautomer of enone 3.78 can eliminate silyl alcohol to afford phenol; the same problem that proved fatal to previous dienophile syntheses from 3.66, 3.74, and 3.75.

Indeed, under various conditions, desired enone 3.78 was obtained as a mixture with under-oxidized ketone 3.80, hydroquinone, and phenol. These side reactions were always observed with prolonged reaction times and elevated temperatures using IBX or standard Seagusa–Ito reaction conditions but full consumption of starting materials required reaction for 12–24 h, resulting in an overall reduced yield. This problem could be somewhat alleviated by stopping reactions early, isolating ketone 3.80, then re-subjecting this material to similar reaction conditions. However, this approach afforded desired enone 3.78 as an inseparable mixture with unreacted ketone. Some effort was put into using the Pd-mediated conditions developed by Stahl but very little oxidation was observed before the Pd catalyst plated out, leading to almost exclusive recovery of alcohol 3.79.32

Having tried more standard oxidation conditions, it was found that IBS, an IBX analogue, was reported31a to be a competent catalyst for oxidative enone formation when used in conjunction with stoichiometric Oxone. Because IBS features a sulfonic acid moiety instead of the carboxylate found in IBX, it is both more acidic and more active. Indeed, in 5 h at 70 °C in MeNO2, with 2.0 equivalents of powdered Oxone, catalytic amounts of IBS readily afforded enone 3.78, albeit with a significant amount of hydroquinone. However, in this case, it was suspected that the over-oxidation was coming from acid-mediated cleavage of the TBS ether, followed by alcohol oxidation rather than oxidation of enone to dienone, followed by tautomerization.
This theory was born out in practice when, with a sufficiently robust alcohol protecting group (TBDPS instead of TBS), IBS yielded desired enone 3.83 as the major product. Despite these favorable results, the greasy TBDPS protecting group led to solubility problems in the subsequent Morita–Baylis–Hilman reaction, where polar solvents (a THF/H₂O mixture) were necessary for desired reactivity, resulting in low yields of 3.84. For that reason, the TBS protecting group continued to be used.

With that concession, it was recognized that the best material throughput was actually obtained by first mono-protecting diol 3.82, oxidizing the free alcohol to the ketone under Swern or Parikh–Doering conditions, then forming the silyl enol ether and oxidizing further using pre-complexed IBX·MPO. This route allowed for the synthesis of 5–10 g batches of enone 3.78 in good yield with a minimum of purification necessary, but the cost of MPO (~$10/gram at the time the research was conducted) and the need for 1.5 equivalents of IBX·MPO made this approach less than ideal. While this route provided sufficient material for a number of studies, ultimately, the published route³³ from diene 3.86 was the preferred method for making enone 3.78. Diene 3.86 could be treated with acid to afford the skipped enone, which was epoxidized cleanly with mCPBA. One-pot, base-mediated opening of the epoxide afforded enone, which was cleanly TBS protected and used in further reactions. While lower yielding than the synthesis from 3.82, this second route were cheap and convenient, allowing for the synthesis of 17 g of 3.78 in a single
batch. The published conditions\textsuperscript{34} for the Morita–Baylis–Hilman reaction on 3.78 using aqueous CH\textsubscript{2}O worked reliably, although yields varied somewhat (isolated yields were generally between 40–70\%). Conversion of the allylic alcohol to the chloride using MsCl then proceeded smoothly, affording desired dienophile 3.85.

3.4 Successful Completion of the Clionastatin Core

The Diels–Alder reaction between enone 3.85 and diene 3.34 worked efficiently to give tricycle 3.65 under the same conditions employed with dienophile 3.33, although there were a few interesting differences from the earlier system. While 1.05 equivalents of
Et₂AlCl was sufficient for complete conversion of dienophile 3.33, dienophile 3.85 required 2.0 equivalents. This is interesting, as silyl ethers are generally considered to be non-coordinating, but preferential coordination of the Lewis acid to the silyl ether over the ketone is the most reasonable explanation for this phenomenon. Furthermore, while up to four diastereomers could result from the Diels–Alder reaction, only two diastereomers were observed. When nOe correlations were obtained for downstream analogues of the Diels–Alder adduct, it was found that the stereochemistry was as shown in Scheme 3.19, with an α-C4 silyl ether. This stereochemistry was at first puzzling, since this relative stereochemistry appears to come from an endo-approach on the more hindered face of the dienophile. This stereochemical outcome had been previously observed in Diels–Alder reactions with 4-silyloxy cyclohexenones and was explained as chelation of the Lewis acid between the dienophile silyl ether and the silyloxy diene. That theory is in agreement with the need for excess Lewis acid with these substrates. However, for Lewis-acid mediated Diels–Alder reactions of this type, a concerted, highly asynchronous reaction seems more consistent with a second explanation, namely, kinetically-favored axial attack of a nucleophile (enol ether 3.34) on the more-stable half-chair conformation of dienophile.

![Diagram of stereochemistry](image)

**Figure 3.3.** Rationale for the observed Diels–Alder diastereoselectivity.
Regardless of the reason, this reaction was highly diastereoselective at low temperature (10:1 dr at \(-78^\circ C, 4\)–6 h), but competitive cleavage of the silyl enol ether over prolonged reaction times encouraged the use of less selective, but ultimately higher yielding conditions (4:1 dr at 0 °C, 5 min). The Diels–Alder adduct 3.86 could be purified on silica (after pretreatment with 1–2% Et\(_3\)N) but partial hydrolysis of the enol ether was still observed. Better results were obtained if the crude mixture was immediately brominated, then heated in DMF with base to effect elimination of HBr and afford enone 3.87.

Reduction of the C1 ketone in the presence of an enone was achieved by addition of 0.4 equivalents of NaBH\(_4\) in EtOH at 0 °C, but elimination of the resulting C1 alcohol on 3.88 was less trivial. Efforts to convert the neopentylic alcohol into either the corresponding tosylate or mesylate were not successful owing to unfavorable steric interactions and attempted elimination using Burgess reagent\(^{36}\) returned only starting material, as did acidic, protic conditions (H\(_2\)SO\(_4\) or pTsOH in toluene). While treatment with Tf\(_2\)O in pyridine/DCM was viable, this procedure gave modest, variable yields (ranging from 10–50%), leading to messy reaction mixtures, presumably owing to an E1 mechanism, where the cation formed at C1 could induce an alkyl shift to give a variety of unidentified skeletal rearrangement products. Pre-formation of the triflate using LDA and PhNTf\(_2\) resulted in similar reaction profiles. Interestingly, elimination using SOCl\(_2\) in pyridine/DCM, which is known to give chlorinated products from 2° alcohols,\(^{37}\) gave slightly higher and much more reproducible yields (40–60%) of alkene 3.89. Martin Sulfurane dehydrating agent gave almost quantitative yield, but the prohibitive cost ($70/gram) and propensity of the
reagent to absorb atmospheric water, even when stored in a desiccator, lead to the use of SOCl₂ most often.

Dichlorination of olefin 3.89 using Et₄NCl₃ in DCM furnished trichlorides 3.90 and 3.91 in high yield as a nearly inseparable mixture of diastereomers, favoring the undesired trichloride. Extensive effort was invested into trying to understand both the cause for this selectivity and possible methods for favoring the desired diastereomer (see Chapter 4). However, even with a mixture of diastereomers, work towards validating our current retrosynthetic strategy continued. Because even partial separation of diastereomers 3.90 and 3.91 was so laborious, a mixture of diastereomers, enriched in 3.91, was often used in the further synthetic studies towards clionastatin core 3.1. For ease of communication, those mixtures enriched in 3.91 will be referred to as 3.91 for the remainder of this chapter.

The next challenge for this synthesis lay in oxidizing the B-ring enone to dienone 3.93. This task was viewed with a certain amount of trepidation, considering the not

![Chemical structure](image)

| Table 3.5. Attempted oxidative dienone formation on tricycle 3.91. |
|---------------------------------|-------------|---------------|----------------|
| Reagent | Solvent | Temperature | Result |
| DDQ | PhMe | 110 °C | trace product |
| DDQ | MeCN | 60 °C | trace product |
| DDQ | 1,4-dioxane | 60 °C | trace product |
| PyHBr•Br₂ | DCM | rt | messy |
| Pd(OAc)₂ | MeCN | 60 °C | no reaction |
| Pd(OAc)₂ | DMSO | 60 °C | no reaction |
| IBX | MeCN | 60 °C | trace product |
| IBX•MPO | DMSO/DCM | rt | cleavage of TMS |
| IBX•MPO | DMSO/DCM | rt | cleavage of TES |
| LDA then PhSeBr | THF | −78 °C to rt | no reaction |
insignificant effort that had previously gone into attempted enone formations on other, related B-rings (see Scheme 3.3 and Tables 3.2, 3.3, and 3.4). However, employing what had been learned from those previous efforts, exploration on oxidative enone formation began on substrates 3.91 and 3.92.

Saegusa–Ito oxidations, unlike with previous substrates, failed completely, returning only starting tricycle 3.91. DDQ resulted in trace amounts of desired dienone 3.93 as observed by ESI-MS, but 1H NMR showed only starting materials. IBX or IBX·MPO failed to give more than trace product from either enone 3.91 or silylenol ether 3.92, returning only enone. At this point, it was suspected that enolization of the C7 ketone might not be facile. Indeed, molecular models showed very poor overlap between the α-protons and the C7 π-system, and all attempts to deprotonate with strong bases (LDA, LiHMDS) and trap with electrophiles afforded only starting material. Furthermore, the ring-strain introduced by enolization of the B-ring to make 3.92 probably resulted in acceleration of silyl enol ether cleavage, as evidenced by the fact that 3.92 deprotected much more rapidly even on base-treated silica than any enol ether previously made for this project. In fact, the TMS-protected variant did not even survive cold aqueous NaHCO₃ washes, and the trace amounts of HBr in PhSeBr were sufficient to completely cleave the TMS group.

With these realizations, it became apparent that in situ formation of a silylenol ether, followed by one-pot trapping with an electrophile, was the most promising route for enone formation. Using the slightly more robust TESOTf to form the desired enol ether, in situ treatment with PhSeBr afforded the desired selenylated compound as a mixture of diastereomers at C6. While selenylated tricycles 3.94α and 3.94β could be isolated, it proved simpler to quench with a large excess of mCPBA and isolate enone 3.93 directly.
The reasonably good yield for those three transformations in a one-pot reaction, when compared with the ratio of $3.94\alpha$ and $3.94\beta$ in isolated mixtures, suggest that, while only selenoxide $3.94\beta$ could undergo syn-β-hydride elimination, the acidity of the doubly-activated C6 proton allowed for facile epimerization, interconverting $3.94\alpha$ and $3.94\beta$ and driving all material to $3.93$ via Le Chatelier’s principle.\textsuperscript{38} This reaction proceeded remarkably well several times on varying scales but started giving a completely different product when a new bottle of PhSeBr was employed. The new product, eventually identified as α-bromo enone $3.95$, comes from a known side reaction\textsuperscript{39} with PhSeBr. Attempts to use PhSeCl instead resulted only in similar α-chlorination products. Because of these inconsistencies between batches of reagent, it was ultimately more consistent to brominate with NBS and eliminate with LiCl/Li$_2$CO$_3$ in DMF at 120 °C.

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**Scheme 3.20 Completion of Clionastatin Cores 3.96 and 3.1**

\begin{itemize}
  \item 1. TESOTf
  \item 2. PhSeBr or NBS
  \item 3. mCPBA, 0–70%

\end{itemize}

$3.94\beta$ undergoes syn-β-hydride elimination to yield $3.93$. In another pathway, $3.95$ is transformed to $3.96$ via LiCl/Li$_2$CO$_3$ in DMF at 120 °C. $3.96$ is a minor diastereomer obtained along with $3.93$ and $3.91$.
With dienone 3.93 in hand, deprotection of the TBS ether with TBAF was followed by elimination using Tf₂O in pyridine to afford both the unnatural clionastatin core (3.96) and the natural clionastatin core (3.1) as a mixture. At this point, it was extremely gratifying to see that the ¹H NMR spectrum for desired trichloride 3.1 very closely resembled the corresponding peaks for clionastatin A (3.97, Figure 3.4). Undesired core 3.96, on the other hand, was in significant disagreement with 3.97. Specifically, the C1 and C2 protons, which should sit in shielded, axial positions in core 3.1, had the expected splitting (J = 8.6 Hz compared with J = 9.0 for 3.97), while the C1 and C2 protons for 3.96 are further downfield and appear as singlets. The ¹³C NMR data was similarly in close agreement for carbons on the A- and B-rings.

3.5 Conclusion
While early attempts to use the Diels–Alder reaction had failed to produce a reasonable route to the clionastatin core, by carefully analyzing the desired structure, we were ultimately able to design several successful sets of diene/dienophile pairs, each of which taught us about some aspect of the desired core. Though much time was, perhaps, wasted on elaborate strategies to synthesize more heavily functionalized dienophiles, the final approach enabled the eventual synthesis of trichlorides 3.90 and 3.91, which could be elaborated into the natural and unnatural clionastatin cores 3.1 and 3.96. Comparison of these products with naturally occurring clionastatin A corroborated the structural assignment of the natural product. Efforts towards applying this synthetic route to the synthesis of the tetracyclic natural products will be discussed in the next chapter.

### 3.6 Experimental Procedures

**9-(*tert*-Butyldimethylsilyloxy)-1,2,4a,4b,5,6,7,8,10,10a-decahydrophenanthrene-4a-carbaldehyde (3.7):** A solution of aldehyde 3.8 (18 mg, 0.18 mmol) in toluene (1 mL) was treated with dry ZnI₂ (57 mg, 0.18 mmol) under argon. Diene 3.9 (41 mg, 0.178 mmol) in toluene (1 mL) was added to the resulting heterogeneous mixture and stirred for 3 h. The reaction was quenched by addition of saturated aqueous NaHCO₃ (2 mL) and extracted with CH₂Cl₂ (2 x 2 mL). The combined organic extracts were washed with H₂O (2 mL) and saturated aqueous NaCl (2 mL). The organic layer was dried with Na₂SO₄, concentrated in vacuo, and purified by column chromatography (SiO₂, 1:19 EtOAc/hexanes, RF = 0.42 in 1:1 DCM/hexanes, KMnO₄) to afford 3.7 (59 mg, 77%) as a pale yellow oil. Data for 3.7: ¹H
NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 9.41 (s, 1H), 5.97 (dt, \(J = 10.0, 3.5, 1H\)), 5.55 (d, \(J = 10.0, 1H\)), 2.93 (d, \(J = 14, 1H\)), 2.45 (d, \(J = 12, 1H\)), 2.20 (m, 1H), 2.13 (m, 3H), 2.05 (dd, \(J = 35, 2.5, 1H\)), 1.80 (d, \(J = 33, 1H\)), 1.71 (m, 2H), 1.63 (m, 2H), 1.31 (m, 1H), 1.28–1.14 (m, 3H), 0.97 (s, 9H), 0.14 (s, 6H); \(^{13}\)C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 204.3, 130.9, 123.9, 53.2, 39.5, 32.6, 32.3, 29.8, 27.0, 26.8, 26.5, 25.9, 24.7, -3.8, -4.0; IR (thin film) 2930, 2856, 1716, 1660, 1471 cm\(^{-1}\); HRMS (Cl/methylene chloride) \(m/z\) calculated for C\textsubscript{21}H\textsubscript{34}O\textsubscript{2}Si (M + H)\(^+\) 347.2406, found 347.2416.

\[9-(\text{tert-Butyldimethylsilyloxy})-1,2,4a,4b,5,6,7,8,10,10a\text{-decahydrophenanthren-4a-yl}]\text{methanol (3.11)}\): Aldehyde 3.7 (29 mg, 0.08 mmol) was dissolved in EtOH (1 mL) and stirred at room temperature. To this solution was added NaBH\(_4\) (4 mg, 0.10 mmol) in one portion and the resulting yellow slurry was stirred for 30 min. The reaction was quenched with H\(_2\)O (1 mL) and extracted with CH\(_2\)Cl\(_2\) (3 x 1 mL); the combined organic layers were washed with brine (1 mL) and dried with Na\(_2\)SO\(_4\). The solvent was removed \textit{in vacuo} and the resulting oil was purified by column chromatography (silica gel, 1:9 EtOAc/hexanes, \(R_f = 0.56\) in 1:9 EtOAc/hexanes, KMnO\(_4\)) to afford 3.11 (15 mg, 50%) as a yellow oil. Data for 3.11: \(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 5.71 (dt, \(J = 10.0, 3.5, 1H\)), 5.21 (d, \(J = 10.0, 1H\)), 4.02 (d, \(J = 8.5, 1H\)), 3.29 (d, \(J = 8.5, 1H\)), 2.06–1.80 (m, 7H), 1.45 (m, 2H), 1.29–1.21, (m, 8H), 0.87 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 128.5, 127.2, 71.4, 52.1, 45.6, 37.9, 37.7, 29.8, 27.3, 27.3, 26.9, 26.7, 26.1, 25.3, 23.9, -2.4, -2.6; IR (thin film) 3394, 3050,
2927, 2900 cm⁻¹; LRMS (Cl/MeOH) m/z calculated for C₂₁H₃₆O₂Si (M + H)⁺ 349.32, found 349.32.

**1,2,5,6,7,8,10,10a-Octahydro-4a,8a-methanophenanthren-9(4bH)-one (3.12):** To a solution of alcohol 3.11 (5.7 mg, 0.02 mmol) in CH₃CN (0.2 mL) was added PPh₃ (7 mg, 0.03 mmol) and CCℓ₄ (5 μL, 0.05 mmol). The solution was stirred at room temperature for 8 h, concentrated *in vacuo*, and purified by column chromatography (silica gel, 1:9 EtOAc/hexanes, Rₚ = 0.61 in 1:19 EtOAc/hexanes, KMnO₄) to afford 3.12 (2 mg, 58%) as a colorless oil. Data for 3.12: ¹H NMR (500 MHz, CDCl₃) δ 5.71 (dt, J = 10.0, 3.5, 1H), 5.21 (d, J = 10.0, 1H), 4.02 (d, J = 8.5, 1H), 3.29 (d, J = 8.5, 1H), 2.06–1.80 (m, 7H), 1.45 (m, 2H), 1.29–1.21, (m, 8H), 0.87 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); IR (thin film) 3394, 3050, 2927, 2900 cm⁻¹. **Note:** could not find target mass.

**9-Oxo-1,2,4a,5,6,7,8,9,10,10a-decahydrophenanthrene-4a-carbaldehyde (3.13):** A solution of silyl enol ether 3.7 (7 mg, 0.02 mmol) and Pd(OAc)₂ (7 mg, 0.03 mmol) in CH₃CN (0.5 mL) was stirred at 45 °C, open to air, for 2 h. The reaction was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel, 1:19 EtOAc/hexanes, Rₚ = 0.33 in 1:3 EtOAc/hexanes, KMnO₄) to afford 3.13 (2 mg, 31%) as a pale yellow solid. Data for 3.13: ¹H NMR (500 MHz, CDCl₃) δ 9.51 (s, 1H), 6.11 (dt, J = 10.0, 3.5, 1H), 5.80 (d, J = 10.0, 1H), 2.61 (dd, J = 16.0, 5.0, 1H), 2.47 (d, J = 5.5, 1H), 2.41 (dd, J =
$16.5, 5.0, 1H), 2.32–2.27 (m, 3H), 2.15 (m, 2H), 1.70–1.63 (m, 3H), 0.95–0.83 (m, 4H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \delta 200.0, 132.6, 122.9, 63.2, 40.0, 29.4, 28.4, 24.3, 24.1, 22.6, 22.1, 21.6; IR (thin film) 2923, 2853, 1723, 1665 cm\textsuperscript{-1}; LRMS (Cl/MeOH) m/z calculated for C\textsubscript{15}H\textsubscript{19}O\textsubscript{2} (M + OH)–247.14, found 247.12.

![Triisopropyl[1-(2-methoxycyclohex-1-enyl)vinyloxy]silane](image)

**Triisopropyl[1-(2-methoxycyclohex-1-enyl)vinyloxy]silane (3.19):** A solution of 2-acetylcyclohexanone (1.5 g, 10.7 mmol) in MeOH (14 mL) with concentrated H\textsubscript{2}SO\textsubscript{4} (0.14 mL) was topped with a water condenser and heated to reflux. After 12 h, the reaction was allowed to cool to rt and the acid was neutralized by addition of KOH pellets (~300 mg). The solution was concentrated to 1/4\textsuperscript{th} volume *in vacuo*, diluted with Et\textsubscript{2}O (10 mL), and washed with saturated aqueous NaCl (10 mL). The organic layer was dried with Na\textsubscript{2}SO\textsubscript{4} and concentrated *in vacuo* to afford the methyl enol ether as a golden-yellow oil (1.59 g), which was used without further purification. The crude enol ether was dissolved in dry THF (18 mL) and cooled to 0 °C under argon. The reaction was stirred and Et\textsubscript{3}N (3.6 mL, 26 mmol) was added dropwise, followed by dropwise addition of TIPSOTf (3.03 mL, 11 mmol). The reaction was stirred at 0 °C for 90 min, quenched with a mixture of Et\textsubscript{3}N (5 mL), hexanes (25 mL), and saturated aqueous NaHCO\textsubscript{3} (50 mL). The organic layer was washed with H\textsubscript{2}O (2 x 50 mL) and brine (50 mL), then dried with Na\textsubscript{2}SO\textsubscript{4}. Concentration *in vacuo* and column chromatography through a short plug (silica gel, 1:1 CH\textsubscript{2}Cl\textsubscript{2}/hexanes with 1% Et\textsubscript{3}N, R\textsubscript{f} = 0.58 in 1:3 EtOAc/hexanes, KMnO\textsubscript{4}) afforded **3.19** (2.8 g, 88%) as a yellow oil in about 90% purity by \textsuperscript{1}H NMR, contaminated with 2-(1-triisopropylsilyloxy)vinyl cyclohexanone. **Note:** Attempts to distill this compound resulted in decomposition, and
some decomposition was observed while collecting fractions during chromatography. Attempts to remove all solvent resulted in further decomposition. Data for 3.19: $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 4.01 (s, 1H), 3.98 (s, 1H), 3.67 (s, 3H), 2.31 (m, 2H), 2.05 (t, $J = 8.4$, 2H), 1.61 (m, 2H), 1.34 (m, 2H), 1.18 (septet, $J = 5.3$, 3H), 1.08 (t, $J = 5.3$, 18H); IR (thin film) 2944, 2866, 1744, 1673, 1654, 1618, 1464 cm$^{-1}$. Note: could not find target mass.

![Structure](image)

**2-(Chloromethyl)cyclohex-2-enone (3.33):** Cyclohexenone (1.92 g, 20 mmol), aqueous CH$_2$O (3.2 mL, 35% solution, 40 mmol), and DMAP (244 mg, 2.0 mmol) in THF (5 mL) were stirred 20 h and acidified by addition of 1N HCl (10 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (4 x 20 mL), washed with saturated aqueous NaHCO$_3$ (20 mL) and saturated aqueous NaCl (20 mL). The organic extracts were dried with Na$_2$SO$_4$ and the solvent was removed in vacuo to produce an orange oil (1.7 g, 72%), which was used without further purification. The resulting allylic alcohol (1.67 g, 13 mmol) was dissolved in CH$_2$Cl$_2$ (15 mL) under argon and cooled to $-20$ °C. Et$_3$N (1.66 mL, 12 mmol) was added slowly and the resulting solution was stirred for 10 min. MsCl (1.48 mL, 32 mmol) was added dropwise, the reaction mixture was warmed to room temperature, and stirred for 3.5 h. The reaction was quenched with saturated aqueous NaHCO$_3$ (20 mL), washed with saturated aqueous NaCl (20 mL), dried with Na$_2$SO$_4$, and concentrated in vacuo. Chloride 3.33 (1.7 g, 91%) was isolated as a pale yellow oil and used without further purification. Data for 3.33 matched literature spectra in all respects: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.12 (t, $J = 4.5$, 1H), 4.18, (s, 2H), 2.46–2.41 (m, 4H), 2.02–1.98 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 197.4, 149.5, 136.0, 41.0, 38.1, 26.0, 22.7; IR (thin film) 2948, 2870, 1672, 1364, 1176 cm$^{-1}$; HRMS
(Cl/methylene chloride) m/z calculated for C\textsubscript{7}H\textsubscript{9}ClO (M + NH\textsubscript{4})\textsuperscript{+} 162.0686, found 162.0690.

4a-(Chloromethyl)-9-(trimethylsilyloxy)-2,3,4a,4b,5,6,7,8,10,10a-decahydrophenanthren-4(1H)-one (3.32): To a solution of enone 3.33 (211 mg, 1.46 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (15 mL) under argon at 0 °C was added Et\textsubscript{2}AlCl (1.53 mL, 1.0 M in hexanes, 1.53 mmol). The resulting mixture was stirred 30 min, after which a solution of diene 3.34 (430 mg, 2.2 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (3 mL) was added and the reaction mixture was stirred for 1 h. The reaction mixture was quenched by sequential addition of Et\textsubscript{3}N (5 mL), saturated aqueous NaHCO\textsubscript{3} (10 mL), and saturated aqueous Rochelle’s salt (20 mL) and allowed to stir an additional 30 min. The aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 20 mL), the organic extracts were dried with Na\textsubscript{2}SO\textsubscript{4}, and concentrated in vacuo to afford a crude yellow oil that was purified by column chromatography (silica gel, 1:19 EtOAc/hexanes, R\textsubscript{f} = 0.6 in 1:19 EtOAc/hexanes, KMnO\textsubscript{4}) to afford 3.32 (590 mg, 94%, 1:1.8 dr) as a yellow oil.

Note: Attempts to separate the diastereomers resulted only in hydrolysis of the silyl enol ether. Data for 3.32: \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 4.31 (d, J = 11.0, 0.35H), 4.16 (d, J = 11.0, 0.65H), 3.38–3.33 (d, J = 11.0, 1H), 2.89 (d, J = 13.5, 1H), 2.71 (m, 0.65H), 2.59–2.43 (m, 2.35H), 2.30–2.24 (m, 1H), 2.04–1.71 (m, 7H), 1.61–1.41 (m, 3H), 1.28–0.90 (m, 3H), 0.20 (s, 9H); IR (thin film) 2931, 2853, 1705 cm\textsuperscript{-1}. LRMS (Cl/MeOH) m/z calculated for C\textsubscript{18}H\textsubscript{29}ClO\textsubscript{2}Si (M + H)\textsuperscript{+} 341.16, found 341.20.
(4a,10a)-4a-(Chloromethyl)-2,3,5,6,7,8,10,10a-octahydrophenanthrene-4,9(1H,4aH)-dione (3.31): To a cooled solution of silyl enol ether 3.32 (27 mg, 0.079 mmol) in wet THF (0.8 mL) at 0 °C was added NBS (21 mg, 0.12 mmol) in one portion. The reaction mixture was stirred for 45 min, quenched with H₂O (2 mL), and extracted with CH₂Cl₂ (3 x 1 mL). The combined organic extracts were dried with Na₂SO₄ and concentrated in vacuo to give a dark brown solid. The crude bromide was dissolved in DMF (0.8 mL) with a minimum amount of CH₂Cl₂ (4 drops), to which Li₂CO₃ (17 mg, 0.23 mmol) and LiCl (5 mg, 0.1 mmol) were added. The resulting homogeneous mixture was stirred vigorously and heated at 120 °C for 1 h. The solution was diluted with H₂O (2 mL) and extracted with CH₂Cl₂ (4 x 2 mL). The combined organic extracts were washed with saturated aqueous NaCl (2 mL), dried with Na₂SO₄, and concentrated in vacuo. The crude brown oil was purified by flash chromatography (silica gel, 1:9 EtOAc/hexanes, Rf = 0.62 in 1:4 EtOAc/hexanes, KMnO₄) to provide 3.31 (15 mg, 70%) as a pale yellow oil. Data for 3.31: ¹H NMR (500 MHz, CDCl₃) δ 4.26 (d, J= 11.4, 1H), 3.57 (d, J= 11.4, 1H), 2.94 (m, 1H), 2.71 (dd, J = 17.6, 3.0, 1H), 2.47 (d, J = 15.7, 1H), 2.35 (dd, J = 17.6, 3.0, 2H), 2.24–2.03 (m, 3H), 2.00–1.96 (m, 2H), 1.82–1.66 (m, 7H), 1.50–1.42 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 207.5, 196.1, 149.3, 135.9, 59.2, 45.2, 40.7, 39.7, 38.5, 27.8, 26.9, 25.5, 22.7, 21.9, 21.4; IR (thin film) 2935, 2862, 1711, 1619, 1432 cm⁻¹; HRMS (Cl/methylene chloride) m / z calculated for C₁₅H₁₉ClO₂ (M + Na)⁺ 289.0971, observed 289.0966.
(±)-(1R,4S,4aS,8aR)-6-(Hydroxymethyl)-2,3,4,4a,8,8a-hexahydro-1,4-methanonaphthalen-5(1H)-one (3.48): To a stirred solution of cyclohexenone 3.43 (8.17 g, 51 mmol) in THF (17 mL) was added DMAP (623 mg, 5.10 mmol) and aqueous CH$_2$O (12 mL, 35% solution, 153 mmol). The reaction was allowed to stir at rt for 4 d, cooled to 0 °C, and acidified by slow addition of 1N HCl (20 mL). The reaction mixture was extracted with EtOAc (4 x 50 mL), the combined organic extracts were washed with saturated aqueous NaHCO$_3$, and saturated aqueous NaCl (50 mL each). The organic layer was dried with Na$_2$SO$_4$ and concentrated in vacuo to viscous orange oil, which was purified by flash chromatography (silica gel, gradient from hexanes to 1:1 EtOAc/hexanes, $R_f$ = 0.16 in 1:1 EtOAc/hexanes, KMnO$_4$) to provide 3.48 (5.88 g, 60%). Data for 3.48: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.59 (s, 1H), 6.15 (s, 1H), 6.09 (s, 1H), 4.16 (m, sH), 3.40 (s, 1H), 3.04 (s, 1H), 2.97 (dd, $J$ = 9.9, 4.2, 1H), 2.76 (m, 1H), 2.65 (m, 1H), 2.54 (t, $J$ = 6.3, 1H), 2.08 (s 1H), 1.45 (d, $J$ = 8.4, 1H), 1.35 (d, $J$ = 8.3, 1H); IR (thin film) 3458, 2981, 1735, 1656 cm$^{-1}$; LRMS (ES+) m / z calculated for C$_{12}$H$_{14}$O$_2$Na (M + Na)$^+$ 213.0892, observed 213.0826.

(±)-(4aS,10aS)-3,4-Dichloro-4a-(chloromethyl)-2,3,4,4a,5,6,7,8,10,10a-decahydrophenanthren-9(1H)-one (3.52): To a cooled solution of ketone 3.31 (235 mg, 0.881 mmol) in EtOH (9 mL) at 0 °C was added NaBH$_4$ (10.1 mg, 0.264 mmol) in one portion. The reaction mixture was stirred for 45 min, quenched with 10% AcOH (10 mL),
and extracted with Et₂O (4 x 10 mL). The combined organic extracts were washed with saturated aqueous NaHCO₃ (10 mL) and saturated aqueous NaCl (10 mL), dried with MgSO₄, and concentrated in vacuo to give alcohol 3.50 as a pale yellow oil. To a cooled solution of crude alcohol 3.50 in 2:1 CH₂Cl₂/pyridine (15 mL) at 0 °C under argon was added Tf₂O (0.38 mL, 2.23 mmol). The resultant solution was allowed to stir overnight, warming slowly to rt, and quenched by the addition of H₂O (10 mL). The organic phase was washed with 1N HCl (10 mL), saturated aqueous NaHCO₃ (10 mL), H₂O (10 mL), and saturated aqueous NaCl (10 mL). The combined organic layers were dried with Na₂SO₄ and concentrated in vacuo to afford triflate 3.51 as an orange oil. To a solution of crude triflate 3.51 in DMF (5 mL) was added LiCl (105 mg, 2.47 mmol). The resulting homogeneous mixture was stirred vigorously and heated at 120 °C for 36 h. The solution was diluted with H₂O (10 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were washed with saturated aqueous NaCl (10 mL), dried with Na₂SO₄, and concentrated in vacuo. The crude olefin 3.51 was passed quickly through a plug of silica and taken on to the next step. Alkene 3.51 was dissolved in CH₂Cl₂ and cooled to 0 °C under argon. Et₄NCl₃ (39 mg, 0.165 mmol) was added in one portion, the reaction mixture was allowed to stir for 20 min and quenched by addition of half-saturated aqueous Na₂S₂O₃ (2 mL). The aqueous phase was extracted with CH₂Cl₂ (3 x 2 mL) and the combined organic extracts were washed with H₂O (2 mL) and saturated aqueous NaCl (1 mL). The organic phase was dried with Na₂SO₄ and concentrated in vacuo to afford a yellow oil, which was purified by column chromatography (silica gel, 1:19 EtOAc/hexanes, Rf = 0.46 in 1:4 EtOAc/hexanes, KMnO₄), then by preparative HPLC (3% acetone/hexane) to provide the major diastereomer of 3.52 (7 mg, 35%) as a white solid. Data for 3.52: 1H NMR (500 MHz, CDCl₃) δ 4.40 (bs, 1H), 4.23
(d, J = 11.4, 1H), 4.17 (bs, 1H), 3.84 (d, J = 12.1, 1H), 2.89 (m, 2H), 2.65–2.40 (m, 3H), 2.40–
2.33 (m, 3H), 2.01 (m, 1H), 1.82 (m, 1H), 1.67–1.56 (m, 5H); IR (thin film) 2935, 2862, 1711,
1619, 1432 cm⁻¹; LRMS (Cl/methanol) m / z calculated for C₁₅H₁₉Cl₃OK (M + K)⁺ 361.2,
observed 361.2.

(±)-Methyl (4aS,4bS,10aS)-1,4-dioxo-9-[(trimethylsilyl)oxy]-1,4b,5,6,7,8,10,10a-
octahydrophenanthrene-4a(4H)-carboxylate (3.54): To a stirred solution of quinone 3.53 (366 mg, 2.20 mmol) in DCM (40 mL) at −78 °C under argon was added enol ether 3.34 (432 mL, 2.20 mmol) in DCM (2 mL). After 1 h, a second portion of 3.34 (432 mL, 2.20 mmol) was added and the reaction was stirred an additional 30 min. The reaction mixture was warmed to rt, concentrated to ~5 mL in vacuo, and passed through a short silica plug,
eluting with EtOAc. The residue was purified by column chromatography (SiO₂, gradient eluent from 1:9 EtOAc/hexanes to 1:4 EtOAc/hexanes, Rf = 0.46 in 1:4 EtOAc/hexanes,
KMnO₄) to afford 3.54 (520 mg, 65%) as a pale orange oil. Data for 3.54: ¹H NMR (500
MHz, CDCl₃) δ 6.84 (d, J = 7.3, 3H), 6.67 (d, J = 10.3, 2H), 6.62 (d, J = 10.3, 1H), 3.83 (d, J =
5.9, 2H), 3.78 (s, 6H), 3.64 (s, 3H), 3.17 (d, J = 11.2, 1H), 3.12 (dd, J = 9.9, 6.5, 1H), 3.07 (d, J =
12.6, 1H), 2.80 (m, 5H), 2.47 (m, 2H), 2.00 (m, 1H), 1.85 (m, 2H), 1.77 (m, 3H), 1.69 (m, 2H),
1.61 (m, 3H), 1.54 (m, 3H), 1.33 (m, 1H), 1.15 (m, 1H), 1.02 (m, 3H), 0.94 (m, 1H), 0.14 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 197.6, 197.0, 196.7, 193.4, 170.2, 168.7, 142.0, 141.4,
139.8, 138.7, 137.9, 137.3, 120.4, 117.9, 100.0, 65.3, 64.5, 63.4, 60.5, 53.6, 53.4, 48.2, 45.4,
42.4, 33.9, 31.0, 30.7, 28.7, 28.4, 28.2, 27.7, 27.6, 27.3, 26.9, 25.2, 19.2, 17.5, 14.3, 13.8, 0.6.
**tert-Butyl[(1-cyclohex-1-en-1-yl)vinyl]oxy]diphenylsilane (3.56):** To a stirred solution of KHMDS (6.5 mL, 1.0 M in THF, 6.50 mmol) under argon at −78 °C was added 1-(cyclohex-1-en-1-yl)ethan-1-one (500 µL, 4.03 mmol) dropwise. The resulting solution was stirred for 20 min before TBDPSCl (1.256 mL, 4.83 mmol) was added dropwise, stirred for an additional 10 min, then allowed to warm to rt. The reaction mixture was stirred at rt for 2 h, concentrated in vacuo, and filtered through celite, rinsing with hexanes. The solution was again concentrated in vacuo and the residue was purified by column chromatography (SiO₂ pre-treated for 30 min by stirring with 1% Et₃N in hexanes, gradient eluent from 1:49 Et₂O/hexanes to 1:24 Et₂O/hexanes, Rᵢ = 0.52 in 1:9 EtOAc/hexanes, KMnO₄) to afford 3.56 (1.26 g, 86%) as a pale yellow oil. Data for 3.56: ¹H NMR (500 MHz, CDCl₃) δ 7.75 (d, J = 7.9, 4H), 7.39 (m, 6H), 6.54 (bs, 1H), 4.18 (s, 1H), 3.80 (s, 1H), 2.21 (m, 2H), 2.11 (m, 2H), 1.69 (m, 2H), 1.61 (m, 2H), 1.06 (s, 9H).

**(±)-Methyl (4aS,4bS,10aS)-9-[[tert-butylidiphenylsilyl]oxy]-1,1-dimethoxy-4-oxo-1,4b,5,6,7,8,10,10a-octahydrophenanthrene-4a(4H)-carboxylate (3.57):** To a stirred solution of quinone 3.55 (1.95 g, 9.17 mmol) in DCM (90 mL) under argon was added enol ether 3.56 (3.32 g, 9.17 mmol) in DCM (5 mL). After 2 d, the reaction mixture was concentrated in vacuo and purified by column chromatography (SiO₂, gradient eluent from 1:6 EtOAc/hexanes to 1:4 EtOAc/hexanes, Rᵢ = 0.36 in 1:4 EtOAc/hexanes, KMnO₄) to
afford 3.57 (789 mg, 23%) as a yellow oil. Data for 3.57: ¹H NMR (500 MHz, CDCl₃) δ 7.67 (d, J = 6.6, 2H), 7.59 (d, J = 6.6, 2H), 7.38 (m, 6H), 6.25 (dd, J = 10.6, 2.4, 1H), 5.92 (d, J = 10.5, 1H), 3.58 (s, 3H), 3.08 (s, 6H), 2.98 (t, J = 10.3, 1H), 2.82 (s, 3H), 1.86 (d, J = 7.4, 1H), 1.70 (d, J = 7.3, 2H), 1.56 (m, 2H), 1.45 (m, 1H), 1.30 (t, J = 12.4, 1H), 1.14 (m, 1H), 1.03 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 193.8, 170.7, 142.6, 138.0, 135.5, 135.4, 134.3, 134.1, 130.2, 129.8, 129.7, 127.7, 117.6, 98.4, 58.3, 51.9, 49.5, 47.4, 40.0, 40.0, 32.0, 29.5, 27.9, 27.5, 27.2, 26.8, 19.5; IR (thin film) 2931, 2855, 1722, 1589 cm⁻¹; HRMS (ES+) m / z calculated for C₃₄H₄₂O₆SiNa [M + Na]⁺ 597.2648, found 597.2471.

(±)-Methyl (4S,4aS,4bS,10aS)-9-[(tert-butyldiphenylsilyl)oxy]-4-hydroxy-1,1-dimethoxy-1,3,4,4b,5,6,7,8,10,10a-decahydrophenanthrene-4a(2H)-carboxylate (3.58): To a flame-dried vial under argon was added enone 3.57 (32 mg, 0.056 mmol) and PtO₂ (1.3 mg, 0.0056 mmol). The flask was evacuated and sparged for 5 min with H₂, after which EtOAc (2 mL) was added. The reaction was allowed to stir at rt for 23 h and poured through a short plug of celite, which was then rinsed with EtOAc. The solution was concentrated in vacuo to afford a white foam. The crude ketone was dissolved in toluene (2 mL) and cooled to -78 °C under argon. Red-Al (4 x 18 µL, ≥60 wt.% in toluene, 4 x 0.056 mmol) was added at 5 min intervals and the reaction mixture was warmed to rt and allowed to stir for an additional 10 min. The solution was cooled back to -78 °C and quenched by dropwise addition of saturated aqueous Rochelle’s salt (2 mL), then diluted with an additional portion of saturated aqueous Rochelle’s salt (2 mL), toluene (4 mL) and
H₂O (2 mL). This biphasic mixture was stirred for 30 min at rt, the aqueous layer was extracted with EtOAc (3 x 3 mL), and the combined organic extracts were washed with saturated aqueous NaCl (3 mL). The organic layer was dried over Na₂SO₄, concentrated in vacuo, and purified by column chromatography (SiO₂, gradient eluent from 1:6 EtOAc/hexanes to 1:4 EtOAc/hexanes, R_f = 0.25 in 1:4 EtOAc/hexanes, KMnO₄) to afford 3.58 (22 mg, 68%) as a pale yellow oil. Data for 3.58: ¹H NMR (500 MHz, CDCl₃) δ 7.74 (d, J = 7.7, 2H), 7.70 (d, J = 7.7, 2H), 7.38 (m, 6H), 3.97 (bs, 1H), 3.58 (s, 3H), 3.19 (d, J = 12.7, 1H), 3.04 (m, 1H), 2.96 (s, 3H), 2.83 (m, 1H), 2.74 (s, 5H), 1.81 (m, 3H), 1.70 (m, 1H), 1.54 (m, 7H), 1.40 (m, 1H), 1.28 (m, 3H), 1.18 (m, 1H), 1.08 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 138.0, 135.7, 135.6, 134.2, 134.1, 129.9, 129.8, 127.7, 127.7, 116.3, 101.6, 69.6, 51.4, 50.3, 47.8, 47.2, 41.2, 37.8, 33.4, 28.7, 28.4, 27.9, 27.7, 27.3, 26.9, 25.9, 19.6; IR (thin film) 3504, 3048, 2932, 2855, 1702 cm⁻¹; HRMS (ES+) m/z calculated for C₃₄H₄₆O₅SiNa [M + Na]^+ 601.2961, found 601.2900.

(±)-Methyl (4aS,4bS,10aS)-9-[(tert-butylidiphenylsilyl)oxy]-1,1-dimethoxy-1,4b,5,6,7,8,10,10a-octahydrophenanthrene-4a(2H)-carboxylate (3.59): To a stirred solution of alcohol 3.58 (94 mg, 0.162 mmol) in pyridine (6 mL) at 0 °C under argon was added Tf₂O (109 µL, 0.648 mmol) dropwise. The resulting orange solution was warmed to rt and stirred for 3 h, at which point the reaction mixture was again cooled to 0 °C and a second portion of Tf₂O (55 µL, 0.324 mmol) was added. A third portion of Tf₂O (109 µL, 0.648 mmol) was added (at 0 °C) after an additional 3 h of stirring at rt. 9 h after the initial
addition of Tf₂O, the reaction was poured into a mixture of ice, aqueous NaHCO₃ (2 mL), and DCM (6 mL). The aqueous layer was extracted with DCM (3 x 3 mL) and the combined organic extracts were dried over Na₂SO₄. The resulting solution was concentrated in vacuo and purified by column chromatography (SiO₂, gradient eluent from 1:20 EtOAc/hexanes to 1:10 EtOAc/hexanes to 1:6 EtOAc/hexanes, Rₜ = 0.50 in 1:4 EtOAc/hexanes, KMnO₄) to afford 3.59 (54 mg, 60%) as a yellow foam. Data for 3.59: ¹H NMR (500 MHz, CDCl₃) δ 7.69 (t, J = 7.6, 4H), 7.38 (m, 6H), 5.42 (m, 2H), 3.59 (s, 3H), 3.09 (d, J = 13.3, 1H), 2.96 (s, 3H), 2.82 (s, 4H), 2.11 (m, 1H), 2.01 (m, 1H), 1.82 (m, 2H), 1.68 (m, 2H), 1.47 (m, 1H), 1.37 (m, 1H), 1.30 (m, 1H), 1.26 (m, 2H), 1.18 (m, 1H), 1.05 (s, 9H); IR (thin film) 2930, 2855, 1732, 1577 cm⁻¹; HRMS (ES+) m / z calculated for C₅₄H₄₄O₅SiNa [M + Na]⁺ 583.2856, found 583.2709.

4-(Ethylsulfinyl)cyclohex-2-en-1-one (3.76): To a stirred solution of diene 3.69 (1.70 g, 10.0 mmol) in DCM (10 mL) at −78 °C was added a premixed solution of NCS (1.40 g, 10.5 mmol) and EtSH (0.76 mL, 10.5 mmol) in DCM (10 mL). The resulting yellow solution was stirred for 20 min and washed with H₂O (10 mL) and saturated aqueous NaCl (10 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The resulting orange oil (510 mg, 33%, Rₜ = 0.13 in 1:9 EtOAc/hexanes, KMnO₄) was used without further purification. Data for 3.76: ¹H NMR (600 MHz, CDCl₃) δ 7.17 (d, J = 8.4, 1H), 6.85 (dd, J = 9.6, 4.2, 1H), 6.71 (d, J = 8.5, 1H), 5.89 (d, J = 10.1, 1H), 3.23 (q, J = 7.3, 1H), 3.06 (q, J = 7.4, 1H), 2.63 (m, 4H), 2.31 (m, 3H), 2.03 (m, 1H), 1.33 (t, J = 7.2, 3H); ¹³C NMR (151 MHz, CDCl₃) δ
Known\textsuperscript{31a} cyclohexenone \textbf{3.83} (22.0 g, 62.9 mmol) and DMAP (7.70 g, 62.9 mmol) in THF (60 mL) were heated to 50 °C and stirred 15 min. Aqueous CH\textsubscript{2}O (74 mL, 35% solution, 943 mmol) was added and stirring was continued for 2 h. The reaction mixture was cooled to 0 °C, quenched by addition of 1N HCl (100 mL), and the aqueous phase was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 200 mL). The combined organic layers were washed with saturated aqueous NaHCO\textsubscript{3} (200 mL), H\textsubscript{2}O (200 mL), and saturated aqueous NaCl (200 mL). The organic layer was dried over Na\textsubscript{2}SO\textsubscript{4}, the solvent was removed \textit{in vacuo}, and the residue was filtered through a short plug of silica to produce the crude alcohol (5.50 g) as an orange oil. The resulting allylic alcohol was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (150 mL) under argon and cooled to 0 °C. Et\textsubscript{3}N (4.04 mL, 29.0 mmol) was added slowly and the resulting solution was stirred for 10 min. MsCl (1.68 mL, 21.8 mmol) was added dropwise, the reaction mixture was warmed to room temperature, and stirred for 19 h. The volume was reduced \textit{in vacuo}, the reaction mixture was washed with saturated aqueous NH\textsubscript{4}Cl (50 mL), and the organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} before being concentrated further \textit{in vacuo}. Purification by column chromatography (SiO\textsubscript{2}, gradient eluent from hexanes to 1:4 EtOAc/hexanes to 1:1 EtOAc/hexanes, \(R_f = 0.58\) in 1:4 EtOAc/hexanes, KMnO\textsubscript{4}) afforded \textbf{3.84} (2.64 g, 11%) as a yellow foam. A roughly equimolar amount of intermediate mesylate (2.76 g, 10%) was also
isolated as an orange oil. Data for 3.84: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.69 (m, 4H), 7.47, (m, 2H), 7.42 (m, 4H), 6.92 (s, 1H), 4.56 (m, 1H), 4.16 (d, $J$ = 12.0, 1H), 4.11 (d, $J$ = 12.0, 1H), 2.59 (m, 1H), 2.22 (m, 1H), 2.08 (m, 2H), 1.10 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 196.7, 151.3, 135.8, 135.7, 130.1, 130.1, 127.9, 127.8, 81.5, 67.7, 35.4, 32.6, 26.9, 14.4.

4-[(tert-Butyldimethylsilyl)oxy]-2-(chloromethyl)cyclohex-2-ene-1-one (3.85): To a stirred solution of 4-[(tert-butyldimethylsilyl)oxy]-2-(hydroxymethyl)cyclohex-2-ene-1-one$^{34}$ (3.10 g, 12.1 mmol) in DCM (150 mL) under argon was added Et$_3$N (1.60 mL, 11.5 mmol) and a catalytic quantity of Et$_4$NCl (20 mg). The reaction mixture was cooled to 0 °C and MsCl (2.81 mL, 36.3 mmol) was added slowly. The ice bath was allowed to warm and the reaction was stirred for 18 h at rt. The pale yellow solution was washed successively with cold saturated aqueous NaHCO$_3$ solution (100 mL) and saturated aqueous NH$_4$Cl solution (100 mL), then the organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by column chromatography (SiO$_2$, gradient eluent from hexanes to 1:9 EtOAc/hexanes, $R_f$ = 0.5 in 1:4 EtOAc/hexanes, KMnO$_4$) to afford 3.85 (2.64 g, 79%) as a colorless oil. Data for 3.85: $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 6.89 (s, 1H), 4.55–4.53 (m, 1H), 4.16 (d, $J$ = 10.5, 1H), 4.09 (d, $J$ = 10.5, 1H), 2.57 (dt, $J$ = 16.8, 4.5, 1H), 2.37–2.27 (m, 1H), 2.18–2.15 (m, 1H), 1.98–1.87 (m, 1H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 196.5, 151.9, 135.0, 67.3, 40.5, 35.8, 33.1, 26.0, 18.3, –4.4, –4.5; IR (thin film) 2952, 2930, 2857, 1694, 1643, 1360, 1253 cm$^{-1}$; HRMS (ES+) m / z calculated for C$_{13}$H$_{23}$ClO$_2$SiNa [M + Na]$^+$ 297.1053, found 297.1048.
To a solution of enone 3.85 (1.53 g, 5.57 mmol) in DCM (60 mL) under argon at \(-78^\circ\text{C}\) was added Et\(_2\)AlCl (11.1 mL, 1.0 M in hexanes, 11.1 mmol). The resulting mixture was stirred for 10 min, then a solution of diene 3.34 (1.6 M in benzene, 3.83 mL, 6.13 mmol) was added and the reaction mixture was stirred for 3 h. The reaction was quenched by sequential addition of Et\(_3\)N (6 mL), cold saturated aqueous NaHCO\(_3\) solution (12 mL), and a saturated aqueous solution of Rochelle’s salt (24 mL), then allowed to stir an additional 30 min. The resulting mixture was extracted with DCM (3 x 30 mL). The combined organic extracts were washed with H\(_2\)O (30 mL), saturated aqueous NaCl solution (30 mL), then dried with Na\(_2\)SO\(_4\) and concentrated in vacuo to afford a crude yellow oil (3.10 g), which was used without further purification.

To a solution of crude silyl enol ether 3.86 (2.62 g, 5.57 mmol) in wet THF (60 mL) at 0 \(^\circ\text{C}\) was added NBS (1.97 g, 11.1 mmol) in one portion. The reaction mixture was stirred for 2 h in the dark, and quenched with saturated aqueous NaHCO\(_3\) solution (50 mL). The aqueous phase was extracted with DCM (3 x 50 mL), and the combined organic extracts were washed with H\(_2\)O (50 mL) and saturated aqueous NaCl solution (50 mL). The organic solution was dried with Na\(_2\)SO\(_4\) and concentrated in vacuo to give a dark orange oil (4.35 g) which was used without further purification. The crude bromide was dissolved in DMF (100 mL) and Li\(_2\)CO\(_3\) (1.23 g, 16.7 mmol) and LiCl (354 mg, 8.36 mmol) were added. The resulting heterogeneous mixture was stirred vigorously and heated at 120 \(^\circ\text{C}\) for 90 min in the dark. The mixture was allowed to cool, diluted with H\(_2\)O (100 mL) and extracted
with EtOAc (5 x 50 mL). The combined organic extracts were washed with H$_2$O (4 x 50 mL) and saturated aqueous NaCl solution (50 mL), dried with Na$_2$SO$_4$, and concentrated in vacuo. The crude brown oil was purified by column chromatography (SiO$_2$, gradient eluent from hexanes to 1:19 to 1:9 EtOAc/hexanes, $R_f = 0.46$ in 1:4 EtOAc/hexanes, KMnO$_4$) to provide 3.87 (1.10 g, 50%) as a pale yellow solid. Data for 3.87: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.17–4.13 (m, 2H), 3.38 (d, $J = 11.4$, 1H), 2.96 (dt, $J = 6.6$, 3.3, 1H), 2.72 (td, $J = 13.6$, 5.0, 1H), 2.65 (dd, $J = 18.0$, 6.5, 1H), 2.45–2.25 (m, 3H), 2.25–1.96 (m, 3H), 1.96–1.72 (m, 2H), 1.65–1.58 (m, 2H), 1.51–1.22 (m, 2H), 0.80 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) 207.9, 195.3, 149.1, 136.9, 70.6, 57.9, 46.0, 42.4, 36.9, 35.2, 32.2, 27.3, 26.1, 23.2, 22.4, 21.5, 18.2, –4.7, –4.9; IR (thin film) 2931, 2857, 1716, 1670, 1626 cm$^{-1}$; HRMS (ES$^+$) m/z calculated for C$_{21}$H$_{33}$ClO$_3$SiNa (M + Na)$^+$ 419.1785, observed 419.1793.

(±)-(1R,4aR,10aS)-1-[(tert-Butyldimethylsilyl)oxy]-4a-(chloromethyl)-1,2,4a,5,6,7,8,9,10,10a-decahydrophenanthren-9-one (3.89): To a stirred solution of ketone 3.87 (1.10 g, 2.77 mmol) in EtOH (60 mL) at 0°C was added NaBH$_4$ (52 mg, 1.39 mmol) in one portion. The reaction mixture was stirred at 0°C for 1 h, then quenched with 1 N HCl (5 mL) and neutralized by addition of saturated aqueous NaHCO$_3$ solution (20 mL). The mixture was extracted with DCM (4 x 20 mL) and the combined organic layers were washed with H$_2$O (2 x 20 mL) and saturated aqueous NaCl solution (20 mL). The organic extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo to afford a pale yellow foam (1.06 g) which was used without further purification. (A) To a stirred solution of crude
alcohol 3.88 (1.06 g, 2.66 mmol) in DCM (60 mL) under argon was added Martin sulfurane (2.68 g, 3.99 mmol) in one portion. The reaction mixture was stirred at room temperature for 2 h and quenched by the addition of H2O (20 mL). The organic phase was washed with saturated aqueous NaHCO3 solution (30 mL) and saturated aqueous NaCl solution (30 mL), and the organic layer was dried over Na2SO4 and concentrated in vacuo. The residue was purified by column chromatography (SiO2, gradient eluent from hexanes to 1:19 EtOAc/hexanes, RF = 0.49 in 1:4 EtOAc/hexanes, KMnO4), then residual l-phenyl-l-(trifluoromethyl)-2,2,2-trifluoroethanol was removed at 0.1 torr to afford 3.89 (805 mg, 79%)40 OR (B) To a stirred solution of alcohol 3.88 (500 mg, 1.35 mmol) in pyridine (20 mL) with DCM (3 mL) under argon at 0 °C was added SOCl2 (0.30 mL, 4.06 mmol) dropwise. The reaction mixture was stirred, warming slowly to room temperature, for 7 h, and quenched by the addition of cold saturated aqueous NaHCO3 solution (30 mL). The aqueous phase was extracted with DCM (3 X 30 mL) and the combined organic layers were washed successively with H2O (2 X 30 mL) and saturated aqueous NH4Cl solution (30 mL). The organic extracts were dried over Na2SO4 and concentrated in vacuo. The residue was purified by column chromatography (SiO2, gradient eluent from hexanes to 1:19 to 1:9 EtOAc/hexanes, RF = 0.49 in 1:4 EtOAc/hexanes, KMnO4) to afford 3.89 (202 mg, 42%) as an amorphous white solid. Data for 3.89: 1H NMR (500 MHz, CDCl3) δ 5.83–5.73 (m, 1H), 5.42 (d, J = 10.4, 1H), 4.20–4.15 (m, 1H), 3.74 (d, J = 12.0, 1H), 3.50 (d, J = 12.0, 1H), 2.73 (d, J = 14.1, 1H), 2.64 (dd, J = 16.1, 4.2, 1H), 2.50 (d, J = 16.1, 1H), 2.39–2.17 (m, 4 H), 2.11–2.02 (m, 2H), 1.87–1.79 (m, 2H), 1.47–1.38 (m, 2H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 198.5, 154.0, 136.0, 129.4, 125.2, 65.6, 48.7, 47.6, 38.6, 33.0, 32.1,
26.1, 25.5, 23.4, 22.6, 21.8, 18.4, -4.4, -4.6; IR (thin film) 2928, 2853, 1721, 1670 cm⁻¹; HRMS (ES+) m/z calculated for C₂₁H₃₃ClO₂SiNa [M + Na]⁺ 403.1836, found 403.1843.

(±)-(1R,3S,4S,4aS,10aS)-1-[(tert-Butydimethylsilyl)oxy]-3,4-dichloro-4a-(chloromethyl)-1,2,3,4,4a,5,6,7,8,9,10,10a-dodecahydrophenanthren-9-one  (3.90)
and  (±)-(1R,3R,4R,4aS,10aS)-1-[(tert-butydimethylsilyl)oxy]-3,4-dichloro-4a-(chloromethyl)-1,2,3,4,4a,5,6,7,8,9,10,10a-dodecahydrophenanthren-9-one  (3.91):
To a stirred solution of alkene 3.89 (92 mg, 2.41 mmol) in DCM (3 mL) at room temperature was added Et₄NCl₃ (86 mg, 0.362 mmol); a second portion of Et₄NCl₃ (20 mg, 0.086 mmol) was added after 50 min. The reaction was stirred for an additional 30 min and quenched with saturated aqueous Na₂S₂O₃ solution (2 mL). The aqueous phase was extracted with DCM (3 x 2 mL), the combined organic extracts were washed with H₂O (2 mL), saturated aqueous NaCl solution (2 mL), and dried over Na₂SO₄. The organic solution was concentrated in vacuo to afford a 4:1 diastereomeric mixture as a yellow oil. The residue was purified by column chromatography (SiO₂, gradient eluent from hexanes to 1:49 to 1:19 EtOAc/hexanes, Rf = 0.57 in 1:4 EtOAc/hexanes, KMnO₄) to afford the minor diastereomer 3.90 (12 mg, 16%) and the major diastereomer 3.91 (71 mg, 65%) as yellow oils. Data for 3.90: ¹H NMR (500 MHz, CDCl₃) δ 4.32 (d, J = 12.4, 1H), 4.19 (d, J = 10.9, 1H), 4.05 (m, 2H), 3.65 (d, J = 12.4, 1H), 2.92–2.87 (m, 2H), 2.75 (dd, J = 14.0, 5.0, 1H), 2.49–2.34 (m, 5H), 1.74 (m, 2H), 1.52–1.36 (m, 1H), 0.90 (s, 9H), 0.08 (s, 6H); IR (thin film) 2932, 2858, 1668, 1628, 1379, 1258, 1105 cm⁻¹; HRMS (ES+) m/z calculated for C₂₁H₃₃ClO₂SiNa
[M + Na]+ 473.1213, found 473.1203. Data for 3.91: 1H NMR (500 MHz, CDCl₃) δ 4.72 (bs, 1H), 4.46–4.38 (m, 1H), 4.38 (d, J = 12.0, 1H), 4.21 (s, 1H), 3.65 (d, J = 12, 1H), 2.90–2.79 (m, 1H), 2.77–2.60 (m, 2H), 2.58–2.46 (m, 2H), 2.33–2.24 (m, 1H), 2.22–2.11 (m, 2H), 2.00 (d, J = 14.8, 1H), 1.92–1.74 (m, 2H), 1.52–1.36 (m, 2H), 0.90 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H); 13C NMR (126 MHz, CDCl₃) δ 198.3, 153.2, 137.4, 63.8, 62.1, 60.1, 51.2, 48.0, 38.0, 33.4, 26.2, 26.2, 25.8, 23.6, 22.4, 21.61, 18.4, −4.5, −4.7; IR (thin film) 2932, 2858, 1668, 1628, 1379, 1258, 1105 cm⁻¹; HRMS (ES+) m/z calculated for C₂₁H₃₃Cl₂O₂SiNa [M + Na]+ 473.1213, found 473.1203.

(±)-(1R,3R,4R,4aR)-1-[[tert-Butydimethylsilyl]oxy]-3,4-dichloro-4a-(chloromethyl)-1,2,3,4,4a,5,6,7,8,9-decahydrophenanthren-9-one (3.93): A stirred solution of trichloride 3.91 (18 mg, 0.040 mmol) and Et₃N (0.11 mL, 0.80 mmol) in DCM (4 mL) under argon was cooled to 0 °C. TESOTf (90 μL, 0.40 mmol) was added dropwise and the reaction mixture was allowed to stir at room temperature for 2 h. PhSeBr (22 mg, 0.093 mmol) was added as a solid and stirring was continued until no enol ether remained as judged by TLC analysis. The reaction was cooled to 0 °C and mCPBA (107 mg, 0.620 mmol) was added portionwise. After 10 min, the reaction was quenched with saturated aqueous Na₂S₂O₃ solution (1 mL), washed with saturated aqueous NaHCO₃ solution (1 mL), and extracted with DCM (3 x 2 mL). The combined organic extracts were washed successively with H₂O (1 mL), saturated aqueous NaHCO₃ solution (2 x 1mL), and saturated aqueous NaCl solution (1 mL). The organic solution was dried with Na₂SO₄ and concentrated in vacuo. The crude
yellow oil was purified by column chromatography (SiO$_2$, gradient eluent from hexanes to 1:19 to 1:9 to 1:4 EtOAc/hexanes, R$_f$ = 0.35 in 1:4 EtOAc/hexanes, KMnO$_4$) to afford 3.93 as a white solid (11 mg, 60%). Data for 3.93: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.77 (s, 1H), 4.78 (dd, $J$ = 11.2, 4.5, 1H), 4.60 (s, 1H), 4.54 (d, $J$ = 11.7, 1H), 4.42 (s, 1H), 3.74 (d, $J$ = 11.7, 1H), 2.56–2.43 (m, 2H), 2.44–2.30 (m, 2H), 2.27–2.18 (m, 2H), 1.86–1.53 (m, 4H), 0.96 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 185.81, 156.15, 151.48, 137.10, 127.78, 64.41, 64.17, 58.33, 54.82, 46.71, 40.60, 26.19, 24.61, 22.67, 22.41, 21.75, 18.68, −4.59, −4.93; IR (thin film) 2932, 2885, 2858, 1672, 1628 cm$^{-1}$; HRMS (CI+) m/z calculated for C$_{21}$H$_{31}$Cl$_3$O$_2$SiNa [M + Na]$^+$ 449.1237, found 449.1241.

(±)-(3R,4R,4aS)-3,4-Dichloro-4a-(chloromethyl)-3,4,4a,5,6,7,8,9-octohydrophenanthren-9-one (3.96) and (±)-(3S,4S,4aS)-3,4-dichloro-4a-(chloromethyl)-3,4,4a,5,6,7,8,9-octohydrophenanthren-9-one (3.1): A stirred solution of silyl ether 3.93 (11 mg, 0.024 mmol) in wet THF (2 mL) was treated with TBAF (0.12 mL, 1.0 M in THF, 0.122 mmol) at room temperature. After 1 h, the reaction was quenched with aqueous HCl (1N, 2 mL) and extracted with EtOAc (3 x 3 mL). The combined organic extracts were washed successively with saturated aqueous NaHCO$_3$ solution, H$_2$O, and saturated aqueous NaCl solution (2 mL portions of each). The organic solution was dried with Na$_2$SO$_4$ and concentrated in vacuo. The crude yellow oil was redissolved in 1:1 DCM/pyridine (2 mL) and cooled to 0 °C under argon. Tf$_2$O (0.2 mL, 0.119 mmol) was added to the reaction mixture, which was allowed to warm to room temperature and stirred for 30 min. The reaction mixture was cooled to −20 °C and allowed to stand for 12 h.
It was quenched by the addition of H₂O (1 mL), the aqueous phase was extracted with DCM (2 x 2 mL), and the combined organic extracts were washed with saturated aqueous NaHCO₃ solution (2 x 1 mL) and saturated aqueous NH₄Cl solution (1 mL). Drying over Na₂SO₄ and concentration in vacuo provided a yellow oil, which was purified by column chromatography (SiO₂, gradient eluent from hexanes to 1:19 to 1:9 EtOAc/hexanes, Rᵢ = 0.33 in 1:4 EtOAc/hexanes, KMnO₄) to afford 3.96 as a white solid (6 mg, 79%). Data for 3.96: ¹H NMR (500 MHz, CDCl₃) δ 6.50 (dd, J = 9.9, 0.6, 1H), 6.44 (s, 1H), 6.01 (dd, J = 9.9, 4.7, 1H), 4.98 (d, J = 4.7, 1H), 4.60 (s, 1H), 4.10 (d, J = 11.2, 1H), 3.80 (d, J = 11.2, 1H), 2.52–2.30 (m, 3H), 2.30–2.19 (m, 1H), 1.87–1.75 (m, 2H), 1.73–1.58 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 185.9, 149.4, 147.3, 138.1, 132.2, 129.7, 126.6, 60.2, 56.2, 51.3, 48.0, 24.3, 22.8, 22.2, 21.7; IR (thin film) 2933, 2860, 1634 cm⁻¹; HRMS (ES+) m/z calculated for C₁₅H₁₅Cl₃ONa [M + Na]⁺ 339.0086, found 339.0088. Data for 3.1, subjected to the preceding synthetic transformations as the minor diastereomer in a mixture of 3.90 and 3.91: ¹H NMR (500 MHz, CDCl₃) δ 6.47–6.39 (m, 2H), 6.05 (d, J = 9.8, 1H), 4.78 (d, J = 8.6, 1H), 4.25 (d, J = 8.6, 1H), 4.22 (d, J = 11, 1H), 3.75 (d, J = 11.0, 1H), 2.89–2.82 (m, 1H), 2.56–2.45 (m, 3H), 1.92–1.83 (m, 2H), 1.58–1.45 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 184.6, 152.7, 150.5, 139.2, 131.0, 130.7, 129.4, 68.9, 62.7, 52.6, 45.0, 30.2, 23.8, 22.9, 21.6; IR (thin film) 2926, 2850, 1653, 1640 cm⁻¹; HRMS (ES+) m/z calculated for C₁₅H₁₅Cl₃ONa [M + Na]⁺ 339.0086, found 339.0078.

3.7 Notes and References


15 A carefully buffered, cold quench was needed to remove all of the aluminum salts during workup of the Diels–Alder reaction and, while silica gel chromatography using 1–2% Et₃N in the eluent afforded some pure material, a significant portion of the desired product
was still hydrolyzed, as judged by comparison with the \( ^1H \) NMR spectrum for the crude reaction mixture.


21 For one reference that notes problems with the key enzymatic step as published, see: Kummer, D. A.; Derun, L.; Dion, A.; Myers, A. G. Chem Sci. 2011, 2, 1710–1718. Also see references therein for other modified acylation conditions.


Ibid.


The Diels–Alder reaction between 3.44 and 3.45 remains the preferred route for obtaining enantioenriched enone 3.78 but is not amenable to a racemic synthesis.


Through personal correspondence with S. S. Stahl and T. Diao, it was concluded that 3.79 was a poorly-behaved substrate for this reaction and gave only moderate yields, even when tested in their specialized reactor. Yields of 3.78 dropped dramatically in their hands when this reaction was attempted in a standard flask or vial.


For the original report of the Burgess reagent and some of its applications, see: Atkins, G. M.; Burgess, E. M. J. Am. Chem. Soc. 1968, 90, 4744–4745.

For the reaction of SOCl₂ with a variety of alcohols to give secondary chlorides, see: van Woerden, H. F. Chem. Rev. 1963, 63, 557–571.


For an exploration of the side reactions possible with PhSeBr, see: Rheinbolt, H.; Perrier, M. Bull. Soc. Chim. Fr. 1950, 17, 759.

Some material was lost by an accidental spill in this reaction, setting an upper limit for the efficiency of this reaction at about 80%.
Chapter 4: Intriguing Stereoselectivity in Dichlorination Reactions

4.1 Introduction

Key to the synthesis of the clionastatin core (4.1) and, ultimately, the clionastatins themselves, was diastereomeric control between the C1 chloride and the C10 chloromethyl group (Figure 4.1). With tricycle 4.2 in hand, stereoselectivity would depend on a diastereoselective dichlorination to afford either desired trichloride 4.3 or undesired 4.4. Dichlorination reactions, while investigated previously both in our own lab\textsuperscript{1} and in other labs,\textsuperscript{2} have not been extensively examined for complex cyclic systems. Hand-held models did not suggest an obvious preference for either desired or undesired dichlorination product, leading us to initiate a more in-depth study of the matter.

![Figure 4.1](image-url)  
*Figure 4.1. The desired clionastatin core (4.1) and the proposed diastereoselective dichlorination of alkene 4.2 towards the synthesis of that core.*

4.2 Background on Dichlorination Reactions in Cyclic Systems

Prior to our synthetic efforts on the clionastatin system, there were several relevant studies on dichlorination and other dihalogenation reactions of steroid systems,\textsuperscript{3} as well as dichlorinations of cyclic alkenes in other natural product scaffolds. Robinson \textit{et al.} showed,\textsuperscript{4} in their work on 9,11-dihalocortacosteroids, that a high degree of stereoselectivity is native to steroid functionalization when dichlorination of pregnane derivative 4.5 gave the 9α,11β-product (4.6) as a single diastereomer. The stereochemical outcome could be explained in several ways. Initial chloronium formation could selectively occur on the α-
face of the steroid, as the β-face is significantly sterically crowded by the C19 methyl group, or chloronium formation could be completely non-selective. The Fürst–Plattner rule\(^5\) then states that nucleophilic attack of chloride on the chloronium intermediate should occur to give the most chair-like trans-diaxial product. This means that the same product would result from α-chloronium opening at the sterically less-congested C11 position and β-chloronium opening at the C9 position, which possess a partial positive charge. Either of these possible explanations are in keeping with the observations of Barton and coworkers,\(^6\) who observed that dichlorination of cholesterol (4.7) produced dichloride 4.8 as the major product. The regioselectivity observed for the bromofluorination of cholesterol acetate\(^7\)

**Scheme 4.1** a) Dichlorination of Pregnane Derivative 4.5; b) Dichlorination of Cholesterol (4.7); c) Bromofluorination of Cholesterol Acetate (4.9); d) Studies Towards Dichloroisoclimide (4.15)
(4.9), on the other hand, may give some insight into whether or not there is any facial selectivity in the initial halonium formation, as it is well known with mixed dihalogen reagents that the less electronegative halogen forms the initial halonium ion. The predominant formation of bromide 4.10 rather than 4.11, then, suggests fluoride opening of an α-bromonium. It is, however, important to keep in mind that bromonium formation is reversible and, in the presence of excess olefin, bromonium ions can undergo alkene-alkene transfer, while evidence suggests that chloronium-ion formation is largely irreversible.8

Jung’s studies9 towards the synthesis of dichlorolissoclimide (4.15), while not performed on a steroidal core, offered further insight into stereochemical olefin-dichlorination on a substituted decalin. While both steroidal examples shown herein feature dichlorination of a tri-substituted alkene, trans-decalin 4.12 features a 1,2-disubstituted olefin, similar to the one found in the clionastatin model 4.2. Additionally, the presence of the gem-dimethyl motif at C4 makes the alkene on 4.12 sterically very similar to the clionastatin system. It was somewhat distressing, then, to see that the dichlorination in Jung’s case greatly favored diaxial dichloride 4.13, obtained from the same facial selectivity that had been observed in the above-mentioned steroid systems. In his case, he was able to equilibrate to thermodynamically preferred 4.14 via a thermal dyotropic shift, although the methoxymethyl ether inexplicably proved vital for the success of that reaction. Other substrates, with differing substitution at C9, failed to equilibrate under the same conditions.

Admittedly, the reagents and conditions used to dichlorinate 4.5, 4.7, and 4.12 differ greatly, which could have a significant impact on the stereochemical outcome for
those reactions. However, the paucity of experimental data for olefin-dichlorination reactions on complex, polycyclic systems forced us to draw what comparisons we could.

4.3 Observed Effects of Solvent and Homoallylic Directing Group

From these three examples, it could be inferred that electrophilic dichlorination of alkenes on decalin systems possessing an angular methyl group generally gives the diaxial dichloride generated by initial attack on the face opposite the C19 angular methyl group. Then, opening by chloride occurs according to the Fürst-Plattner rule, giving the diaxial dichloride product. Application of these principles to tricycle 4.2 suggested that the major product should be undesired diastereomer 4.4 (Scheme 4.2).

Scheme 4.2 Anticipated Stereochemical Outcomes for Dichlorination of Tricycle 4.2

![Scheme 4.2](image)

However, unlike the literature examples shown above, tricycle 4.2 possessed both a Δ1,2-alkene and a cis-fused decalin motif, which could have a significant effect on the stereochemical outcome of the dichlorination reaction. These two structural features result in 4.2 adopting a distinctly cup-shaped conformation. Thus, while the C19 chloromethyl group would direct chloronium formation to the α-face, matching literature precedent, reaction on the more accessible convex face would result in β-chloronium formation. Additionally, the proximity of the C11 methylene to the C1 α-face could further favor β-
chloronium formation, leading to formation of desired trichloride 4.3 by chloride attack at the more accessible C2 position (pathway A) or trichloride 4.4 by Fürst–Plattner attack (pathway B). Indeed, the fact that dichlorination of olefin 4.16 resulted in nearly equal amounts of 4.17 and 4.18 (Equation 4.1) suggested that our system was distinct from previously published examples.

\[
\text{Et}_4\text{NCl}_3 \rightarrow \begin{array}{c}
\text{Cl} \\
\text{DCM, 0 °C}
\end{array}
\]

4.16: \( R = H \)
4.2: \( R = \text{OTBS} \)

4.17/4.18: 65% (1:1.2 dr)
4.3/4.4: 90% (1:4 dr)

A careful conformational analysis of tricycle 4.2, based on COSY and \(^1\)H NMR spectra, also showed almost no coupling between H4 and H5 (\( J = 3.6 \) Hz), suggesting that the silyloxy group was positioned axially, under the steroidal A-ring, a conclusion that was supported by later computational analysis. The role that an axial, homoallylic silyloxy group might play in dichlorination reactions was completely unknown but it was envisioned that it could potentially block the \( \alpha \)-face from attack. Thus, while there might be some bias for the undesired anti,anti relationship between C2-C1-C10, there did not appear to be an overwhelming barrier to obtaining the desired stereochemistry.

However, while dichlorination of tricycle 4.2 proceeded cleanly under the same conditions used for 4.16, a 1:4 ratio was obtained favoring the undesired trichloride 4.4, as shown by NOESY correlations (Figure 4.2). The fact that these first attempts resulted in mostly

\text{Figure 4.2. Observed NOESY correlations for 4.3 and 4.4.}
undesired product, while disappointing, was by no means discouraging. Indeed, this was viewed as a very promising starting point for optimization of reaction conditions.

While 2.0 equivalents\textsuperscript{10} of Et\textsubscript{4}NCl\textsubscript{3} were sufficient to see complete consumption of starting material over a range of temperatures (Table 4.1), below \textasciitilde 20 °C, little or no reaction was observed, highlighting the sterically hindered nature of this particular \( \Delta^{1,2} \)-alkene. For comparison, in several acyclic systems,\textsuperscript{1,2} Et\textsubscript{4}NCl\textsubscript{3} was capable of dichlorinating alkenes completely in 1.5 hours at \textasciitilde 78 °C. Milder chlorinating agents, such as PhICl\textsubscript{2}, failed to react even at room temperature, despite the fact that it was found to be a competent chlorinating agent for cholesterol and other related steroid systems (Equation 4.2).\textsuperscript{11} However, a lack of reactivity at lower temperatures was ultimately unimportant, as slightly more of the desired diastereomer was formed at ambient temperature (Table 4.1, compare entry 2 and 4).

![Chemical structure](image)

**Table 4.1. Temperature dependence for dichlorination of alkene 4.2.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent (equivalents)</th>
<th>Temperature</th>
<th>Ratio of 4.3 : 4.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et\textsubscript{4}NCl\textsubscript{3} (2.0)</td>
<td>\textasciitilde 78 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>Et\textsubscript{4}NCl\textsubscript{3} (2.0)</td>
<td>0 °C</td>
<td>&gt;90%, 1 : 4</td>
</tr>
<tr>
<td>3</td>
<td>Et\textsubscript{4}NCl\textsubscript{3} (2.0)</td>
<td>12 °C</td>
<td>clean, 1 : 3</td>
</tr>
<tr>
<td>4</td>
<td>Et\textsubscript{4}NCl\textsubscript{3} (2.0)</td>
<td>23 °C</td>
<td>clean, 1 : 3</td>
</tr>
<tr>
<td>5</td>
<td>PhICl\textsubscript{2} (1.5)</td>
<td>0 °C to 23 °C</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

![Chemical structure](image)

(4.2)
Because there was a clear difference in diastereoselectivity between the chlorination of 4.16 and 4.2, an obvious strategy for obtaining more of the desired dichlorination product involved varying the protecting group on the C4 alcohol. The TBDPS protected substrate 4.20 (Table 4.2, entry 3), although more difficult to make and sluggish to react with Et₄NCl₃, could also be dichlorinated cleanly to provide a 1:2 ratio of diastereomers, still favoring the undesired isomer. These three substrates, considered together, suggested that no purely electronic or steric trend could be used to explain the dichlorination diastereoselectivity. Possibly, conformation plays a major role in determining the dichlorination outcome, as the TBS protected alcohol in 4.2 is clearly axial and the TBDPS protected alcohol of 4.20, while difficult to positively assign due to poor resolution of protons in the ¹H NMR spectrum, appears to be equatorial. From simple hand-held models, it appears that the equatorial silyloxy group forces the Δ¹²-olefin slightly downward, further opening the β-face of the alkene to attack on electrophilic chlorine and resulting in less α-chloronium formation than was observed with the TBS substrate 4.2. This rationale, however, in no way explains diastereocntrol observed for unsubstituted tricycle 4.16.

Table 4.2. Experimental outcomes for dichlorination on various substituted tricycles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.16: H</td>
<td>65%</td>
<td>4.17/4.18: 1 : 1.2 dr</td>
</tr>
<tr>
<td>2</td>
<td>4.2: OTBS</td>
<td>90%</td>
<td>4.3/4.4: 1 : 4 dr</td>
</tr>
<tr>
<td>3</td>
<td>4.20: OTBDPS</td>
<td>96%</td>
<td>4.21/4.22: 1 : 2 dr</td>
</tr>
<tr>
<td>4</td>
<td>4.23: OH</td>
<td>65–78%</td>
<td>4.24/4.25: 2.5 : 1 dr</td>
</tr>
<tr>
<td>5</td>
<td>4.26: OTCA</td>
<td>95%</td>
<td>4.27/4.28: 1 : 9 dr</td>
</tr>
<tr>
<td>6</td>
<td>4.29: OAc</td>
<td>messy</td>
<td>4.30/4.31: 1 : 5 dr</td>
</tr>
<tr>
<td>7</td>
<td>4.32: OMe</td>
<td>90%</td>
<td>4.33/4.34: 1 : 2.5 dr</td>
</tr>
</tbody>
</table>
In order to further explore the directing effect of the homoallylic alcohol on the stereochemical outcome of the dichlorination reaction, my undergraduate research assistant, Sean Feng, deprotected silyl ether 4.2 with TBAF in THF and re-protected alcohol 4.23 with a variety of sterically and electronically different groups. She then performed dichlorination reactions under standard conditions (DCM, 2.0 equivalents Et₄NCl₃, 0 °C). Electron withdrawing groups (entries 5 and 6) clearly increased the preference for the undesired diastereomer, although analysis was complicated in the case of acetate-protected substrate 4.29, which was unusual in that the dichlorination reaction did not proceed cleanly.

A chloronium intermediate on the β-face of the ring (4.35, Scheme 4.3) could have been opened via anchimeric assistance by the acetate carbonyl to give intermediate 4.36, which would then be displaced by chloride with double inversion of stereochemistry, leading to trichloride 4.37, with a syn,syn relative stereochemistry between C2-C1-C10. This could account for the one additional product that was observed in the crude reaction mixture and would result in less of the desired diastereomer than would otherwise be expected, skewing the results for that compound. While the desired diastereomer was observed as the major product with free alcohol 4.23, it was surprising that the substrate with the small, electron donating methyl protected alcohol (4.32) still favored the undesired diastereomer.

**Scheme 4.3 Achimeric Participation in the Dichlorination Reaction Homoallylic Acetate 4.29**
While alcohol 4.23 was not originally intended as a dichlorination substrate, but was instead made as an intermediate to test the effects of non-silyl protecting groups on this chlorination reaction, it proved to be the only substrate tested that afforded the desired diastereomer as the major product (4.224 instead of 4.225). The respective $^1$H NMR for the TBS protected substrate 4.2 and the alcohol 4.23 were virtually superimposable, suggesting that the conformations of both molecules were very similar. Furthermore, it was initially predicted that the reduced steric of the free alcohol would open up the α-face of the steroid, resulting in increased amounts of undesired diastereomer. Despite these reservations, dichlorination under identical conditions (Table 4.2, entries 2 and 4) resulted in an inversion of the observed diastereoselectivity, although accompanied by significant amounts of decomposition for the free alcohol.

With this promising lead, optimization of reaction conditions was attempted for the dichlorination of alcohol 4.23 (Table 4.3). Low yields and poor selectivity at rt with excess Et$_4$NCl$_3$ (entry 1) improved somewhat by cooling to 0 °C and using only 2.0 equivalents of Et$_4$NCl$_3$ (entry 2). However, this also resulted in low conversion (<50%), suggesting that the Et$_4$NCl$_3$ was being consumed in some undesired manner, resulting in the observed decomposition. By lowering the reaction temperature to −78 °C and quenching at the same temperature (Entry 3), both improved selectivity and reduced decomposition were observed, but useful conversion could not be achieved under those conditions. Even maintaining low temperature for several days did not result in any increased conversion. It seems probable, given other observations about low-temperature dichlorinations, that any observed reactivity under these conditions was occurring at interfaces, as reactants were being added or quenched, due to local elevated temperatures. Best results were, therefore,
obtained when the Et₄NCl₃ (4–5 equivalents) was added at −78 °C and the reaction was allowed to warm to 0 °C, then quenched rapidly by addition of aqueous Na₂S₂O₃. This procedure resulted in reproducible yields between 65–78% with a 2.5:1 dr favoring the desired diastereomer.

![Chemical structures](image)

**Table 4.3.** Reaction conditions screened for dichlorination of alkene 4.23.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent (equivalents)</th>
<th>Solvent (temperature)</th>
<th>Ratio of 4.24 : 4.25</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₄NCl₃ (&gt;5.0)</td>
<td>DCM (rt)</td>
<td>messy, 1.6 : 1</td>
</tr>
<tr>
<td>2</td>
<td>Et₄NCl₃ (2.0)</td>
<td>DCM (0 °C)</td>
<td>33%, 3 : 1</td>
</tr>
<tr>
<td>3</td>
<td>Et₄NCl₃ (2.0)</td>
<td>DCM (−78 °C)</td>
<td>low conversion, 6 : 1</td>
</tr>
<tr>
<td>4</td>
<td>Et₄NCl₃ (4.0)</td>
<td>DCM (−78 °C to rt)</td>
<td>50% conversion, 2.5 : 1</td>
</tr>
<tr>
<td>5</td>
<td>Et₄NCl₃ (10.0 in DCM)</td>
<td>DCM (−78 °C)</td>
<td>low conversion, 2 : 1</td>
</tr>
<tr>
<td>6</td>
<td>Et₄NCl₃ (&gt;5.0)</td>
<td>HFIP (−78 °C to rt)</td>
<td>messy, 1 : 1</td>
</tr>
<tr>
<td>7</td>
<td>Et₄NCl₃ (&gt;5.0)</td>
<td>DCE (−78 °C to rt)</td>
<td>messy, 5 : 1</td>
</tr>
<tr>
<td>8</td>
<td>Et₄NCl₃ (3.0)</td>
<td>DCE (−5 °C)</td>
<td>clean, 1.8 : 1</td>
</tr>
<tr>
<td>9</td>
<td>Et₄NCl₃ (&gt;5.0)</td>
<td>o-PhCl₂ (−78 °C to rt)</td>
<td>clean, 2.5 : 1</td>
</tr>
<tr>
<td>10</td>
<td>Et₄NCl₃ (3.0)</td>
<td>o-PhCl₂ (−5 °C)</td>
<td>clean, 1.3 : 1</td>
</tr>
<tr>
<td>11</td>
<td>Et₄NCl₃ (&gt;5.0)</td>
<td>DCM (−78 °C to −30 °C)</td>
<td>messy, 2 : 1</td>
</tr>
<tr>
<td>12</td>
<td>Et₄NCl₃ (&gt;5.0)</td>
<td>PhCl (−78 °C to rt)</td>
<td>clean, 1 : 1</td>
</tr>
<tr>
<td>13</td>
<td>Et₄NCl₃ (&gt;5.0)</td>
<td>PhCF₃ (−78 °C to rt)</td>
<td>decomposition</td>
</tr>
<tr>
<td>14</td>
<td>Et₄NCl₃ (&gt;5.0)</td>
<td>o-PhCl₂/DCE (−78 °C to rt)</td>
<td>clean, 3 : 1</td>
</tr>
<tr>
<td>15</td>
<td>Et₄NCl₃ (&gt;5.0)</td>
<td>Et₂O (−78 °C to rt)</td>
<td>no reaction</td>
</tr>
<tr>
<td>16</td>
<td>Et₄NCl₃ (&gt;5.0)</td>
<td>THF (−78 °C to rt)</td>
<td>no reaction</td>
</tr>
<tr>
<td>17</td>
<td>Et₄NCl₃ (&gt;5.0)</td>
<td>MTBE (−78 °C to rt)</td>
<td>no reaction</td>
</tr>
<tr>
<td>18</td>
<td>Et₄NCl₃ (&gt;5.0)</td>
<td>EtOAc (−78 °C to rt)</td>
<td>decomposition</td>
</tr>
<tr>
<td>19</td>
<td>Et₄NCl₃ (&gt;5.0)</td>
<td>MeCN (−78 °C to rt)</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

Using this optimized protocol, several halogenated solvents were screened (entries 6–14) to see if improved diastereoselectivity or reaction profile could be observed. Individually, DCE afforded improved selectivity, albeit with much more decomposition, while o-PhCl₂ gave fairly clean reactivity but with modest diastereoselectivity. Unfortunately, no combination of these two solvents across a range of temperatures gave...
overall improved reactivity, leading to the continued use of DCM. One additional set of experiments was designed to test non-halogenated, moderately polar solvents but use of ethereal solvents (entries 15–17) resulted in rapid consumption of Et₄NCl₃, presumably via oxidation of the solvent, and both EtOAc and MeCN (entries 18–19) led to complete decomposition of alcohol 4.23 with no identifiable dichlorination products.

It should be noted that, while no decomposition product could be positively identified, the appearance of multiple signals in the ^1H NMR spectrum between 6–7 ppm suggested the formation of several different A-ring enones. This was not entirely surprising, as oxidation of the homoallylic alcohol on cholesterol (4.7) had previously been seen under dichlorination conditions. Given that these products were never observed when dichlorination was performed on a protected alcohol, that Et₄NCl₃ is a competent oxidant, and that cleaner reactivity could be observed at low temperature with low conversion, it seemed consistent that initial olefin dichlorination occurs competitively with alcohol oxidation (Scheme 4.4).
From trichlorides 4.24 and 4.25, alcohol oxidation to β-chloroketone 4.38 and elimination of HCl from would lead to enone 4.39 as a mixture of diastereomers at C1. If alcohol oxidation occurred before dichlorination, then acid-mediated isomerization of olefin 4.40 would lead to enone 4.41. Ketones 4.38, 4.39, 4.40, and 4.41 could also all tautomerize, leading to isomerization at C5 and formation of the corresponding thermodynamically preferred trans-decalins. $^1$H NMR analysis could have been complicated by the presence of any or all of these proposed side products, in addition to the desired dichlorination products.

With undesired trichloride 4.4 being the most easily accessed compound in this series, some effort was invested into possible methods for conversion of 4.4 into desired trichloride 4.3. Based on the work of Jung, as well as the observations made in our own group, it seemed possible that a heat- or Lewis acid-mediated dyotropic shift could interconvert these two compounds, leading to formation of the desired, thermodynamically favored di-equatorial dichlorination product. However, heating tricycle 4.4 up to 150 °C in toluene or up to 120 °C with excess ZnCl$_2$ in toluene returned only starting material. Heating to 150 °C with ZnCl$_2$ resulted in consumption of starting material with no identifiable chlorinated product.

**4.4 Computational Insights into Dichlorination Mechanism and Selectivity**

While the reversal in diastereoselectivity for the dichlorination reaction was advantageous and suggested that this proposed route towards the clionastatin core was viable, it raised two questions that the experimental data could not answer: 1) why did the diastereoselectivity switch if, by $^1$H NMR analysis, the ground-state conformations of both 4.2 and 4.23 were nearly identical and 2) for alcohol 4.23, why did we appear to be getting
diequitorial dichlorination when precedent for dichlorination of every other steroidal system examined appeared to favor diaxial products? While other substrates were designed to further investigate this problem experimentally (see Section 5.6), we also turned to a computational collaboration for some insight.

Using the results from dichlorination of 4.2 and 4.23 as a starting point, Mr. Hung Pham from the Houk research group at UCLA began a computational study\textsuperscript{13} of the diastereomeric pairs of trichlorides 4.3/4.4 and 4.24/4.25. Starting with a comparison of ground-state energies, Hung found the undesired TBS-protected diastereomer 4.4 is favored by 0.4 kcal/mol over desired 4.3, while for the free alcohol, desired diastereomer 4.24 is favored by 2.9 kcal/mol over undesired 4.25. These numbers agree qualitatively with the major and minor products obtained from both reactions but, quantitatively, do not match the observed product ratios, predicting >100:1 ratio in the unprotected case. Furthermore, these results don’t address the expectation that dichlorination reactions are largely irreversible and, so, are under kinetic control\textsuperscript{14}.

With that in mind, Hung next endeavored to model the intermediates and transition states that would lead to formation of the respective trichloride products (Scheme 4.5).\textsuperscript{15} We had initially expected that the kinetically-controlled formation of 4.42 or 4.43 would be the point of stereochemical divergence but the $\Delta \Delta G^+$ for the two corresponding transition states was found to be 1.4 kcal/mol which, according to this model, would result in $\sim$9:1 ratio favoring the undesired trichloride 4.24. It was, furthermore, puzzling that Mr. Pham could not find a transition state for direct chloride attack at C1 or C2, suggesting a more complex mechanism.
Indeed, additional computational exploration found a low-energy pathway for conversion of 4.43 into either 4.44 or 4.45. The $\Delta \Delta G^\ddagger$ for this transformation was calculated to be 2.7 kcal/mol but the ground-state energy of 4.45 is significantly lower (6.6 kcal/mol), suggesting that if any equilibration could occur at this point, all of the material would funnel through intermediate 4.45 to produce undesired trichloride diastereomer 4.24. However, the transitions from 4.44/4.45 to 4.24/4.25 via chloride attack at C19 were found to be nearly barrierless, precluding any equilibration. These findings qualitatively explain the observed selectivity for formation of 4.24 but predict a product ratio of ~95:1, pointing to a significant disconnect between experimental results and this mechanistic prediction. Furthermore, computational analysis of this mechanistic pathway
for TBS-protected substrate 4.2 gave relative energies for each intermediate and transition state that were remarkably similar, predicting a 49:1 ratio, still favoring the desired diastereomer (4.3). Clearly, this is in significant disagreement with the experimental observations.

Therefore, while computational methods pointed to the possible participation of the C19 chloride in these dichlorination reactions, which explains the presence of perceived β-chloronium formation that is not normally seen on steroid systems, more time and effort must be put into both the computation and experiments before anything definitive can be said about the mechanism for these dichlorination reactions. One possible explanation for this discrepancy between computational and experimental results is that chloronium ions may not be the relevant species under our reaction conditions, existing instead as discrete β-chloro carbocation intermediates.16

### 4.5 Conclusion

While initial efforts at forming a trichlorotricycle resulted predominantly in the undesired diastereomer, extensive optimization paid off in the discovery that alcohol 4.23 could be dichlorinated to give desired trichloride 4.24 as the major product. Studies directed at stereochemical solvent- and temperature-dependence led to several interesting observations and inspired further synthetic methodologies (see Section 5.6). Computational studies also pointed to possible unexpected anchimeric assistance from the C19 chloromethyl group. Unfortunately, despite attention to detail in both synthetic and computational efforts, the separate data from those two endeavors is in significant disagreement and further studies are required to resolve this conflict.

### 4.6 Experimental Procedures
(±)-(1R,4aR,10aS)-1-[[tert-Butyldiphenylsilyl]oxy]-4a-(chloromethyl)-2,4a,5,6,7,8,10,10a-octahydrophenanthren-9(1H)-one (4.20): To a stirred solution of (1R,4S,4aR,10aS)-1-[[tert-Butyldiphenylsilyl]oxy]-4a-(chloromethyl)-4-hydroxy-2,3,4,4a,5,6,7,8,10,10a-decahydrophenanthren-9(1H)-one\(^\text{17}\) (430 mg, 0.822 mmol) in pyridine (10 mL) with DCM (10 mL) was added Tf\(_2\)O (0.55 mL, 3.29 mmol) dropwise. The bright orange reaction mixture was stirred, warming slowly to room temperature, for 21 h, and quenched by the addition of cold H\(_2\)O (10 mL). The organic layer was washed with saturated aqueous NaCl solution (10 mL). The organic extracts were dried over Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. The residue was purified by column chromatography (SiO\(_2\), gradient eluent from hexanes to 1:4 to 1:1 EtOAc/hexanes, R\(_f\) = 0.36 in 1:4 EtOAc/hexanes, KMnO\(_4\)) to afford 4.20 (99 mg, 20%) as an amorphous white solid, as well as re-isolated starting material (197 mg, 46%). Data for 4.20: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.81 (d, \(J = 7.8\), 4H), 7.50 (m, 6H), 5.69 (dd, \(J = 9.7, 2.3\), 1H), 5.36 (d, \(J = 10.1\), 1H), 4.27 (m, 1H), 3.61 (d, \(J = 11.9\), 1H), 3.19 (d, \(J = 11.9\), 1H), 2.95 (m, 2H), 2.56 (m, 1H), 2.35 (m, 3H), 2.16 (m, 3H), 1.86 (m, 2H), 1.46 (m, 2H), 1.14 (s, 9H).

(±)-(1R,3S,4S,4aS,10aS)-1-[[tert-Butyldiphenylsilyl]oxy]-3,4-dichloro-4a-(chloromethyl)-1,2,3,4a,5,6,7,8,9,10,10a-dodecahydrophenanthren-9-one \textit{(4.21)} and (±)-(1R,3R,4R,4aS,10aS)-1-[[tert-butyldiphenylsilyl]oxy]-3,4-dichloro-4a-
(chloromethyl)-1,2,3,4,4a,5,6,7,8,9,10,10a-dodecahydrophenanthren-9-one (4.22): To a stirred solution of alkene 4.20 (120 mg, 0.23 mmol) in DCM (2 mL) at 0 °C was added Et4NCl3 (220 mg, 0.95 mmol). The reaction was stirred for an additional 30 min and quenched with saturated aqueous Na2S2O3 solution (5 mL). The aqueous phase was extracted with DCM (3 x 5 mL), the combined organic extracts were washed with H2O (5 mL), saturated aqueous NaCl solution (5 mL), and dried over Na2SO4. The organic solution was concentrated in vacuo to afford a 2:1 diastereomeric mixture as a yellow oil. The residue was purified by column chromatography (SiO2, 1:19 EtOAc/hexanes, Rf = 0.50 in 1:4 EtOAc/hexanes, KMnO4) to afford the minor diastereomer 4.21 (12 mg, 9%) and the major diastereomer 4.22 (70 mg, 52%) as yellow oils. Data for a mixture of 4.21 and 4.22: 1H NMR (500 MHz, CDCl3) δ 7.79 (m, 8H), 7.51 (m, 12H), 4.61 (s, 1H), 4.55 (dt, J = 11.6, 4.0, 1H), 4.16 (m, 8H), 3.82 (td, J = 11.6, 5.9, 1H), 3.57 (d, J = 12.0, 1H), 3.38 (d, J = 11.9, 1H), 3.10 (m, 1H), 3.01 (m, 2H), 2.91 (m, 3H), 2.57 (m, 5H), 2.41 (m, 2H), 2.25 (m, 6H), 1.88 (m, 4H), 1.76 (m, 2H), 1.64 (m, 2H), 1.50 (m, 2H), 1.19 (s, 9H), 1.19 (s, 9H); LRMS (ES+) m/z calculated for C31H37Cl3O2SiNa [M + Na]+ 597.2, found 597.3.

(±)-(1R,4aR,10aS)-4a-(Chloromethyl)-1-hydroxy-2,4a,5,6,7,8,10,10a-octahydrophenanthren-9(1H)-one (4.23): To a stirred solution of silyl ether 4.2 (80 mg, 2.10 mmol)18 in THF (5 mL) was added TBAF (1.05 mL, 1.0 M solution in THF, 1.05 mmol) and the reaction mixture was stirred at rt for 4 h. The reaction was quenched by the addition of cold HCl (1 N, 5 mL), the aqueous phase was extracted with EtOAc (2 x 10 mL),
and the combined organic layers were washed successively with saturated aqueous NaHCO₃ (5 mL), H₂O (5 mL), and saturated aqueous NaCl solution (5 mL). The organic extracts were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, gradient eluent from 1:9 to 1:4 to 1:1 EtOAc/hexanes, Rf = 0.33 in 1:1 EtOAc/hexanes, KMnO₄) to afford 4.23 (50 mg, 90%) as a microcrystalline white solid. Data for 4.23: ¹H NMR (500 MHz, CDCl₃) δ 5.83–5.73 (ddd, J = 10.0, 4.5, 2.8, 1H), 5.47 (d, J = 10.1, 1H), 4.26 (m, 1H), 3.73 (d, J = 12.0, 1H), 3.51 (d, J = 12.0, 1H), 2.78 (dt, J = 12.9, 3.6, 1H), 2.64 (dd, J = 16.1, 4.3, 1H), 2.47 (m, 1H), 2.29 (m, 3H), 2.11–2.02 (m, 2H), 1.87–1.79 (m, 3H), 1.47–1.38 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 198.0, 153.9, 136.1, 128.8, 125.6, 65.8, 48.3, 47.8, 38.4, 33.2, 31.3, 25.7, 23.3, 22.6, 21.7; IR (thin film) 3420 (broad), 3028, 2931, 2860, 1659, 1621 cm⁻¹; HRMS (ES⁺) m / z calculated for C₁₅H₁₉ClO₂Na [M + Na]⁺ 289.0971, found 289.0958.

(±)-(1R,3S,4S,4aS,10aS)-3,4-Dichloro-4a-(chloromethyl)-1-hydroxy-2,3,4,4a,5,6,7,8,10,10a-decahydrophenanthren-9(1H)-one (4.24) and (±)-(1R,3R,4R,4aS,10aS)-3,4-dichloro-4a-(chloromethyl)-1-hydroxy-2,3,4,4a,5,6,7,8,10,10a-decahydrophenanthren-9(1H)-one (4.25): To a stirred solution of alkene 4.23 (39 mg, 0.146 mmol) in DCM (7 mL) at -78 °C was added Et₄NCl₃ (104 mg, 0.439 mmol). The reaction was stirred for 2 min, removed from the ice bath, and warmed to rt. As soon as the frost on the flask melted completely, the reaction was quenched with saturated aqueous Na₂S₂O₃ solution (3 mL). The organic phase was washed with H₂O (3
mL), saturated aqueous NaCl solution (3 mL), and dried over Na₂SO₄. The organic solution was concentrated \textit{in vacuo} to afford a 2.5:1 diastereomeric mixture as a yellow oil. The residue was purified by column chromatography (SiO₂, gradient eluent from 1:4 to 1:1 EtOAc/hexanes, R_f = 0.30 in 1:1 EtOAc/hexanes, KMnO₄) to afford a mixture of diastereomers (\textbf{4.24} and \textbf{4.25}) (30 mg, 61%) as a white solid. Data for \textbf{4.24} (tabulated from spectra of a 2:1 diastereomeric mixture): \(^1\)H NMR (500 MHz, CDCl₃) δ 4.34 (d, \(J = 12.0, 1\)H), 4.26–4.03 (m, 3H), 3.65 (d, \(J = 12.0, 1\)H), 3.09–3.02 (m, 1H), 2.88 (d, \(J = 18.2, 1\)H), 2.82–2.75 (dd, \(J = 18.2, 5.3, 1\)H), 2.59–2.41 (m, 3H), 2.38–2.29 (m, 2H), 1.72–1.62 (m, 2H), 1.65–1.49 (m, 4H); \(^13\)C NMR (126 MHz, CDCl₃) δ 196.9, 157.2, 137.3, 69.4, 64.6, 59.9, 49.5, 43.3, 40.8, 39.0, 31.9, 28.7, 23.8, 22.5, 21.5; IR (thin film) 3411 (broad), 2937, 2862, 1657 cm\(^{-1}\); HRMS (ES+) m / z calculated for C\(_{15}\)H\(_{19}\)Cl\(_3\)O\(_2\)Na [M + Na]\(^+\) 359.0348, found 359.0339.

\(\text{(-)}\text{-}(\mathbf{1R,4aR,10aS})\text{-}4\text{-}(\text{Chloromethyl})\text{-}9\text{-oxo-1,2,4a,5,6,7,8,9,10,10a-decahydrophenanthren-1-yl \ 2,2,2-trichloroacetate (4.26):} \)

To a stirred solution of alcohol \textbf{4.23} (16 mg, 0.06 mmol) in pyridine (0.12 mL) at 0 °C under argon was added trichloroacetyl chloride (11 \(\mu\)L, 0.10 mmol). The reaction mixture was stirred, warming slowly to room temperature, for 6 h, and quenched by the addition of cold saturated aqueous NaHCO\(_3\) solution (0.5 mL). The aqueous phase was extracted with DCM (3 x 0.5 mL) and the combined organic layers were washed successively with H\(_2\)O (1 mL). The organic extracts were dried over Na₂SO₄ and concentrated \textit{in vacuo}. The residue was purified by column chromatography (SiO₂, gradient eluent from hexanes to 1:19 to 1:9
EtOAc/hexanes, R\textsubscript{f} = 0.71 in 1:1 EtOAc/hexanes, KMnO\textsubscript{4}) to afford 4.26 (7 mg, 28%) as a colorless film. Data for 4.26: \(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 5.86 (d, \(J = 10.1, 1H\)), 5.60 (d, \(J = 10.1, 1H\)), 5.38 (m, 1H), 3.78 (d, \(J = 12.1, 1H\)), 3.56 (d, \(J = 12.1, 1H\)), 3.07 (d, \(J = 11.6, 1H\)), 2.67 (m, 2H), 2.45 (dd, \(J = 16.1, 11.3 2H\)), 2.38 (m, 3H), 2.11 (m, 1H), 1.80 (m, 2H), 1.53 (m, 2H), 0.89 (m, 1H); \(^{13}\)C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 195.7, 161.4, 153.4, 135.7, 126.6, 126.1, 74.5, 47.5, 35.2, 33.8, 29.8, 27.5, 25.6, 23.0, 22.2, 21.2; IR (thin film) 2934, 1763, 1668 cm\(^{-1}\); HRMS (ES\textsuperscript{+}) \(m/z\) calculated for C\textsubscript{17}H\textsubscript{18}Cl\textsubscript{4}O\textsubscript{3}Na [M + Na\textsuperscript{+}] 432.9908, found 432.9894.

(±)-(1R,3S,4S,4aS,10aS)-3,4-Dichloro-4a-(chloromethyl)-9-oxo-1,2,3,4,4a,5,6,7,8,9,10,10a-dodecahydrophenanthren-1-yl 2,2,2-trichloroacetate (4.27) and (±)-(1R,3R,4R,4aS,10aS)-3,4-dichloro-4a-(chloromethyl)-9-oxo-1,2,3,4,4a,5,6,7,8,9,10,10a-dodecahydrophenanthren-1-yl 2,2,2-trichloroacetate (4.28): To a stirred solution of alkene 4.26 (7 mg, 0.02 mmol) in DCM (0.3 mL) at 0 °C was added Et\textsubscript{4}NCl\textsubscript{3} (7 mg, 0.03 mmol); a second portion of Et\textsubscript{4}NCl\textsubscript{3} (1 mg, 0.004 mmol) was added after 3 h. The reaction was stirred for an additional 1 h and quenched with saturated aqueous Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} solution (0.5 mL). The aqueous phase was extracted with DCM (3 x 0.5 mL), the combined organic extracts were dried over Na\textsubscript{2}SO\textsubscript{4}, and the organic solution was concentrated \textit{in vacuo} to afford a 9:1 diastereomeric mixture as a yellow oil. The residue was purified by preparatory TLC (SiO\textsubscript{2}, 1: 9 EtOAc/hexanes, R\textsubscript{f} = 0.65 in 1:1 EtOAc/hexanes, KMnO\textsubscript{4}) to afford the major diastereomer (4.28) (9 mg, 90%) as a yellow oil. Data for 4.28: \(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 5.63 (m, 1H), 4.79 (bs, 1H), 4.43 (d, \(J = 12.1, 1H\)), 4.32 (s, 1H),...
3.72 (d, J = 12.1, 1H), 3.25 (m, 1H), 2.92 (t, J = 14.7, 1H), 2.80 (ddd, J = 14.7, 11.5, 3.5, 1H),
2.65 (dd, J = 14.7, 3.1, 1H), 2.51 (d, J = 14.7, 1H), 2.37 (m, 2H), 2.21 (m, 2H), 1.88 (m, 2H),
1.58 (m, 3H), 1.49 (m, 3H), 0.83 (m, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 195.7, 161.0, 152.6,
137.3, 58.1, 50.7, 47.5, 36.7, 33.3, 29.7, 25.7, 24.7, 23.2, 22.0, 21.1; IR (thin film) 2925, 1768,
1667 cm⁻¹.

(±)-(1R,4aR,10aS)-4a-(Chloromethyl)-9-oxo-1,2,4a,5,6,7,8,9,10,10a-decahydrophenanthren-1-yl acetate (4.29): To a stirred solution of alcohol 4.23 (15 mg, 0.071 mmol) in DCM/pyr (1:1 mixture, 0.7 mL) was added Ac₂O (10 µL, 0.106 mmol). The reaction mixture was stirred at rt for 5 h and quenched by the addition of cold saturated aqueous NaHCO₃ solution (1 mL). The aqueous phase was extracted with DCM (3 x 3 mL) and the combined organic layers were washed successively with H₂O (3 mL) and saturated aqueous NaCl solution (3 mL). The organic extracts were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, gradient eluent from 1:9 to 1:4 to 1:1 EtOAc/hexanes, Rf = 0.74 in 1:4 EtOAc/hexanes, KMnO₄) to afford 4.29 (14 mg, 64%) as an amorphous white solid. Data for 4.29: ¹H NMR (500 MHz, CDCl₃) δ 5.83 (ddd, J = 10.0, 4.5, 2.8, 1H), 5.52 (d, J = 10.0, 1H), 5.27 (m, 1H), 3.76 (d, J = 12.0, 1H), 3.58 (d, J = 12.0, 1H), 2.91 (dt, J = 12.5, 3.8 1H), 2.68 (dd, J = 13.6, 4.5, 1H), 2.45 (m, 5H), 2.13 (m, 4H), 2.02 (s, 3H), 1.80 (m, 2H), 1.46 (m, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 197.0, 170.4, 153.6, 135.4, 127.8, 125.4, 67.9, 47.3, 35.4, 33.7, 28.0, 25.4, 23.0, 22.2, 21.4,
21.1; IR (thin film) 2926, 1753, 1665 cm\(^{-1}\); HRMS (ES+) \(m/z\) calculated for \(C_{17}H_{21}ClO_3Na\) 
\([M + Na]^+\) 331.1077, found 331.1074.

\[
\begin{align*}
\text{(±)-(1R,3S,4S,4aS,10aS)-3,4-Dichloro-4a-(chloromethyl)-9-oxo-} \\
1,2,3,4,4a,5,6,7,8,9,10,10a-	ext{dodecahydrophenanthren-1-yl acetate (4.30) and (±)}
\end{align*}
\]

\[
\begin{align*}
\text{(±)-(1R,3R,4R,4aS,10aS)-3,4-dichloro-4a-(chloromethyl)-9-oxo-} \\
1,2,3,4,4a,5,6,7,8,9,10,10a-	ext{dodecahydrophenanthren-1-yl acetate (4.31)}: \text{To a stirred solution of alkene 4.29 (14 mg, 0.044 mmol) in DCM (0.5 mL) at 0 °C was added Et}_4\text{NCl}_3 \\
(19 mg, 0.079 mmol). The reaction was stirred for 1 h and quenched with saturated aqueous Na\(_2\text{S}_2\text{O}_3\) solution (2 mL). The aqueous phase was extracted with DCM (3 x 2 mL), the combined organic extracts were washed with H\(_2\text{O}\) (3 mL), saturated aqueous NaCl solution (3 mL), and dried over Na\(_2\text{SO}_4\). The organic solution was concentrated \textit{in vacuo} to afford a 5:1 diastereomeric mixture as a yellow oil. The residue was purified by column chromatography (SiO\(_2\), gradient eluent from hexanes to 1:19 to 1:9 to 1:4 EtOAc/hexanes, \(R_f = 0.83\) in 1:1 EtOAc/hexanes, KMnO\(_4\)) to afford a mixture of diastereomers (4.30 and 4.31) (11 mg, 65%) as yellow oils. Data for 4.30: \(^1\text{H NMR (500 MHz, CDCl}_3\) \(\delta\) 5.13 (dt, \(J = 11.8, 2.8, 1\text{H}\)), 4.34 (d, \(J = 12.5, 1\text{H}\)), 4.25 (d, \(J = 10.9, 1\text{H}\)), 4.08 (td, \(J = 11.5, 5.7, 1\text{H}\)), 3.70 (d, \(J = 12.6, 1\text{H}\)), 3.15 (m, 1H), 2.90 (m, 1H), 2.69 (m, 2H), 2.55 (dd, \(J = 13.8, 8.9, 1\text{H}\)), 2.53 (m, 1H), 2.34 (bs, 2H), 2.15 (m, 1H), 2.06 (s, 3H), 1.72 (m, 2H), 1.63 (m, 2H), 0.87 (m, 3H); \(^{13}\text{C NMR (126 MHz, CDCl}_3\) \(\delta\) 195.6, 169.9, 144.4, 111.7, 68.7, 66.3, 59.0, 42.9, 37.9, 35.6, 32.4, 29.8, 28.4, 23.5, 22.2, 21.2; IR (thin film) 2929, 2857, 1738, 1666 cm\(^{-1}\); HRMS (ES+) \(m/z\)
calculated for C_{17}H_{21}Cl_{3}O_{3}Na [M + Na]^+ 401.0454, found 401.0446. Data for **4.31**: 1H NMR (500 MHz, CDCl_{3}) δ 5.52 (m, 1H), 4.72 (bs, 1H), 4.42 (d, J = 12.0, 1H), 4.29 (s, 1H), 3.68 (d, J = 12.1, 1H), 3.06 (m, 1H), 2.84 (t, J = 15.2, 1H), 2.62 (m, 2H), 2.59 (q, J = 14.3, 1H), 2.38 (m, 1H), 2.22 (m, 3H), 2.08 (m, 3H), 1.90 (m, 2H), 1.56 (m, 4H), 1.28 (m, 3H), 0.92 (m, 3H); 13C NMR (126 MHz, CDCl_{3}) δ 169.9, 153.0, 137.1, 58.6, 50.7, 47.9, 36.8, 33.9, 29.8, 28.7, 25.8, 24.8, 23.3, 22.2, 21.3; IR (thin film) 2929, 2857, 1738, 1666 cm^{-1}; HRMS (ES+) m / z calculated for C_{17}H_{21}Cl_{3}O_{3}Na [M + Na]^+ 401.0454, found 401.0427.

(±)-(1R,4aR,10aS)-4a-(chloromethyl)-1-methoxy-2,4a,5,6,7,8,10,10a-octahydrophenanthren-9(1H)-one (4.32): To a stirred solution of alcohol **4.23** (22 mg, 0.077 mmol) in DMF (0.7 mL) at 0 °C under argon was added NaH (17 mg, 60% in mineral oil, 0.39 mmol) and MeI (47 µL, 0.77 mmol). The reaction mixture was stirred at rt for 1 h and quenched by the addition of cold saturated aqueous NH_{4}Cl solution (1 mL). The aqueous phase was extracted with EtOAc (3 x 1 mL) and the combined organic layers were washed with saturated aqueous NaCl solution (1 mL). The organic extracts were dried over Na_{2}SO_{4} and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_{2}, gradient eluent from 1:19 to 1:9 to 1:4 EtOAc/hexanes, R_{f} = 0.38 in 1:4 EtOAc/hexanes, KMnO_{4}) to afford **4.32** (19 mg, 88%) as an amorphous white solid. Data for **4.32**: 1H NMR (500 MHz, CDCl_{3}) δ 5.82 (ddd, J = 10.0, 4.7, 2.7 1H), 5.46 (d, J = 10.0, 1H), 3.75 (d, J = 12.0, 1H), 3.71 (m, 1H), 3.50 (d, J = 12.0, 1H), 3.34 (s, 3H), 3.01 (d, J = 13.6, 1H), 2.54 (dd, J = 13.6, 2.5, 2H), 2.49 (m, 1H), 2.29 (m, 2H), 2.26 (dd, J = 13.8, 8.6, 1H), 2.06 (m, 2H),
1.84 (m, 2H), 1.45 (m, 2H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 197.9, 153.7, 135.7, 128.6, 125.1, 73.8, 64.8, 56.0, 53.7, 47.9, 47.2, 33.9, 32.7, 28.6, 25.2, 23.0, 22.3, 21.4; IR (thin film) 3026, 2928, 2855, 1668, 1614, 1593 cm\(^{-1}\); HRMS (ES+) \(m / z\) calculated for C\(_{16}\)H\(_{21}\)ClO\(_2\)Na [M + Na]\(^+\) 303.1128, found 303.1127.

(±)-(1\(R\),3\(S\),4\(S\),4\(a\)\(S\),10\(a\)\(S\))-3,4-Dichloro-4\(a\)-(chloromethyl)-1-methoxy-2,3,4,4\(a\),5,6,7,8,10,10\(a\)-decahydrophenanthren-9(1\(H\))-one (4.33) and (±)-(1\(R\),3\(R\),4\(R\),4\(a\)\(S\),10\(a\)\(S\))-3,4-dichloro-4\(a\)-(chloromethyl)-1-methoxy-2,3,4,4\(a\),5,6,7,8,10,10\(a\)-decahydrophenanthren-9(1\(H\))-one (4.34): To a stirred solution of alkene 4.30 (19 mg, 0.066 mmol) in DCM (0.6 mL) at 0 °C was added Et\(_4\)NCl\(_3\) (28 mg, 0.119 mmol). The reaction was stirred for 40 min and quenched with saturated aqueous Na\(_2\)S\(_2\)O\(_3\) solution (2 mL). The aqueous phase was extracted with DCM (3 x 1 mL), the combined organic extracts were washed with H\(_2\)O (1 mL), saturated aqueous NaCl solution (1 mL), and dried over Na\(_2\)SO\(_4\). The organic solution was concentrated in vacuo to afford a 2.5:1 diastereomeric mixture as a yellow oil. The residue was purified by column chromatography (SiO\(_2\), gradient eluent from 1:19 to 1:9 to 1:4 EtOAc/hexanes, \(R_f\) = 0.50 in 1:4 EtOAc/hexanes, KMnO\(_4\)) to afford a mixture of diastereomers (4.33 and 4.34) (21 mg, 90%) as a yellow oil. Data for a mixture of 4.33 and 4.34: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.74 (bs, 1H), 4.35 (d, \(J\) = 12.0, 1H), 4.27 (m, 1H), 4.22 (d, \(J\) = 10.9, 1H), 4.05 (m, 1H), 3.89 (m, 1H), 3.66 (d, \(J\) = 12.0, 2H), 3.57 (m, 1H), 3.36 (s, 4H), 3.22 (m, 2H), 3.07 (m, 1H), 2.90 (m, 1H), 2.58 (m, 6H), 2.34 (m, 3H), 2.18 (m, 4H), 1.83 (m, 3H), 1.72 (m, 2H), 1.60 (m, 4H), 1.47.
(m, 3H), 0.86 (m, 2H); IR (thin film) 2930, 1665 cm⁻¹; HRMS (ES⁺) m / z calculated for C₁₆H₂₂Cl₃O₂ [M + H]⁺ 350.0685, found 351.0674.

### 4.7 Notes and References


3 For synthetic work towards halogenated synthetic steroids and studies of their biological activities, see: Mattox, V. R.; Mason, H. L.; Albert, A. *J. Biol. Chem.* **1956**, *218*, 359–364.


10 For the original preparation of Mioskowski’s reagent, see: Schlama, T.; Gabriel, K.; Gouverneur, V.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1997**, *36*, 2342–2344. Et₄NCl₃ was prepared as outlined in this paper and titrated using either styrene or cyclohexene. The Et₄NCl₃ thus prepared requires 1.6–1.8 equivalents for delivery of 1.0 equivalent of active Cl₂.


Mr. Pham performed these calculations using a M06-2X density functional and a 6-31+G(d,p) basis set in implicitly modeled dichloromethane.

Mr. Pham did model the interconversion of 4.21 and 4.22 and found a barrier of >34 kcal/mol, which is prohibitive under these reaction conditions.

For these experiments, Mr. Pham modeled Et₄NCl₃ as Cl₂ with an equivalent of Et₄NCl in solution.


This alcohol was made following the same series of experimental conditions used to make alcohol 3.88 except that enone 3.84 was used instead of 3.85 for the initial Diels–Alder reaction.

Silyl ether 4.2 was prepared as discussed in Chapter 3.
Chapter 5: Synthetic Efforts Towards the CD-Ring Diene and Studies Towards Tetracyclic Clionastatin A

5.1 Introduction

Optimistic that our convergent Diels–Alder approach to the clionastatin core would be applicable to the fully functionalized clionastatin ring system, we next endeavored to put that plan into practice. To do this, we needed to synthesize a trans-hydrindane based diene for our key Diels–Alder reaction. We were confident that the synthesis of this substrate would prove a trivial task for two major reasons. First, trans-hydrindanes are a common motif in many natural products,\(^1\) including clionastatins A (5.1) and B (5.2), suggesting a possible thermodynamic preference. Indeed, the existence of a C15 ketone in the clionastatins suggested that the C14 stereocenter could be epimerizable under physiological conditions, further supporting the idea that the natural products exist as the thermodynamically preferred epimer. Additionally, numerous total syntheses have featured the construction of trans-hydrindanes, offering several known methods, from which we could draw inspiration. Flush with confidence, we set out on what we assumed would be the final leg of the synthetic efforts towards 5.1 and 5.2.

5.2 Background on the Thermodynamics of trans-Hydrindanes

It seems prudent to disabuse the reader at this early point in the chapter of any false ideas they might harbor, as we did, about the thermodynamics of cis- vs. trans-hydrindanes. It is indisputable that there exist a wealth of naturally occurring trans-hydrindane-containing natural products,\(^2\) with a considerable number of studies on both natural and
unnatural systems. However, as several of these studies show, the majority of naturally occurring trans-hydrindanes can be explained by the steric constraints of specific substitution patterns rather than by any general stability of the trans-hydrindane motif per se. Indeed, several different papers (Scheme 5.1) use almost identical reaction conditions (NaOMe or KOMe solutions) to equilibrate from either cis- or trans-hydrindanones to the opposite epimer, citing the thermodynamically preferred ring-junction as the driving force. While there are sufficient examples of this sort of equilibration for one to make conjectures about the influence of substitution on thermodynamic preference, there are relatively few systematic studies of this phenomenon. One exceptional study on this topic, by Dana et al., looked at the effect of C15 and C13 stereochemistry on the relative favorability of cis- vs. trans-ring fusion (Table 5.1).

For this study, a series of methyl-substituted cis-hydrindanes were made with varying stereochemistry, then treated with NaOMe for 24 days (calculated as 8 times the
half-life of the epimerization reaction). A quick look at the data immediately shows that the only pair of substrates that favored trans-ring fusion were the pair of 15α-methyl substituted hydrindanes. This was rationalized, after examining relevant coupling constants, by the fact that 15α-substitution on the cis-hydrindane projects the methyl group under the 6-membered ring, causing unfavorable steric interactions with the C11 and C12 methylenes. Relief of these steric interactions is significant enough to compensate for the strain introduced by formation of the trans-hydrindane. A more careful examination of the data also shows that the angular methyl group, in most cases, disfavors the trans-ring fusion as compared with the des-methyl variant (R₁ = Me vs. H). This piece of information suggested that literature precedent for formation of trans-hydrindanes that lack a C18 alkyl group might be irrelevant to our synthetic efforts, as application to the clionastatins, which possess a C18 methyl, would likely still afford the cis-hydrindane.

While this analysis of the influence on structural relationship to cis vs. trans preference was instructive and informed our later synthetic efforts towards CD-ring diene synthesis, the presence of the epimerizable α-C14 position in the clionastatins continued to

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>Cis</th>
<th>Trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>76</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>92</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>CH₃</td>
<td>H</td>
<td>6</td>
<td>94</td>
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<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>100</td>
<td>0</td>
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<tr>
<td>6</td>
<td>CH₃</td>
<td>H</td>
<td>CH₃</td>
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</tr>
</tbody>
</table>
trouble us. It seemed likely that, given the isolation of this particular stereoisomer, some additional aspect of the clionastatins unique structure was leading to a thermodynamic preference for that product. However, application of computational methods\textsuperscript{6} by Mr. Hung Pham on the structure of clionastatin A (5.1) revealed that the cis-ring fusion was, in fact, almost 15 kcal/mol lower in energy than the trans-ring fusion. The existence of the metastable trans-ring fusion as the naturally occurring epimer is caused by an overwhelming \(>40\) kcal/mol barrier to enolization of the C15 ketone. As previously stated, while this thermodynamic information was not known at the outset of the project, it was quickly uncovered and informed our synthetic efforts for the remainder of the project.

5.3 \textit{De Novo} Approaches to the \textit{trans}-Hydrindane

5.3.1 Ring-Closing Metathesis for Diene Synthesis

\begin{center}
\textbf{Scheme 5.2 Proposed Retrosynthesis of Diene 5.11 via Ring-Closing Metathesis}
\end{center}

While the experimental and computational data discussed above was not known to us at the outset of this project, our synthetic efforts rapidly made it apparent that formation of the \textit{trans}-hydrindane would not be as facile as anticipated. Our initial approach featured a tandem-vicinal difunctionalization of cyclohexenone 5.15 to install the stereochemistry at what would become C13 and C14 in the steroid core, followed by ring-closing metathesis to form the 5-membered ring (Scheme 5.2). The C-ring ketone could then be converted into the kinetic enolate, trapped as the corresponding triflate (5.13), and a Heck reaction with a suitable vinyl ether could form the hydrindene 5.12. Enol ether formation would then
afford the desired diene 5.11. A similar strategy, featuring a ring-closing metathesis reaction, was employed by the Leighton group\(^7\) for the formation of the (iso)cyclocitrinol ring-system (Scheme 5.3), although (iso)cyclocitrinol core 5.16 possesses additional stereochemical complexity that favored establishment of the trans-disposed vinyl and allyl groups, prior to the key metathesis step.

![Scheme 5.3](image)

Our efforts to employ ring-closing metathesis towards the synthesis of 5.11 were initially undertaken by Borja López-Perez, a visiting graduate student from the Universidade de Santiago de Compostela. After minor optimization, conjugate vinylation\(^8\),\(^9\) proceeded smoothly using catalytic CuBr\(\cdot\)SMe\(_2\), although direct allylation of the resulting magnesium or copper enolate proved unsuccessful. Trapping as the corresponding silyl enol ether 5.18 and subsequent treatment with MeLi allowed for regioselective generation of the lithium enolate, which could be allylated in reasonable yield to afford 5.14, although a significant amount of double allylation product 5.19 was also observed. 5.14 was isolated as a roughly 1:1.2 mixture of diastereomers, favoring the undesired one. This low selectivity was not unexpected, as the steric difference between the β-methyl and β-vinyl groups is not large (A-values of 1.7 and 1.35 respectively translates into ~1:2 dr), resulting in poor facial selectivity for the allylation. This was not seen as a problem, since it was presumed that optimization of conditions could improve selectivity at a later point. The
diastereomeric mixture of 5.14 was carried forward and the need for such optimization never arose.

**Scheme 5.4 Sythetic Efforts Towards Diene 5.11**

With this substrate, ring-closing metathesis was attempted using several different catalysts, including Grubbs 1\textsuperscript{st} generation, Grubbs 2\textsuperscript{nd} generation, Hoveyda–Grubbs, and Stewart–Grubbs\textsuperscript{10}, but ring closure was never observed. Conditions were varied with each of the preceding catalysts, examining toluene and DCM across a range of temperatures, either under an argon or ethylene atmosphere but none of these changes resulted in any product formation. However, formation of kinetic vinyl triflate 5.20 and Pd-mediated Heck reaction with ethyl vinyl ether, followed by acidic workup, resulted in enone 5.21. This diastereomeric mixture of enones could be subjected to a variety of metathesis catalysts to afford a mixture of what was tentatively assigned as undesired cis-hydrindene 5.22 and the unreacted trans-isomer of 5.21.
Confirmation of the relative stereochemistry of hydrindene 5.22 proved challenging, as most of the peaks in the $^1$H NMR spectra are overlapping. However, a perusal of the literature$^5$ shows that, for analogous trans-hydrindanes, the C19 methyl (using steroid numbering for simplicity) generally appears between 0.6–0.8 ppm, while for cis-hydrindanes, the same methyl signal appears at 0.9–1.3 ppm. In the case of 5.22, the C19 methyl shift was observed at 1.27 ppm, making assignment as the cis-hydrindane fairly certain. Later hydrogenation of a mixture of 5.25 and 5.26 (Scheme 5.5) allowed for a direct comparison with known hydrindanones 5.9 and 5.10 (Table 5.1), leading to unambiguous assignment of the major products as cis-fused rings.

These results were not entirely unexpected, as the mechanism for this metathesis should involve Ru first engaging the sterically more accessible allyl group. In the case of ring closure for the cis-substrate 5.21, the resulting ruthenium alkylidene could easily
reach the vinyl group and perform the desired metathesis. However, for the trans-substrate 5.21, the allyl and vinyl groups, while equatorial, are also on opposite faces of the cyclohexanone. It was reasoned that elevated temperatures should allow access to a conformation that would enable closure to the trans-fused hydrindane but at higher temperatures, only catalyst decomposition was observed.\textsuperscript{11} Grubbs catalysts are also known to decompose in the presence of terminal olefins, as the more stable benzylidene from the pre-catalyst is replaced with a methyldiene, leading to catalyst death.\textsuperscript{12}

The solution to this problem seemed to be as simple as adding a propenyl Grignard reagent into cyclohexenone 5.15 instead of using a vinyl Grignard reagent. However, when propenylmagnesium bromide was employed for the conjugate addition, trapping of the resulting enolate with TMSCl was never observed. This minor problem was solved by trapping as enol acetate 5.23 instead, followed by the same treatment with MeLi to generate the desired lithium enolate. Allylation with allyl bromide gave 5.24 with a similar diastereomeric mixture to that previously observed for 5.14. However, unlike diene 5.14, which failed to engage in ring-closing metathesis, diene 5.24 readily closed under standard metathesis conditions to afford a 4:1 ratio of diastereomers 5.25 and 5.26, enriched in the undesired cis-fused hydrindene. Based on the high yield for this reaction and both the starting and final diastereomeric ratios, it seems that the presence of an acidic proton α to the carbonyl leads to enolization and an equilibrium mixture of cis and trans products is formed.

To remove the possibility for epimerization, 5.24 was converted to the vinyl triflate 5.27 and treated to the Heck conditions previously employed. Unfortunately, as previously observed with enone 5.21, with a variety of catalysts and conditions, only the cis-isomer of
5.28 engaged in ring-closing metathesis to afford 5.22. While this series of experiments provided us with access to several grams of bicycle 5.22, which could have allowed us to carry forward with model studies on the clionastatin system, Mr. Pham’s earlier calculations suggested that we were unlikely to convert this material into the desired trans-hydridane and, so, no efforts were made to test the Diels–Alder reaction at that time.

At this juncture, it occurred to us that allylic alcohol 5.30 might perform better under ring-closing metathesis conditions than the simple allyl compound 5.24. It is well documented\(^\text{13}\) that secondary allylic alcohols accelerate the rate of many metathesis reactions by coordinating to the catalyst through both an oxygen p-orbital and the alkene π-bond. This route had the added advantage of not requiring isolation of an intermediate enol ether, as one-pot conjugate addition and aldol reaction provided a sufficient quantity of 5.30, albeit as an inseparable mixture of diastereomers, in a roughly 1:1:1:1 ratio. Metathesis on this substrate did, as predicted, proceed much more rapidly at lower temperature, but still resulted in only cis-fused 5.31. Based on the influence that the C15

---

**Scheme 5.6 Attempted Aldol/Metathesis for Trans-Hydridane Formation**

1. \[\text{MgBr, CuCl}\]
2. \[\text{ZnCl}_2, \text{H}\]

\[
\begin{align*}
5.15 & \quad \text{ZnCl}_2, \text{H} \quad \rightarrow \quad 5.30 \\
& \quad \text{NaOMe, MeOH} \quad \rightarrow \quad 5.32 \\
& \quad 5.30 \quad \rightarrow \quad 5.33 \\
& \quad \text{Grubbs-II} \quad \rightarrow \quad 5.31 \\
& \quad \text{DCM, 35 °C} \\
& \quad 5.32 \quad \rightarrow \quad 5.34
\end{align*}
\]
stereochemistry exerts on the thermodynamic preference of cis- vs. trans-hydrindanes (Table 5.1), we did examine possible equilibration of cis-fused 5.31 to 5.32 via a base-mediated retro-aldol/aldol mechanism but these attempts resulted only in decomposition. The increased reactivity of 5.30 suggested that conversion to 5.33 should provide a non-epimerizable substrate with the potential to close the trans-isomer, forming 5.34. However, the return of Borja to Spain and promising developments in other synthetic efforts prevented studies in that direction.

5.3.2 Meinwald Rearrangement for trans-Hydrindane Synthesis

When it became apparent that ring-closing metathesis was unlikely to afford the desired substrate, we began investigating several other synthetic approaches simultaneously. Dr. Allen Hong reasoned that, despite the thermodynamic preference for cis-ring fusion, the trans-hydrindane might still be formed kinetically by some stereospecific process. Specifically, under Lewis acidic conditions, epoxide 5.35 could undergo a Meinwald rearrangement,14 in which epoxide opening to a β-hydroxy cation is followed by a 1,2-hydride shift, resulting in redox-neutral formation of ketone 5.32 (Scheme 5.7). This method has been used several times in natural-product synthesis, notably to make trans-hydrindane 5.38.

![Scheme 5.7 Proposed Meinwald Rearrangement for the Formation of Hydrindanone 5.32](image)
To build the required substrate for the Meinwald rearrangement, a series of known transformations\(^{15}\) was performed to make enone 5.42. Starting with \(\alpha\)-methyl cyclohexanone 5.39, doubly lithiated propargyl alcohol was added to form diol 5.40 (Scheme 5.8). Rupe rearrangement\(^{16}\) transiently formed diene 5.41, which underwent facile Nazarov cyclization\(^{17}\) to afford enone 5.42 in serviceable yields. Nucleophilic epoxidation of enone 5.42 under basic conditions, followed by reduction of the ketone and protection with TBSCl produced the desired epoxide 5.43. When epoxide 5.43 was treated with any of several different catalysts, cis-hydrindanone 5.45 was isolated in good yields. The stereospecific nature of the Meinwald rearrangement points to initial formation of \(\text{trans}\)-hydrindane 5.44, followed by rapid enolization and protonation. Indeed, molecular models show a nearly perfect overlap between the C14 C–H bond and the C9 carbonyl in \(\text{trans}\)-hydrindane 5.44. Epoxide 5.46, diastereomeric at C15, could also be made from enone 5.42 by a known 1,2-reduction,\(^{18}\) TBS protection, and DMDO-mediated epoxidation under basic conditions. However, treatment of this epoxide with ZnBr\(_2\) or Zn(OTf)\(_2\)

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**Scheme 5.8 Attempted Meinwald Rearrangement on Epoxides 5.43 and 5.46**

\[
\begin{align*}
\text{5.39} & \xrightarrow{nBuLi} \text{5.40} & \text{H}_2\text{SO}_4, \text{MeOH, 0 °C} & \rightarrow [\text{5.41}] \xrightarrow{\text{H}_2\text{O}_2, \text{LiOH}} \text{5.42} \\
\text{1. H}_2\text{O}_2, \text{LiOH} & \xrightarrow{\text{2. NaBH}_4} \xrightarrow{\text{3. TBSCI}} 48\% \text{ over 3 steps} & \text{5.40} \rightarrow \text{5.43} & \xrightarrow{\text{ZnBr}_2, 23 °C \text{ to reflux}} 60\% \text{ not observed} \\
\text{5.43} & \xrightarrow{\text{1. NaBH}_4, \text{CeCl}_3\cdot\text{H}_2\text{O}} \xrightarrow{\text{2. TBSCI}} \xrightarrow{\text{3. DMDO, NaHCO}_3} 31\% & \text{5.46} & \xrightarrow{\text{ZnBr}_2, 23 °C \text{ to reflux}} \text{5.47}
\end{align*}
\]
afforded only elimination product 5.47.

5.3.3 Ring Contraction for \textit{trans}-Hydrindane Synthesis

Because many of our problems were being caused by the thermodynamic preference for \textit{cis}-hydrindane formation, Dr. Allen Hong conceived of route that would monopolize on the thermodynamic preferences of other ring systems. Bicyclo[5.3.0]decanes are computationally predicted,\textsuperscript{19} in several cases where equilibration is possible, to favor the \textit{trans}-ring fusion (Figure 5.2). If, therefore, we could perform a ring-contraction on a \textit{trans}-fused bicyclo[5.3.0]decane in such a way that equilibration was not possible afterwards, we could readily access the desired substitution pattern for diene 5.57 (Scheme 5.9).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{example}
\caption{The calculated relative energies and equilibrium ratios for several relevant bicyclo[4.3.0]nonanes and bicyclo[5.3.0]decanes.}
\end{figure}

This route proved disappointing. Starting from 1,3-dione 5.48, the known\textsuperscript{20} β,β-substituted enol ether 5.50 could be formed but the unoptimized conjugate methylation was extremely unreliable, likely due to a temperature-sensitive cuprate intermediate. The desired methallylation to make 5.51 also never proceeded, despite extensive efforts using both enolate\textsuperscript{21} and Pd-mediated\textsuperscript{22} conditions. Alternatively, methallylation of sterically less-demanding 5.48 proceeded smoothly and could be followed by treatment with diazomethane, Stork–Danheiser addition/transposition,\textsuperscript{23} then ring-closing metathesis to
afford bicyclo[5.3.0]decane 5.53. Direct conjugate addition of a methyl nucleophile to provide 5.55/5.56 was not successful at this point but cyclopropanation24 afforded 5.54 and reductive ring-opening25 did yield modest amounts of 5.55/5.66. Unfortunately, conditions using either SmI₂ or Li⁰/NH₃ gave similar yields and an almost identical ratio of 5.55 to 5.56 (1:2.5 and 1:2.4 respectively), while efforts to equilibrate the mixture using NaOMe in MeOH either returned similar ratios or resulted in decomposition. Based on these results, it seemed certain that for this particular substitution pattern, the cis-ring fusion was thermodynamically preferred. In retrospect, this is perfectly understandable. For cis-configured ring-systems such as those shown in Figure 5.2, there can be a significant steric clash between C15 or C16 and those labeled C9 or C7, causing the trans-ring system to be favored. However, because three of those four carbons are sp² hybridized in 5.56, those unfavorable interactions are largely minimized, meaning that the strained

Scheme 5.9 Efforts to Make trans-Bicyclo[5.3.0]decane 5.55

For cis-configured ring-systems such as those shown in Figure 5.2, there can be a significant steric clash between C15 or C16 and those labeled C9 or C7, causing the trans-ring system to be favored. However, because three of those four carbons are sp² hybridized in 5.56, those unfavorable interactions are largely minimized, meaning that the strained
trans-ring 5.55 is comparatively higher energy.

5.4 Trans-Hydrindanes from the Hajos–Parrish Ketone

The several synthetic routes discussed above were all designed to install functionality where it was needed in the natural product, with a minimum of functional-group interconversion and manipulation late-stage. However, these theoretically concise syntheses failed to deliver the desired diene and the key Diels–Alder reaction to form a tetracyclic steroid skeleton remained untested. With an eye towards making the desired trans-hydrindane by any means possible, we turned our attention towards known methods for making the trans-ring fusion with functionality that would be usable, if not ideal.

Aside from semi-synthetic approaches, there seemed to be two major methods for the formation of trans-hydrindanes with relevant oxidation patterns to the clionastatin synthesis. One method utilizes a Type-I intramolecular Diels–Alder reaction (Scheme 5.10a).26 This method was briefly examined and synthetic efforts towards triene 5.59 were
begun. However, further examination of the literature (Scheme 5.10b)\textsuperscript{27} showed that, even when \textit{trans}-hydrindanes are formed as the major products in intramolecular Diels–Alder reactions, significant amounts of the corresponding \textit{cis}-hydrindanes are also formed (e.g. formation of \textit{5.61} and \textit{5.62}). Furthermore, in the absence of other stereochemically directing substitution on the triene precursor, \textit{cis}-hydrindane products usually predominate (e.g. \textit{5.65} vs. \textit{5.64}). A closer look at our proposed triene (\textit{5.59}) showed a significant amount of strain in the requisite conformation for the Diels–Alder reaction leading to the \textit{trans}-hydrindane, suggesting that, if the reaction proceeded at all, desired bicycle \textit{5.58} was unlikely to be formed as the major product.

The second common method for accessing \textit{trans}-hydrindane systems is from the Hajos–Parrish ketone (\textit{5.66}).\textsuperscript{28} While initially unattractive because the oxidation pattern found on this dione does not match the desired pattern for the clionastatins (Figure 5.1), this approach all but guaranteed access to the desired diene, and so, it was adopted.

\subsection*{5.4.1 Utilizing a Diazene Sigmatropic Rearrangement}

It was shown\textsuperscript{29} in 1971 that allylic diazenes could undergo concerted, [3,3]-sigmatropic rearrangements to afford reduced olefinic products with [1,3]-transposition of the alkene (Scheme 5.11a). It was later shown\textsuperscript{30} to do so with complete fidelity to the starting stereochemistry (Scheme 5.11b). Unfortunately, the requisite allylic diazenes could be challenging to form stereoselectively and the precursors were often difficult to handle, leading to the development of more stable, substituted hydrazines, which could be unmasked \textit{in situ} under mild conditions to afford the requisite diazenes.\textsuperscript{31} Specifically,
Myers\textsuperscript{32} recognized that NBSH (o-nitrobenzenesulfonylhydrazide) was ideally suitable for this transformation. The acidifying effect of the Ns group gives NBSH the proper pK\textsubscript{a} to participate effectively in Mitsunobu reactions on allylic alcohols to provide, after spontaneous elimination of o-nitrosulfonic acid, the desired diazene, which immediately undergoes the desired [3,3]-rearrangement. Myers further showed that this method was applicable on complex, steroidal cores (conversion of 5.72 to 5.73). Because it had previously been shown that allylic alcohol 5.74 could be made with high diastereoselectivity\textsuperscript{33} from ketone 5.66, use of NBSH seemed like an ideal method for formation of trans-hydridane 5.75. However, it seemed unlikely that 5.75 could be
further elaborated to a suitable diene (5.76) for our synthesis of the clionastatins.

Our total synthesis would require a more oxidized substrate than 5.74 but we thought that the literature precedent would be largely applicable to our desired system. We started from the Hajos–Parrish ketone (5.66), which can be made in either racemic form or enantioselectively by a number of methods. Of those tested by us, we found the method of Weichert et al. to be the easiest and most readily scalable. It did not require multiple days at low temperature, as did the original Hajos procedure, and afforded material with 95% ee after a single recrystallization.

A known reduction and various protection conditions provided access to enones 5.78–5.81 in good yield. For initial studies, 5.78 was employed owing to the ease with

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### Scheme 5.13 Allylic Transposition via Diazene Intermediates Towards Diene 5.87

![Scheme diagram showing steps for allylic transposition via diazene intermediates towards diene 5.87.]

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which it could be made and its comparative spectroscopic simplicity. In order to install the desired C15 oxidation found in the clionastatins, conditions\textsuperscript{35} were employed to form the thermodynamic dienyl acetate \textit{5.82}, followed by epoxidation with \textit{mCPBA} and base-mediated acetate cleavage/epoxide opening to afford the allylic alcohol as a single diastereomer, resulting from epoxidation on the less hindered face, away from the angular methyl group. This alcohol was protected as benzoyl ester \textit{5.83}.

For the synthesis of diene \textit{5.87}, a functional handle was required at C8 that would allow later cross-coupling or nucleophilic addition into an acyl equivalent. We examined both the vinyl bromide \textit{5.84} and iodide \textit{5.85} for this purpose and, while both could be made,\textsuperscript{36} neither was obtained in high yields. Interestingly, allylic oxidation of the C15 benzoyl-protected alcohol to the corresponding ketone was a major competing reaction. Nonetheless, the \(\alpha\)-bromo enone could be obtained and converted into bromide \textit{5.84} by stereoselective 1,2-reduction.\textsuperscript{37} Unfortunately, this substrate failed to undergo the desired Mitsunobu reaction under standard conditions (using equimolar portions of NBSH, DIAD, and \(\text{Ph}_3\text{P}\) in \(N\)-methylmorpholine [NMM]). Varying temperatures, concentrations, order of addition, reagent ratios, and reaction times also all failed to produce any desired product. Use of sterically less hindered DEAD in place of DIAD was no more successful, nor was the use of THF as a replacement for NMM or as a co-solvent. Further investigation of the literature on the Hajos–Parrish derived substrates showed that, while unsubstituted allylic alcohol \textit{5.78} is readily substituted, C8 methyl or halide substitution, which we required, produced a steric problem that was known to limit Mitsunobu reaction at C9.\textsuperscript{38}

Even use of more active \(n\text{Bu}_3\text{P}\) initially resulted in no product. However, when alcohol \textit{5.84} was stirred with \(\text{Ph}_3\text{P}\) and DIAD at 0 °C, then cooled to \(-30\) °C for addition of
the NBSH, up to a 20% yield of desired vinyl bromide 5.86 was obtained, although mixed with side products and significant amounts of starting alcohol. These results are consistent with a careful examination of the mechanism for the Mitsunobu reaction (Scheme 5.14). It is well documented that a mixture of DIAD and trialkylphosphine form phosphorane 5.91 in the absence of acid, and the addition of acid creates an equilibrium between 5.92 and 5.91, favoring the phosphonium, which is eventually converted into product. The recovery of only starting alcohol 5.84 at low temperature suggested that the problematic step was the initial activation of the hindered alcohol (formation of 5.92), as elimination products would be an expected side reaction if activation were occurring. At 0 °C, exclusive formation of 5.91 was probably occurring in our case but, because NBSH is not stable under these reaction conditions above –30 °C, cooling was necessary before addition of the acid. This resulted in formation of phosphonium 5.92, with fully 50% of the alcohol 5.84 unreactive, as reactivation of the dissociated alcohol could not occur at that low temperature. One attempt was made to use Movassaghi’s more stable IPNBSH (the condensation product of acetone and NBSH), allowing for the entire reaction to be run at 0 °C, but no Misunobu reaction was observed with this reagent at all, presumably due to the

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**Scheme 5.14 Mechanism for the General Mitsunobu Reaction Using DIAD**

![Scheme 5.14 Mechanism for the General Mitsunobu Reaction Using DIAD](image-url)
increased steric bulk of IPNBSH.

It was also known that sulfinic acids could undergo a similar, spontaneous, sigmatropic rearrangement to afford, after expulsion of SO₂, reduced allylic-transposition products. Unfortunately, the harsh conditions usually required to unveil the desired sulfinic acid from the thioacetate precursors (excess LiAlH₄ at rt, then excess mCPBA) somewhat limited the application of this methodology (Scheme 5.15, conversion of 5.94 to 5.96).

This limitation led to the development of benzenethiothiazole (BTT) as an alternative to thioacetic acid for this tandem Mitsunobu reaction/[3,3]-rearrangement. The benefits of BTT for this sequence were showcased in the conversion of allylic alcohol 5.97 to hydrindene 5.99. Similar to us, Wicha et al. had also observed the need for (nBu)₃P to obtain efficient activation of the hindered allylic alcohol 5.97. The BTT-substituted 5.98

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**Scheme 5.15 Allylic Transposition via Sulfinic Acid Sigmatropic Rearrangement**

1. DEAD, Ph₃P 2. LiAlH₄ 78%  

1. mCPBA 2. DCM, 40–50 °C 80%

1. DIAD, PBu₃, BTT 2. mCPBA 58%

1. NaBH₄ 2. aq. tartaric acid 71%

---

5.84  

BTT, DIAD, (nBu)₃P 95%

5.100  

×

5.86
could then be oxidized by several methods, although \( m \text{CPBA} \) was the most efficient. Reductive cleavage of the benzenethiazole could be performed at 0 °C with \( \text{NaBH}_4 \) to unmask a sodium salt of the sulfinic acid, which could be acidified under carefully controlled conditions to afford the rearranged product 5.99.

On our system, Mitsunobu product 5.100 was readily formed in high yield but treatment with \( m \text{CPBA} \) gave a mixture of products, possibly from incomplete oxidation and formation of several sulfoxide or epoxide diastereomers. One product was also isolated that might have been the product of competitive N-oxidation, a known, albeit minor, side reaction previously reported by Wicha. Attempts to purify or directly reduce this mixture were never successful and no rearranged product 5.86 was ever obtained. Efforts to reductively cleave the benzenethiazole 5.100 first, then oxidize the resulting thiol to the sulfinic acid, were also not successful.

Notwithstanding the continuing problems with this [3,3]-rearrangement strategy, with the few milligrams of vinyl bromide 5.86 that could be obtained, several cross coupling reactions were tested (Scheme 5.13). Intermolecular Heck reaction using various palladium sources, solvents, and bases with \( n \)-butyl vinyl ether returned only starting 5.86 or dehalogenated material. Lithiation and attempted addition into acetyl chloride was also unsuccessful but Stille reaction with tributyl(1-ethoxyvinyl)stannane, followed by TMS enol ether formation resulted in diene 5.87. As exciting as it was to finally make the desired bicyclic, \( \text{trans} \)-fused diene, it was painfully apparent that this route was not going provide the material throughput required to optimize the Diels–Alder reaction conditions, let alone the remainder of the clionastatin synthesis. Therefore, despite having validated this synthetic route, it was set aside in search of a more reliable method.
5.4.2 *Trans*-Hydrindane Synthesis Via Hydrogenation

Hydrogenation or other direct reductions of enones 5.78–5.81 are generally known to afford *cis*-hydrindanes.\(^\text{42}\) However, under very specific conditions, or with the proper functionality to provide conformational bias or to act as a directing group, *trans*-hydrindanes have been made in this way. Two ideas in particular attracted our attention. The first was to use the allylic C15 alcohol to direct catalytic hydrogenation or 1,4-reduction to the α-face of the hydrindane (Table 5.2). The second idea was to use a bulky Cu-catalyst with DIBAL-H, which is known to give *trans*-hydrindanes on similar systems.

On a hydrindane system similar to the one that we sought to employ (5.101), while Pd/C resulted in highly selective *cis*-ring fusion, Crabtree’s catalyst, which readily coordinates to free alcohols, reversed the native preference of the substrate (Equation 5.1).\(^\text{43}\) It was reasoned that, due to the α-allylic alcohol on our system (Table 5.2, 5.104), a similar directing effect might be observed. However, because we needed further functionalization at C8, simple 1,4-reduction of the enone or hydrogenation of the Δ⁸¹⁴-alkene would afford a C9 ketone that could not be regioselectively enolized in the direction that we needed.\(^\text{44}\) With this in mind, we ultimately hoped to apply a 1,4-hydrosilylation, which would afford the silyl enol ether of 5.105. However, for simplicity in comparing screening results, hydrosilylation attempts were treated immediately with TBAF in THF to

\[
\begin{align*}
\text{5.101} & \xrightarrow{\text{catalyst, } H_2} \text{5.102} + \text{5.103} \\
\text{Pd/C} & \quad \text{Crabtree’s Catalyst} \\
\text{5:95} & \quad 96:4
\end{align*}
\]
afford the parent ketones (5.105 and 5.106).

Unfortunately, under all conditions tried, little or none of the trans-fusion was observed (Table 5.2). Crabtree’s catalyst,\textsuperscript{45} which is known to be selective by nature of its reduced reactivity, failed to give more than trace conversion after several attempts and we were not able to determine the cis/trans ratio due to the low conversion. Reactions with Wilkinson’s catalyst\textsuperscript{46} could be forced to complete conversion but 1,2-reduction was the major product, while Karstedt’s catalyst\textsuperscript{47} resulted in multiple products, even at very low conversion. Use of Ni or Fe under transfer hydrogenation conditions resulted in either predominantly cis-hydrindane or 1,2-reduction. Bulky Cu catalysts,\textsuperscript{48} which were reported to give up to 10:1 trans: cis selectivity on Hajos–Parrish derived systems, also afford predominantly cis-fusion in low yield. Given all of these results and the fact that many of the conditions are known to work on very similar systems, it seems probable that, rather than having a directing effect, the C15 α-OH group provides steric hindrance that leads to kinetic formation of the β-reduction products.

![Diagram](image_url)

Table 5.2. Reduction conditions for attempted trans-hydrindane formation from 5.104.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Catalyst</th>
<th>Reductant</th>
<th>Conversion (%)</th>
<th>5.105:5.106:5.107</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>[(cod)IrP(cy)\textsubscript{3}(pyr)]PF\textsubscript{6}</td>
<td>H\textsubscript{2} (~20 psi)</td>
<td>5</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>RhCl(PP\textsubscript{3})\textsubscript{3}</td>
<td>TESH, rt−70 °C</td>
<td>10−100</td>
<td>20:20:60</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>Pt\textsubscript{5}[(Me\textsubscript{2}SiCH=CH\textsubscript{2})\textsubscript{2}O]\textsubscript{3}</td>
<td>TESH</td>
<td>10</td>
<td>messy</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>NiCl\textsubscript{2}·6H\textsubscript{2}O</td>
<td>NaBH\textsubscript{4}</td>
<td>100</td>
<td>25:75:0</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>Fe\textsubscript{2}(ox)\textsubscript{3}</td>
<td>NaBH\textsubscript{4}</td>
<td>100</td>
<td>0:0:100</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>Fe\textsubscript{2}(ox)\textsubscript{3}</td>
<td>TESH</td>
<td>100</td>
<td>messy</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>Fe(acac)\textsubscript{3}</td>
<td>NaBH\textsubscript{4}</td>
<td>100</td>
<td>0:0:100</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>Fe(acac)\textsubscript{3}</td>
<td>TESH</td>
<td>100</td>
<td>messy</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>none</td>
<td>NaBH\textsubscript{4}</td>
<td>100</td>
<td>0:0:100</td>
</tr>
<tr>
<td>10</td>
<td>TES</td>
<td>tBuLi, Cul</td>
<td>DIBAL-H</td>
<td>29</td>
<td>10:90:0</td>
</tr>
<tr>
<td>11</td>
<td>TES</td>
<td>TMSLi, Cul</td>
<td>DIBAL-H</td>
<td>30</td>
<td>5:95:0</td>
</tr>
</tbody>
</table>
Ultimately, in the face of all of these marginal successes and failures, and with dwindling time left to complete this project, we turned our attention to known enone 5.109, reported by Bagnirollini of Hoffmann-La Roche.\textsuperscript{49} In many ways, this felt like a concession. The D-ring on 5.109 is clearly underoxidized for later conversion to the desired clionastatin system and would require several additional late-stage manipulations, on top of the 5 steps already required to transpose the C9 ketone into the oxidation pattern needed for our desired substrate. However, despite these apparent drawbacks, this route proved robust and scalable. Enone 5.81, which we had already made for a different synthetic route, reacted readily with methoxymagnesium methyl carbonate\textsuperscript{50} (MMC), whereupon hydrogenation afforded a 9:1 mixture of diastereomers, favoring the trans-hydrindane. The resulting keto acid was known to spontaneously decarboxylate at rt but we found that a one-pot hydrogenation/NaBH\textsubscript{4} reduction procedure nicely circumvented isolation of the unstable intermediate and afforded 5.108 in good yield. Conversion of the hydroxyacid to the methyl ketone, followed by elimination of the β-hydroxy group, provided desired enone 5.109 in multi-gram quantities.
Finally, with a robust synthesis of a sufficiently functionalized trans-hydridane diene (5.110 or 5.111), the key Diels–Alder reaction could be tested for formation of a tetracyclic clionastatin precursor and the total synthesis could be completed.

5.5 Diels–Alder Reaction to Make Tetracycle 5.121

One major concern going into the Diels–Alder reaction with the fully-functionalized CD-ring diene was whether the conditions developed for the model system (see Section 3.4) would be relevant to this more complex system. This worry was largely inspired by Corey’s studies on the nicandrenone system,51 where he had observed facile endo-selective Diels–Alder reactivity on a tricyclic model system (5.112), but when making the tetracycle (5.116), selectivity switched to predominantly the exo-approach. In our system, the reversal in selectivity might be even more pronounced, since instead of the flat, aromatic D-ring possessed by nicandrenone, we would be using a stereochemically-rich trans-hydridane, with an angular C18 methyl group. While endo-/exo-selectivity would not be vital to our synthesis, the relative stereochemistry of our C18 and C19 methyl groups was

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Scheme 5.17 Stereochemical Outcome of the Nicandrenone Diels–Alder Studies

[Diagram showing stereochemical outcomes of the reaction with endo and exo configurations]
important. Thus, either an endo-Diels–Alder reaction from the α-face or an exo-Diels–Alder reaction from the β-face would be needed. While the α-face endo reaction seemed reasonable, if the Diels–Alder reaction did switch to an exo-selective mode, we had no reasonable expectation of selectivity.

It proved true that steric interactions retarded the Diels–Alder reaction, as our model diene and dienophile reacted almost immediately at 0 °C (Scheme 3.13) but CD-ring diene 5.110 underwent acid-mediated deprotection before any Diels–Alder reaction was observed with dienophile 5.117. Efforts to make and use more robust enol ethers were largely unsuccessful. The TBDPS enol ether could never be made, nor could the methyl analogue. The dienyl acetate (5.111) was made and could be handled easily but it proved unreactive under a variety of forcing conditions. This matched observations in the literature\textsuperscript{52} which point to vinyl acetates being \(~100\) times less reactive than the corresponding silyloxydienes.

A screen of Lewis acids suggested that a stepwise, double-Michael reaction might be
occurring competitively with the concerted Diels–Alder reaction (Scheme 5.18). This would be problematic, because an intermediate β-chloroenolate (5.118) could rapidly eliminate to give structure 5.119. Indeed, 1H NMR and MS data suggest that this product was formed when strong Lewis acids (BF₃·Et₂O, TMSOTf) were used.

Ultimately, the use of a toluene solution of diene 5.110 with excess Et₃N (residual from the formation of the enol ether) not only served to stabilize the diene for storage but also served to quench trace HCl formed by the Et₂AlCl Lewis acid, resulting in desired Diels–Alder reaction rather than simple protodesilylation, affording 5.120 as a single diastereomer, although difficulty in handling the sensitive silyl enol ether precluded full characterization of the compound at that point. Treatment of crude enol ether 5.120 with NBS, as previously done for the ABC-ring system, resulted in an α-bromo ketone, which was somewhat purified by chromatography. The thermal elimination conditions previously employed (LiCl, Li₂CO₃, DMF, 120 °C) proved effective in this case, giving predominantly a single product, but resulted in formation of undesired enone 5.122 rather than the desired regioisomer. While somewhat surprising (both alkenes are tetrasubstituted but the

Scheme 5.19 Successful Diels–Alder Reaction and Further Manipulations of Tetracycle 1.21

156
undesired enone appears to have more ring strain), this result simply pointed to the need for other oxidation conditions. Selenenylation, which would probably add to the β-face of the steroid (5.123), after oxidation to the selenoxide, could only eliminate to form the Δ⁸,⁹-alkene (5.124). Unfortunately, analysis of a NOESY spectrum for 5.122 showed the undesired relative stereochemistry between C18 and C19 (Figure 5.4). This product comes from the exo-Diels–Alder reaction, as expected based on the precedent from Corey's nicandrenone synthesis, with dienophile approach from the α-face of the hydrindane, away from the angular C18 methyl group. The fact that this is the only diastereomer formed in the Diels–Alder reaction after several hours at rt suggests that flipping this diastereoselectivity may be very challenging.

5.6 Future Directions

As with any complex, multi-year project, there were many avenues that were not thoroughly investigated en route to the synthesis of the clionastatins. The difficulty lies not in identifying these unfinished facets, but rather in identifying which are worth pursuing further. In an immediate sense, forming the desired relative stereochemistry in the Diels–Alder reaction is the first concern. Use of a modified diene (5.126, Scheme 5.20) could allow for either tethering to the dienophile through the 4-hydroxy group or Lewis acid-mediated direction of the dienophile to the β-face of the diene, resulting in desired cycloadduct 5.127. Should that prove successful, application of the synthetic route from the
model system would allow for completion of clionastatins A (5.1) and B (5.2). Also, development of a better understanding of the dichlorination diastereoselectivity is a
project that has both immediate application to the clionastatin total synthesis, as well as farther-reaching implications for stereodefined vicinal alkyl dihalide formation. For that study, further model systems will be key to understanding the role of the C19 chloride in the final stereochemical outcome of the chlorination reactions (Scheme 5.21). Finally, a study of Diels–Alder reactions using both enantioenriched 5.117 and enantioenriched 5.110 should point to matched and mismatched cases and tell us about the balance of steric and electronic effects operative in these complex cycloadditions.

5.7 Conclusion

In the course of the investigations outlined in this chapter, many reasonable approaches to trans-hydrindane formation were investigated. Some of these approaches had a high degree of novelty and some were nearly identical to published substrates. The result was an increased understanding of the thermodynamics that governs stereocontrol in these systems and an appreciation for the subtle conformational and electronic effects that influence reactivity in complex settings. Ultimately, a satisfactorily substituted diene (5.110) was synthesized and employed in a Diels–Alder reaction to form a tetracyclic steroid core (5.121), albeit with the incorrect relative stereochemistry between C18 and C19. However, the general synthetic strategy employed will be further improved and applied to the synthesis of clionastatins A and B in due time.

5.8 Experimental Procedures
2- Allyl-3-methyl-3-vinylcyclohexan-1-one (5.14): To a stirred solution of known enol ether 5.18 (760 mg, 3.61 mmol) in THF (18 mL) at 0 °C was added MeLi-LiBr (2.00 mL, 1.81 M in THF, 3.61 mmol). The reaction was stirred for 1 h and DMPU (463 mg, 3.61 mmol) and allylbromide (568 mg, 4.69 mmol) were added. After an additional 22 h, the reaction was quenched with saturated aqueous NaCl solution (10 mL) and the aqueous phase was extracted with Et₂O (3 x 10 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, 1:49 Et₂O/hexanes, Rf = 0.28 in 1:9 EtOAc/hexanes, KMnO₄) to afford 5.14 (371 mg, 58%) as an ~1:1.2 mixture of diastereomers. Data for 5.14: ¹H NMR (500 MHz, CDCl₃) δ 5.84 (m, 1.4H), 5.67 (d, J = 10.9, 6H), 5.08 (m, 3H), 2.59 (m, 1.4H), 2.47 (d, J = 11.4, 0.4H), 2.38 (m, 0.4H), 2.27 (m, 1.4H), 2.06 (m, 1.8H), 1.68 (m, 3.4H), 1.15 (s, 1.6H), 0.89 (s, 0.8H); ¹³C NMR (126 MHz, CDCl₃) δ 211.3, 144.6, 136.5, 136.4, 116.5, 116.3, 114.0, 110.8, 52.1, 51.4, 49.3, 49.2, 42.5, 37.1, 35.6, 33.7, 33.5, 29.9, 28.4, 28.3, 23.5.

6-Allyl-5-methyl-5-vinylcyclohex-1-en-1-yl trifluoromethanesulfonate (5.20): To a stirred solution of DIPA (291 mg, 2.88 mmol) in THF (10 mL) at ~78 °C was added nBuLi (1.02 mL, 2.50 M in hexanes, 2.56 mmol) and the solution was allowed to stir for 30 min, whereupon ketone 5.14 (285 mg, 1.60 mmol) was added. After 2 h, PhNTf₂ (915 mg, 2.56 mmol) was added in one portion and the resulting solution was allowed to stir overnight, warming slowly to rt. The reaction mixture was filtered through SiO₂, eluting with DCM, then concentrated in vacuo. The residue was purified by column chromatography (SiO₂, 1:199 Et₂O/hexanes, Rf = 0.80 in 1:19 EtOAc/hexanes, KMnO₄) to afford 5.20 (350 mg,
70%) as an ~1:1.2 mixture of diastereomers. Data for 5.20: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\Delta 5.78\) (m, 2H), 5.59 (m, 1H), 5.14 (m, 3H), 5.00 (d, \(J = 17.3\) Hz), 2.54 (m, 2H), 2.19 (m, 1H), 1.85 (m, 1H), 1.58 (m, 3H); 13C NMR (126 MHz, CDCl\(_3\)) \(\Delta 151.7, 145.0, 144.8, 135.3, 134.6, 125.7, 125.6, 117.7, 117.5, 114.1, 113.9, 40.0, 39.8, 37.4, 36.9, 35.7, 35.6, 33.5, 31.3, 27.9, 27.5, 24.8, 23.2.

**1-(6-Allyl-5-methyl-5-vinylcyclohex-1-en-1-yl)ethan-1-one (5.21):** To a vigorously stirred solution of triflate 5.20 (86 mg, 0.277 mmol), freshly fused LiCl (82 mg, 1.94 mmol), and Pd(Ph\(_3\)P)\(_4\) (32 mg, 0.028 mmol) in THF (4 mL) was added ethyl vinyl ether (55 \(\mu\)L, 0.554 mmol). The reaction was heated to reflux and stirred for 16 h, then quenched by the addition of saturated aqueous NaCl solution (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL), the combined organic extracts were dried over Na\(_2\)SO\(_4\), and concentrated \textit{in vacuo}. The residue was purified by column chromatography (SiO\(_2\), 1:199 EtOAc/hexanes, \(R_f = 0.37\) in 1:19 EtOAc/hexanes, KMnO\(_4\)) to afford 5.21 (21 mg, 38%) as an ~1:1.2 mixture of diastereomers. Data for 5.21: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\Delta 6.54\) (s, 1H), 5.84 (m, 3H), 5.06 (m, 6H), 2.78 (m, 1H), 2.38 (s, 3H), 2.30 (m, 1H), 1.97 (m, 2H), 1.75–1.39 (m, 9H), 1.35–1.13 (m, 12H); 13C NMR (126 MHz, CDCl\(_3\)) \(\Delta 192.0, 191.0, 146.5, 137.6, 118.0, 116.1, 112.7, 37.6, 31.8, 31.0, 26.4, 26.1, 22.6.

![Diagram](image-url)
(+)-1-[(3αR,7αS)-3a-Methyl-3a,4,5,7a-tetrahydro-(1H)-inden-7-yl]ethan-1-one (5.22): To a stirred solution of enone 5.21 (15 mg, 0.073 mmol) in DCM (1 mL) was added Grubbs’ second generation catalyst (~1 mg, 0.002 mmol). The reaction was heated to 50 °C and stirred for 3 h, then quenched by the addition of HCl (1 mL, 1 M). The aqueous phase was extracted with DCM (3 x 5 mL), the combined organic extracts were dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, 1:49 EtOAc/hexanes, Rf = 0.44 in 1:19 EtOAc/hexanes, KMnO₄) to afford 5.22 (7 mg, 54%) as a single diastereomer. Data for 5.22: ¹H NMR (500 MHz, CDCl₃) δ 7.18 (s, 1H), 5.55 (d, J = 10.9, 1H), 5.33 (d, J = 10.9, 1H), 3.34 (m, 1H), 2.38 (s, 3H), 2.21 (m, 3H), 1.97 (m, 1H), 1.86 (m, 1H), 1.52 (m, 2H), 1.32 (s, 6H), 1.26 (s, 3H), 0.92 (m, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 197.6, 154.4, 142.4, 136.0, 127.8, 39.0, 36.5, 34.4, 29.9, 28.4, 27.9, 26.2, 24.9.

(±)-(E)-3-Methyl-3-(prop-1-en-1-yl)cyclohex-1-en-1-yl acetate (5.23): To a stirred suspension of CuBr·SMe₂ (22 mg, 0.106 mmol) in THF (6 mL) at ~78 °C under argon was added propenylmagnesium bromide [prepared fresh from propenyl bromide (523 mg, 4.32 mmol) and magnesium turnings (105 mg, 4.32 mmol) in THF (5.6 mL)] and DMPU (0.47 mL, 3.88 mmol). After 10 min, commercially available enone 5.15 (194 mg, 1.76 mmol) was added in THF (1 mL) and the reaction was allowed to warm to 0 °C. The reaction mixture was stirred for an additional 1.5 h and Ac₂O (719 mg, 7.04 mmol) was added. After an additional 1 h, the reaction was quenched by the addition of saturated aqueous NaHCO₃ (5 mL), the aqueous phase was extracted with hexanes (3 x 5 mL), the combined organic extracts were dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by
column chromatography (SiO$_2$, 1:199 EtOAc/hexanes, $R_f = 0.75$ in 1:9 EtOAc/hexanes, KMnO$_4$) to afford 5.23 (174 mg, 51%) as a mixture of diastereomers. Data for 5.23: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.41 (m, 2H), 5.29 (m, 1H), 2.25–2.05 (m, 6H), 1.77 (m, 5H), 1.70–1.62 (m, 2H), 1.46 (m, 1H), 1.19 (s, 3H), 1.10 (s, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 169.3, 169.2, 147.9, 147.1, 139.5, 138.8, 124.4, 123.7, 122.9, 121.4, 37.7, 37.5, 36.4, 35.5, 29.5, 28.7, 26.8, 26.7, 21.1, 19.7, 19.1, 18.0, 14.0.

2-Allyl-3-methyl-3-[(E)-prop-1-en-1-yl]cyclohexan-1-one (5.24): To a stirred solution of vinyl acetate 5.23 (174 mg, 0.896 mmol) in THF (5 mL) at 0 °C was added MeLi·LiBr (550 µL, 1.81 M in THF, 0.985 mmol) and the reaction was allowed to stir for an additional 2 h, after which DMPU (0.12 mL, 0.985 mmol) and allyl bromide (0.16 mL, 1.792 mmol) were added. The reaction was allowed to warm to rt and stirred overnight, then quenched by the addition of saturated aqueous NaHCO$_3$ (5 mL). The aqueous phase was extracted with hexanes (3 x 5 mL), the combined organic extracts were dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO$_2$, 1:49 EtOAc/hexanes, $R_f = 0.63$ in 1:19 EtOAc/hexanes, KMnO$_4$) to afford 5.24 (78 mg, 45%) as an ~1.6:1 mixture of diastereomers. Data for 5.24: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.72 (m, 2H), 5.43 (m, 1H), 5.26 (d, $J = 11.9$, 1H), 5.11 (m, 4H), 2.57 (d, $J = 13.9$, 1H), 2.37 (m, 6H), 2.01 (m, 1H), 1.72 (m, 8H), 1.35 (m, 3H), 1.22 (s, 3H), 1.02 (s, 1H), 0.94 (s, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 211.4, 138.8, 136.6, 136.4, 134.8, 126.0, 124.1, 116.4, 116.2, 55.0, 53.8, 49.3, 42.3, 38.3, 37.6, 36.8, 33.8, 33.5, 31.6, 29.3, 28.9, 28.4, 24.4, 22.7, 14.5, 14.2.
(±)-(3aR,7aR)-7a-methyl-3,3a,5,6,7,7a-hexahydro-(4H)-inden-4-one (5.25) and (±)-(3aS,7aR)-7a-methyl-3,3a,5,6,7,7a-hexahydro-(4H)-inden-4-one (5.26): To a stirred solution of ketone 5.24 (23 mg, 0.119 mmol) in DCM (3 mL) was added Grubbs’ second generation catalyst (7 mg, 0.009 mmol) and the reaction was heated to 50 °C for 2.5 h. The reaction mixture was filtered through SiO₂, rinsing with DCM, and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, 1:33 Et₂O/hexanes, Rf = 0.22 in 1:19 EtOAc/hexanes, KMnO₄) to afford a 1:4 mixture of 5.25 and 5.26 (78 mg, 45%). Data for a 1:1.8 diastereomeric mixture of 5.25 and 5.26: ¹H NMR (500 MHz, CDCl₃) δ 5.69 (m, 2.8H), 5.51 (m, 1H), 5.45 (m, 1.8H), 2.74–2.51 (m, 8H), 2.48–2.17 (m, 9H), 2.15–1.90 (m, 9H), 1.84–1.55 (m, 11H), 1.17 (s, 5H), 1.17 (s, 7H), 0.86 (m, 9H).

6-Allyl-5-methyl-5-[(E)-prop-1-en-1-yl]cyclohex-1-en-1-yl trifluoromethanesulfonate (5.27): To a stirred solution of DIPA (0.19 mL, 1.33 mmol) in THF (6 mL) at −78 °C under argon was added nBuLi (0.46 mL, 2.5 M in hexanes, 1.18 mmol) dropwise. The resulting solution was stirred 30 min before ketone 5.24 (142 mg, 0.738 mmol) was added. The reaction mixture was stirred an additional 1 h, after which PhNTf₂ (422 mg, 1.18 mmol) was added via cannula in THF (2 mL). The reaction was allowed to warm to rt and stirred overnight, then filtered through SiO₂, rinsing with DCM, and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, 1:99 Et₂O/hexanes, Rf = 0.72 in 1:19 EtOAc/hexanes, KMnO₄) to afford 5.27 (159 mg, 67%) as a
mixture of diastereomers. Data for the diastereomeric mixture of 5.27: ¹H NMR (500 MHz, CDCl₃) δ 5.90 (s, 1.5H), 5.79 (m, 1.5H), 5.49 (m, 1.5H), 5.34 (m, 1.5H), 5.15 (m, 2.5H), 2.99 (m, 0.5H), 2.65–2.40 (m, 3H), 2.36–2.12 (m, 2.5H), 1.98–1.62 (m, 9.5H), 1.62–1.43 (m, 2.5H), 1.37 (m, 6.5H), 1.14 (m, 1.5H), 1.04 (m, 0.5H), 0.93 (m, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 151.3, 150.4, 142.2, 138.1, 137.9, 137.2, 137.2, 136.7, 136.6, 135.4, 134.9, 134.9, 134.7, 133.7, 132.1, 132.1, 131.0, 130.0, 128.1, 128.1, 127.8, 126.6, 126.4, 125.7, 125.4, 125.3, 124.9, 124.8, 120.7, 119.9, 118.1, 117.7, 117.6, 117.4, 117.3, 117.3, 117.2, 116.4, 116.3, 41.7, 38.9, 38.3, 37.3, 37.0, 35.5, 35.5, 34.7, 34.7, 34.6, 34.5, 33.6, 31.6, 29.1, 28.9, 26.1, 26.0, 25.3, 25.0, 24.7, 22.7, 20.7, 14.3, 14.3, 14.1, 14.1, 11.4.

![Structural diagram of 1-{6-Allyl-5-methyl-5-[(E)-prop-1-en-1-yl]cyclohex-1-en-1-yl}ethan-1-one](image)

1-{6-Allyl-5-methyl-5-[(E)-prop-1-en-1-yl]cyclohex-1-en-1-yl}ethan-1-one (5.28): To a stirred solution of triflate 5.27 (121 mg, 0.373 mmol), Et₃N (0.10 mL, 0.746 mmol), and ethyl vinyl ether (0.18 mL, 1.87 mmol) in DMSO (0.5 mL) was added a solution of Pd(OAc)₂ (3 mg, 0.011 mmol) in DMSO (2 mL). The reaction mixture was stirred at 65 °C for 3 h and quenched with saturated aqueous NaHCO₃ (3 mL). The aqueous phase was extracted with Et₂O (3 x 3 mL), dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, 1:49 Et₂O/hexanes, Rf = 0.22 in 1:19 EtOAc/hexanes, KMnO₄) to afford 5.28 (54 mg, 67%) as a mixture of diastereomers. Data for the diastereomeric mixture of 5.28: ¹H NMR (500 MHz, CDCl₃) δ 6.91 (s, 1H), 6.82 (s, 2H), 6.52 (s, 0.5H), 5.83 (m, 4.5H), 5.47 (m, 7.5H), 5.29 (d, J = 11.7, 2.5H), 5.03 (m, 8.5H), 3.00 (m, 2H), 2.81 (m, 3.5H), 2.41–2.23 (m, 23.5H), 2.23–1.73 (m, 12.5H) 1.73–1.60 (m, 42.5H), 1.53 (m, 12H), 1.46–1.01 (m, 95.5H), 0.93 (m, 43H); ¹³C NMR (126 MHz, CDCl₃) δ 199.7, 149.2,
148.5, 138.7, 137.9, 137.6, 124.6, 124.4, 115.9, 115.8, 65.9, 38.3, 37.5, 37.0, 34.7, 34.6, 32.8, 31.6, 31.5, 31.3, 29.8, 29.1, 29.0, 28.4, 26.1, 26.0, 25.3, 22.7, 22.3, 20.7, 15.3, 14.4, 14.3, 14.2, 11.5.

\((\pm)-(3aR,7aS)-3a-Methyl-3a,4,5,7a-tetrahydro-(1H)-inden-7-yl\)

 trifluoromethanesulfonate (5.29): To a stirred solution of DIPA (0.07 mL, 0.47 mmol) in THF (3 mL) at -78 °C under argon was added nBuLi (0.17 mL, 2.5 M in hexanes, 0.42 mmol) dropwise. The resulting solution was stirred 30 min before ketone 5.26 (40 mg, 0.263 mmol) was added. The reaction mixture was stirred an additional 1 h, after which PhNTf\(_2\) (150 mg, 0.42 mmol) was added. The reaction was allowed to warm to rt and stirred overnight, then filtered through SiO\(_2\), rinsing with DCM, and concentrated \textit{in vacuo}. The residue was purified by column chromatography (SiO\(_2\), 1:99 Et\(_2\)O/hexanes, \(R_f = 0.72\) in 1:19 EtOAc/hexanes, KMnO\(_4\)) to afford 5.29 (56 mg, 76%). Data for 5.29: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 6.05\) (s, 1H), 5.63 (d, \(J = 11.1\), 1H), 5.34 (d, \(J = 11.1\), 1H), 2.71 (bs, 1H), 2.54 (m, 1H), 2.17 (m, 3H), 1.98 (m, 1H), 1.60 (m, 1H), 1.23 (s, 3H).

\((\pm)-(3R)-2-[(E)-1-Hydroxybut-2-en-1-yl]-3-methyl-3-vinylcyclohexan-1-one\) (5.30): To a stirred suspension of CuCl (219 mg, 2.21 mmol) in Et\(_2\)O (8 mL) at -78 °C under argon was added vinylmagnesium bromide (4.4 mL, 1.0 M in THF, 4.41 mmol). After 10 min, a solution of enone 5.15 (243 mg, 2.21 mmol) in Et\(_2\)O (2 mL) was added and stirring was continued for 20 min. A solution of ZnCl\(_2\) (601 mg, 4.41 mmol) in Et\(_2\)O (3 mL) was then
added, followed by crotonaldehyde (0.92 mL, 11.1 mmol). The black solution was stirred for 1 h and quenched with saturated aqueous NH₄Cl solution (10 mL, adjusted to pH 9 with NaOH), and the aqueous layer was extracted with Et₂O (3 x 10 mL). The organic layer was washed with H₂O (10 mL) and saturated aqueous NaCl solution (10 mL), dried over Na₂SO₄, and concentrated in vacuo to afford 5.30 as a roughly 1:1:1:1 mixture of diastereomers, which was used in subsequent reactions without further purification. Data for 5.30: ¹H NMR (500 MHz, CDCl₃) δ 5.93 (m, 1H), 5.79 (m, 1H), 5.61 (m, 1H), 5.20–4.95 (m, 3H), 2.76 (dd, J = 14.9, 4.2, 1H), 2.61–2.12 (m, 4H), 1.68 (m, 6H), 1.59–1.35 (m, 3H), 1.23 (m, 7H), 1.08 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 212.9, 212.3, 146.8, 146.8, 146.0, 144.9, 132.2, 131.3, 130.8, 130.2, 129.2, 128.6, 127.6, 127.3, 112.8, 112.8, 112.3, 112.3, 112.2, 110.7, 71.8, 71.7, 66.9, 66.8, 66.7, 65.6, 65.1, 63.7, 63.6, 60.0, 53.8, 44.4, 44.2, 43.4, 42.1, 42.0, 41.2, 41.2, 41.1, 41.0, 39.8, 39.6, 38.6, 36.7, 36.6, 34.9, 29.7, 28.5, 25.8, 25.7, 25.3, 24.7, 23.4, 22.4, 22.2, 22.1, 21.7, 21.5, 19.3, 19.0, 18.8, 17.8, 17.7, 13.2.

(±)-(3aR,7aR)-3-Hydroxy-7a-methyl-3,3a,5,6,7,7a-hexahydro-(4H)-inden-4-one (5.31): To a stirred solution of ketone 5.30 (310 mg, 1.39 mmol) in DCM (25 mL) was added Grubbs’ second generation catalyst (94 mg, 0.112 mmol) and the reaction was stirred at rt for 2 h. The reaction mixture was filtered through SiO₂, rinsing with EtOAc, and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, gradient eluent from 1:9 to 9:41 EtOAc/hexanes, Rf = 0.17 in 1:4 EtOAc/hexanes, KMnO₄) to afford 5.31 (99 mg, 43%) as a ~1:2 mixture of diastereomers. Data for the diastereomeric mixture of 5.31: ¹H NMR (500 MHz, CDCl₃) δ 6.29 (d, J = 5.7, 1H), 5.92 (dd, J = 5.7, 2.6, 1H),
4.89 (t, J = 2.9, 1H), 3.43 (bs, 1H), 2.61 (m, 1H), 2.41 (m, 2H), 2.15 (m, 2H), 1.94 (m, 1H), 1.82 (td, J = 12.2, 6.3, 2H), 1.23 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 212.5, 146.5, 130.3, 73.1, 61.4, 52.5, 40.8, 34.8, 23.1, 23.0.

($\pm$)-tert-Butyldimethyl([(1aS,4aR,7R,7aR)-4a-methyloctahydroindeno[3a,4b]oxireno-7-yl]oxy)silane (5.43): A stirred solution of enone 5.42 (179 mg, 1.19 mmol) in MeOH (12 mL) was cooled to 0 °C and LiOH-H$_2$O (75 mg, 1.78 mmol) was added in one portion, followed by dropwise addition of H$_2$O$_2$ (0.40 mL, 30 wt. % in H$_2$O, 3.56 mmol). The reaction was allowed to stir at that temperature for 7 h, then diluted with DCM (20 mL) and NaHCO$_3$ (20 mL). The aqueous layer was extracted with DCM (3 x 10 mL), the combined organic extracts were dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO$_2$, gradient eluent from 1:10 to 1:6 EtOAc/hexanes, $R_f$ = 0.38 in 1:4 EtOAc/hexanes, KMnO$_4$) to afford epoxyketone (134 mg, 68%), which was then redissolved in MeOH (8 mL). The solution was cooled to 0 °C with stirring and NaBH$_4$ (15 mg, 0.40 mmol) was added in one portion. After 10 min, the reaction mixture was diluted with DCM (10 mL) and NaHCO$_3$ (10 mL), then the organic layer was extracted with DCM (5 x 10 mL). The combined organic layers were dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude concentrate was filtered through SiO$_2$, rinsing with Et$_2$O, and used in the next reaction without further purification. The epoxy alcohol thus obtained was dissolved in DCM (4 mL) under argon and imidazole was added (121 mg, 1.77 mmol), followed by TBSCl (134 mg, 0.89 mmol). The cloudy white suspension was stirred for 4 h, then quenched with saturated aqueous NHCO$_3$ solution (5 mL). The aqueous layers was extracted with DCM (3
x 5 mL), the combined organic layers were dried over Na₂SO₄, concentrated *in vacuo*, and purified by column chromatography (SiO₂, gradient eluent from 1:99 to 1:33 EtOAc/hexanes, Rₜ = 0.85 in 1:4 EtOAc/hexanes, KMnO₄) to afford epoxide **5.43** (82 mg, 24%) as a pale yellow oil. Data for **5.43**: ¹H NMR (500 MHz, CDCl₃) δ 3.73 (s, 1H), 3.06 (s, 2H), 2.01 (m, 2H), 1.68 (m, 2H), 1.56 (m, 2H), 2.01 (m, 1H), 1.27 (m, 2H), 1.09 (s, 3H), 0.86 (m, 11H), 0.06 (s, 3H), 0.01 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 77.4, 77.4, 77.2, 76.9, 70.0, 58.2, 38.5, 36.6, 34.8, 31.1, 26.0, 25.9, 24.1, 18.3, 16.0, -4.5, -5.0; LRMS (ES+) m / z calculated for C₁₆H₃₀O₂SiNa [M + Na]⁺ 305.19, found 305.18.

(±)-(3R,3aR,7aR)-3-[(tert-Butyldimethylsilyl)oxy]-7a-methyloctahydro-(4H)-inden-4-one (**5.45**): To freshly dried ZnBr₂ (2.0 mg, 0.004 mmol) under argon was added a solution of epoxide **5.43** (1.9 mg, 0.007 mmol) in benzene (0.5 mL) and the mixture was allowed to stir for 1.5 h, then heated to reflux and stirred an additional 40 min. The reaction was quenched with 1:4 saturated aqueous NaHCO₃/H₂O (2 mL), diluted with EtOAc (2 mL), and the aqueous layer was extracted with EtOAc (3 x 2 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, gradient eluent from 1:99 to 1:33 EtOAc/hexanes, Rₜ = 0.50 in 1:10 EtOAc/hexanes, PAA) to afford ketone **5.45** (minute amount isolated). Data for **5.45**: ¹H NMR (500 MHz, CDCl₃) δ 4.27 (dd, J = 9.5, 5.1, 1H), 2.53 (t, J = 8.2, 1H), 2.00 (m, 2H), 1.86 (m, 3H), 1.74 (m, 2H), 1.66 (m, 1H), 1.56 (m, 2H), 1.36 (m, 1H), 1.25 (m, 1H), 1.08 (s, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.03 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 212.6, 74.1, 59.5, 48.6, 38.9, 32.9, 30.8, 27.5, 26.6, 25.9, 22.4, 18.6, -4.5, -5.2; IR
(thin film) 2964, 2920, 2856, 1717, 1462 cm⁻¹; LRMS (ES+) m / z calculated for C16H30O2SiNa [M + Na]⁺ 305.19, found 305.16.

(±)-tert-Butyldimethyl([(1aS,4aR,7S,7aR)-4a-methyloctahydroindeno[3a,4b]oxireno-7-yl]oxy)silane (5.46): A solution of enone 5.42 (316 mg, 2.10 mmol) and CeCl₃·7H₂O (392 mg, 1.05 mmol) in MeOH (20 mL) was sonicated until all solids dissolved, then cooled to 0 °C. NaBH₄ (120 mg, 3.16 mmol) was added in small portions and the reaction was stirred for 3 min before being quenched with saturated aqueous NaHCO₃ solution (10 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic extracts were dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, 1:10 EtOAc/hexanes, Rf = 0.38 in 1:4 EtOAc/hexanes, PAA) to afford the allylic alcohol (255 mg, 81%) as a 3:1 mixture of diastereomers. This material was dissolved in DCM (17 mL), to which imidazole (457 mg, 6.71 mmol) and TBSCl (505 mg, 3.35 mmol) were added. The reaction was stirred at rt for 3 h, filtered to remove solids (rinsing with DCM), and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, gradient eluent from hexanes to 1:99 EtOAc/hexanes, Rf = 0.85 in 1:10 EtOAc/hexanes, PAA) to afford the desired silyl ether (253 mg) as a single diastereomer. This silyl ether was dissolved in a mixture of DCM (2.5 mL), saturated aqueous NaHCO₃ (4 mL), aqueous EDTA buffer (1.5 mL, 1 x 10⁻⁴ M), and acetone (0.25 mL). This solution was cooled to 0 °C and Oxone (644 mg, 1.37 mmol) was added with vigorous stirring. After 40 min, the reaction was warmed to rt and stirring was continued for 8 h. Additional acetone (5 mL), DCM (10 mL), saturated aqueous NaHCO₃ (5 mL), and aqueous
EDTA buffer (5 mL) were added after 2 h and additional portions of Oxone (4.2 g total) were added roughly every 2 h until the reaction was complete, as judged by TLC analysis. The reaction was quenched with 2-methyl-2-butene (5 mL), the aqueous phase was extracted with DCM (3 x 10 mL), the organic layers were dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, 1:19 Et₂O/hexanes, R_f = 0.38 in 1:20 EtOAc/hexanes, PAA) to afford the desired epoxide 5.46 (248 mg, 42%). Data for 5.46: ¹H NMR (500 MHz, CDCl₃) δ 4.12 (t, J = 7.7, 1H), 3.33 (s, 1H), 2.02 (d, J = 15.1, 1H), 1.92 (m, 1H), 1.60 (m, 5H), 1.37 (d, J = 13.2, 1H), 1.29 (m, 2H), 1.24 (m, 1H), 1.04 (m, 1H), 0.98 (s, 3H), 0.86 (s, 9H), 0.03 (s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 73.3, 71.2, 54.4, 36.7, 36.7, 34.3, 30.8, 29.8, 25.9, 25.4, 23.9, 18.4, 15.9, -4.6, -4.8; IR (thin film) 2929, 2856, 1463 cm⁻¹; LRMS (ES+) m / z calculated for C₁₆H₃₀O₂SiNa [M + Na]⁺ 305.19, found 305.18.

(±)-7a-Methyl-1,2,5,6,7,7a-hexahydro-(4H)-inden-4-one (5.47): To freshly dried ZnBr₂ (8.5 mg, 0.038 mmol) under argon was added a solution of epoxide 5.46 (22 mg, 0.079 mmol) in benzene (1.0 mL) and the mixture was heated at reflux for 32 h. The reaction was diluted with EtOAc (2 mL), poured into 50% saturated aqueous NaHCO₃ (5 mL), and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, gradient eluent from 1:99 to 1:49 to 1:24 to 1:19 Et₂O/hexanes, R_f = 0.31 in 1:10 EtOAc/hexanes, PAA) to afford enone 5.47 (6 mg, 51%), which was identical in all respects to reported spectroscopic values.⁵³
**3-Methoxy-2-(2-methylallyl)cyclopent-2-en-1-one (5.52):** A stirred solution of KOH (3.36 g, 60.0 mmol) in H₂O (50 mL) was cooled to 0 °C and 1,3-cyclopentanedione (5.98 g, 60.0 mmol) was added. The reaction was sonicated until a brown, uniform suspension was formed and 3-bromo-2-methylpropene (7.26 ml, 72.0 mmol) was added dropwise with vigorous stirring. After 5 d, the reaction was filtered through a Buchner funnel, washing gummy solids with H₂O. The solids were allowed to air-dry and harden, then collected and dried further under reduced pressure on a high-vacuum pump (0.5 mm Hg). The aqueous washes were rendered basic by addition of aqueous NaOH (6 M), washed with hexanes (3 x 10 mL) to remove non-polar impurities, then acidified with aqueous HCl (1 M). The aqueous solution was extracted with EtOAc (4 x 10 mL), the combined organic phases were dried over Na₂SO₄, and concentrated *in vacuo* before being combined with the previously isolated solids. The residue was purified by column chromatography (SiO₂, gradient eluent from DCM to 1:19 to 1:9 MeOH/DCM, Rf = 0.38 in 1:9 MeOH/DCM, PAA) to afford desired the vinylogous acid (4.8658 g), which was redissolved in minimal amount of MeOH. The solution was cooled to 0 °C and a solution of CH₂N₂ was added dropwise until starting material was consumed by TLC analysis and a yellow color persisted. The reaction was quenched by the addition of 10% AcOH in MeOH (15 mL) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, gradient eluent from 1:1 to 4:1 EtOAc/hexanes to EtOAc, Rf = 0.74 in 1:9 MeOH/DCM, PAA) to afford vinylogous ester 5.52.
Data for 5.52: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.70 (s, 1H), 4.60 (s, 1H), 3.95 (s, 3H), 2.84 (s, 2H), 2.69 (t, $J$ = 4.8, 2H), 2.48 (t, $J$ = 4.8, 2H), 1.72 (s, 3H).

7-Methyl-3,4,5,8-tetrahydroazulen-1(2H)-one (5.53): To flame-dried Mg powder (926 mg, 38.1 mmol) in THF (15 mL) under argon was added DIBAL-H (0.1 mL) and the reaction was stirred for 15 min. 4-Bromo-1-butene (2.32 mL, 22.9 mmol) in THF (5 mL) was added dropwise, giving a bubbling dark grey reaction mixture. After the bubbling subsided, the reaction was heated to 90 °C and stirred for 20 min. The resulting Grignard reagent was added dropwise to a suspension of anhydrous CeCl$_3$ (5.63 g, 22.9 mmol) in THF (10 mL) at rt. The mixture was stirred for 30 min and vinylogous ester 5.52 (1.27 g, 7.62 mmol) in THF (5 mL) was added. After 10 min of stirring, the reaction was cooled to 0 °C and quenched with aqueous HCl (10 mL, 1 M). The reaction mixture was diluted with H$_2$O and EtOAc, then the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried over Na$_2$SO$_4$ and concentrated in vacuo. The black residue was purified by column chromatography (SiO$_2$, gradient eluent from 1:9 to 1:6 to 1:4 EtOAc/hexanes, $R_f$ = 0.48 in 1:1 EtOAc/hexanes, PAA) to give bicyclic enone (824 mg) as an red oil. A portion of this enone (394 mg, 1.91 mmol) was dissolved in degassed benzene (100 mL, degassed by bubbling argon for ≥1 h), the septum was quickly removed, and Hoveyda–Grubbs second generation catalyst (125 mg, 0.200 mmol) was added in on portion. The flask was quickly resealed and heated, with stirring, at 80 °C for 30 min. The reaction was cooled to rt, ethyl vinyl ether (1 mL) was added, and the reaction was stirred an additional 5 min. The reaction mixture was concentrated in vacuo and the black residue
was purified by column chromatography (SiO$_2$, gradient eluent from 1:10 to 1:6 to 1:4 EtOAc/hexanes, $R_f = 0.29$ in 1:4 EtOAc/hexanes, PAA) to afford alkene **5.53** (71 mg, 6%). Data for **5.53**: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.64 (t, $J = 6.5$, 1H), 2.94 (s, 2H), 2.43 (m, 5H), 2.31 (m, 4H), 2.31 (s, 3H).

**(+)-(3a$R$,8a$R$)-7-Methyl-2,3,5,8-tetrahydro-(1H,4H)-3a,8a-methanoazulen-1-one (5.54)**: To a cooled mixture of NaH (90 mg, 2.24 mmol) and trimethylsulfoxonium iodide (550 mg, 2.50 mmol) under argon at 5 °C, DMSO (3 mL) was added dropwise. The mixture was warmed to rt by removal of the cooling bath and sonicated for several minutes. The reaction was then stirred at rt for 45 min to form a clear, colorless, viscous mixture. Enone **5.53** (33 mg, 0.204 mmol) in DMSO (0.5 mL + 0.5 mL to rinse) was added and the resulting mixture was stirred vigorously. After 15 min, the reaction was heated at 75 °C for 15 min, then cooled to rt and poured onto ice. The mixture was extracted with Et$_2$O (3 x 10 mL), the combined organic phases were dried over MgSO$_4$, and concentrated in vacuo (ca. 50 mm Hg) The residue was purified by column chromatography (SiO$_2$, gradient eluent from 1:19 to 1:9 to 1:6 to 1:4 Et$_2$O/hexanes, $R_f = 0.61$ in 1:4 EtOAc/hexanes, PAA) to afford cyclopropane **5.54** (18 mg, 50%). Data for **5.54**: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.21 (s, 1H), 2.82 (d, $J = 16.6$, 1H), 2.30 (m, 1H), 2.20 (d, $J = 16.3$, 1H), 2.11 (m, 3H), 2.04 (m, 1H), 2.00 (m, 1H), 1.96 (m, 1H), 1.92 (m, 1H), 1.87 (m, 1H), 1.70 (m, 3H), 1.32 (m, 1H), 1.21 (d, $J = 4.6$, 1H), 1.13 (d, $J = 4.6$, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 215.3, 134.7, 123.5, 41.4, 35.7, 33.3, 30.4, 30.3, 27.3, 26.4, 26.2, 26.0; LRMS (ES+) m / z calculated for C$_{12}$H$_{17}$O [M + H]$^+$ 177.1279, found 177.1100.
(±)-(3aR,8aS)-3a,7-Dimethyl-3,3a,4,5,8,8a-hexahydroazulen-1(2H)-one (5.55) and (±)-(3aR,8aR)-3a,7-dimethyl-3,3a,4,5,8,8a-hexahydroazulen-1(2H)-one (5.56): A) NH₃ (4 mL) was condensed into pre-cooled (−78 °C) flask and a freshly cut, hexanes-washed piece of Li wire (3.9 mg, 0.556 mmol) was added, giving the reaction mixture a blue color. Cyclopropyl ketone 5.54 (20 mg, 0.111 mmol) in THF (1 mL + 1 mL to rinse) was added dropwise and the reaction was stirred for 15 min, after which the reaction was quenched with excess solid NH₄Cl. THF (5 mL) was added and the NH₃ was allowed to slowly evaporate as the reaction warmed to rt. The reaction mixture was extracted with Et₂O (3 x 10 mL), the combined organic phases were dried over MgSO₄, and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, gradient eluent from 1:19 to 1:9 Et₂O/hexanes, R_f = 0.56 in 1:4 EtOAc/hexanes, PAA) to afford diastereomeric ketones 5.55 and 5.56 (7 mg, 35%) in a 1:2.5 ratio; B) To a stirred solution of cyclopropane 5.54 (10 mg, 0.057 mmol) in THF (0.4 mL) and DMPU (0.1 mL) under argon at −78 °C was added SmI₂ solution (0.5 mL, 0.05 M in THF, 0.025 mmol) dropwise. The reaction was stirred for 10 min, then warmed to rt and stirred for an additional 5 min. Additional aliquots of SmI₂ (2 x 0.5 mL, 0.05 M in THF, 0.050 mmol total) were added at −78 °C and the reaction was warmed to rt, to be monitored by TLC. When the reaction was judged to be complete, the reaction was quenched by addition of saturated aqueous NaHCO₃ solution and stirred vigorously. The aqueous phase was extracted with Et₂O (3 x 10 mL), the combined organic phases were dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO₂, gradient eluent from 1:49 to 1:24 to
3:47 to 1:9 Et₂O/hexanes, \( R_f = 0.56 \) in 1:4 EtOAc/hexanes, PAA) to afford diastereomeric ketones 5.55 and 5.56 (3 mg, 30%) in a 1:2.4 ratio. Data for 5.55 and 5.56: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 5.49 (m, 1H), 5.41 (m, 2.5H), 2.38–2.09 (m, 21H), 2.06 (m, 3H), 1.97 (m, 6H), 1.84–1.41 (m, 33H), 1.17 (s, 9H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \): 221.1, 218.9, 136.8, 136.6, 125.7, 125.4, 66.0, 58.7, 58.4, 42.6, 42.5, 41.2, 36.5, 36.0, 35.8, 34.5, 29.8, 29.4, 28.6, 27.5, 27.2, 26.9, 24.3, 23.9, 17.2, 15.5, 15.4; LRMS (ES+) m / z calculated for C\(_{12}\)H\(_{18}\)ONa [M + Na]\(^{+}\) 201.1255, found 201.3274.

(±)-(1S,3S,3aS,6S)-7-Bromo-6-hydroxy-3-methoxy-3a-methyl-2,3,3a,4,5,6-hexahydro-(1H)-inden-1-yl benzoate (5.84): An analogue of enone 5.83 (591 mg, 1.90 mmol), protected with TES on the C15 hydroxyl, was dissolved in DCM (10 mL) and cooled to \(-78^\circ\)C. \( \text{Br}_2 \) (0.11 mL, 2.09 mmol) was added, the reaction was warmed to 0 °C, and the reaction was allowed to stir for several minutes before Et\(_3\)N (0.32 mL, 2.28 mmol) was added. The reaction was stirred for an additional 3 h and quenched with saturated aqueous NaHCO\(_3\) solution (10 mL). The aqueous phase was extracted with DCM (2 x 10 mL), the combined organic layers were dried over Na\(_2\)SO\(_4\), and concentrated \textit{in vacuo} to afford, after column chromatography (SiO\(_2\), gradient eluent from 1:9 to 1:4 to 1:1 EtOAc/hexanes, \( R_f = 0.08 \) in 1:4 EtOAc/hexanes, KMnO\(_4\)) deprotected alcohol 5.104 (R = H, 245 mg, 47%). This alcohol (245 mg, 0.89 mmol) was dissolved in DCM (10 mL) with DMAP (261 mg, 2.14 mmol) under argon and cooled to 0 °C. BzCl (0.11 mL, 0.89 mmol) was added dropwise and stirring was continued for 2 h, after which the reaction was quenched with saturated
aqueous NH$_4$Cl (10 mL), the organic phase was dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO$_2$, gradient eluent from 1:19 to 1:9 to 1:4 EtOAc/hexanes, R$_f$ = 0.22 in 1:4 EtOAc/hexanes, KMnO$_4$) to afford a bromoenone (260 mg, 77%). This enone (260 mg, 0.686 mmol) was dissolved in MeOH/THF (1:3, 9 mL) and stirred vigorously. CeCl$_3$$ \cdot $7H$_2$O (511 mg, 1.37 mmol) was added and stirred until completely dissolved, after which NaBH$_4$ (39 mg, 1.03 mmol) was added. The reaction was stirred for 3 h and quenched with acetone (1 mL), diluted with H$_2$O (10 mL), and the aqueous phase was extracted with DCM (4 x 10 mL). The combined organics were dried over Na$_2$SO$_4$ and concentrated in vacuo to afford 5.84 (220 mg, 84%), which was used without further purification. Data for 5.84: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.04 (d, $J$ = 7.2, 2H), 7.57 (t, $J$ = 7.4, 1H), 7.41 (t, $J$ = 7.8, 2H), 5.84 (d, $J$ = 7.4, 1H), 4.37 (t, $J$ = 8.0, 1H), 3.62 (dd, $J$ = 10.8, 7.1, 1H), 3.37 (s, 3H), 2.58 (bs, 1H), 2.23 (m, 3H), 2.03 (m, 2H), 1.73 (dd, $J$ = 13.8, 3.1, 1H), 1.10 (s, 3H).

(±)-(1S,3S,3aS,7aS)-7-Bromo-3-methoxy-3a-methyl-2,3,3a,4,5,7a-hexahydro-(1H)-inden-1-yl benzoate (5.86): A stirred solution of alcohol 5.84 (54 mg, 0.142 mmol) in THF (1.5 mL) under argon was cooled to 0 °C and nBu$_3$P (115 µL, 0.467 mmol) was added. DIAD (83 µL, 0.425 mmol) was then added and the resulting solution was stirred for 30 min, cooled between −30 °C and −40 °C, and NBSH (92 mg, 0.425 mmol) was added. After 1 h, the reaction was warmed to rt and quenched with saturated aqueous NaHCO$_3$ solution (2 mL). The aqueous phase was extracted with EtOAc (3 x 3 mL), the combined organic layers were dried over Na$_2$SO$_4$, and concentrated in vacuo to afford, after column chromatography
(SiO$_2$, gradient eluent from 1:19 to 1:9 to 1:4 to 1:1 EtOAc/hexanes, $R_f = 0.67$ in 1:1 EtOAc/hexanes, KMnO$_4$) vinyl bromide 5.86 (12 mg, 23%). Data for 5.86: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.09 (d, $J = 7.1$, 2H), 7.59 (t, $J = 8.8$, 1H), 7.44 (t, $J = 7.6$, 2H), 6.02 (s, 1H), 5.27 (t, $J = 9.9$, 1H), 3.62 (t, $J = 8.3$, 1H), 3.32 (s, 3H), 2.85 (m, 1H), 2.47 (m, 1H), 2.26 (m, 2H), 2.10 (m, 1H), 1.94 (m, 1H), 0.96 (s, 3H).

(±)-(1S,3S,3aS,7aR)-3-methoxy-3a-methyl-7-{1-[(trimethylsilyl)oxy]vinyl}-2,3,3a,4,5,7a-hexahydro-(1H)-inden-1-yl benzoate (5.87): A stirred solution of vinyl bromide 5.86 (6 mg, 0.016 mmol), (Ph$_3$P)$_2$PdCl$_2$ (~1 mg), tributyl(1-ethoxyvinyl)stannane (6 µL, 0.018 mmol) in DMF (0.3 mL) under argon was heated at 70 °C for 4.5 h. The reaction was cooled to rt and quenched with saturated aqueous NaHCO$_3$ solution (2 mL). The aqueous phase was extracted with DCM (3 x 3 mL), the combined organic layers were dried over Na$_2$SO$_4$, and concentrated in vacuo to afford, after column chromatography (SiO$_2$, gradient eluent from 1:19 to 1:9 to 1:4 EtOAc/hexanes, $R_f = 0.50$ in 1:4 EtOAc/hexanes, KMnO$_4$) desired enone (5 mg, 95%), which could be elaborated into unstable silyl enol ether 5.87 by treatment with excess TMSOTf and Et$_3$N in DCM. Data for the intermediate enone: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.13 (d, $J = 8.1$, 2H), 7.61 (t, $J = 7.6$, 1H), 7.50 (t, $J = 7.5$, 2H), 6.05 (s, 1H), 5.33 (t, $J = 11.5$, 1H), 3.65 (t, $J = 8.7$, 1H), 3.40 (s, 3H), 2.88 (m, 1H), 2.50 (dt, $J = 15.1$, 8.3,1H), 2.30 (m, 2H), 2.16 (m, 1H), 2.03 (m, 1H), 1.67 (m, 1H), 1.31 (m, 7H), 1.01 (s, 3H), 0.91 (m, 5H).
(±)-(15S,3S,3aS,6R)-6-(Benzo[d]thiazol-2-ylthio)-7-bromo-3-methoxy-3a-methyl-2,3,3a,4,5,6-hexahydro-(1H)-inden-1-yl benzoate (5.100): A stirred solution of alcohol 5.84 (36 mg, 0.094 mmol) and benzo[d]thiazole-2-thiol (24 mg, 0.144 mmol) in THF (1 mL) at 0 °C under argon was added nBu3P (43 µL, 0.176 mmol). DIAD (35 µL, 0.176 mmol) was then added and the reaction was allowed to stir for 5 h at 0 °C. The reaction mixture was concentrated in vacuo and purified by column chromatography (SiO2, gradient eluent from 1:19 to 1:9 to 1:4 EtOAc/hexanes, RF = 0.40 in 1:4 EtOAc/hexanes, KMnO4) to afford 5.100 (45 mg, 90%) as a white solid. Data for 5.100: 1H NMR (500 MHz, CDCl3) δ 8.08 (d, J = 7.3, 2H), 7.88 (d, J = 8.1, 1H), 7.75 (d, J = 8.0, 1H), 7.59 (t, J = 7.6, 1H), 7.45 (m, 3H), 7.30 (m, 2H), 5.96 (d, J = 8.1, 1H), 4.99 (d, J = 4.6, 1H), 3.68 (dd, J = 10.7, 7.2, 1H), 3.41 (s, 3H), 2.61 (td, J = 14.3, 3.9, 1H), 2.42 (d, J = 15.0, 1H), 2.30 (d, J = 7.2, 1H), 2.19 (d, J = 7.1, 1H), 1.93 (m, 2H), 1.40 (m, 4H), 1.10 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 166.1, 165.5, 153.2, 148.8, 135.4, 133.1, 129.9, 129.9, 128.5, 127.2, 126.2, 124.6, 124.5, 121.8, 121.4, 121.1, 118.1, 112.1, 87.2, 21.8, 58.2, 54.3, 48.3, 36.2, 30.7, 28.7, 24.7, 19.1, 13.9.

(±)-(15S,3S,7aS)-3-Hydroxy-1-methoxy-7a-methyl-1,2,3,6,7,7a-hexahydro-(5H)-inden-5-one (5.104): To a stirred solution of enone 5.78 (2.50 g, 13.9 mmol) in isopropenyl acetate (60 mL) was added pTsOH·H2O (660 mg, 3.47 mmol). The mixture was heated at reflux for 3 h, diluted with EtOAc (50 mL), and quenched with saturated aqueous NaHCO3
solution (30 mL). The organic phase was washed with H₂O (30 mL), saturated aqueous NaCl (30 mL), dried over Na₂SO₄, and concentrated in vacuo. The crude dienyl acetate was dissolved in acetone (80 mL), H₂O (30 mL), and saturated aqueous NaHCO₃ (30 mL), then cooled to 0 °C. Oxone (27.8 g, 45.2 mmol) to the vigorously stirred solution and the reaction was allowed to stir for 1 h. The mixture was diluted with H₂O (100 mL), the aqueous phase was extracted with EtOAc (4 x 50 mL), the combined organics were washed with saturated aqueous NaCl (50 mL), and dried over Na₂SO₄. The organic solution was concentrated in vacuo and to afford alcohol 5.104 (1.36 g, 45%). Data for 5.104: ¹H NMR (500 MHz, CDCl₃) δ 4.84 (d, J = 7.7, 1H), 3.79 (dd, J = 11.0, 6.7, 1H), 3.42 (s, 3H), 3.02 (s, 1H), 2.81 (dd, J = 16.3, 5.5, 1H), 2.69 (d, J = 16.3, 1H), 2.34 (dd, J = 13.8, 6.7, 1H), 2.19 (dd, J = 13.1, 5.5, 1H), 2.05 (m, 3H), 1.16 (s, 3H).

(±)-(1S,3S,7aS)-1-Methoxy-7a-methyl-3-[(triethylsilyl)oxy]-1,2,3,6,7,7a-hexahydro-(5H)-inden-5-one (5.104): To a stirred solution of crude enone 5.104 (R = H, 3.70 g, ~13.9 mmol) and imidazole (2.08 g, 30.6 mmol) in DCM (70 mL) was added TESCl (3.03 mL, 18.1 mmol). The mixture was allowed to stir at rt for 1.5 h, quenched with saturated aqueous NaCl solution (30 mL), and the aqueous phase was extracted with DCM (30 mL). The combined organic layers were washed with H₂O (30 mL), saturated aqueous NaHCO₃ (30 mL), saturated aqueous NaCl (30 mL), dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, gradient eluent from 1:9 to 1:4 EtOAc/hexanes, Rf = 0.33 in 1:4 EtOAc/hexanes, KMnO₄) to afford silyl ether 5.104 (1.93 g,
Data for 5.104: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.98 (s, 1H), 4.82 (ddd, $J$ = 10.0, 4.6, 2.0, 1H), 3.62 (t, $J$ = 8.2, 1H), 3.36 (s, 3H), 2.53 (ddd, $J$ = 16.3, 14.6, 5.2, 1H), 2.38 (ddd, $J$ = 14.6, 4.8, 2.3, 1H), 2.20–2.03 (m, 5H), 1.99 (dd, $J$ = 13.8, 4.7, 1H), 1.16 (s, 3H), 0.99 (t, $J$ = 7.9, 14H), 0.61 (m, 9H).

![Diagram of molecule](image)

($\pm$)-1-(1S,3aR,7aS)-1-(tert-Butoxy)-7a-methyl-2,3,3a,6,7,7a-hexahydro-(1H)-inden-4-yl)ethan-1-one (5.109): Enone 5.109 was made by the known route,$^{49}$ and selected characterization data are as follows: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.68 (bs, 1H), 3.48 (t, $J$ = 8.1, 1H), 2.38 (m, 2H), 2.26 (s, 4H), 2.17 (m, 1H), 2.00 (m, 1H), 1.81 (dt, $J$ = 12.7, 4.1, 1H), 1.52 (m, 1H), 1.42 (m, 1H), 1.27 (m, 1H), 1.15 (s, 12H), 0.72 (s, 3H).

![Diagram of molecule](image)

($\pm$)-{(1-[1S,3aR,7aS]-1-(tert-Butoxy)-7a-methyl-2,3,3a,6,7,7a-hexahydro-(1H)-inden-4-yl]vinyl}oxy)trimethylsilane (5.110): To a stirred solution of enone 5.109 (421 mg, 1.68 mmol) in DCM (20 mL) at 0 °C was added Et$_3$N (0.35 mL, 2.52 mmol) and TMSOTf (0.37 mL, 2.02 mmol). The mixture was allowed to stir at rt for 4 h, quenched with cold saturated aqueous NaHCO$_3$ solution (20 mL), and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was dissolved in benzene (5 mL) and used as an ~0.21 M solution for further reactions. Data for 5.110: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.91 (bs, 1H), 4.28 (s, 1H),
4.13 (s, 1H), 3.49 (m, 1H), 2.59 (m, 1H), 2.19 (m, 3H), 1.94 (m, 4H), 1.75 (m, 1H), 1.53 (m, 3H), 1.15 (s, 14H), 0.73 (s, 3H), 0.21 (s, 12H).

(±)-1-[(1S,3aR,7aS)-1-(tert-Butoxy)-7a-methyl-2,3,3a,6,7,7a-hexahydro-(1H)-inden-4-yl]vinyl acetate (5.111): To a stirred solution of DIPA (32 µL, 0.226 mmol) in THF (1 mL) at -78 °C under argon was added nBuLi (0.11 mL, 2.05 M, 0.226 mmol). This mixture was stirred for 5 min, then added to a stirred solution of enone 5.109 (47 mg, 0.188 mmol) in THF (2 mL) at -78 °C under argon. The reaction was stirred for an additional 15 minutes, treated with Ac₂O (32 µL, 0.339 mmol), and allowed to warm slowly to rt. After 3 h, the reaction was quenched with saturated aqueous NH₄Cl solution (2 mL) and the aqueous phase was extracted with EtOAc (3 x 2 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, gradient eluent from hexanes to 1:19 to 1:9 EtOAc/hexanes, Rf = 0.57 in 1:4 EtOAc/hexanes, KMnO₄) to afford 5.111 (10 mg, 18%). Data for 5.111: ¹H NMR (500 MHz, CDCl₃) δ 5.84 (m, 1H), 4.89 (s, 1H), 4.69 (s, 1H), 3.50 (m, 1H), 2.26–2.10 (m, 8H), 2.01 (m, 3H), 1.76 (m, 2H), 1.61 (m, 5H), 1.29 (m, 3H), 1.15 (s, 12H), 0.74 (s, 3H).
(±)-(4S,5R,9R,10R,13S,17S)-17-(tert-Butoxy)-4-[(tert-butyldimethylsilyl)oxy]-10- (chloromethyl)-13-methyl-3,4,5,6,9,10,11,12,13,15,16,17-dodecahydro-(1H)-
cyclopenta[a]phenanthrene-1,7(2H)-dione (5.122): To a stirred solution of enone 5.117 (41 mg, 0.149) in DCM (1 mL) at 0 °C under argon was added Et2AlCl (0.25 mL, 1.0 M in hexanes, 0.250 mmol). After 5 min, a solution of 5.110 (0.50 mL, ~0.21 M in toluene, 0.105 mmol) was added and the reaction was allowed to stir for 3 h. The reaction was quenched with Et₃N (1 mL), saturated aqueous Rochelle’s salt (2 mL), and saturated aqueous NaHCO₃ solution (4 mL) and the resulting biphasic mixture was stirred for an additional 20 min. The aqueous phase was extracted with DCM (3 x 2 mL), the combined organic layers were washed with saturated aqueous NaCl (2 mL), dried over Na₂SO₄, and concentrated in vacuo. The residue was redissolved in DCM (1 mL), cooled to 0 °C, and treated with NBS (80 mg, 0.448 mmol). After 15 min stirring, the reaction was quenched with saturated aqueous Na₂S₂O₃ (2 mL), the aqueous phase was extracted with DCM (3 x 1 mL), and the combined organic layers were dried over Na₂SO₄. The resulting organic solution was concentrated in vacuo and purified by column chromatography (SiO₂, gradient eluent from 1:19 to 1:9 EtOAc/hexanes, Rₚ = 0.44 in 1:4 EtOAc/hexanes, KMnO₄) to afford bromoketone (13 mg, 20%) as a 1:1 mixture of diastereomers. This bromoketone was dissolved in DMF (0.5 mL), along with LiCl (10 mg, 0.236 mmol) and Li₂CO₃ (40 mg, 0.541 mmol) and heated at 100 °C for 2 h. The reaction was allowed to cool to rt, quenched with H₂O (2 mL), and extracted with Et₂O (3 x 2 mL). The combined organic layers were dried over Na₂SO₄, concentrated in vacuo, and purified by column chromatography (SiO₂, gradient eluent from hexanes to 1:19 to 1:9 EtOAc/hexanes, Rₚ = 0.48 in 1:4 EtOAc/hexanes, KMnO₄) to afford enone 5.122 (3 mg, 27%). Data for 5.122: ¹H NMR (500
MHz, CDCl$_3$) $\delta$ 4.27 (d, $J = 11.3$, 1H), 4.17 (m, 1H), 4.02 (m, 1H), 3.33 (m, 1H), 3.31 (d, $J = 11.3$, 1H), 2.92 (m, 2H), 2.79 (m, 1H), 2.45 (m, 2H), 2.33 (m, 1H), 2.18 (s, 1H), 2.13 (m, 1H), 1.97 (m, 1H), 1.87 (m, 1H), 1.73 (m, 2H), 1.64 (m, 2H), 1.16 (s, 11H), 0.94 (m, 11H), 0.87 (s, 3H), 0.82 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 210.0, 198.8, 161.7, 158.3, 126.6, 79.7, 57.9, 43.5, 42.0, 41.3, 37.4, 33.0, 32.7, 32.5, 30.0, 29.7, 28.8, 28.7, 25.9, 25.8, 25.7, 18.6, 16.2, –4.4, –5.3; HRMS (ES+) m/z calculated for C$_{29}$H$_{47}$ClO$_4$SiNa [M + Na]$^+$ 545.28, found 545.30.

5.9 Notes and References


2 A quick literature search shows 9796 trans-hydrindane containing natural products and only 1523 cis-hydrindane containing natural products.


6 Mr. Hung Pham from the Houk lab at UCLA performed these calculations using a M06-2X density functional and a 6-31+G(d,p) basis set in implicitly modeled THF.

7 This unpublished example from Dr. Christopher Plummer's work in the Leighton group (Columbia University) was made known to us through personal communication after our work on this retrosynthetic route was already well underway.


9 For the synthesis and characterization of 5.18 by Cu-mediated conjugate addition, see: Rafferty, R. J.; Williams, R. M. J. Org. Chem. 2012, 77, 519–524.
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Appendix: NMR Data
OTBPs