Development of Tandem Chemical Processes for the Synthesis of Bioactive Natural Products

by

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Dedication

To Mom and Dad

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Abstract

The discovery of new reagents and the development of new tandem chemical processes, which permit access to bioactive natural products and therapeutic agents, is an area of great interest. Described herein is the development of two new tandem chemical processes: the synthesis of conjugated polyenes utilizing designed sulfonylphosphonate reagents and the stereoselective rapid assembly of steroid skeletons via a Michael-aldol-aldol cascade.

Chapter 1 provides an overview of polyenes including their importance in medicine and materials science and synthetic advancements. Discussed is synthetic methods and strategies employed in polyene synthesis including the historically employed linear installation approach and recent advancements using iterative cross-coupling.

Chapter 2 describes the development of sulfonylphosphonate reagents for the synthesis of unsymmetrical all *trans*-polyenes. Selective metalation of sulfonylphosphonate results in sufficiently stable carbanions that undergo chemoselective Julia-Kocienski condensation with aldehydes to provide (*E*)-allylic phosphonates in good yields and selectivities (16 examples, up to 85% yield, and up to >95:5 *E*:*Z*). The subsequent Horner-Wadsworth-Emmons condensation with aldehydes is used to synthesize various unsymmetrical *trans*-dienes, trienes, and tetraenes. This methodology was utilized in the concise synthesis (5 linear steps, 6 total steps) of a naturally occurring fluorescent probe, β-parinaric acid.

Chapter 3 provides an overview of cardiotonic steroids including their structure, biological activity, and historical importance. The chapter focuses on synthetic strategies including semi-synthetic and synthetic methods and highlights the inherent challenges that prevent appreciable quantities of cardiotonic steroids to be synthesized.

Chapter 4 describes a rapid conceptually new asymmetric approach to functionalized oxygenated steroid cores. Developed is the unprecedented chiral bis(oxazoline) copper(II) complex-catalyzed enantioselective and diastereoselective Michael reaction of cyclic ketoesters and enones to install challenging vicinal quaternary and tertiary stereocenters (8 examples, up to 95% yield, up to >20:1 dr, and up to 96% ee). These products subsequently undergo base-promoted diastereoselective aldol cascade reactions resulting in the natural (3 examples, up to 59% yield, up to >20:1 dr, and up to 92% ee) or unnatural (6 examples, up to 86% yield, >20:1 dr, and up to 99% ee) steroid skeletons.

Chapter 1

Polyenes: An Overview of the Biology and Chemistry of Polyenes

1.1. Introduction

Conjugated polyenes represent an important and diverse class of natural and unnatural products. Polyenes that possess interesting biological properties are produced by nearly every organism. Due to their unique properties, polyenes are increasingly being used in medicine (e.g. drugs and biological probes) and materials science (e.g. non-linear optics). As a result, polyenes continue to be a research topic of great interest.[1]

1.2. Brief Overview of Polyenes in Nature

An important class of polyenes are retinoids (Figure 1.1).[2] Retinoids are natural and unnatural compounds structurally related to vitamin A (retinol, **1**). Retinoic acid (**2**) is a vital component of embryo development. Retinal (**3**) and 11-*cis*-retinal (**5**) are chemically responsible for vision in vertebrates.[3] 9-*cis*-Retinoic acid (**4**) is a FDA-approved anti-cancer agent for the treatment of Kaposi's sarcoma.[4] 13-*cis*-Retinoic acid (**5**) is used as an acne drug.[5] It is worth noting that as a result of retinoic acid's (**2**) role in embryo development, retinoic acid derivatives are often teratogens. Due to the importance of their biological roles and use in medicine, retinoids have become common synthetic targets.

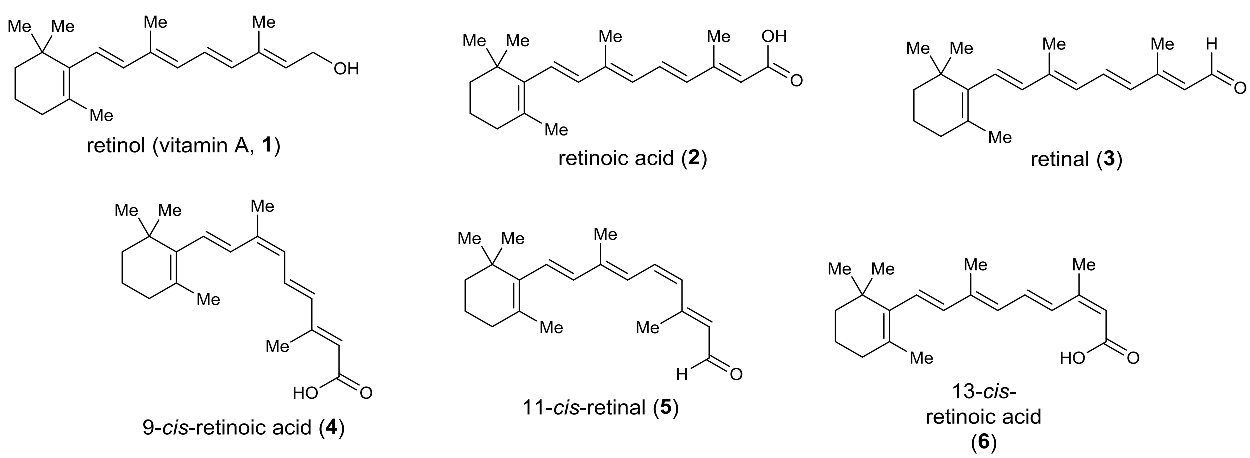


Figure 1.1. Structures of selected examples of retinoids.

Another important class of polyenes are the polyene macrolide antimycotics (**Figure 1.2**).[6] Polyenes in this group are typically obtained from *Streptomyces* soil bacteria and are significant due to their anti-fungal activity. Examples of polyene macrolide antimycotics include amphotericin B (**7**), natamycin (**8**), and nystatin (**9**). Amphotericin B and nystatin are anti-fungal drugs that are listed on the World Health Organization's List of Essential Medicines.[7] Natamycin is also an anti-fungal drug, but is also used as a food preservative.[8] Although not fully understood, the mechanism of action for their anti-fungal properties is proposed to be fungal cell death due to ion leakage. The polyene macrolide antimycotic binds to ergosterol of the fungal cell membrane. This interaction weakens the cell membrane forming a transmembrane channel. This causes ion leakage through the formed pore, which leads to cell death.[9] Polyene macrolide antimycotics have also been widely-studied and synthetically targeted due to their unique properties.

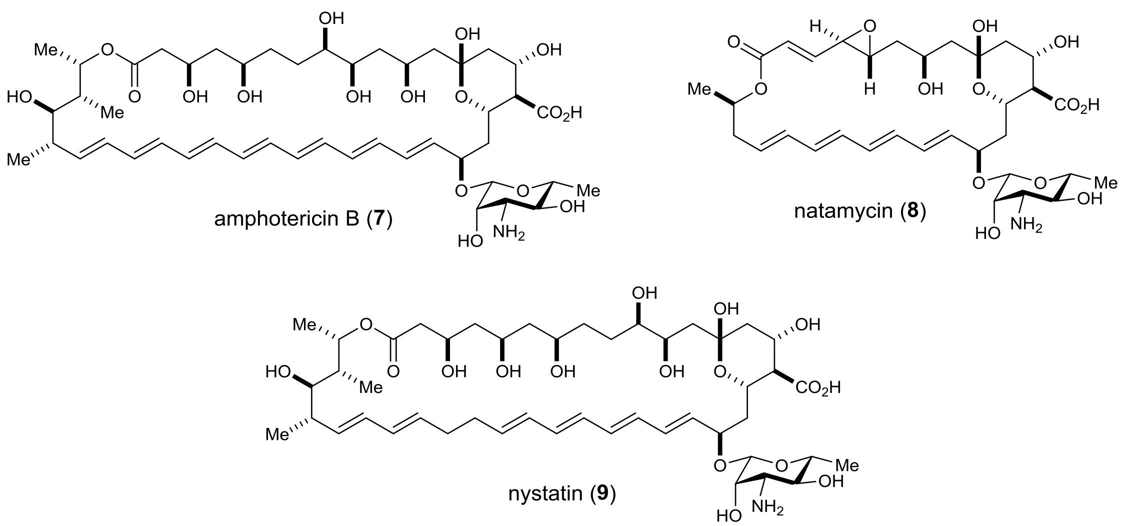


Figure 1.2. Structures of amphotericin B, natamycin, and nystatin.

1.3.0. Synthetic Strategies in Polyene Synthesis

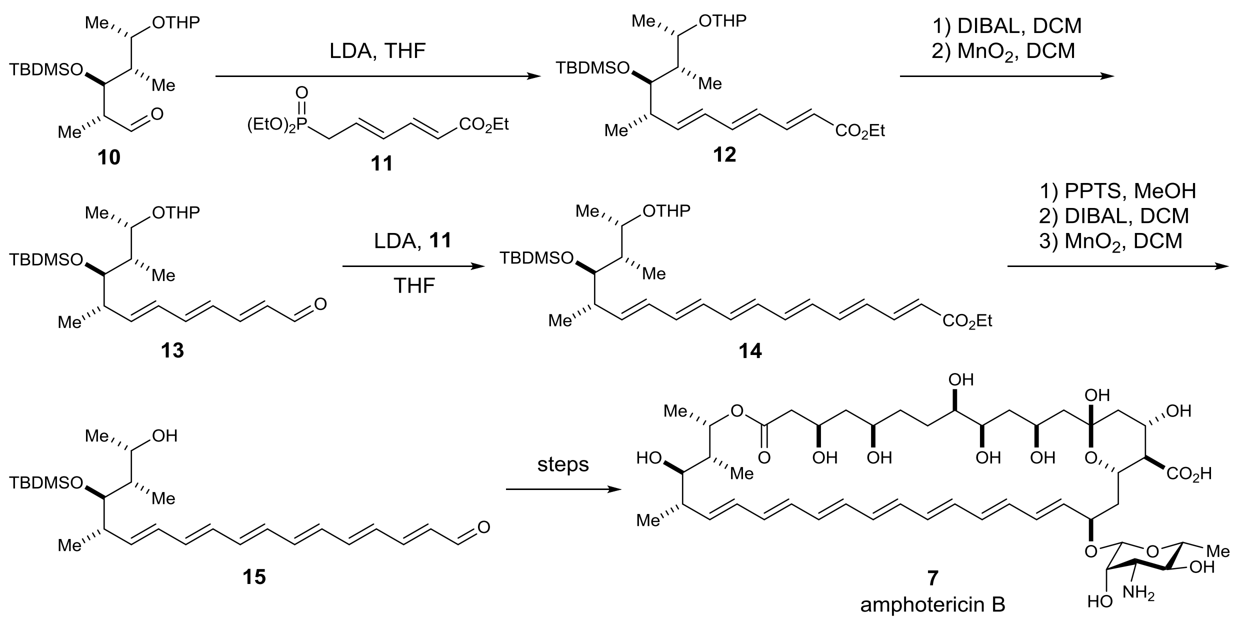
Although the synthesis of polyene systems containing up to 15 double bonds has been accomplished nearly 80 years ago,[10] synthesizing polyene-containing compounds still remains a formidable task due to their reactivity. Depending on their structure, polyenes can readily undergo oxidation, cycloaddition, polymerization, and/or isomerization reactions. Therefore, strategies in polyene synthesis must be cognizant of this instability by employing mild conditions.

1.3.1. Linear Installation

Historically, polyene moieties have been constructed by utilizing stereoselective condensation reactions (e.g. Wittig reaction) or transition metal catalyzed cross-coupling reactions (e.g.

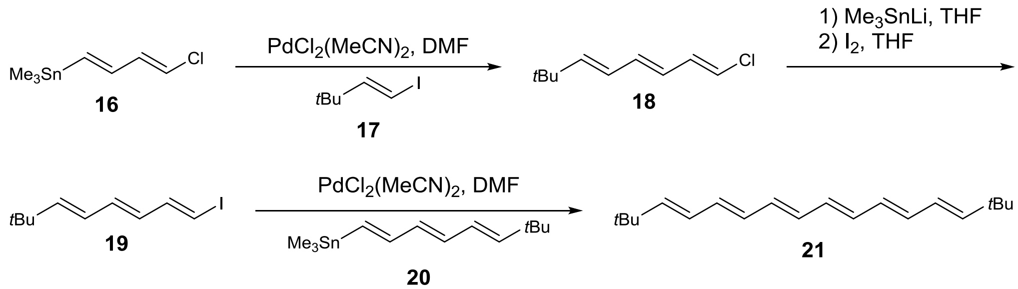
Stille coupling) in a linear approach with stepwise carbon-carbon double bond (condensation reaction) or carbon-carbon bond (cross-coupling reaction) formation.[1]

An example of constructing complex polyenes using stereoselective condensation reactions in a linear approach is the synthesis of amphotericin B by the Nicolaou group.[11] Nicolaou and co-workers' utilized iterative Horner-Wadsworth-Emmons (HWE) reactions to construct the 7 double bond-containing polyene system. The construction of the polyene system started with aldehyde **10** (Scheme 1.1). Aldehyde **10** was condensed with phosphonate **11** to give triene ester **12**. Trine ester **12** was converted to trienal **13** in two steps by reduction with DIBAL to the alcohol followed by oxidation with MnO_2. This procedure of condensation followed by reduction then oxidation was then reiterated. Trienal **13** was condensed with phosphonate **11** to give hexaene ester **14**. After removal of the tetrahydropyranyl ether, the ester was then reduced and oxidized to afford hexaenal **15**. Hexaenal **15** was then converted to amphotericin B after coupling with another fragment, a ring-closing HWE reaction to install the final double bond and to construct the macrolide ring, and glycosylation.



Scheme 1.1. Nicolaou and co-workers' synthesis of amphotericin B by consecutive HWE reactions.

An example of constructing polyenes using transition metal catalyzed cross-coupling reactions in a linear approach is Müllen and co-workers' synthetic efforts towards synthesizing conducting polymers.[12] The synthesis relies on consecutive Stille reactions to generate symmetric hexaene **21** (Scheme 1.2). Bifunctional butadiene **16** undergoes palladium-catalyzed coupling reaction with vinyl iodide **17** to generate chlorotriene **18**. Due to the incompatibility of chlorotriene **18** to undergo cross-coupling with organotin compounds, chlorotriene **18** was converted to a more reactive iodotriene **19** after stannylation and iodination. Symmetric hexaene **21** was then formed after another palladium-catalyzed coupling reaction with stannyltriene **20**.



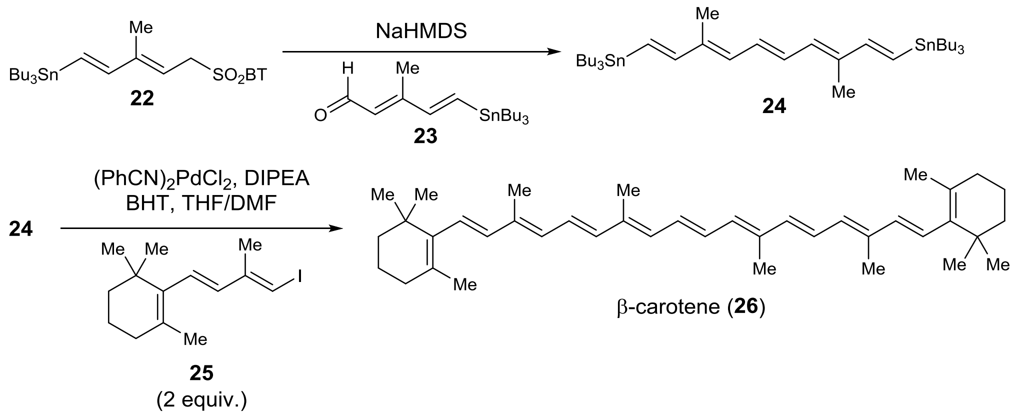
Scheme 1.2. Müllen and co-workers' synthetic studies of conducting polymers by consecutive palladium-catalyzed coupling reactions.

Although effective in synthesizing polyenes, as demonstrated by the syntheses of Nicolaou and Müllen, synthesizing polyenes in this stepwise fashion is often lengthy as it can require multiple post-coupling manipulations such as oxidation state adjustments (Scheme 1.1) or transmetalations (Scheme 1.2). Additionally, obtaining high stereocontrol can become cumbersome.

1.3.2. Sequential Cross-Coupling/Iterative Cross-Coupling of Bifunctional Reagents

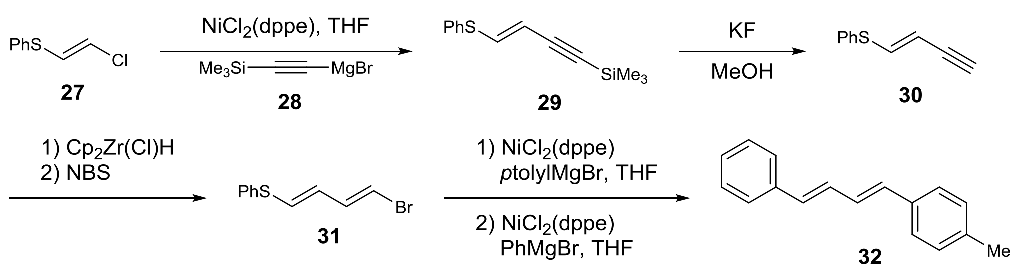
Recently, more concise methods based on transition metal catalyzed cross-coupling reactions have been developed for synthesizing polyenes. These methods rely on the design of bifunctional reagents that allow for a streamline synthesis of polyene systems. Symmetrical bifunctional substrates suitable for double couplings to form symmetrical polyenes have been reported. Similarly, unsymmetrical bifunctional substrates have been developed to undergo iterative cross-coupling (sequential cross-coupling) to generate unsymmetrical polyenes. Several examples of these substrates have been utilized in the synthesis of polyene systems and natural products.

De Lera and workers developed a convergent synthesis of symmetrical polyene β-carotene (**26**) that quickly generates a highly conjugated system after double coupling of bisstannane **24** (Scheme 1.3).[13] β-Carotene is a naturally occurring pigment in plants and its structural similarity to vitamin A is not surprising as it is a dietary source of vitamin A.[14] Bisstannane **24** was formed after condensation of sulfone **22** with aldehyde **23**. The resulting bisstannae **24** then undergoes a two-fold Stille reaction with vinyl iodide **25** to form β-carotene.



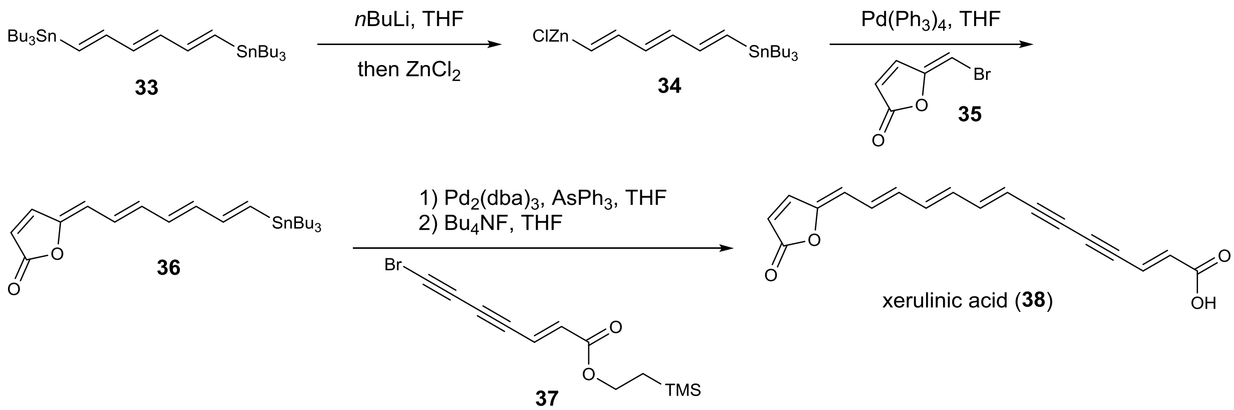
Scheme 1.3. De Lera and co-workers' synthesis of β-carotene by a two-Stille reaction.

Naso and co-workers developed an approach to synthesizing unsymmetrical *trans*-dienes through sequential couplings of bifunctional diene **31** with Grignard reagents (Scheme 1.4). Bifunctional diene **31** was synthesized from vinyl chloride **27**. Kumada coupling of vinyl chloride **27** and Grignard reagent **28** gave enyne **29**. Enyne **29** was then desilylated to form enyene **30**. After hydrozirconation with Schwartz's reagent followed by bromination, bifunctional diene **31** was obtained. Bifunctional diene **31** then underwent sequential nickel catalyzed cross-coupling reactions to afford unsymmetrical diene **32**.



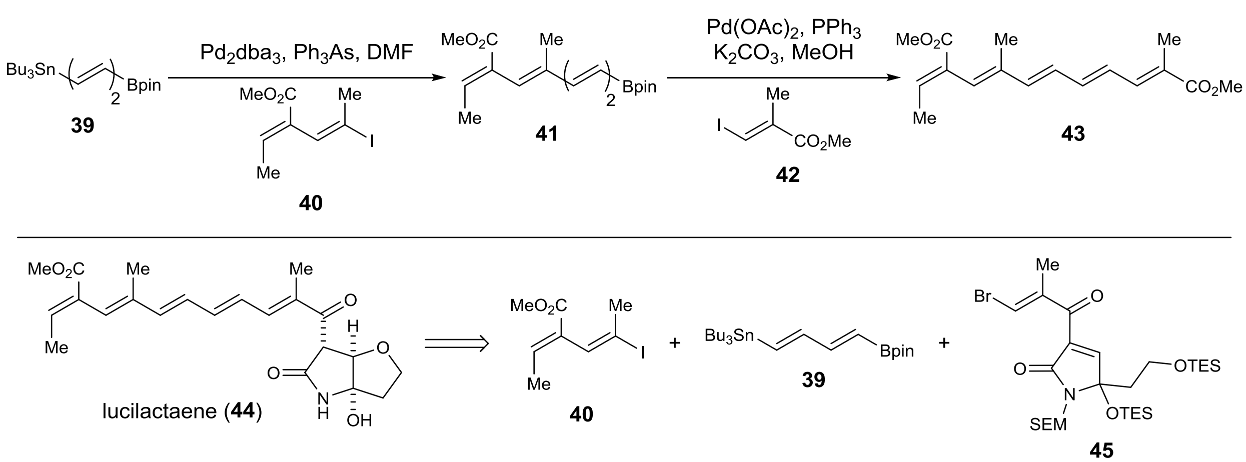
Scheme 1.4. Naso and coworkers' synthesis of unsymmetrical dienes by sequential nickel catalyzed cross-couplings with diene **31**.

Brückner and Sorg reported the synthesis of xerulinic acid by using hetero-bis-metalated triene **34**, which was coupled with vinyl bromide **35** and alkynyl bromide **37** by Negishi and Stille couplings, respectively (Scheme 1.5).[15] Xerulinic acid has been shown to inhibit the biosynthesis of cholesterol and RNA in HeLa S3 cells. Initial synthetic efforts were focused on coupling bisstannane **33** directly with vinyl bromide **35** and alkynyl bromide **37** by consecutive Stille couplings. However, low yields of stannane **36** through coupling of bisstannane **33** and vinyl bromide **35** were observed due to the similar reactivity of bisstannae **33** and stannane **36**. To circumvent this problem, bisstannane **33** was first converted to hetero-bis-metalated triene **34**, which selectively underwent Negishi coupling with vinyl bromide **35** to afford stannane **36**. The synthesis of xerulinic acid was completed after stannane **36** was coupled with alkynyl bromide **37** followed by a deprotection.



Scheme 1.5. Brückner and Sorg synthesis of xerulinic acid by successive Negishi and Stille couplings.

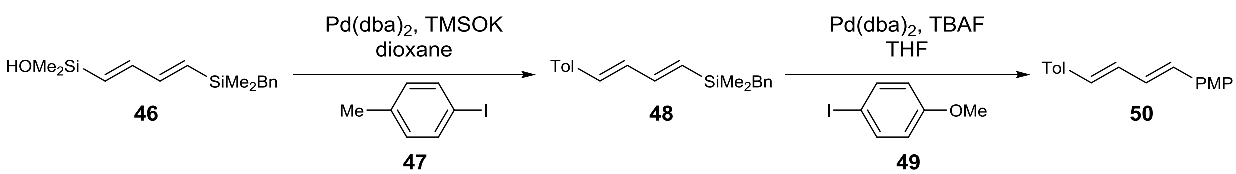
Coleman and Walczak designed hetero-bis-metalated diene **39**, which is suited for tandem Stille/Suzuki-Miyaura coupling to assemble polyene systems (Scheme 1.6).[16] Unsymmetrical bifunctional diene **39** is able to undergo selective Stille coupling with the tin-bearing terminus due to the need for basic conditions for transmetalation to occur at the boron-bearing terminus. This method was first used to assemble the pentaene side chain of lucilactaene (**43**). Lucilactaene (**44**) is a cell cycle inhibitor in p53-inactive cells. The pentaene side chain was synthesized by using



Scheme 1.6. Synthesis of polyene systems using Coleman and Walczak's hetero-bis-metalated diene reagent (**39**) for Stille/Suzuki-Miyaura coupling sequence.

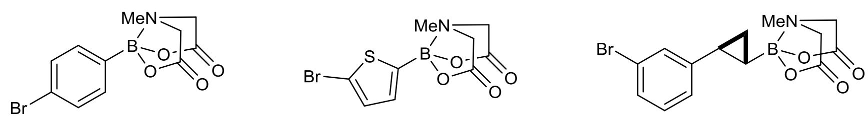
bifunctional diene **39** as a lynchpin reagent in the orthogonal Stille coupling with vinyl iodide **40** and Suzuki-Miyaura coupling with vinyl iodide **42**. Coleman and co-workers later reported the total synthesis of lucilactaene utilizing this protocol, but modifying the Suzuiki-Miyaura coupling fragment.[17]

Denmark and Tymonko reported the synthesis of unsymmetrical dienes from bissilylbutadiene **46** (Scheme 1.7).[18] By design, the bissilylbutadiene **46** is comprised of an alkyl silane terminus and a silanol terminus. Alkyl silanes and silanols undergo transmetalation by different modes of activation. Alkyl silanes are activated by formation of a pentavalent silicon center with fluoride, while silanols can be activated by formation of silanolate with base. Due to the different modes of activation, the alkyl silane terminus and silanol terminus can be chemically differentiated. Denmark and Tymonko used this strategy in their synthesis of diene **50** from bissilylbutadiene **46**. The silanol terminus of bissilylbutadiene **46** was activated with base to undergo a modified Hiyama coupling (Hiyama-Denmark coupling) with aryl iodide **47** to afford silane **48**. Silane **48** was then activated with fluoride to undergo Hiyama coupling with aryl iodide **49** to give unsymmetrical diene **50**.



Scheme 1.7. Denmark and Tymonko's synthesis of unsymmetrical dienes from bissilylbutadiene **46** by sequential cross-coupling reactions.

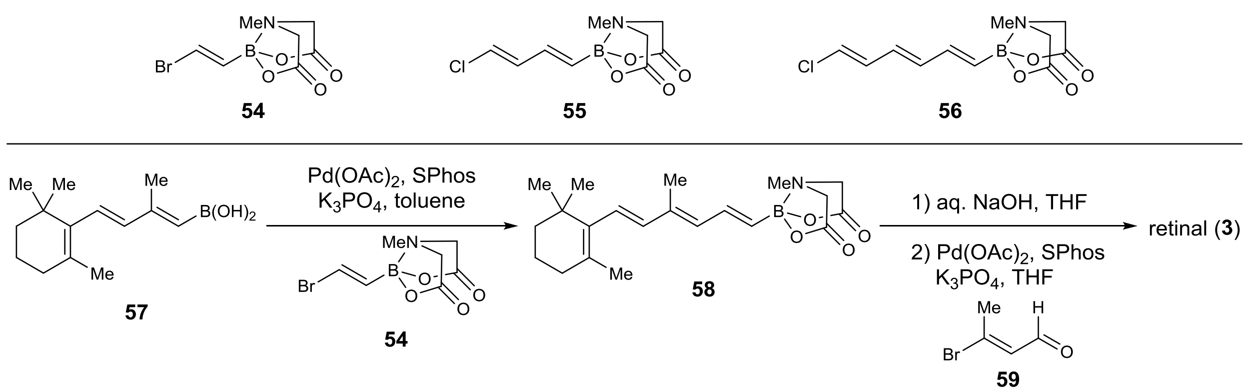
Burke and Gillis first reported the design of several B-protected haloboronic acid building blocks (Figure 1.3).[19] These building blocks rely on protection of boronic acid functionality with the trivalent ligand *N*-methyliminodiacetic acid (MIDA), which enables selective coupling with the halide terminus without affecting the MIDA boronate ester. The MIDA ligand can then be removed under mild basic conditions to restore the boronic acid functionality for further coupling. The use of B-protected organoboranes for selective coupling with a halide terminus had previously been reported. However, these examples are incompatible for complex substrate synthesis (e.g. polyenes) as they involve strong heteroatom-boron bonds that require harsh conditions to cleave the ligand.



51 52 (±) 53

Figure 1.3. Structures of MIDA B-protected haloboronic acid building blocks synthesized by Burke and Gillis.

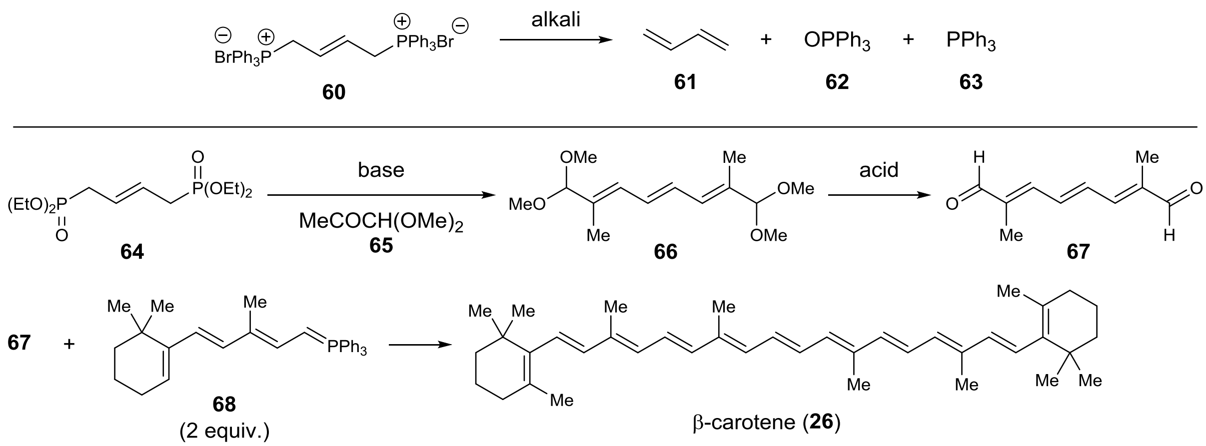
Due to the mild conditions for cleavage of the MIDA ligand, Burke and co-workers were able to adopt MIDA B-protected boronic acids in the synthesis of polyenes. Burke and co-workers described the synthesis of polyene systems based on B-protected haloalkenylboronic acids (**54**-**56**), which were demonstrated to undergo selective coupling with the halide terminus (Scheme 1.8).[20] These B-protected haloaklenylboronic acid building blocks were shown to be compatible for selective cross-coupling under Suzuki-Miyaura, Stille, Negishi, Sonogashira, and Heck coupling reaction conditions. Burke and co-workers were able to synthesize retinal (**3**) by using B-protected haloalkenylboronic acid **54**. B-protected haloalkenylboronic acid **54** was coupled with boronic acid **57** to afford B-protected haloalkenylboronic acid **58**. The MIDA ligand was then cleaved and resulting boronic acid was coupled with bromide **59** to complete the synthesis of retinal (**3**). Burke and co-workers have since expanded the scope of this methodology including the introduction of *cis* olefins.[21]



Scheme 1.8. MIDA boronates designed by Burke and co-workers for the synthesis of polyene systems by iterative cross-coupling and their application in synthesis of retinal.

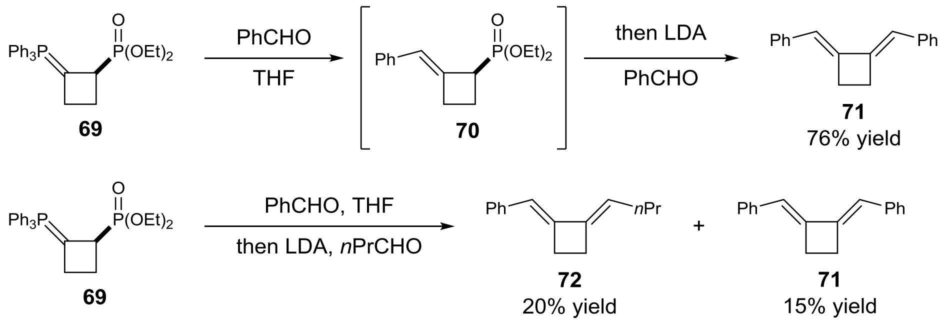
1.3.3. Sequential Condensations of Bifunctional Reagents

In contrast to the variety of bifunctional substrates that have been designed and employed in the synthesis of polyenes by sequential transition metal catalyzed cross-coupling reactions, the use of bifunctional substrates in double condensation protocols is rare. Stilz proposed the use of symmetrical bistriphenylphosphonium salts (e.g. **60**) for the synthesis of symmetrical polyenes by double Wittig reactions, but they were found to be incompatible for double condensation as fragmentation occurs upon treatment with base (Scheme 1.9). Stilz and Pommer later demonstrated that the use of vinylogous α,β-bisphosphonates (e.g **64**) were an improvement and suitable for double condensations. In fact, vinylogous α,β-bisphosphonate **64** was used in the industrial synthesis of β-carotene (**26**). Triacetal **66** was formed after double HWE reactions of bisphosphonate **64** and ketone **65**. Triacetal **66** was then converted to dialdehyde **67** after treatment with acid. Double Wittig reaction of dialdehyde **67** and phosphorane **68** to afford β-carotene.[22]



Scheme 1.9. Double condensations of symmetrical bistriphenylphosphonium salts and vinylogous α,β-bisphosphonates in the synthesis of β-carotene.

Although Stilz and Pommer were able to apply vinylogous α,β-bisphosphonates in the synthesis of symmetrical polyenes, there is no reports of their application in the synthesis of unsymmetrical polyenes. Essentially, there are no general methods for the synthesis of unsymmetrical polyenes. Minami and co-workers described the use of bifunctional cyclobutane **69**, which by sequential Wittig and HWE reactions afforded symmetrical and unsymmetrical 1,2-bis(ylidene)cyclobutanes.[23] Symmetrical 1,2-bis(ylidene)cyclobutane **71** was synthesized from bifunctional cyclobutane **69** by first Wittig reaction with benzaldehyde then treatment of the resulting phosphonate with base and benzaldehyde (HWE reaction). While this procedure gave synthetically useful yields for the synthesis of symmetrical 1,2-bis(ylidene)cyclobutanes, the application of bifunctional cyclobutane **69** in the synthesis of unsymmetrical 1,2-bis(ylidene)cyclobutanes proved to be difficult. Bifunctional cyclobutane **69** was subjected to Wittig reaction with benzaldehyde followed by HWE reaction with propanal. This reaction resulted in a low yield of the desired unsymmetrical 1,2-bis(ylidene)cyclobutanes **72** and the symmetrical 1,2-bis(ylidene)cyclobutanes **71** was observed as a major side product.



Scheme 1.10. Minami and co-workers' synthesis of symmetrical and unsymmetrical 1,2-bis(ylidene)cyclobutanes.

1.4 Conclusion

The synthesis of conjugated polyenes is a synthetic challenge due to the potential instability of polyenes; polyenes can readily undergo oxidation, cycloaddition, polymerization, and/or isomerization reactions. Significant progress has been made in recent years to develop general and succinct methods for their synthesis. The use of bifunctional substrates in the synthesis of symmetrical and unsymmetrical polyenes by sequential transition metal catalyzed cross-coupling reactions proves promising, while the use of bifunctional substrates in the synthesis of unsymmetrical polyenes remains unexplored. Due to their importance in medicine and materials science, polyenes and methods for their synthesis will remain a research area of great interest.

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Chapter 2

Synthesis of Conjugated Polyenes via Sequential Condensation of Sulfonylphosphonate and Aldehydes[a]

2.1 Strategy to Synthesizing Unsymmetrical Polyenes by Sequential Condensations

Polyenes remain important synthetic targets due to their importance in medicine and materials science.[1] Methods for the synthesis of conjugated polyenes are typically based on the use of transition metal catalyzed cross-coupling couplings or stereoselective condensation reactions. Traditionally, polyene systems have been constructed in a linear fashion by stepwise carbon-carbon double bond (condensation reaction) or carbon-carbon bond (cross-coupling) formation. The drawback of this approach is generally multiple post-coupling manipulations are required after the installation each olefin functionality.

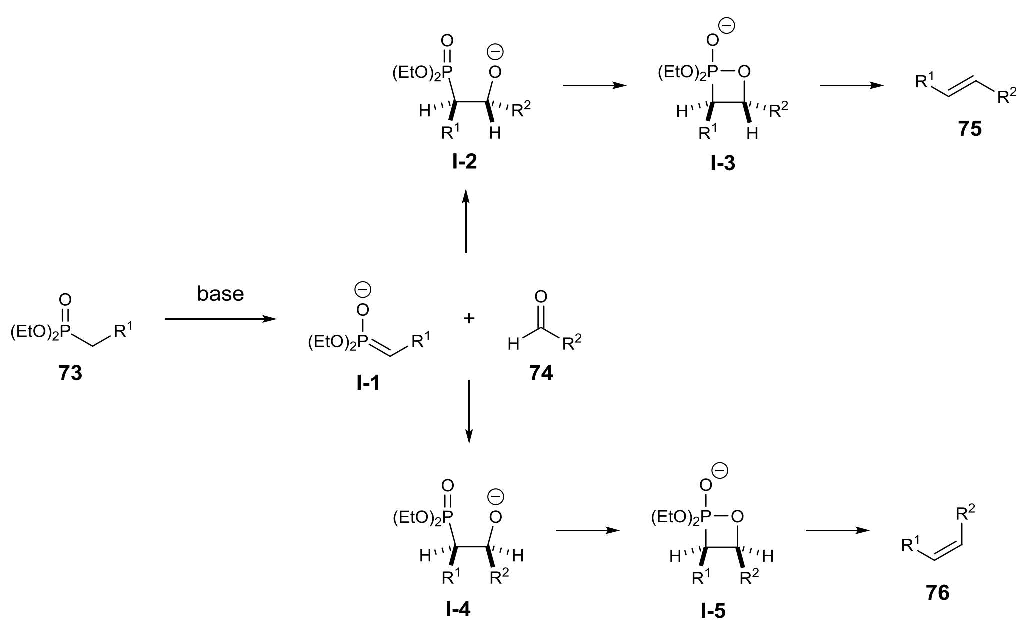
Recently, to avoid post-coupling manipulations and a more succinct synthesis, transition metal catalyzed double couplings and iterative cross-coupling methods have been developed to synthesize symmetrical and unsymmetrical polyenes.[2] The advantage of utilizing transition metal catalyzed cross-couplings in the synthesis of polyenes is the high degree of stereocontrol that can be achieved. However, building blocks required for these couplings (i.e. vinyl halides and vinyl metals) are often not commercially available and can be cost-prohibitive. Additionally, the synthesis of required building blocks are not always trivial and low and medium levels of stereo- and regiocontrol are occasionally observed.[3]

In contrast to double coupling and iterative cross-coupling methods, double condensation and sequential condensation protocols are rare. Stilz and Pommer developed a procedure for the synthesis of symmetrical polyenes from the double condensation of vinylogous α,β-bisphosphonates with aldehydes.[4] No general method for the synthesis of unsymmetrical polyenes via double condensation or sequential condensation has been described. In juxtaposition to cross-coupling reactions, condensation reactions may not have the same high degree of stereocontrol (notably in the synthesis of polyenes containing *cis* olefins), but typically employ cheaper building blocks

[a] Cichowicz, N. R.; Nagorny, P. *Org. Lett.* **2012**, *14*, 1058-1061.

(e.g. aldehydes) that are often the direct products of petrochemical processing. Therefore, a double condensation or sequential condensation method could be advantageous in the synthesis of all *trans*-polyenes, in which a high degree of stereocontrol can be achieved. The method could drastically improve step economy by taking advantage of readily available building blocks and avoiding additional steps required for the synthesis of vinyl haldies, boronic acids, stannanes, and silanes.

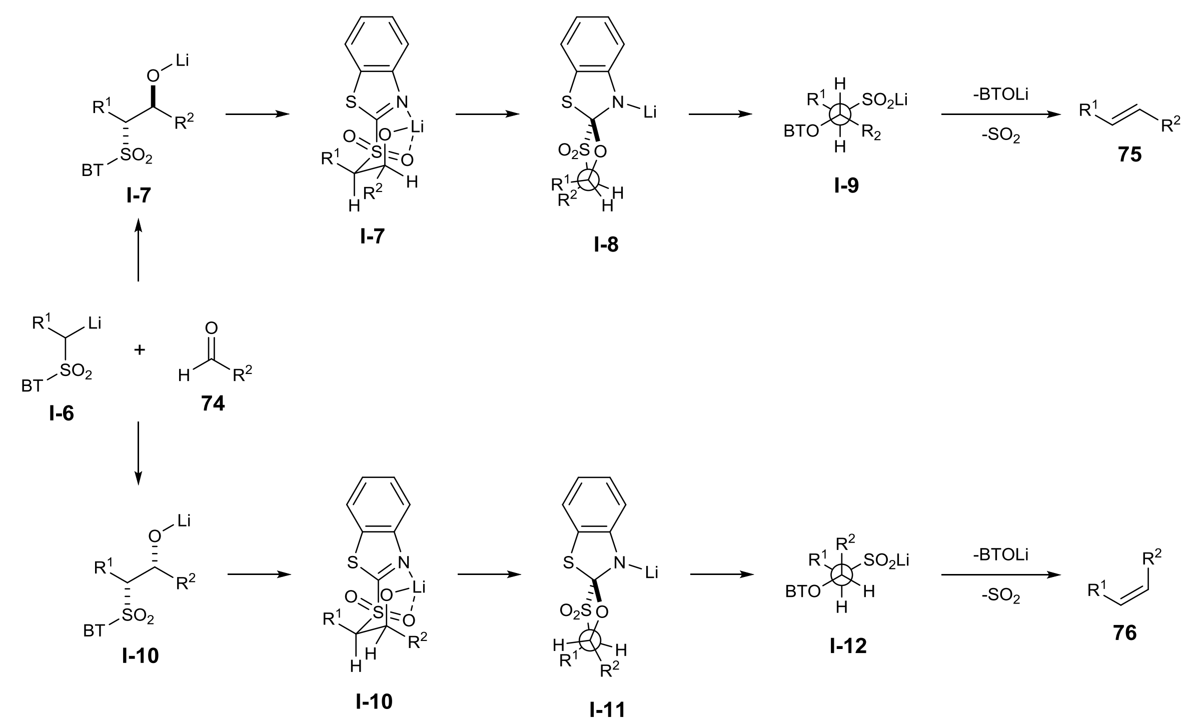
In 1954, Georg Wittig discovered the synthesis of olefins by a condensation reaction of aldehydes and phosphonium ylides.[5] Since then, additional condensation reactions have been developed that involve direct olefination of aldehydes. An example is the Horner-Wadsworth-Emmons (HWE) reaction.[6] First reported as a modification of the Wittig reaction, the HWE reaction produces olefins from the reaction of aldehydes and phosphonates. The use of phosphonates is viewed as an improvement to the Wittig reaction as the byproducts of the reaction are easier to remove. Typically, HWE reactions provide (*E*)-alkenes selectivity. The selectivity can be rationalized based on the reaction mechanism (Scheme 2.1). In an HWE reaction, a stabilized (R^1 = EWG) phosphonate carbanion (**I-1**) is formed after deprotonation with base. The generated phosphonate carbanion (**I-1**) can then couple with an aldehyde (**74**) by nucleophilic attack. This rate-limiting step dictates the stereochemical outcome of the reaction: *threo* β-alkoxyphosphonate **I-2** leads to the formation of an (*E*)-alkene (**75**) as the *erythro* β-alkoxyphosphonate **I-4** leads to the



Scheme 2.1. Mechanism of HWE reaction.

formation of a (*Z*)-olefin. β-Alkoxyphosphonate (**I-2** and **I-4**) then cyclizes to oxaphosphetane (**I-3** and **I-5**), which eliminates to the resulting alkene (**75** and **76**) and phosphate byproduct.

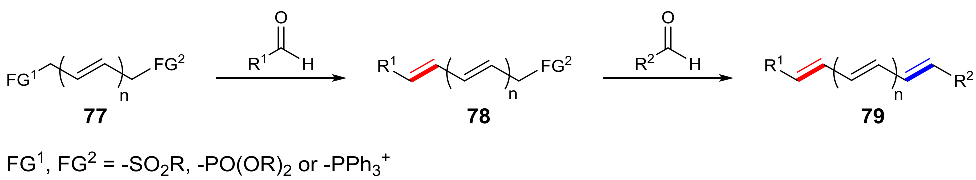
A more recently developed condensation reaction is the Julia-Kocienski reaction (or modified Julia olefination).[7] The Julia-Kocienski involves direct olefination of aldehydes by reaction with heteroaryl sulfones. The nature of the heteroaryl group affects the stereochemical outcome of the reactions. Benzothiazolyl (BT) and 1-phenyl-1*H*-tetrazol-5-yl (PT) are among the most commonly used heteroaryl groups that provide (*E*)-alkenes in high selectivity. The mechanism involves nucleophilic attack of aldehyde **74** by metalated sulfone **I-6** (formed after deprotonation) to form either *anti* β-alkoxidesulfone **I-7** or *syn* β-alkoxidesulfone **I-10** (Scheme 2.2). Formation of *anti* β-alkoxidesulfone **I-7** yields an (*E*)-alkene as *syn* β-alkoxidesulfone **I-10** yields a (*Z*)-alkene. The β-alkoxidesulfones (**I-7** and **I-10**) undergo Smiles rearrangement through spirocyclic **I-8** and **I-11** to give **I-9** and **I-12**. Alkenes **75** and **76** are then formed after antiperiplanar elimination of the heteroaryl group by extrusion of sulfur dioxide.



Scheme 2.2. Mechanism of Julia-Kocienski reaction.

Taking advantage of direct olefination of aldehydes methods, proposed is the rapid construction of all-*trans* unsymmetrical polyenes by sequential condensation reactions (Scheme 2.3).

The proposed method would entail the design of a bifunctional substrate (**77**) with sulfone, phosphonate, or phosphorane terminus to permit Julia-Kocienski, HWE, or Wittig condensation reactions, respectively. The proposed method would entail monodeprotonation of bifunctional substrate **77**, which upon condensation with an equivalent of aldehyde would provide allylic monofunctional substrate **78**. The unsymmetrical polyene (**79**) synthesis would then be completed by monodeprotonation of allylic monofunctional substrate **78** followed by condensation with an equivalent of a different aldehyde.

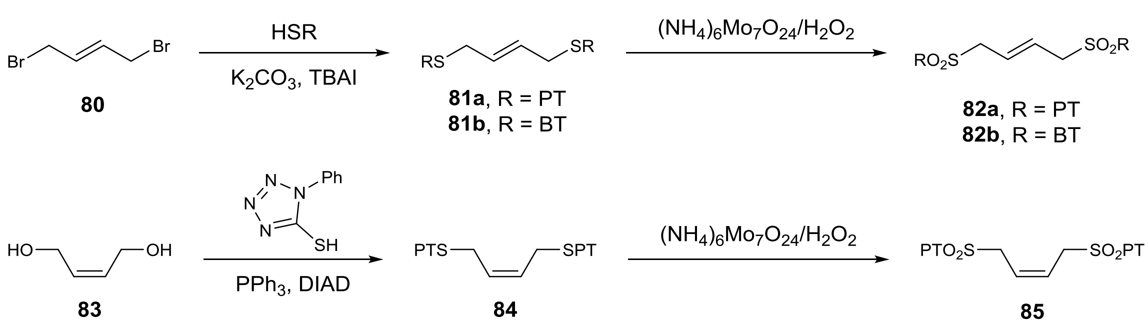


Scheme 2.3. Proposed synthesis of unsymmetrical polyenes via sequential condensation with readily available aldehydes.

2.2 *Bis*-Sulfones

Initial efforts focused on the development and application of symmetrical *bis*-sulfones. Envisioned was the possibility of selective mondeprotonation followed by condensation with aldehyde (Julia-Kocienski reaction) to give an allylic sulfone. The formed allylic sulfone could then be condensed with a different aldehyde to furnish an unsymmetrical polyene.

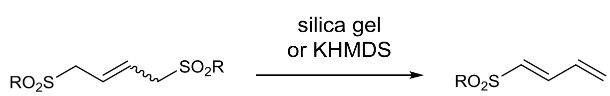
To begin, three vinylogous α,β-unsaturated *bis*-sulfones were synthesized (Scheme 2.4). These particular sulfones were sought in efforts to explore the difference in reactivity and selectivity that could be achieved by varying the olefin geometry and heteroarylsulfone of the *bis*-sulfone. (*E*)-*bis*-Sulfones **82** were synthesized in two steps from commercially available (*E*)-1,4-dibromobut-2-ene (**80**). Dibromide **80** was treated with thiol and catalytic iodide to undergo S_N2



Scheme 2.4. Synthesis of *bis*-sulfones.

reaction to give *bis*-sulfide **81**. *bis*-Sulfide **81** was then oxidized to the corresponding *bis*-sulfone **82** utilizing ammonium molybdate with hydrogen peroxide. Similarly, (*Z*)-*bis*-Sulfone **85** was synthesized in two steps from commercially available (*Z*)-but-2-ene-1,4-diol (**83**). Under Mitsunobu reaction conditions, diol **83** was converted to *bis*-sulfide **84**, which was then oxidized to the desired *bis*-sulfone **85**.

Although *bis*-sulfones could be easily synthesized, handling and purification of *bis*-sulfones proved to be difficult. *bis*-Sulfones are not very soluble in common organic solvents and upon exposure to silica gel underwent elimination (Scheme 2.3). The purification problem was ultimately circumvented by utilizing recrystallization. Unfortunately, it was soon realized that the synthesized *bis*-sulfones undergo the same elimination upon treatment with base under condensation conditions. Therefore, due to their instability, *bis*-sulfones were deemed unsuitable for this method and not further pursued.



82a, R = PT, *E* olefin
82b, R = BT, *E* olefin
85, R = PT, *Z* olefin

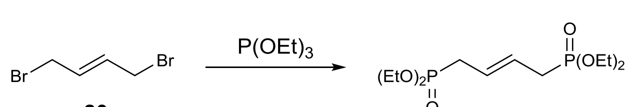
86a, R = PT
86b, R = BT

Scheme 2.5. Elimination of *bis*-sulfones upon exposure to silica gel or base.

2.3 Bisphosphonates

Although the use of symmetrical bisphosphonates in the synthesis of symmetrical polyenes via double condensation with aldehydes, there is no evidence of its application in the synthesis of unsymmetrical polyenes. Similar to symmetrical *bis*-sufone, the desired outcome would be condensation with one equivalent of aldehyde to provide selectively allylic phosphonate. The allylic phosphonate would in turn undergo condensation with another aldehyde to yield an unsymmetrical polyene.

Vinylogous α,β-bisphosphonate **64** was synthesized in one step from commercially available dibromide **80** under Arbuzov reaction conditions (Scheme 2.6).[8] An improvement from *bis*-sulfones, bisphosphonates were found to be soluble in common organic solvents and stable to silica gel chromatography.

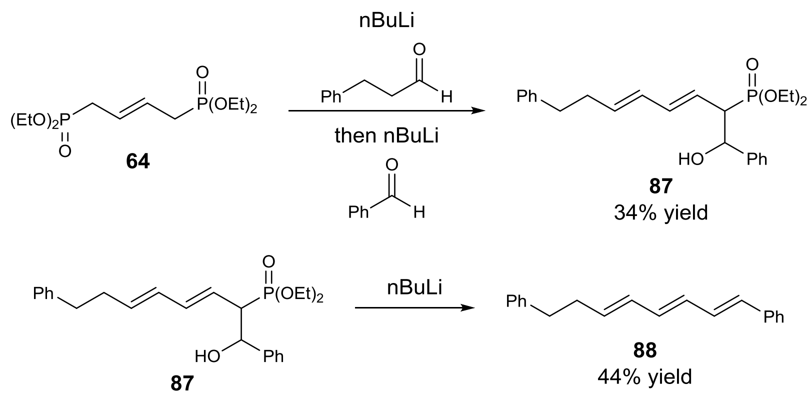


80

64

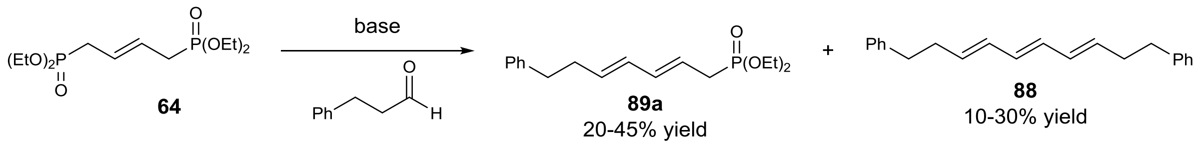
Scheme 2.6. Synthesis of known bisphosphonate **64**.

Known bisphosphonate **64** was first evaluated in a one-pot doubled condensation protocol (Scheme 2.7). In the one-pot procedure, bisphosphonate was treated with one equivalent of base and 3-phenylpropanal followed by treatment with another equivalent of base and benzaldehyde. Although the expected triene product was not observed, β'-hydroxy allylic phosphonate **87**, resulting from incomplete double condensation, was isolated in 34% yield. This suggests that the second condensation is sluggish. Resubmitting β'-hydroxy allylic phosphonate **87** to basic conditions afforded the desired triene **88** in 44% yield.



Scheme 2.7. Synthesis of triene **88** from bisphosphonate **64**.

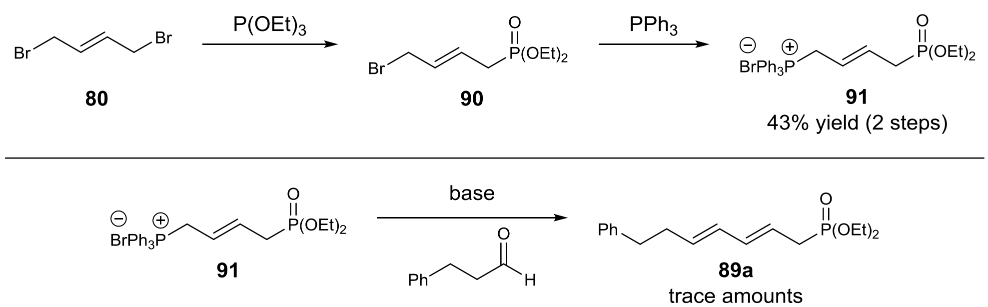
Although this two-step procedure provided the desired product, the overall 15% yield was unsatisfactory. In effort to understand the intricacies of the proposed double condensation procedure, the initial condensation was to be investigated. The single condensation of bisphosphonate **64** was first screened with the bases KHMDS, NaHMDS, LiHMDS, and *n*BuLi. Bisphosphonate **64** was treated with one equivalent of base followed by one equivalent of 3-phenylpropanal. By crude ^{1}H NMR analysis, the use of NaHMDS and LiHMDS resulted in decomposition of the starting material, while the use of KHMDS and *n*BuLi resulted in formation of both allylic phosphonate **89a** and undesired triene **88**. Unfortunately, further experimentation demonstrated the difficulties in selectively accomplishing single condensation of bisphosphonate with aldehyde. This is due to the similar reactivity of bisphosphonate **64** and allylic phosphonate **89a**. As a result, bisphosphonates were considered unsuitable for the synthesis of unsymmetrical polyenes.



Scheme 2.8. Condensation of bisphosphonate **64** with 3-phenylpropanal.

2.4 Sulfonophosphorane

Based on the studies with *bis*-sulfones and bisphosphonates, it became evident that an advantageous alteration would be an unsymmetrical bifunctional substrate. Removing the symmetry of the substrate could significantly improve the inadequacies observed with *bis*-sulfones and bisphosphonates. Proposed was the design of an unsymmetrical bifunctional substrate **91** with a phosphonate and triphenylphosphonium terminus was synthesized (Scheme 2.9). It was perceived that the more acidic protons adjacent to the triphenylphosphonium terminus would result in chemoselective formation of allylic phosphonates after Wittig condensation with an aldehyde. However, attempted Wittig condensation of **91** with 3-phenylpropanal provided only trace amounts of the desired allylic phosphonate **89a**. As a result, bifunctional substrate **91** was not further studied.



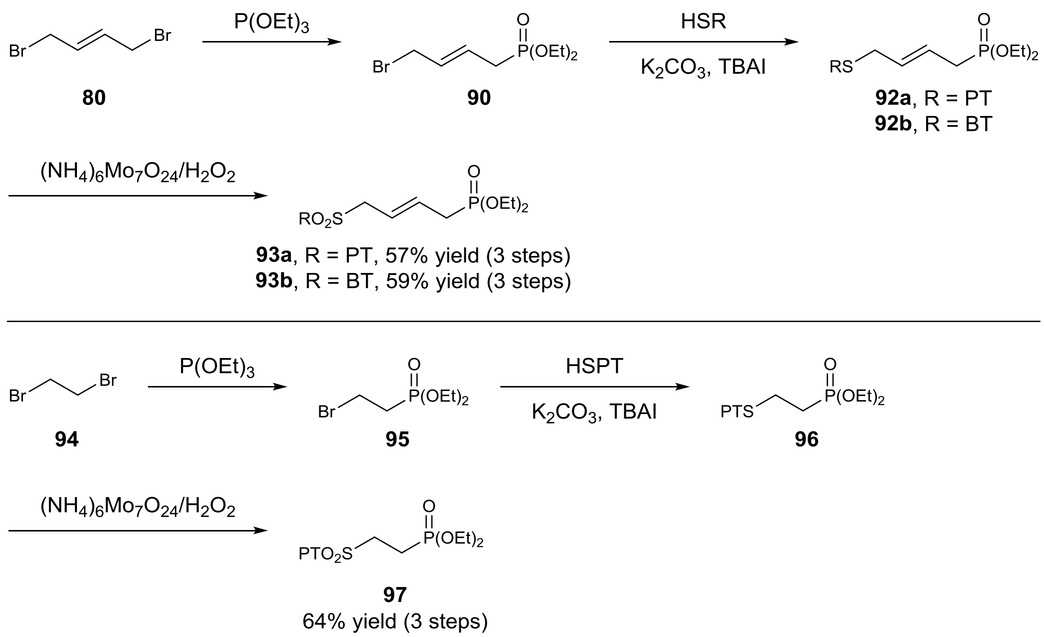
Scheme 2.9. Synthesis of bifunctional substrate **91**.

2.5 Sulfonylphosphonates

Similar in design to sulfonophosphorane, proposed was the design of an unsymmetrical bifunctional substrate with a phosphonate and arylsulfone terminus: sulfonylphosphonate. It was surmised that the protons next to the arylsulfone functionality would be more acidic than the protons adjacent to the phosphonate functionality. This difference in acidity would result in chemoselective Julia-Kocienski condensation with an aldehyde resulting in an allylic phosphonate. The unsymmetrical polyene synthesis could then be completed by HWE condensation of the allylic phosphonate with another aldehyde.

2.5.1 Synthesis of Sulfonylphosphonates

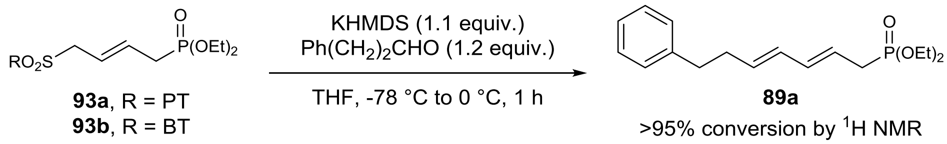
Sulfonylphosphonates **93** and **97** were synthesized on a multigram scale from commercially available dibromide **80** and **94** in three steps (Scheme 2.10). Arbuzov reaction conditions desymmetrize the symmetrical dibromide (**80**/**94**) to give bifunctional substrate with a bromide and phosphonate terminus (**90**/**95**). The bromide of the bifunctional substrate was then converted to the arylsulfone by substitution with thiol followed by oxidation resulting in the synthesis of the desired sulfonylphosphonate (**93**/**97**).



Scheme 2.10. Synthesis of sulfonylphosphonates.

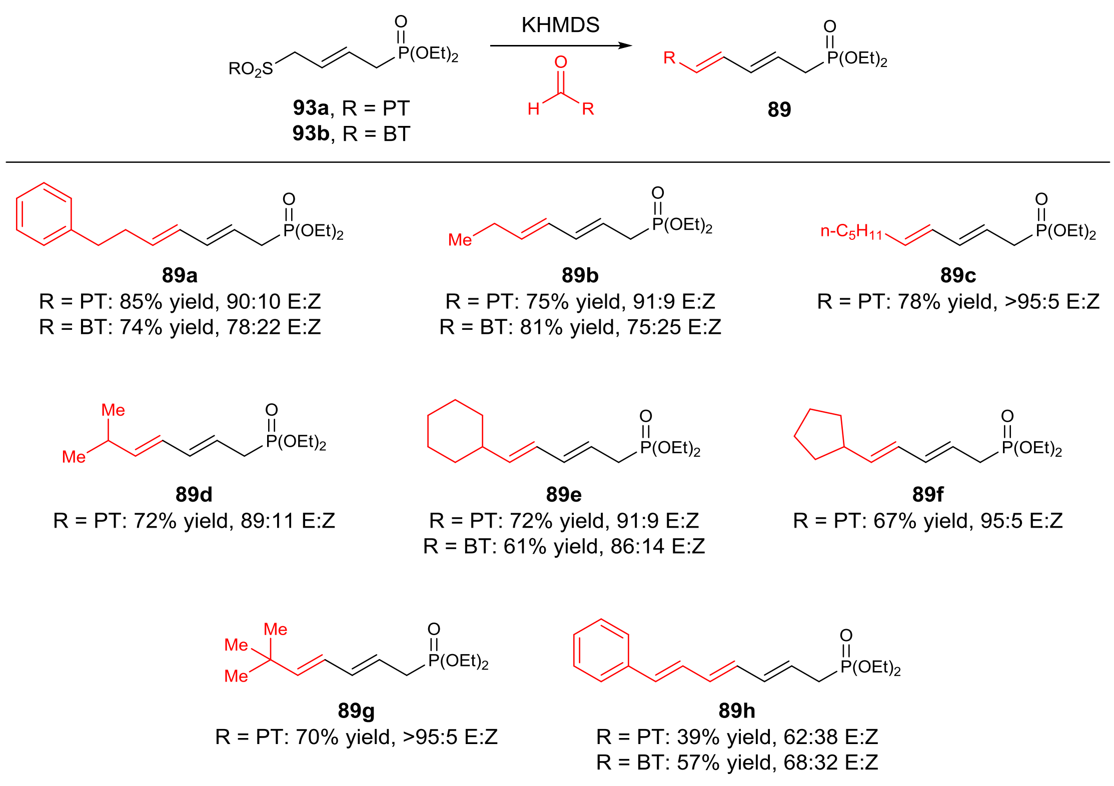
2.5.2 Chemoselective Julia-Kocienski Condensation of Sulfonylphosphonate

In order to test the hypothesis that sulfonylphosphonates would be an improvement, sulfonylphosphonates **93a** and **93b** were subjected to Julia-Kocienski conditions to understand if chemoselectivity could be achieved. The treatment of sulfonylphosphonates **93a** and **93b** with KHMDS (1.1 equiv.) followed by the addition of 3-phenylpropanal (1.2 equiv.) resulted in the clean formation of **89a** (Scheme 2.11). Both reactions proceeded with remarkable levels of chemoselectivity and no competing HWE condensation was detected by ^{1}H NMR analysis of the crude mixture. Additionally, the formation of symmetrical triene side product and elimination of the arylsulfone were not observed.



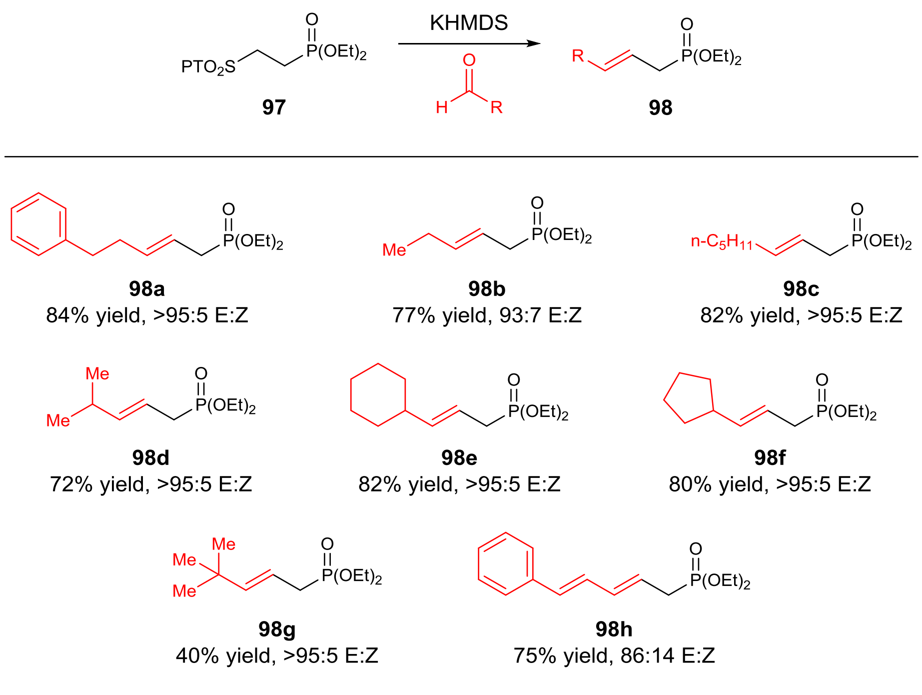
Scheme 2.11. Monocondensation of 3-phenylpropanal and **93a** and **93b**.

Based on these encouraging results, the effect of the aldehyde structure on the yields and selecivities of this reaction was explored next (Scheme 2.12). General comparison of the reactions of metalated **93a** and **93b** with aldehydes illustrates that both substrates react with comparable efficiencies to provide allylic phosphonates **89**. However, olefinations with metalated 1-phenyl-1H-tetrazole-sulfone **93a** proceed with higher selectivities. The Julia-Kocienski condensations with metalated **93a** proceed with good yields and selectivities with both the unbranched (**89a-c**) and β-substituted aliphatic aldehydes (**89d-g**). However, condensations with α,β-unsaturated aldehydes such as 3-phenyl-2-propenal proceed with moderate yields and selectivities (**89h**). To demonstrate that these reactions are not sensitive to scale up, a condensation of **93a** and 3-phenylpropenal was carried out on a gram scale without any erosion in yield or selectivity.



Scheme 2.12. Synthesis of allylic phosphonates **89** from sulfonylphosphonate **93** by chemoselective Julia-Kocienski reaction.

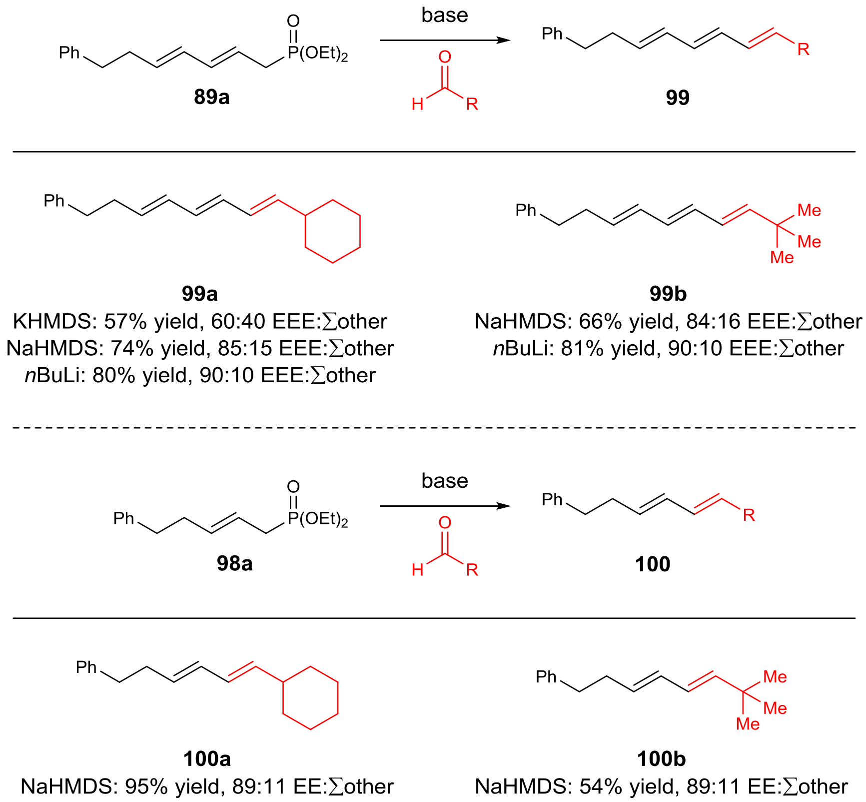
While sulfonylphosphonates **93a** and **93b** could be converted to polyene systems of trienes or higher, they are not suitable for the synthesis of dienes. However, sulfonylphosphonate **97** could specifically designed to allow access to dienes. Similar to sulfonylphosphonates **93a** and **93b**, sulfonylphosphonate **97** could be monodeprotonated with KHMDS and reacted with various aldehydes to provided allylic phosphonates **98a-h** (Scheme 2.13). Importantly, these reactions were completely chemoselective and no HWE or double condensation products were detected. In general, the yields and selectivities for the condensations with **97** were superior to the corresponding yields and selectivities of olefinations with **93a** and **93b**. Both the unbranched (**98a-c**) and β-substituted (**98c-g**) aliphatic aldehydes reacted with sulfonylphosphonate **97** to provide allylic phosphonates in 40-84% yields and excellent selectivities. Additionally, sulfonylphosphonate **97** could be condensed with α,β-unsaturated aldehydes such as 3-phenyl-2-propenal to the corresponding allylic phosphonate (**98h**) in 75% isolated yield with an 86:14 E/Z ratio. Furthermore, the condensations with sulfonylphosphonate **97** could be carried out on a gram scale without any erosion of yield or selectivity (**98a**).



Scheme 2.13. Synthesis of allylic phosphonates **98** from sulfonylphosphonate **97** by chemoselective Julia-Kocienski reaction.

2.5.3 Synthesis of Unsymmetrical Polyenes

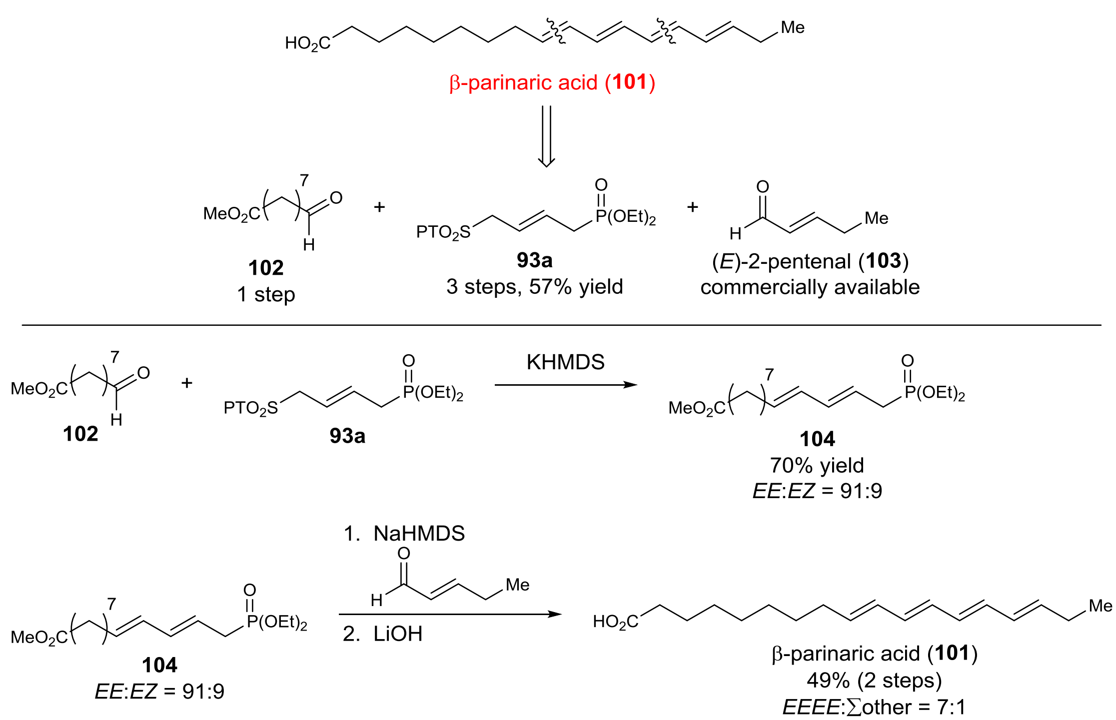
In order to demonstrate that sulfonylphosphonates could be used for the convergent synthesis of polyenes (*cf*. Scheme 2.3), the HWE condensation of allylic phosphonates **89a** and **98a** with aldehydes was investigated (Scheme 2.14). It is known that allylic phosphonates can be utilized in (*E*)-selective HWE condensations to provide (*E*)-polyenes in good yields and selectivities, and the results with allylic phosphonates **89a** and **98a** reinforce these findings.[9] Evaluation of the optimal base for reactions with allylic phosphonate **89a** revealed that the deprotonation of dienyl phosphonates with *n*BuLi provides superior yields and selectivities. However, NaHMDS was found to be the base of choice for the reactions of allylic phosphonate **98a**.



Scheme 2.14. Synthesis of unsymmetrical trienes **99** and **100** from allylic phosphonates **89a** and **98a** by (*E*)-selective HWE reaction.

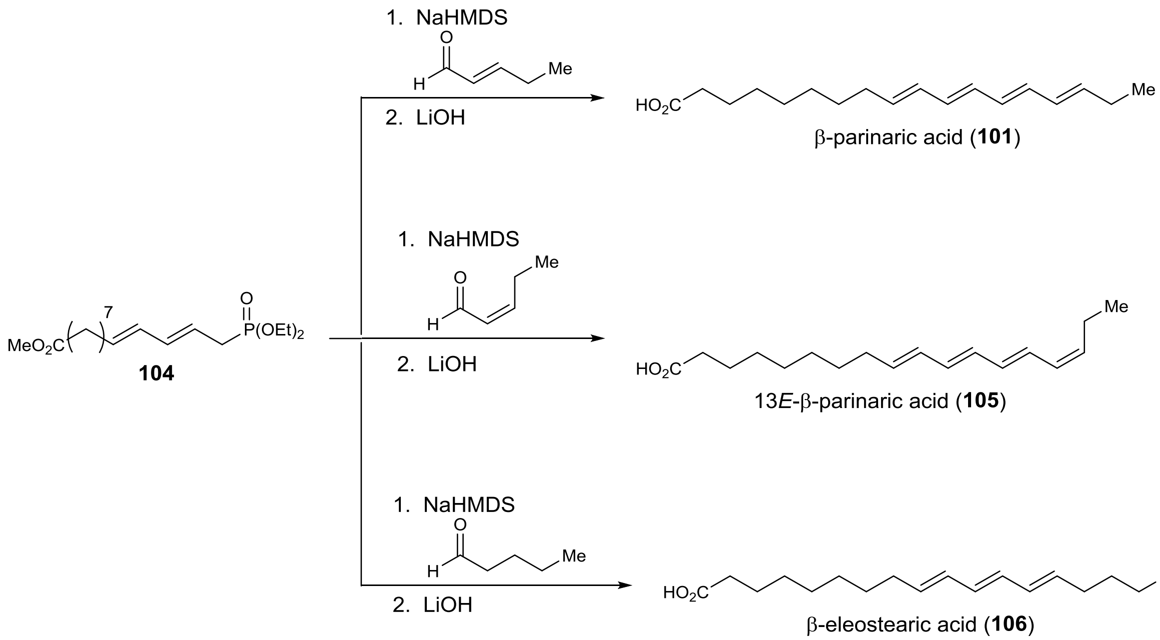
2.5.4 Synthesis of β-Parinaric Acid

Ultimately, sulfonylphosphonate **93a** was applied in the synthesis of β-parinaric acid, a naturally occurring tetraene fatty acid that is a widely used fluorescent membrane probe (Scheme 2.15).[10] Using sulfonylphosphonate **93a**, β-parinaric acid could be assembled from three readily available building blocks: aldehyde **102**,[11] sulfonylphosphonate **93a**, and aldehyde **103**. The synthesis commenced with the condensation of aldehyde **102** with sulfonylphosphonate **93a** providing allylic phosphonate **104** (70% yield, 91:9 9*E*,11*E*:9*Z*,11*E*). Allylic phosphonate **104** was then used in the HWE condensation with commercially available (*E*)-2-pentenal. Due to the light and air sensitivity of the resultant tetraene, the hydrolysis of the β-parinaric acid methyl ester was conducted in situ without isolation of this intermediate. The resultant acid was obtained in 49% yield and 7:1 ratio of the desired all-(*E*)-isomer to the sum of (*Z*)-olefin containing isomers.[12] The synthesis included 5 linear steps (6 steps total and is among the shortest approaches to β-parinaric acid.[13] The previously published route employing iterative cross-coupling reported the synthesis of β-parinaric acid in 10 steps total.[13c]



Scheme 2.15. Synthesis of β-parinaric acid utilizing sulfonylphosphonate **93a**.

Given that sulfonylphosphonates can be condensed with aldehydes including α,β-unsaturated aldehydes to generate allylic phosphonates (Scheme 2.12 and Scheme 2.13) and the generated allylic phosphonates can be condensed with an additional aldehyde to provide unsymmetrical polyenes (Scheme 2.14), several synthetic routes could be envisioned in the synthesis of β-parinaric acid using sulfonylphosphonates. The strategy that was employed (Scheme 2.15), however, was designed purposefully to include the synthesis of allylic phosphonate **104** (Scheme 2.16). Yet to be attempted, allylic phosphonate was proposed to serve as a common synthetic intermediate in the synthesis of 13*E*-β-parinaric acid and β-eleostearic acid, in addition to β-parinaric acid, as these lipids have strong growth-inhibitory effects on human tumor cell lines in addition to being common molecular probes of lipid-protein and lipid-lipid interactions.[10,14]

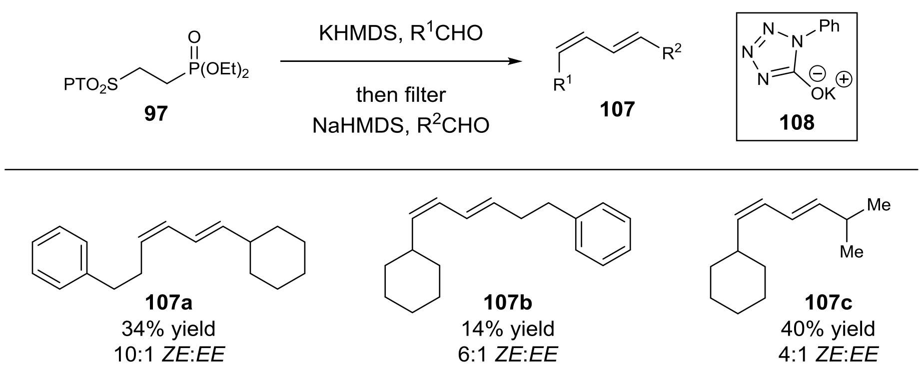


Scheme 2.16. Proposed synthesis of 13*E*-β-parinaric acid and β-eleostearic acid from sulfonylphosphonate **93a**.

2.5.5 One-Pot Modification

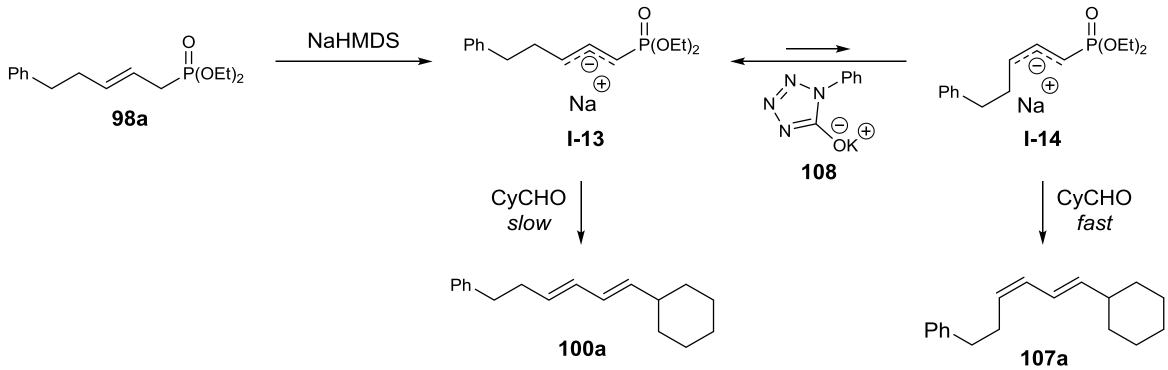
A procedure in which sulfonylphosphonates would be sequentially condensed by Julia-Kocienski and HWE reactions with two different aldehydes in one-pot was investigated. The advantage of this modification would be increased step economy and reducing the need for multiple purifications. Attempts to produce triene **99a** and diene **100a** by one-pot modification, however, was unsuccessful in regards to improving the efficiency of the procedure. Yields were difficult to reproduce and the two-step procedure consistently gave higher yields.

In attempts to optimize the one-pot synthesis of diene **100a** it was discovered that the stereochemical outcome could be altered with formation of the *ZE*-isomer being preferred (Scheme 2.17). Since sulfonylphosphonate **97** was shown to provide allylic phosphonates in good yields (*cf*. Scheme 2.13), it was understood that the HWE condensation was the source of the decreased one-pot yields. Through the course of all Julia-Kocienski reactions, a noticeable precipitate was formed. Although not proven experimentally, the formed precipitate was proposed to be tetrazole salt **108**, which is formed based on the reaction mechanism. (Scheme 2.2). It was hypothesized that the presence of the precipitate was inhibiting the HWE condensation, which would have been removed by purification in the two-step procedure. As a result, a procedure was developed that involved filtering the reaction after the Julia-Kocienski reaction, but before being subjected to the HWE conditions. This alteration resulted in the formation of diene **107a** (*ZE*-isomer) and not expected diene **98a** (*EE*-isomer). Interestingly, the (*Z*)-olefin was formed with the aldehyde that is condensed during the Julia-Kocienski conditions, which suggest that the olefin is isomerized (allylic phosphonate **98a** was formed with >95:5 *E*:*Z* selectivity). This effect was observed in the synthesis of dienes **107b** and **107c**. While a protocol that could synthesize *ZE*-dienes would be highly valuable, the telescopic procedure with filtering provided synthetically low yields that were difficult to reproduce. As a result, the procedure was not further optimized and the cause of isomerization was not determined experimentally.



Scheme 2.17. Synthesis of *ZE*-diene **107** from sulfonylphosphonate **97** by telescopic procedure.

Although not proven experimentally, a mechanism was proposed for the observed isomerization. The source of isomerization is attributed to the presence of a catalytic amount of tetrazole salt **108** after filtration (Scheme 2.18). During the course of the two-step procedure, *EE*-diene **100a** is formed through intermediate **I-13**. However, in the presence of a catalytic amount of tetrazole salt **108** during the course of the telescopic procedure, formation of *ZE*-diene **107a** is favored through intermediate **I-14**. The tetrazole salt **108** is predicted to decelerate the conversion of intermediate **I-13** to *EE*-diene **100a**, lowering the barrier for interconversion between intermediates **I-13** and **I-14** or accelerating the conversion of intermediate **I-14** to *ZE*-diene **107a**. Based on the proposed mechanism, it was proposed that the addition of additives such as tetrazole salt **108** could be used in the synthesis of *Z*,*E*-dienes in HWE reactions of allylic phosphonates.



Scheme 2.18. Proposed mechanism of isomerization.

2.6 Conclusion

Developed was a new protocol for the synthesis of *trans*-dienes, trienes, and tetraenes that is based on chemoselective condensation of monometalated sulfonylphosphonates and aldehydes followed by Horner-Wadsworth-Emmons olefination of the resultant allylic phosphonates. Envisioned is the application of this strategy for the rapid generation of *trans*-polyene libraries as well as for the convergent synthesis of polyene-containing natural products.

2.7 Experimentals

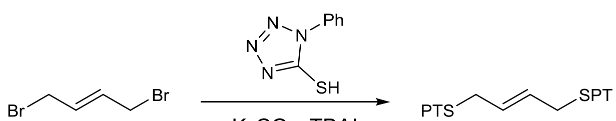
2.7.1 General

All reagents and solvents were purchased from Sigma-Aldrich or Fisher Scientific and were used as received without further purification unless specified. The following aldehydes were distilled from calcium hydride under an atmosphere of nitrogen or under vacuum prior to use: pivaldehyde, hexanal, hydrocinnamaldehyde, propionaldehyde, isobutyraldehyde, cyclohexanecarbaldehyde, cyclopentanecarbaldehyde, and *trans*-cinnamaldehyde. *trans*-2-Pentenal was freshly distilled from calcium chloride prior to use under an atmosphere of nitrogen. THF and DMF were purified by Innovative Technology's Pure-Solve System. Methyl 9-oxononanoate[11] was prepared according to literature precedent.

All reactions were carried out under a positive pressure of nitrogen in flame- or oven-dried glassware with magnetic stirring. Reactions were cooled using external cooling baths: ice water (0 °C) or dry ice/acetone (-78°C). Heating was achieved by use of a silicone bath with heating controlled by electronic contact thermometer. Deionized water was used in the preparation of all aqueous solutions and for all aqueous extractions. Solvents used for extraction and chromatography were ACS or HPLC grade. Purification of reactions mixtures was performed by flash chromatography using SiliCycle SiliaFlash P60 (230-400 mesh).

[1]H NMR spectra were recorded on Varian vnmrs 700 (700 MHz), Varian vnmrs 500 (500 MHz), or Varian INOVA 500 (500 MHz) spectrometers and chemical shifts (δ) are reported in parts per million (ppm) with solvent resonance as the internal standard ($CDCl_3$ at δ 7.26). Data are reported as (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, m = multiplet; coupling constant(s) in Hz; integration). Isomeric purity of compounds containing olefin(s) was determined by ^{1}H NMR. Two-dimenstional COSY experiments were performed to resolve ambiguous assignments. Proton-decoupled ^{13}C NMR spectra were recorded on Varian vnmrs 700 (700 MHz), Varian vnmrs 500 (500 MHz), or Varian INOVA 500 (500 MHz) spectrometers and chemical shifts (δ) are reported in ppm with solvent resonance as the internal standard ($CDCl_3$ at δ 77.0). High resolution mass spectra (HRMS) were recorded on Micromass AutoSpec Ultima or VG (Micromass) 70-250-S Magnetic sector mass spectrometers in the University of Michigan mass spectrometry laboratory. Infrared (IR) spectra were recorded as thin films on NaCl plates on a Perkin Elmer Spectrum BX FT-IR spectrometer. Absorption peaks were reported in wavenumbers (cm^{-1}).

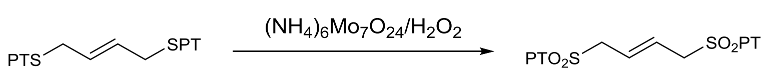
2.7.2 Experimental Procedures and Compound Characterizations



80 **81a**

(*E*)-1,4-bis((1-phenyl-1*H*-tetrazol-5-yl)thio)but-2-ene (81a)

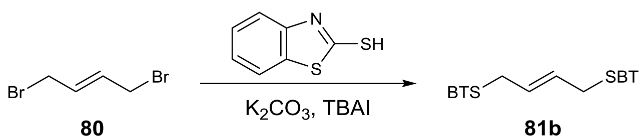
1-Phenyl-1*H*-tetrazole-5-thiol (0.91 g, 5.13 mmol, 2.2 equiv.) was taken in DMF (9.3 mL, 0.2 M). K_2CO_3 (1.45 g, 10.5 mmol, 4.5 equiv.), TBAI (86 mg, 0.23 mmol, 0.1 equiv.), and (*E*)-1,4-dibromobut-2-ene (0.5 g, 2.33 mmol, 1 equiv.) were added. The reaction mixture was then heated to 70 °C and stirred for 20 hours. The reaction mixture was then diluted with EtOAc and washed with a solution of 1:1 brine:H_2O. Product crashed out of organic layer so DCM was added. The DCM organic layer was then washed with a solution of 1:1 brine:H_2O (2 times) and then brine. The organic layer was dried over $MgSO_4$, filtered, and then concentrated *in vacuo* to afford (*E*)-1,4-bis((1-phenyl-1*H*-tetrazol-5-yl)thio)but-2-ene (quantitative). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66-7.26 (m, 10H), 6.14-6.11 (m, 2H), 4.48-4.46 (m, 4H).



81a **82a**

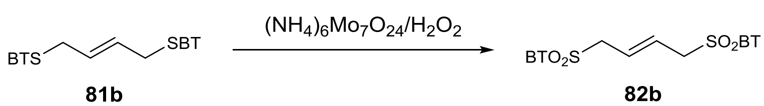
(*E*)-1,4-bis((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)but-2-ene (82a)

bis-Sulfide (1 equiv.) was taken in a 12:1 EtOH/DCM solution (0.08 M). A solution of $(NH_4)_6Mo_7O_{24}$ (0.2 equiv.) in 35% H_2O_2 (0.2 M) was added. The reaction mixture was stirred overnight and was then diluted with DCM and H_2O. The organic layer was extracted and washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was recrystallized from methanol/ethanol to afford (*E*)-1,4-bis((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)but-2-ene . ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57-7.53 (m, 10H), 6.03-6.01 (m, 2H), 3.99-3.97 (m, 4H).



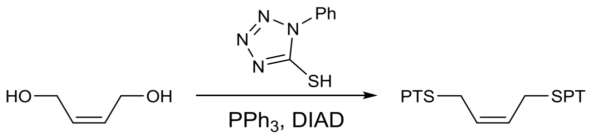
(*E*)-1,4-bis(benzo[*d*]thiazol-2-ylthio)but-2-ene (81b)

2-Mercaptobenzothiazole (2.2 equiv.) was taken in DMF (9.3 mL, 0.2 M). K_2CO_3 (4.5 equiv.), TBAI (0.1 equiv.), and (*E*)-1,4-dibromobut-2-ene (1 equiv.) were added. The reaction mixture was then heated to 70 °C and stirred for 20 hours. The reaction mixture was then diluted with EtOAc and washed with a solution of 1:1 brine:H_2O. Product crashed out of organic layer so DCM was added. The DCM organic layer was then washed with a solution of 1:1 brine:H_2O (2 times) and then brine. The organic layer was dried over $MgSO_4$, filtered, and then concentrated *in vacuo* to afford (*E*)-1,4-bis(benzo[*d*]thiazol-2-ylthio)but-2-ene. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 8.3 Hz, 2H), 7.70 (d, J = 8.1 Hz, 2H), 7.39 (t, J = 7.7 Hz, 2H), 7. 28 (t, J = 7.7 Hz, 2H), 6.03-6.01 (m, 2H), 3.97-3.96 (m, 4H).



(*E*)-1,4-bis(benzo[*d*]thiazol-2-ylsulfonyl)but-2-ene (82b)

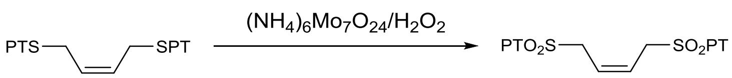
bis-Sulfide (1 equiv.) was taken in a 12:1 EtOH/DCM solution (0.08 M). A solution of $(NH_4)_6Mo_7O_{24}$ (0.2 equiv.) in 35% H_2O_2 (0.2 M) was added. The reaction mixture was stirred overnight and was then diluted with DCM and H_2O. The organic layer was extracted and washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was recrystallized from methanol/ethanol to afford (*Z*)-1,4-bis((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)but-2-ene. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 7.6 Hz, 2H), 7.76 (d, J = 7.6 Hz, 2H), 7.29-7.23 (m, 4H), 5.40-5.38 (m, 2H), 4.15-4.13 (m, 4H).



83 **84**

(*Z*)-1,4-bis((1-phenyl-1*H*-tetrazol-5-yl)thio)but-2-ene (84)

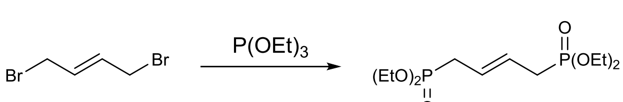
cis-Diol (1 equiv.) was taken in DCM (0.5M) and cooled to 0 °C. 1-Phenyl-1*H*-tetrazole-5-thiol (3 equiv.) and triphenylphosphine (3 equiv.) were added subsequently. The white, turbid reaction mixture was stirred for five minutes and then treated with DIAD (3 equiv.). The clear yellow solution was stirred at 0 °C for 1 hour. The reaction mixture was then quenched with brine solution. Organic layer was removed and aqueous layer was extracted with EtOAc (3 times). Organics layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 0%→40% EtOAc in hexanes) to afford (*Z*)-1,4-bis((1-phenyl-1*H*-tetrazol-5-yl)thio)but-2-ene. ^1H NMR (500 MHz, $CDCl_3$) δ 7.58-7.53 (m, 10H), 5.86-5.83 (m, 2H), 4.23-4.21 (m, 4H).



84 **85**

(*Z*)-1,4-bis((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)but-2-ene (85)

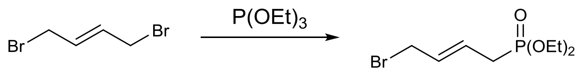
bis-Sulfide (1 equiv.) was taken in a 12:1 EtOH/DCM solution (0.08 M). A solution of $(NH_4)_6Mo_7O_{24}$ (0.2 equiv.) in 35% H_2O_2 (0.2 M) was added. The reaction mixture was stirred overnight and was then diluted with DCM and H_2O. The organic layer was extracted and washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was recrystallized from methanol/ethanol to afford (*Z*)-1,4-bis((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)but-2-ene. ^1H NMR (500 MHz, $CDCl_3$) δ 7.72-7.56 (m, 10H), 6.15-6.12 (m, 2H), 5.03-4.95 (m, 4H).



80 **64**

tetraethyl but-2-ene-1,4-diyl(*E*)-bis(phosphonate) (64)[8]

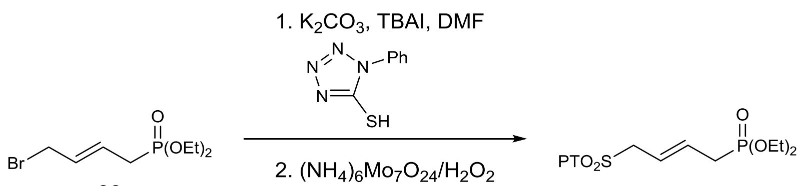
(*E*)-1,4-Dibromobut-2-ene (1 equiv.) and triethylphosphite (3 equiv.) were heated at 160 °C for 2 hours. The reaction mixture was purified by short path distillation (13 Torr at 188 °C) to afford tetraethyl but-2-ene-1,4-diyl(*E*)-bis(phosphonate).



80 **90**

(*E*)-diethyl (4-bromobut-2-en-1-yl)phosphonate (90)[15]

(*E*)-1,4-Dibromobut-2-ene (10.0 g, 46.8 mmol, 1 equiv.) and triethylphosphite (8.6 mL, 51.4 mmol, 1.1 equiv.) were taken in a round-bottom flask fitted with a rubber septum. A needle was placed in the septum to allow bromoethane to evolve. The mixture was heated at 85 °C and stirred for 4 hours. The reaction mixture was cooled and purified by column chromatography (grad. 50% EtOAc in hexanes→EtOAc) to afford (*E*)-diethyl (4-bromobut-2-en-1-yl)phosphonate (7.20 g, 26.5 mmol, 57%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dt, *J* = 7.5, 15.1 Hz, 1H), 5.76 (dt, *J* = 7.0, 14.0 Hz, 1H), 4.11 (m, 4H), 3.95 (dd, *J* = 3.1, 7.4 Hz, 2H), 2.62 (dd, *J* = 7.4, 22.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 6H).

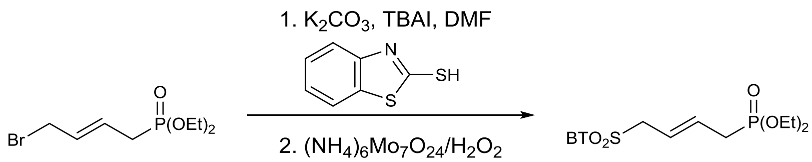


90 **93a**

(*E*)-diethyl (4-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)but-2-en-1-yl)phosphonate (93a)

1-Phenyl-1*H*-tetrazole-5-thiol (9.78 g, 54.9 mmol, 1.2 equiv.) was taken in DMF (146 mL, 0.2 M). K_2CO_3 (28.4 g, 205.8 mmol, 4.5 equiv.) and TBAI (1.7 g, 4.6 mmol, 0.1 equiv.) were added. Phosphonate (12.4 g, 45.7 mmol, 1 equiv.) was added dropwise as a solution in DMF (37 mL, 1.25 M). The reaction was stirred overnight and was then diluted with EtOAc and washed with a solution of 1:1 brine:H_2O (2 times) and then brine. The organic layer was dried over $MgSO_4$ and then concentrated *in vacuo*. The unpurified reaction mixture (~16 g) was then taken in EtOH (416 mL). A solution of $(NH_4)_6Mo_7O_{24}$ (2.4 g, 2.01 mmol) in 35% H_2O_2 (10 mL) was added. The reaction mixture was stirred overnight and was then diluted with DCM and H_2O. The organic layer was extracted and washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 50% EtOAc in hexanes→EtOAc) to afford (*E*)-diethyl (4-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)but-2-en-1-yl)phosphonate (16.9 g, 42.2 mmol, 92%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.56 (m, 5H), 5.99 (dt, *J* = 7.3, 14.8 Hz, 1H), 5.71 (dt, *J* = 7.1, 15.0 Hz, 1H), 4.42 (dd, *J* = 2.5, 7.1 Hz, 2H), 4.08 (m, 4H), 2.63 (dd, *J* = 7.5, 22.2 Hz, 2H), 1.30 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.5 (d, *J* =

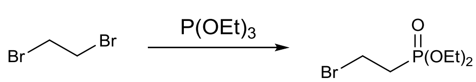
11.1 Hz), 132.9, 131.5, 129.7, 125.1, 118.2 (d, *J* = 14.8 Hz), 62.2 (d, *J* = 6.6 Hz), 59.4 (d, *J* = 2.3 Hz), 31.0 (d, *J* = 139.8 Hz), 16.4 (d, *J* = 5.9 Hz); HRMS (ES) *m/z* calcd for $C_{15}H_{21}N_4O_5PS$ $[M+H]^+$ 401.1043, found 401.1050; IR (thin film, cm^{-1}) 3063, 2984, 2931, 2908, 1595, 1498, 1462, 1444, 1394, 1349, 1251, 1154, 1099, 1050, 1025, 969, 835, 793, 766, 739, 691, 628.



90 93b

(*E*)-diethyl (4-(benzo[*d*]thiazol-2-ylsulfonyl)but-2-en-1-yl)phosphonate (93b)

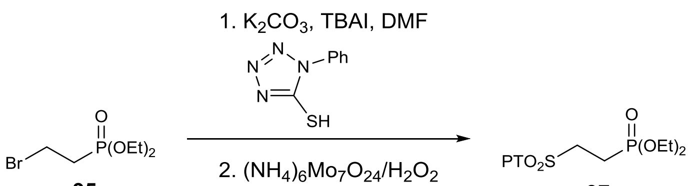
2-Mercaptobenzothiazole (5.77 g, 34.5 mmol, 1.2 equiv.) was taken in DMF (92 mL, 0.2 M). K_2CO_3 (17.86 g, 129.5 mmol, 4.5 equiv.) and TBAI (1.06 g, 2.88 mmol, 0.1 equiv.) were added. Phosphonate (7.80 g, 28.8 mmol, 1 equiv.) was added dropwise as a solution in DMF (23 mL, 1.25 M). The reaction mixture was allowed to stir overnight and then was diluted with EtOAc and washed with a solution of 1:1 brine:H_2O (2 times) and then brine. The organic layer was dried over $MgSO_4$ and then concentrated *in vacuo*. The unpurified reaction mixture (~ 11 g) was then taken in EtOH (286 mL). A solution of $(NH_4)_6Mo_7O_{24}$ (1.65 g, 1.42 mmol) in 35% H_2O_2 (7.5 mL) was added. The reaction was allowed to stir overnight and then was diluted with DCM and H_2O. The organic layer was extracted and washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 50% EtOAc in hexanes→EtOAc) to afford (*E*)-diethyl (4-(benzo[*d*]thiazol-2-ylsulfonyl)but-2-en-1-yl)phosphonate (11.2 g, 28.8 mmol, quantitative) as a white solid. ^1H NMR (700 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.9 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.65 (dt, *J* = 1.1, 7.2 Hz, 1H), 7.60 (dt, *J* = 1.1, 7.1 Hz, 1H), 5.80 (dt, *J* = 7.3, 14.2 Hz, 1H), 5.71 (dt, *J* = 7.3, 14.0 Hz, 1H), 4.24 (dd, *J* = 3.3, 7.0 Hz, 2H), 4.01 (m, 4H), 2.58 (dd, *J* = 7.0, 22.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 165.4, 152.7, 136.9, 131.8 (d, *J* = 10.9 Hz), 128.0, 127.7, 125.5, 122.3, 119.5 (d, *J* = 14.9 Hz), 62.1 (d, *J* = 6.6 Hz), 58.1, 30.9 (d, *J* = 140.0 Hz), 16.4 (d, *J* = 5.9 Hz); HRMS (ES) *m/z* calcd for $C_{15}H_{20}NO_5PS_2$ $[M+H]^+$ 390.0593, found 390.0601; IR (thin film, cm^{-1}) 2982, 2906, 1472, 1393, 1334, 1250, 1149,1127, 1052, 1025, 967, 853, 765, 731, 690, 666, 629.



94 95

diethyl (2-bromoethyl)phosphonate (95)[16]

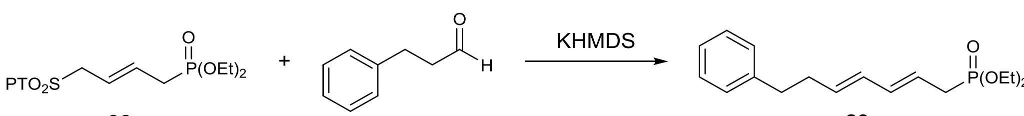
1,2-Dibromoethane (22.3 mL, 258.3 mmol, 7.9 equiv.) and triethylphosphite (5.2 mL, 32.8 mmol, 1 equiv.) were taken neat in a round-bottom flask equipped with a reflux condenser. The reaction mixture was heated at 160 °C and stirred for 4 hours. The reaction mixture was cooled and purified by vacuum distillation (1-5 mbar at 105-130 °C) to afford diethyl (2-bromoethyl)phosphonate (5.61 g, 26.2 mmol, 80%) as a colorless oil. Unreacted 1,2-dibromoethane was recovered (26.0 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 (m, 4H), 3.51 (q, J = 8.5 Hz, 2H), 2.42-2.31 (m, 2H), 1.32 (t, J = 7.1 Hz, 6 H).



diethyl (2-((1-phenyl-1H-tetrazol-5-yl)sulfonyl)ethyl)phosphonate (97)

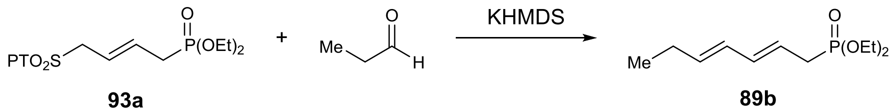
1-Phenyl-1*H*-tetrazole-5-thiol (6.90 g, 38.7 mmol, 1.2 equiv.) was taken in DMF (102 mL, 0.2 M). K_2CO_3 (13.30g, 96.6 mmol, 4.5 equiv.) and TBAI (1.20g, 3.22 mmol, 0.1 equiv.) were added. Phosphonate (6.90 g, 32.2 mmol, 1 equiv.) was added dropwise as a solution in DMF (26 mL, 1.25 M). The reaction was allowed to stir overnight and was then diluted with EtOAc and washed with a solution of 1:1 brine:H_2O (2 times) and then brine. The organic layer was dried over $MgSO_4$ and then concentrated *in vacuo*. The reaction mixture (~10 g) was then taken in EtOH (129 mL). A solution of $(NH_4)_6Mo_7O_{24}$ (1.07g, 0.92 mmol) in 35% H_2O_2 (4.7 mL) was added. The reaction mixture was allowed to stir overnight and was then diluted with DCM and H_2O. The organic layer was extracted and washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 50% EtOAc in hexanes→EtOAc) to afford diethyl (2-((1-phenyl-1H-tetrazol-5-yl)sulfonyl)ethyl)phosphonate (10.12 g, 27,1 mmol, 84%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.59 (m, 5H), 4.18 (m, 4H), 3.95 (m, 2H), 2.42 (ddt, J = 4.0, 8.2, 17.3 Hz, 2H), 1.37 (t, J = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.8, 131.6, 129.8, 124.9, 62.6 (d, J = 6.4 Hz), 50.8, 19.6 (d, J = 143.1 Hz), 16.4 (d, J = 5.9 Hz); HRMS (ES) *m/z* calcd for $C_{13}H_{19}N_4O_5PS$ $[M+H]^+$ 375.0887, found 375.0892; IR (thin film, cm^{-1}) 2985, 2933, 2911, 1498, 1350, 1248, 1212, 1155, 1099, 1053, 1023, 971, 767, 691.

General Procedure for Julia-Kocienski olefinations: Sulfonylphosphonate (1 equiv.) was dissolved in THF (0.25 M) and cooled to -78 °C. KHMDS (1.2 equiv., 1 M in THF) was added slowly. After five minutes at -78 °C, aldehyde (1.5 equiv.) was added to the solution. After 20 minutes, the reaction mixture was warmed up to 0 °C. After 1 hour, the reaction was quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes). Isomeric purity was determined by ^{1}H NMR, based on coupling constants and integration, in conjunction with GC-MS.



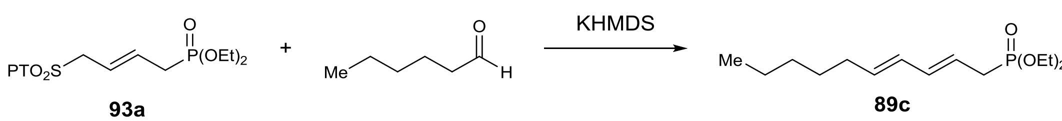
diethyl ((2*E*,4*E*)-7-phenylhepta-2,4-dien-1-yl)phosphonate (89a)

Sulfonylphosphonate **93a** (1.06 g, 2.65 mmol, 1 equiv.) was dissolved in THF (10.6 mL, 0.25 M) and cooled to -78 °C. KHMDS (635 mg, 3.l8 mmol, 1.2 equiv., 1 M in THF) was added slowly. After five minutes at -78 °C, hydrocinnamaldehyde (0.53 mL, 3.99 mmol, 1.5 equiv.) was added to the solution. After 20 minutes, the reaction mixture was warmed up to 0 °C. After 1 hour, the reaction was quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford diethyl ((2*E*,4*E*)-7-phenylhepta-2,4-dien-1-yl)phosphonate (719 mg, 2.33 mmol, 88%, 90:10 *EE:EZ* by ^{1}H NMR) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.24 (m, 2H), 7.21-7.15 (m, 3H), 6.13 (ddd, *J* = 4.9, 10.4 15.1 Hz, 1H), 6.05 (dd, *J* = 10.4, 14.8 Hz, 1H), 5.67 (dtd, *J* = 2.4, 6.9, 14.5 Hz, 1H), 5.52 (dt, *J* = 7.4, 14.8 Hz, 1H), 4.10 (m, 4H), 2.70 (t, *J* = 7.9 Hz, 2H), 2,62 (dd, *J* = 7.7, 22.4, 2H), 2.39 (q, 7.4 Hz, 2H), 1.31 (t, *J* = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 135.1 (d, *J* = 14.9 Hz), 133.4 (d, *J* = 4.3 Hz), 130.1 (d, *J* = 4.8 Hz), 128.4, 128.3, 125.8, 119.9 (d, *J* = 12.5 Hz), 61.9 (d, *J* = 6.7 Hz), 35.6, 34.4, 30.7 (d, *J* = 139.5), 16.4 (d, *J* = 5.8 Hz); HRMS (ES) *m/z* calcd for $C_{17}H_{25}O_3P$ $[M+H]^+$ 309.1614, found 309.1618; IR (thin film, cm^{-1}) 3026, 2982, 2930, 2907, 1497, 1454, 1392, 1251, 1212, 1163, 1098, 1056, 1027, 990, 962, 843, 806, 781, 748, 700.



diethyl (2*E*,4*E*)-octa-2,4-dien-1-ylphosphonate (89b)

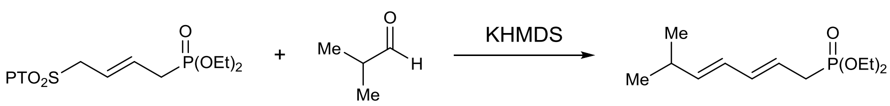
Sulfonylphosphonate **93a** (259 mg, 0.65 mmol, 1 equiv.) was dissolved in THF (2.6 mL, 0.25 M) and cooled to -78 °C. KHMDS (155 mg, 0.78 mmol, 1.2 equiv., 1 M in THF) was added slowly. After five minutes at -78 °C, propionaldehyde (70 µL, 0.97 mmol, 1.5 equiv.) was added to the solution. After 20 minutes, the reaction mixture was warmed up to 0 °C. After 1 hour, the reaction was quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford diethyl (2*E*,4*E*)-octa-2,4-dien-1-ylphosphonate (114 mg, 0.49 mmol, 76%, 91:9 *EE:EZ* by ^{1}H NMR) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14 (ddd, *J* = 5.0, 10.4, 15.2 Hz, 1H), 6.02 (dd, *J* = 10.6, 15.1 Hz, 1H), 5.68 (dtd, *J* = 2.3, 6.5, 15.2 Hz, 1H), 5.51 (dt, *J* = 7.3, 14.9 Hz, 1H), 4.10 (m, 4H), 2.62 (dd, *J* = 7.6, 22.3 Hz, 2H), 2.09 (qn, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 6H), 1.00 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2 (d, *J* = 4.3 Hz), 135.3 (d, *J* = 14.9 Hz), 128.5 (d, *J* = 4.7 Hz), 119.3 (d, *J* = 12.5 Hz), 61.9 (d, *J* = 6.7 Hz), 30.6 (d, *J* = 140.0 Hz), 25.6, 16.4 (d, *J* = 5.8 Hz), 13.4; HRMS (ES) *m/z* calcd for $C_{11}H_{21}O_3P$ $[M+H]^+$ 233.1301, found 233.1301; IR (thin film, cm^{-1}) 3019, 2966, 2933, 2907, 2874, 1478, 1457, 1443, 1392, 1368, 1252, 1212, 1164, 1098, 1058, 1028, 989, 962, 844, 811, 790.



diethyl (2*E*,4*E*)-undeca-2,4-dien-1-ylphosphonate (89c)

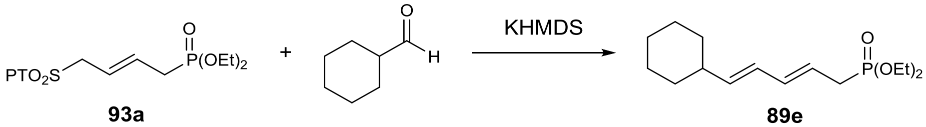
Sulfonylphosphonate **93a** (258 mg, 0.64 mmol, 1 equiv.) was dissolved in THF (2.6 mL, 0.25 M) and cooled to -78 °C. KHMDS (154 mg, 0.77 mmol, 1.2 equiv., 1 M in THF) was added slowly. After five minutes at -78 °C, hexanal (0.12 mL, 0.97 mmol, 1.5 equiv.) was added to the solution. After 20 minutes, the reaction mixture was warmed up to 0 °C. After 1 hour, the reaction was quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford diethyl (2*E*,4*E*)-undeca-2,4-dien-1-ylphosphonate (142 mg, 0.52 mmol, 80%, >95:5

EE:EZ by ^{1}H NMR) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13 (ddd, *J* = 5.0, 10.4, 15.2 Hz, 1H), 6.01 (dd, *J* = 10.6, 15.2 Hz, 1H), 5.64 (dtd, *J* = 2.3, 7.0, 14.9 Hz, 1H), 5.50 (dt, *J* = 7.5, 14.9 Hz, 1H), 4.10 (m, 4H), 2.61 (dd, *J* = 7.6, 22.4 Hz, 2H), 2.06 (q, *J* = 7.3 Hz, 2H), 1.42-1.22 (m, 12H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4 (d, *J* = 15.2 Hz), 134.9 (d, *J* = 4.4 Hz), 129.5 (d, *J* = 4.9 Hz), 119.2 (d, *J* = 12.7 Hz), 61.9 (d, *J* = 6.9 Hz), 32.5 (d, *J* = 1.5 Hz), 31.4, 30.6 (d, *J* = 139.9 Hz), 28.9 (d, *J* = 1.5 Hz), 22.5, 16.4 (d, *J* = 5.9 Hz); HRMS (ES) *m/z* calcd for $C_{15}H_{29}O_3P$ $[M+H]^+$ 275.1769, found 275.1771; IR (thin film, cm^{-1}) 2958, 2928, 2858, 1468, 1443, 1392, 1368, 1252, 1213, 1164, 1098, 1027, 988, 961, 837, 807, 780, 710, 665.



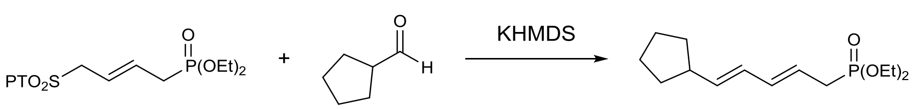
diethyl ((2*E*,4*E*)-6-methylhepta-2,4-dien-1-yl)phosphonate (89d)

Sulfonylphosphonate **93a** (210 mg, 0.52 mmol, 1 equiv.) was dissolved in THF (2.1 mL, 0.25 M) and cooled to -78 °C. KHMDS (126 mg, 0.63 mmol, 1.2 equiv., 1 M in THF) was added slowly. After five minutes at -78 °C, isobutyraldehyde (72 µL, 0.79 mmol, 1.5 equiv.) was added to the solution. After 20 minutes, the reaction mixture was warmed up to 0 °C. After 1 hour, the reaction was quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford diethyl ((2*E*,4*E*)-6-methylhepta-2,4-dien-1-yl)phosphonate (93 mg, 0.38 mmol, 72%, 89:11 *EE:EZ* by ^{1}H NMR) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.12 (ddd, *J* = 5.0, 10.4, 15.2 Hz, 1H), 5.98 (dd, *J* = 10.4, 15.2 Hz, 1H), 5.62 (ddd, *J* = 1.7, 6.7, 15.0 Hz, 1H), 5.51 (dt, *J* = 7.5, 14.9 Hz, 1H), 4.10 (m, 4H), 2.62 (dd, *J* = 7.6, 22.2 Hz, 2H), 2.31 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 6H), 0.99 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7 (d, *J* = 4.4 Hz), 135.5 (d, *J* = 15.1), 126.6 (d, *J* = 4.4 Hz), 119.4 (d, *J* = 12.7 Hz), 61.9 (d, *J* = 6.8 Hz), 31.0, 30.6 (d, *J* = 139.9 Hz), 22.2 (d, *J* = 1.5 Hz), 16.4 (d, *J* = 5.9 Hz); HRMS (ES) *m/z* calcd for $C_{12}H_{23}O_3P$ $[M+H]^+$ 247.1458, found 247.1461; IR (thin film, cm^{-1}) 3012, 2961, 2932, 2906, 2869, 1465, 1440, 1392, 1366, 1293, 1253, 1212, 1164, 1098, 1027, 989, 960, 841, 810, 782, 711.



diethyl ((2*E*,4*E*)-5-cyclohexylpenta-2,4-dien-1-yl)phosphonate (89e)

Sulfonylphosphonate **93a** (228 mg, 0.57 mmol, 1 equiv.) was dissolved in THF (2.3 mL, 0.25 M) and cooled to -78 °C. KHMDS (136 mg, 0.68 mmol, 1.2 equiv., 1 M in THF) was added slowly. After five minutes at -78 °C, cyclohexanecarbaldehyde (0.10 mL, 0.85 mmol, 1.5 equiv.) was added to the solution. After 20 minutes, the reaction mixture was warmed up to 0 °C. After 1 hour, the reaction was quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford diethyl ((2*E*,4*E*)-5-cyclohexylpenta-2,4-dien-1-yl)phosphonate (122 mg, 0.43 mmol, 75%, 91:9 *EE:EZ* by ^{1}H NMR) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.11 (ddd, *J* = 4.9, 10.4, 15.2 Hz, 1H), 5.98 (dd, *J* = 10.4, 15.3 Hz, 1H), 5.59 (ddd, *J* = 2.2, 6.8, 15.3 Hz, 1H), 5.50 (dt, *J* = 7.5, 14.9 Hz, 1H), 4.09 (m, 4H), 2.61 (dd, *J* = 7.6, 22.3 Hz, 2H), 1.97 (m, 1H), 1.74-1.67 (m, 4H), 1.67-1.60 (m, 1H), 1.35-0.97 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5 (d, *J* = 4.3 Hz), 135.6 (d, *J* = 14.9 Hz), 126.9 (d, *J* = 4.8 Hz), 119.3 (d, *J* = 12.5 Hz), 61.9 (d, *J* = 6.7 Hz), 40.6, 32.7 (d, *J* = 1.0 Hz), 30.6 (d, *J* = 139.5 Hz), 26.1, 26.0, 16.4 (d, *J* = 5.8 Hz); HRMS (ES) *m/z* calcd for $C_{15}H_{27}O_3P$ $[M+H]^+$ 287.1771, found 287.1770; IR (thin film, cm^{-1}) 2980, 2925, 2852, 1448, 1392, 1368, 1252, 1214, 1164, 1098, 1058, 1028, 987, 962, 891, 840, 788, 709, 665.

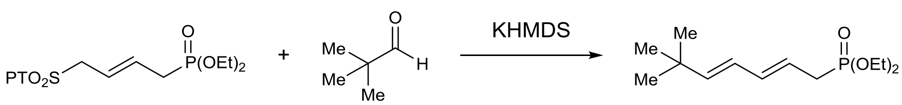


93a 89f

diethyl ((2*E*,4*E*)-5-cyclopentylpenta-2,4-dien-1-yl)phosphonate (89f)

Sulfonylphosphonate **93a** (248 mg, 0.62 mmol, 1 equiv.) was dissolved in THF (2.5 mL, 0.25 M) and cooled to -78 °C. KHMDS (148 mg, 0.74 mmol, 1.2 equiv., 1 M in THF) was added slowly. After five minutes at -78 °C, cyclopentanecarbaldehyde (0.10 mL, 0.93 mmol, 1.5 equiv.) was added to the solution. After 20 minutes, the reaction mixture was warmed up to 0 °C. After 1 hour, the reaction was quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford diethyl ((2*E*,4*E*)-5-cyclopentylpenta-2,4-dien-1-yl)phosphonate (137 mg, 0.50 mmol, 81%, 95:5 *EE:EZ* by ^{1}H NMR) as a colorless oil. ^{1}H NMR (500

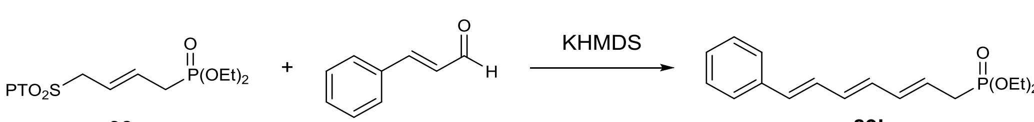
MHz, $CDCl_3$) δ 6.13 (ddd, *J* = 4.9, 10.5, 15.1 Hz, 1H), 6.01 (dd, *J* = 10.5, 15.1 Hz, 1H), 5.63 (ddd, *J* = 2.2, 7.8, 15.1 Hz, 1H), 5.50 (dt, *J* = 7.5, 15.0 Hz, 1H), 4.10 (m, 4H), 2.61 (dd, *J* = 7.6, 22.3 Hz, 2H), 2.44 (sext, *J* = 8.3 Hz, 1H), 1.82-1.74 (m, 2H), 1.69-1.52 (m, 4H), 1.34-1.24 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4 (d, *J* = 3.9 Hz), 135.4 (d, *J* = 15.2 Hz), 127.6 (d, *J* = 4.9 Hz), 119.2 (d, *J* = 12.7 Hz), 61.9 (d, *J* = 6.9 Hz), 43.3, 33.1 (d, *J* = 1.5 Hz), 30.6 (d, *J* = 139.9 Hz), 25.1, 16.5 (d, *J* = 6.0 Hz); HRMS (ES) *m/z* calcd for $C_{14}H_{25}O_3P$ $[M+H]^+$ 273.1614, found 273.1615; IR (thin film, cm^{-1}) 3021, 2978, 2953, 2908, 2868, 1478, 1445, 1392, 1367, 1253, 1213, 1164, 1098, 1058, 1028, 987, 961, 842, 808, 782, 711, 665.



93a 89g

diethyl ((2*E*,4*E*)-6,6-dimethylhepta-2,4-dien-1-yl)phosphonate (89g)

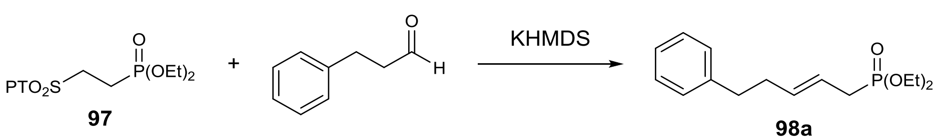
Sulfonylphosphonate **93a** (228 mg, 0.57 mmol, 1 equiv.) was dissolved in THF (2.3 mL, 0.25 M) and cooled to -78 °C. KHMDS (136 mg, 0.68 mmol, 1.2 equiv., 1 M in THF) was added slowly. After five minutes at -78 °C, pivaldehyde (93 µL, 0.85 mmol, 1.5 equiv.) was added to the solution. After 20 minutes, the reaction mixture was warmed up to 0 °C. After 1 hour, the reaction was quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford diethyl ((2*E*,4*E*)-6,6-dimethylhepta-2,4-dien-1-yl)phosphonate (104 mg, 0.40 mmol, 70%, >95:5 *EE:EZ* by ^1H NMR) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 6.13 (ddd, *J* = 4.9, 10.2, 15.1 Hz, 1H), 5.95 (dd, *J* = 10.3, 15.5 Hz, 1H), 5.66 (dd, *J* = 2.3, 15.5 Hz, 1H), 5.52 (dt, *J* = 7.5, 14.9 Hz, 1H), 4.10 (m, 4H), 2.61 (ddd, *J* = 1.1, 7.6, 22.2 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 6H), 1.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.6 (d, *J* = 4.4 Hz), 135.7 (d, *J* = 14.7 Hz), 124.4 (d, *J* = 4.9 Hz), 119.3 (d, *J* = 12.7 Hz), 61.9 (d, *J* = 6.4 Hz), 33.1 (d, *J* = 1.5 Hz), 30.6 (d, *J* = 139.9 Hz), 29.5 (d, *J* = 1.0 Hz), 16.4 (d, *J* = 5.9 Hz); HRMS (ES) *m/z* calcd for $C_{13}H_{25}O_3P$ $[M+H]^+$ 261.1614, found 261.1616; IR (thin film, cm^{-1}) 3026, 2957, 2904, 2867, 1476, 1462, 1444, 1392, 1364, 1333, 1253, 1216, 1164, 1098, 1055, 1029, 990, 961, 874, 846, 831, 812, 784, 712.



93a 89h

diethyl ((2*E*,4*E*,6*E*)-7-phenylhepta-2,4,6-trien-1-yl)phosphonate (89h)

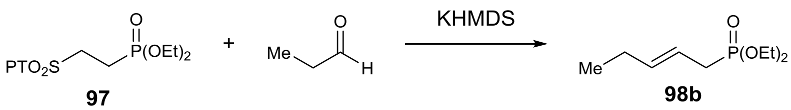
Sulfonylphosphonate **93a** (227 mg, 0.57 mmol, 1 equiv.) was dissolved in THF (2.3 mL, 0.25 M) and cooled to -78 °C. KHMDS (136 mg, 0.68 mmol, 1.2 equiv., 1 M in THF) was added slowly. After five minutes at -78 °C, *trans*-cinnamaldehyde (0.11 mL, 0.85 mmol, 1.5 equiv.) was added to the solution. After 20 minutes, the reaction mixture was warmed up to 0 °C. After 1 hour, the reaction was quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford diethyl ((2*E*,4*E*,6*E*)-7-phenylhepta-2,4,6-trien-1-yl)phosphonate (67 mg, 0.22 mmol, 39%, 62:38 *EE:EZ* by ^{1}H NMR) as a colorless oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 6.80 (ddd, *J* = 5.0, 9.6, 15.7 Hz, 1H), 6.57 (d, *J* = 15.4 Hz, 1H), 6.36-6.33 (m, 2H), 6.27 (ddd, *J* = 4.9, 9.9, 14.9 Hz, 1H), 5.70 (dt, *J* = 7.7, 15.3 Hz, 1H), 4.11 (m, 4H), 2.69 (dd, *J* = 7.7, 22.7 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 137.7, 135.1 (d, *J* = 15.3 Hz), 132.7 (d, *J* = 2.6 Hz), 132.7 (d, *J* = 4.8 Hz), 132.5 (d, *J* = 5.3 Hz), 128.8 (d, *J* = 2.9 Hz), 128.6, 127.5, 126.3, 122.6 (d, *J* = 13.1 Hz), 62.0 (d, *J* = 6.8 Hz), 31.1 (d, *J* = 140.0 Hz), 16.5 (d, *J* = 5.9 Hz); HRMS (ES) *m/z* calcd for $C_{17}H_{23}O_3P$ $[M+H]^+$ 307.1458, found 307.1463; IR (thin film, cm^{-1}) 3023, 2985, 2929, 2906, 1597, 1491, 1448, 1392, 1368, 1295, 1243, 1161, 1097, 1027, 965, 864, 838, 814, 785, 752, 695.



(*E*)-diethyl (5-phenylpent-2-en-1-yl)phosphonate (98a)

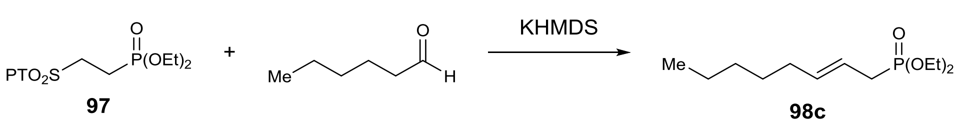
Sulfonylphosphonate **97** (1.04 g, 2.78 mmol, 1 equiv.) was dissolved in THF (11.1 mL, 0.25 M) and cooled to -78 °C. KHMDS (666 mg, 3.34 mmol, 1.2 equiv., 1 M in THF) was added slowly. After five minutes at -78 °C, hydrocinnamaldehyde (0.55 mL, 3.99 mmol, 1.5 equiv.) was added to the solution. After 20 minutes, the reaction mixture was warmed up to 0 °C. After 1 hour, the reaction was quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford (*E*)-diethyl (5-phenylpent-2-en-1-yl)phosphonate (663 mg, 2.35 mmol, 85%, >95:5 *E:Z* by ^{1}H NMR) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (m, 2H), 7.19-7.16

(m, 3H), 5.65 (dt, J = 6.6, 15.3 Hz, 1H), 5.45 (dt, J = 7.3, 15.2 Hz, 1H), 4.07 (m, 4H), 2.69 (t, J = 7.4 Hz, 2H), 2.54 (dd, J = 7.3, 21.6 Hz, 2H), 2.37 (m, 2H), 1.30 (t, J = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 135.1 (d, J = 14.3 Hz), 128.4, 128.3, 125.8, 119.2 (d, J = 11.0 Hz), 61.8 (d, J = 6.7 Hz), 35.5 (d, J = 3.8 Hz), 34.3 (d, J = 2.4 Hz), 30.4 (d, J = 139.5), 16.4 (d, J = 6.23 Hz); HRMS (ES) *m/z* calcd for $C_{15}H_{23}O_3P$ $[M+H]^+$ 283.1458, found 283.1460; IR (thin film, cm^{-1}) 3062, 3027, 2982, 2930, 2907, 2857, 1496, 1479, 1454, 1444, 1392, 1368, 1252, 1215, 1164, 1098, 1054, 1029, 963, 785, 748, 700.



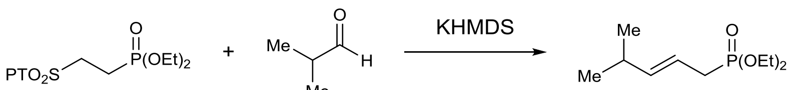
(*E*)-diethyl hex-2-en-1-ylphosphonate (98b)

Sulfonylphosphonate **97** (227 mg, 0.61 mmol, 1 equiv.) was dissolved in THF (2.4 mL, 0.25 M) and cooled to -78 °C. KHMDS (145 mg, 0.73 mmol, 1.2 equiv., 1 M in THF) was added slowly. After five minutes at -78 °C, propionaldehyde (66 µL, 0.91 mmol, 1.5 equiv.) was added to the solution. After 20 minutes, the reaction mixture was warmed up to 0 °C. After 1 hour, the reaction was quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford (*E*)-diethyl hex-2-en-1-ylphosphonate (96 mg, 0.47 mmol, 77%, 93:7 *E:Z* by ^{1}H NMR) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (dt, J = 6.3, 15.3 Hz, 1H), 5.39 (dt, J = 7.3, 15.2 Hz, 1H), 4.09 (m, 4H), 2.54 (dd, J = 7.3, 21.5 Hz, 2H), 2.05 (qn, J = 6.6 Hz, 2H), 1.31 (t, J = 7.1 Hz, 6H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7 (d, J = 14.4 Hz), 117.5 (d, J = 11.0 Hz), 61.8 (d, J = 6.2 Hz), 30.4 (d, 139.5 Hz), 25.6 (d, 2.4 Hz), 16.4 (d, 6.2 Hz), 13.4 (d, 3.4 Hz); HRMS (ES) *m/z* calcd for $C_9H_{19}O_3P$ $[M+H]^+$ 207.1145, found 207.1146; IR (thin film, cm^{-1}) 2980, 2966, 2934, 2907, 2874, 1458, 1444, 1392, 1368, 1293, 1252, 1164, 1098, 1052, 1029, 963, 856, 828, 796, 708.



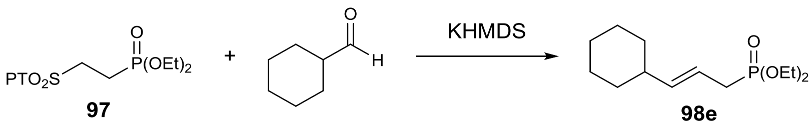
(*E*)-diethyl non-2-en-1-ylphosphonate (98c)

Sulfonylphosphonate **97** (476 mg, 1.27 mmol, 1 equiv.) was dissolved in THF (5.1 mL, 0.25 M) and cooled to -78 °C. KHMDS (304 mg, 1.53 mmol, 1.2 equiv., 1 M in THF) was added slowly. After five minutes at -78 °C, hexanal (0.23 mL, 1.91 mmol, 1.5 equiv.) was added to the solution. After 20 minutes, the reaction mixture was warmed up to 0 °C. After 1 hour, the reaction was quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford (*E*)-diethyl non-2-en-1-ylphosphonate (274 mg, 1.10 mmol, 87%, >95:5 *E:Z* by ^{1}H NMR) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.60 (dt, *J* = 6.6, 15.2 Hz, 1H), 5.39 (dt, *J* = 7.3, 15.2 Hz, 1H), 4.09 (m, 4H), 2.54 (dd, *J* = 7.3, 21.5 Hz, 2H), 2.03 (q, *J* = 6.5 Hz, 2H), 1.40-1.22 (m, 12H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3 (d, *J* = 4.7 Hz), 118.4 (d, *J* = 11.3 Hz), 61.8 (d, *J* = 6.4 Hz), 32.5 (d, *J* = 2.5 Hz), 31.3, 30.5 (d, *J* = 139.9 Hz), 29.9, 28.8 (d, *J* = 3.4 Hz), 22.5, 16.4 (d, *J* = 5.9 Hz), 14.0; HRMS (ES) *m/z* calcd for $C_{13}H_{27}O_3P$ $[M+H]^+$ 249.1614, found 249.1614; IR (thin film, cm^{-1}) 2980, 2958, 2928, 2858, 1458, 1444, 1392, 1368, 1254, 1215, 1164, 1098, 1054, 1030, 963, 835, 783, 708, 666.



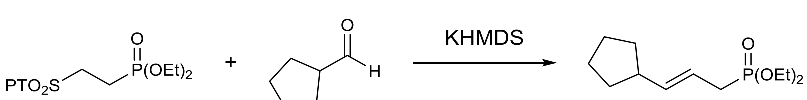
(*E*)-diethyl (4-methylpent-2-en-1-yl)phosphonate (98d)

Sulfonylphosphonate **97** (246 mg, 0.66 mmol, 1 equiv.) was dissolved in THF (2.6 mL, 0.25 M) and cooled to -78 °C. KHMDS (157 mg, 0.79 mmol, 1.2 equiv., 1 M in THF) was added slowly. After five minutes at -78 °C, isobutyraldehyde (90 µL, 0.99 mmol, 1.5 equiv.) was added to the solution. After 20 minutes, the reaction mixture was warmed up to 0 °C. After 1 hour, the reaction was quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford (*E*)-diethyl (4-methylpent-2-en-1-yl)phosphonate (106 mg, 0.48 mmol, 72%, >95:5 *E:Z* by ^{1}H NMR) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57 (ddd, *J* = 6.3, 6.3, 15.3 Hz, 1H), 5.36 (dt, *J* = 7.2, 14.9 Hz, 1H), 4.09 (m, 4H), 2.54 (dd, *J* = 7.3, 21.4 Hz, 2H), 2.30 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 6H), 0.98 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1 (d, *J* = 14.5 Hz), 115.6 (d, *J* = 11.3 Hz), 61.8 (d, *J* = 6.9 Hz), 31.2 (d, *J* = 2.0 Hz), 20.4 (d, *J* = 139.4 Hz), 22.3 (d, J = 3.4), 16.4 (d, 5.9 Hz); HRMS (ES) m/z calcd for $C_{10}H_{21}O_3P$ $[M+H]^+$ 221.1301, found 221.1302; IR (thin film, cm^{-1}) 2960, 2932, 2907, 2870, 1467, 1445, 1392, 1366, 1253, 1164, 1098, 1060, 1029, 965, 867, 789, 712.



(*E*)-diethyl (3-cyclohexylallyl)phosphonate (98e)

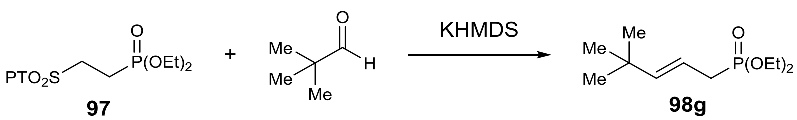
Sulfonylphosphonate **97** (1.05 g, 2.80 mmol, 1 equiv.) was dissolved in THF (11.2 mL, 0.25 M) and cooled to -78 °C. KHMDS (671 mg, 3.37 mmol, 1.2 equiv., 1 M in THF) was added slowly. After five minutes at -78 °C, cyclohexanecarbaldehyde (0.51 mL, 4.21 mmol, 1.5 equiv.) was added to the solution. After 20 minutes, the reaction mixture was warmed up to 0 °C. After 1 hour, the reaction was quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford (*E*)-diethyl (3-cyclohexylallyl)phosphonate (577 mg, 2.20 mmol, 79%, >95:5 *E:Z* by ^{1}H NMR) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (ddd, J = 6.2, 6.2, 15.4 Hz, 1H), 5.36 (dt, J = 6.5, 15.1 Hz, 1H), 4.09 (m, 4H), 2.54 (dd, J = 7.3, 21.4 Hz, 2H), 2.01-1.92 (m, 1H), 1.74-1.67 (m, 4H), 1.67-1.60 (m, 1H), 1.33-1.01 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.0 (d, J = 14.4 Hz), 116.0 (d, J = 11.0 Hz), 61.8 (d, J = 6.2 Hz), 40.8, 32.8 (d, J = 2.9 Hz), 30.6 (d, J = 139.5 Hz), 26.1, 26.0, 16.5 (d, J = 6.2 Hz); HRMS (ES) m/z calcd for $C_{13}H_{25}O_3P$ $[M+H]^+$ 261.1614, found 261.1615; IR (thin film, cm^{-1}) 2980, 2952, 2852, 1478, 1448, 1392, 1367, 1253, 1164, 1098, 1059, 1029, 965, 893, 858, 832, 781, 712.



(*E*)-diethyl (3-cyclopentylallyl)phosphonate (98f)

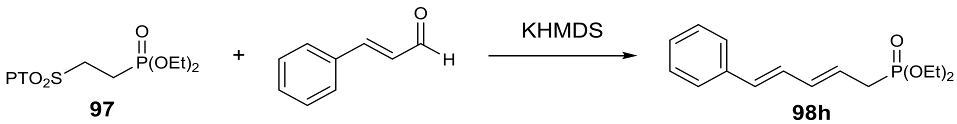
Sulfonylphosphonate **97** (224 mg, 0.60 mmol, 1 equiv.) was dissolved in THF (2.4 mL, 0.25 M) and cooled to -78 °C. KHMDS (143 mg, 0.72 mmol, 1.2 equiv., 1 M in THF) was added slowly. After five minutes at -78 °C, cyclopentanecarbaldehyde (96 µL, 0.90 mmol, 1.5 equiv.) was added to the solution. After 20 minutes, the reaction mixture was warmed up to 0 °C. After 1 hour, the reaction was quenched by addition of aqueous NH_4Cl solution and the product was extracted with

EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford (*E*)-diethyl (3-cyclopentylallyl)phosphonate (122 mg, 0.50 mmol, 83%, >95:5 *E:Z* by ^{1}H NMR) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68 (ddd, *J* = 6.3, 6.3, 15.1 Hz, 1H), 5.39 (dt, *J* = 7.1, 15.1 Hz, 1H), 4.09 (m, 4H), 2.54 (dd, *J* = 7.3, 21.4 Hz, 2H), 2.43 (sext, *J* = 7.3 Hz, 1H), 1.81-1.77 (m, 2H), 1.68-1.51 (m, 4H), 1.34-1.23 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8 (d, *J* = 14.7 Hz), 116.5 (d, *J* = 11.3 Hz), 61.8 (d, *J* = 6.4 Hz), 43.3 (d, *J* = 2.5 Hz), 32.9 (d, *J* = 2.9 Hz), 30.5 (d, *J* = 139.9 Hz), 25.1, 16.4 (d, *J* = 5.9 Hz); HRMS (ES) *m/z* calcd for $C_{12}H_{23}O_3P$ $[M+H]^+$ 247.1458, found 247.1459; IR (thin film, cm^{-1}) 2979, 2953, 2909, 2869, 1478, 1445, 1392, 1367, 1252, 1214, 1164, 1098, 1058, 1029, 964, 862, 831, 786, 713, 665.



(*E*)-diethyl (4,4-dimethylpent-2-en-1-yl)phosphonate (98g)

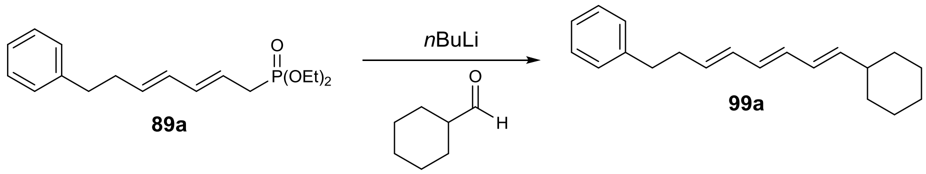
Sulfonylphosphonate **97** (488 mg, 1.30 mmol, 1 equiv.) was dissolved in THF (5.2 mL, 0.25 M) and cooled to -78 °C. KHMDS (312 mg, 1.56 mmol, 1.2 equiv., 1 M in THF) was added slowly. After five minutes at -78 °C, pivaldehyde (0.21 mL, 1.96 mmol, 1.5 equiv.) was added to the solution. After 20 minutes, the reaction mixture was warmed up to 0 °C. After 1 hour, the reaction was quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford (*E*)-diethyl (4,4-dimethylpent-2-en-1-yl)phosphonate (124 mg, 0.53 mmol, 41%, >95:5 *E:Z* by ^{1}H NMR) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 (dd, *J* = 4.9, 15.7 Hz, 1H), 5.32 (dt, *J* = 7.1, 15.4 Hz, 1H), 4.08 (m, 4H), 2.54 (dd, *J* = 7.3, 21.4 Hz, 2H), 1.31 (t, *J* = 7.0 Hz, 6H), 1.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.9 (d, *J* = 14.1 Hz), 113.5 (d, *J* = 10.8), 61.8 (d, *J* = 6.9 Hz), 33.3 (d, *J* = 2.0 Hz), 30.5 (d, *J* = 139.4), 29.4 (d, *J* = 2.5 Hz), 16.4 (d, *J* = 5.9 Hz); HRMS (ES) *m/z* calcd for $C_{11}H_{23}O_3P$ $[M+H]^+$ 235.1458, found 235.1454; IR (thin film, cm^{-1}) 2959, 2905, 2867, 1478, 1464, 1444, 1320, 1364, 1253, 1164, 1098, 1031, 963, 862, 838, 793, 712, 665.



diethyl ((2*E*,4*E*)-5-phenylpenta-2,4-dien-1-yl)phosphonate (98h)

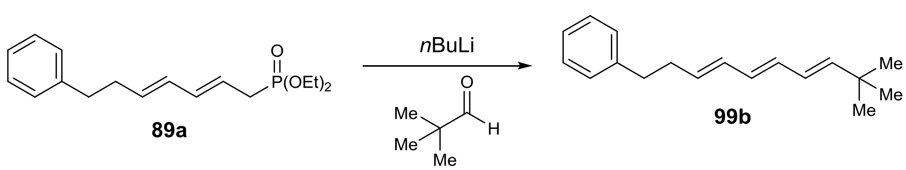
Sulfonylphosphonate **97** (218 mg, 0.58 mmol, 1 equiv.) was dissolved in THF (2.3 mL, 0.25 M) and cooled to -78 °C. KHMDS (139 mg, 0.70 mmol, 1.2 equiv., 1 M in THF) was added slowly. After five minutes at -78 °C, *trans*-cinnamaldehyde (0.11 mL, 0.87 mmol, 1.5 equiv.) was added to the solution. After 20 minutes, the reaction mixture was warmed up to 0 °C. After 1 hour, the reaction was quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford diethyl ((2*E*,4*E*)-5-phenylpenta-2,4-dien-1-yl)phosphonate (142 mg, 0.51 mmol, 87%, 86:14 *E:Z* by ^{1}H NMR) as a yellow solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 6.75 (dd, *J* = 10.5, 15.6 Hz, 1H), 6.49 (dd, *J* = 1.8, 15.7 Hz, 1H), 6.33 (ddd, 4.5, 10.5, 14.8 Hz, 1H), 5.76 (dt, *J* = 7.6, 15.3 Hz, 1H), 4.11 (m, 4H), 2.69 (dd, *J* = 7.6, 22.6 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 137.1, 135.2 (d, *J* = 15.0 Hz), 132.0 (d, *J* = 4.5 Hz), 128.5, 128.3 (d, *J* = 5.0 Hz), 127.5, 126.3, 122.6 (d, *J* = 12.8 Hz), 62.0 (d, *J* = 6.8 Hz), 31.0 (d, *J* = 140.0 Hz), 16.4 (d, *J* = 5.9 Hz); HRMS (ES) *m/z* calcd for $C_{15}H_{21}O_3P$ $[M+H]^+$ 281.1301, found 281.1300; IR (thin film, cm^{-1}) 3027, 2989, 2907, 1494, 1479, 1450, 1391, 1242, 1222, 1158, 1028, 1011, 970, 956, 819, 787, 753, 695.

General Procedure for Horner-Wadsworth-Emmons olefinations with *n*BuLi: Allylic phosphonate (1 equiv.) was dissolved in THF (0.25 M) and cooled to -78 °C. *n*BuLi (1.1 equiv., 2.5 M in hexanes) was added slowly. After 20 minutes at -78 °C, aldehyde (1.5 equiv.) was added to the solution. After 15 minutes, the reaction mixture was warmed up to rt and allowed to stir for 10-12 hours. The reaction was then quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 0%→2% EtOAc in hexanes). Isomeric purity was determined by ^{1}H NMR, based on coupling constants and integration.



((*3E,5E,7E*)-8-cyclohexylocta-3,5,7-trien-1-yl)benzene (99a)

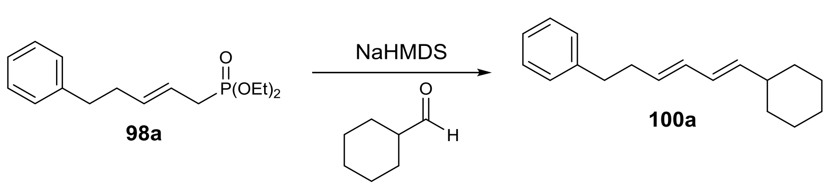
Allylic phosphonate **89a** (257 mg, 0.83 mmol, 1 equiv.) was dissolved in THF (3.3 mL, 0.25 M) and cooled to -78 °C. *n*BuLi (0.35 mL, 0.91 mmol, 1.1 equiv., 2.5 M in hexanes) was added slowly. After 20 minutes at -78 °C, cyclohexanecarbaldehyde (0.15 mL, 1.25 mmol, 1.5 equiv.) was added to the solution. After 15 minutes, the reaction mixture was warmed up to rt and allowed to stir for 12 hours. The reaction was then quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 0%→2% EtOAc in hexanes) to afford ((*3E,5E,7E*)-8-cyclohexylocta-3,5,7-trien-1-yl)benzene (185 mg, 0.70 mmol, 83%, 90:10 *EEE:Σ*other by ^1H NMR) as a colorless oil. ^1H NMR (700 MHz, $CDCl_3$) δ 7.30-7.24 (m, 2H), 7.22-7.15 (m, 3H), 6.11-6.05 (m, 3H), 6.01 (dd, *J* = 8.9, 15.2 Hz, 1H), 5.68 (dt, *J* = 7.0, 14.0 Hz, 1H), 5.63 (dd, *J* = 6.9, 15.1 Hz, 1H), 2.71 (t, *J* = 7.6 Hz, 2H), 2.42 (q, *J* = 7.6 Hz, 2H), 2.01 (m, 1H), 1.78-1.70 (m, 4H), 1.68-1.61 (m, 1H), 1.32-1.05 (m, 5H), 1.09 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 141.8, 140.6, 133.0, 131.6, 131.0, 130.7, 128.4, 128.3, 127.8, 125.8, 40.9, 35.8, 34.6, 32.8, 26.1, 26.0; HRMS (EI) *m/z* calcd for $C_{20}H_{26}$ $[M]^+$ 266.2034, found 266.2039; IR (thin film, cm^{-1}) 3085, 3062, 3015, 2924, 2851, 1496, 1449, 1030, 994, 966, 754, 698.



((*3E,5E,7E*)-9,9-dimethyldeca-3,5,7-trien-1-yl)benzene (99b)

Allylic phosphonate **89a** (257 mg, 0.83 mmol, 1 equiv.) was dissolved in THF (3.3 mL, 0.25 M) and cooled to -78 °C. *n*BuLi (0.35 mL, 0.91 mmol, 1.1 equiv., 2.5 M in hexanes) was added slowly. After 20 minutes at -78 °C, pivaldehyde (0.14 mL, 1.24 mmol, 1.5 equiv.) was added to the solution. After 15 minutes, the reaction mixture was warmed up to rt and allowed to stir for 12 hours. The reaction was then quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 0%→2% EtOAc in hexanes) to afford ((*3E*,*5E*,*7E*)-9,9-dimethyldeca-3,5,7-trien-1-yl)benzene (172 mg, 0.72 mmol, 86%, 90:10 *EEE:Σ*other by ^{1}H NMR) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H), 7.20-7.16 (m, 2H), 6.13-6.05 (m, 3H), 5.98 (dd, *J* = 9.5, 15.4 Hz, 1H), 5.70 (d, *J* = 15.4 Hz, 1H), 5.69 (dt, *J* = 7.1, 15.0 Hz, 1H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.41 (q, *J* = 7.7 Hz, 2H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.6, 141.8, 133.0, 131.6, 131.0, 130.8, 128.4, 128.3, 125.8, 125.2, 35.8, 34.6, 33.3, 29.5; HRMS (EI) *m/z* calcd for $C_{18}H_{24}$ $[M]^+$ 240.1878, found 240.1877; IR (thin film, cm^{-1}) 3085, 3063, 3018, 2959, 2902, 2864, 1496, 1474, 1454, 1362, 1266, 995, 745, 698.

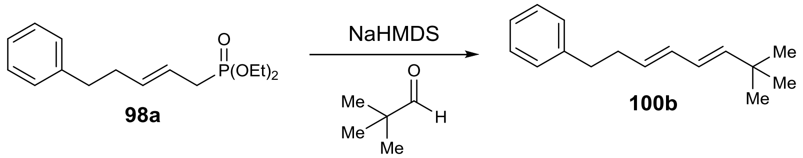
General Procedure for Horner-Wadsworth-Emmons olefinations with NaHMDS: Allylic phosphonate (1 equiv.) was dissolved in THF (0.25 M) and cooled to -78 °C. NaHMDS (1.1 equiv., 2.5 M in hexanes) was added slowly. After 1 hour at -78 °C, aldehyde (1.5 equiv.) was added to the solution. After 15 minutes, the reaction mixture was warmed up to rt and allowed to stir for 10-12 hours. The reaction was then quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 0%→2% EtOAc in hexanes). Isomeric purity was determined by ^{1}H NMR, based on coupling constants and integration.



((*3E*,*5E*)-6-cyclohexylhexa-3,5-dien-1-yl)benzene (100a)

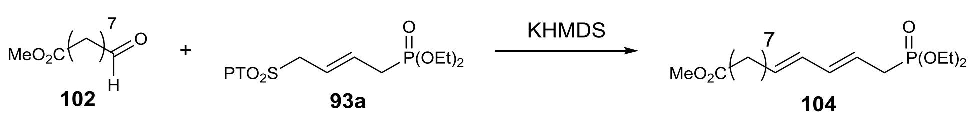
Allylic phosphonate **98a** (228 mg, 0.81 mmol, 1 equiv.) was dissolved in THF (3.2 mL, 0.25 M) and cooled to -78 °C. NaHMDS (163 mg, 0.89 mmol, 1.1 equiv., 2.5 M in hexanes) was added slowly. After 1 hour at -78 °C, cyclohexanecarbaldehyde (0.15 mL, 1.22 mmol, 1.5 equiv.) was added to the solution. After 15 minutes, the reaction mixture was warmed up to rt and allowed to stir for 12 hours. The reaction was then quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 0%→2% EtOAc in hexanes) to afford ((*3E*,*5E*)-6-cyclohexylhexa-3,5-dien-1-yl)benzene

(184 mg, 0.77 mmol, 95%, 89:11 *EE:Σ*other isomers by ^{1}H NMR) as a colorless oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.30-7.25 (m, 2H), 7.22-7.17 (m, 3H), 6.05 (dd, *J* = 10.4, 15.0 Hz, 1H), 5.97 (dd, *J* = 10.2, 15.2 Hz, 1H), 5.62 (dt, *J* = 6.8, 14.2 Hz, 1H), 5.55 (dd, *J* = 6.9, 15.2 Hz, 1H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.38 (q, *J* = 7.2 Hz, 2H), 1.97 (m, 1H), 1.74-1.68 (m, 4H), 1.67-1.61 (m, 1H), 1.31-1.05 (m, 5H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 141.9, 138.9, 131.2, 131.1, 128.4, 128.3, 127.5, 125.8, 40.7, 35.9, 34.5, 32.9, 26.2, 26.0; HRMS (EI) *m/z* calcd for $C_{18}H_{24}$ $[M]^+$ 240.1878, found 240.1882; IR (thin film, cm^{-1}) 3024, 2924, 2851, 1496, 1449, 1030, 987, 966, 745, 698.



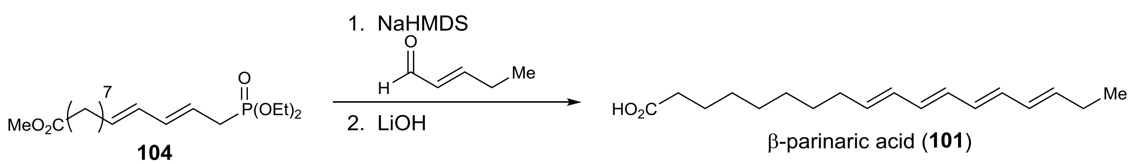
((*3E,5E*)-7,7-dimethylocta-3,5-dien-1-yl)benzene (100b)

Allylic phosphonate **98a** (172 mg, 0.61 mmol, 1 equiv.) was dissolved in THF (2.4 mL, 0.25 M) and cooled to -78 °C. NaHMDS (123 mg, 0.67 mmol, 1.1 equiv., 2.5 M in hexanes) was added slowly. After 1 hour at -78 °C, pivaldehyde (99 µL, 0.92 mmol, 1.5 equiv.) was added to the solution. After 15 minutes, the reaction mixture was warmed up to rt and allowed to stir for 12 hours. The reaction was then quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 0%→2% EtOAc in hexanes) to afford ((*3E,5E*)-7,7-dimethylocta-3,5-dien-1-yl)benzene (72 mg, 0.34 mmol, 55%, 89:11 *EE:Σ*other isomers by ^{1}H NMR) as a colorless oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.3-7.27 (m, 2H), 7.23-7.17 (m, 3H), 6.06 (dd, *J* = 10.7, 15.2 Hz, 1H), 5.95 (dd, *J* = 10.2, 15.5 Hz, 1H), 5.67-5.60 (m, 2H), 2.71 (t, *J* = 7.6 Hz, 2H), 2.39 (q, *J* = 8.0, 2H), 1.03 (s, 9H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 144.0, 142.0, 131.3, 131.3, 128.4, 128.3, 125.8, 125.0, 35.9, 34.5, 33.0, 29.6; HRMS (EI) *m/z* calcd for $C_{16}H_{22}$ $[M]^+$ 214.1721, found 214.1719; IR (thin film, cm^{-1}) 3025, 2959, 2929, 2904, 2864, 1496, 1476, 1461, 1454, 1361, 1270, 1258, 1030, 989, 745, 698.



(9*E*,11*E*)-methyl 13-(diethoxyphosphoryl)trideca-9,11-dienoate (104)

Sulfonylphosphonate **93a** (904 mg, 2.26 mmol, 1 equiv.) was dissolved in THF (9.04 mL, 0.25 M) and cooled to -78 °C. KHMDS (505 mg, 2.71 mmol, 1.2 equiv., 1 M in THF) was added slowly. After five minutes at -78 °C, methyl 9-oxononanoate[11] (496 mg, 2.49 mmol, 1.2 equiv., 1 M in THF) was added to the solution. After 20 minutes, the reaction mixture was warmed up to 0 °C. After 1 hour, the reaction was quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The unpurified reaction mixture was purified by column chromatography (grad. 15%→30% acetone/hexanes) to afford phosphonate (570 mg, 1.58 mmol, 70% yield; 91:9 *EE:EZ* by ^{1}H NMR) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13 (ddd, *J* = 4.9, 10.4, 15.1 Hz, 1H), 6.01 (dd, *J* = 10.8, 15.0 Hz, 1H), 5.62 (dt, *J* = 7.6, 14.7 Hz, 1H), 5.50 (dt, *J* = 7.5, 14.9 Hz, 1H), 4.14-4.05 (m, 4H), 3.66 (s, 3H), 2.61 (dd, *J* = 7.6, 22.3 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.07-2.01 (m, 2H), 1.67-1.56 (m, 2H), 1.39-1.23 (m, 14H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 135.3 (d, *J* = 14.9 Hz), 134.7 (d, *J* = 4.3 Hz), 129.5 (d, *J* = 4.6 Hz), 119.2 (d, *J* = 12.5 Hz), 61.9 (d, *J* = 6.7 Hz), 51.4, 34.1, 32.5 (d, *J* = 1.3 Hz), 30.6 (d, *J* = 139.9 Hz), 29.1 (d, *J* = 1.5 Hz), 29.1, 29.1, 29.0, 24.9, 16.4 (d, *J* = 5.9 Hz); HRMS (ES) *m/z* calcd for $C_{18}H_{33}O_5P$ $[M+H]^+$ 361.2138, found 361.2144; IR (thin film, cm^{-1}) 3019, 2982, 2929, 2855, 1739, 1438, 1392, 1367, 1251, 1210, 1167, 1098, 1056, 1028, 989, 961, 841, 807, 780, 710.



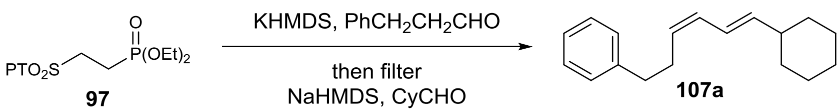
β-parinaric acid

Phosphonate (267 mg, 0.74 mmol, 1 equv.) was dissolved in THF (0.25 M) and cooled to -78 °C. NaHMDS (1.1 equiv., 1 M in hexanes) was added slowly. After five minutes at -78 °C, *trans*-2-pentenal (109 µL, 1.11 mmol, 1.5 equiv.) was added to the solution. After 15 minutes, the reaction mixture was warmed up to rt and allowed to stir for 10 hours. Added LiOH (177 mg, 7.4 mmol, 10 equiv.) as a solution in 1:1 H_2O:MeOH (2 mL) and heated the reaction mixture to 50 °C for 5 hours. The reaction was diluted with EtOAc and washed with 1M HCl. Extracted the aqueous layer with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated *in vacuo*. The unpurified reaction mixture was purified by column chromatography (grad. 0%→10% ether/hexanes) to afford β-parinaric acid (99 mg, 0.36 mmol, 48%; 7:1 all-

*E:*Σother isomers by ^{1}H NMR) as a white solid. ^{1}H and ^{13}C NMR matched previously reported assignments.[13] ^{1}H NMR (700 MHz, $CDCl_3$) δ 10.64 (br s, 1 H), 6.20-6.11 (m, 4H), 6.10-6.04 (m, 2H), 5.73 (dt, *J* = 6.6, 14.2 Hz, 1H), 5.68 (dt, *J* = 7.1, 14.6 Hz, 1H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.15-2.07 (m, 4H), 1.67-1.60 (m, 2H), 1.43-1.18 (m, 8H), 1.01 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 179.0, 136.6, 135.0, 132.5, 132.4, 130.9, 130.8, 130.6, 129.6, 33.8, 32.8, 29.2, 29.1, 29.0, 28.9, 25.9, 24.6, 13.5; HRMS (EI) *m/z* calcd for $C_{18}H_{28}O_2$ $[M]^+$ 276.2089, found 276.2095; IR (thin film, cm^{-1}) 3011, 2960, 2919, 2848, 1711, 1460, 991.

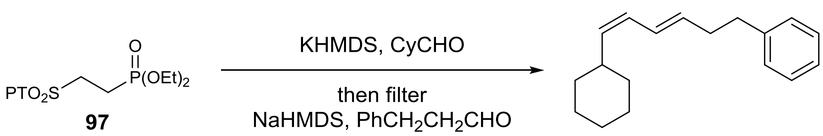
Previously reported[13b] ^{13}C NMR (125 MHz, $CDCl_3$)	Previously reported[13c] ^{13}C NMR (125 MHz, $CDCl_3$)	Synthetic ^{13}C NMR (175 MHz, $CDCl_3$)
179.0	179.4	179.0
137.0	136.6	136.6
135.4	135.0	135.0
132.9	132.5	132.5
132.8	132.4	132.4
131.3	130.9	130.9
131.3	130.8	130.8
131.1	130.6	130.6
130.0	129.6	129.6
34.2	33.9	33.8
33.2	32.8	32.8
29.6	29.2	29.2
29.5	29.1	29.1
29.4	29.0	29.0
29.4	28.9	28.9
26.3	25.9	25.9
25.1	24.6	24.6
13.9	13.5	13.5

General Procedure for Telescopic Synthesis of *ZE* dienes: Sulfonylphosphonate (1 equiv.) was dissolved in THF (0.25 M) and cooled to -78 °C. KHMDS (1.1 equiv., 1 M in THF) was added slowly. After five minutes at -78 °C, aldehyde (1.05 equiv.) was added to the solution. After 20 minutes, the reaction mixture was warmed up to 0 °C. After 1 hour, the reaction was filtered via cannula through a syringe sealed with a rubber septum, packed with $MgSO_4$ and celite and a cotton plug. The reaction was then cooled to -78 °C. NaHMDS (1.1 equiv., 2.5 M in hexanes) was added slowly. After 1 hour at -78 °C, aldehyde (1.5 equiv.) was added to the solution. After 15 minutes, the reaction mixture was warmed up to rt and allowed to stir for 10-12 hours. The reaction was then quenched by addition of aqueous NH_4Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then concentrated *in vacuo*. The reaction mixture was purified by column chromatography (grad. 0%→2% EtOAc in hexanes). Isomeric purity was determined by ^{1}H NMR, based on coupling constants and integration.



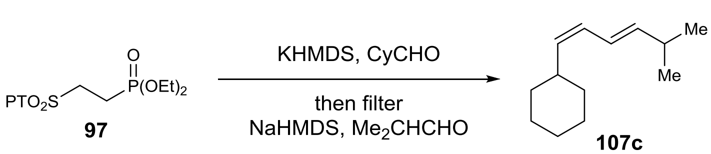
((3*Z*,5*E*)-6-cyclohexylhexa-3,5-dien-1-yl)benzene (107a)

Following the general procedure, ((3*Z*,5*E*)-6-cyclohexylhexa-3,5-dien-1-yl)benzene was obtained in 34% yield, 10:1 *ZE*:*EE*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.22-7.17 (m, 3H), 6.23 (dd, *J* = 11.0, 15.3 Hz, 1H), 5.96 (t, *J* = 10.8 Hz, 1H), 5.62 (dd, *J* = 6.8, 15.1 Hz, 1H), 5.34 (dt, *J* = 7.4, 10.8 Hz, 1H), 2.70 (t, *J* = 7.4 Hz, 2H), 2.47 (q, *J* = 7.2 Hz, 2H), 1.73-1.63 (m, 5H), 1.33-1.03 (m, 6H).



((3*E*,5*Z*)-6-cyclohexylhexa-3,5-dien-1-yl)benzene (107b)

Following the general procedure ((3*E*,5*Z*)-6-cyclohexylhexa-3,5-dien-1-yl)benzene was obtained in 14% yield, 6:1 *ZE*:*EE*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H), 7.16-7.15 (m, 3H), 6.31 (dd, *J* = 11.1, 15.1 Hz, 1H), 5.83 (t, *J* = 11.0 Hz, 1H), 5.67 (dt, *J* = 6.9, 14.7 Hz, 1H), 5.15 (t, *J* = 10.0 Hz, 1H), 2.70 (t, *J* = 7.4 Hz, 2H), 2.42 (q, *J* = 7.0 Hz, 2H), 1.71-1.59 (m, 5H), 1.33-1.03 (m, 6H).



((1Z,3E)-5-methylhexa-1,3-dien-1-yl)cyclohexane (107c)

Following the general procedure ((1Z,3E)-5-methylhexa-1,3-dien-1-yl)cyclohexane was obtained in 40% yield, 4:1 *ZE*:*EE*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.26 (dd, *J* = 11.0, 15.1 Hz, 1H), 5.84 (t, *J* = 11.0 Hz, 1H), 5.61 (dd, *J* = 7.1, 15.3 Hz, 1H), 5.16 (t, *J* = 10.2 Hz, 1H), 2.40-2.32 (m, 1H), 1.73-1.64 (m, 5H), 1.36-0.97 (m, 12H).

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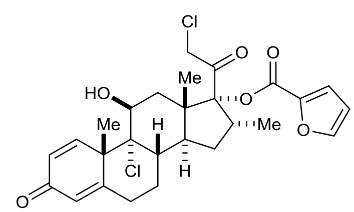
Chapter 3

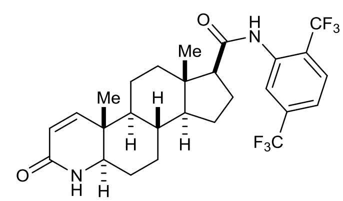
Cardiotonic Steroids: An Overview of Semi-Syntheses and Synthetic Strategies

3.1 Introduction

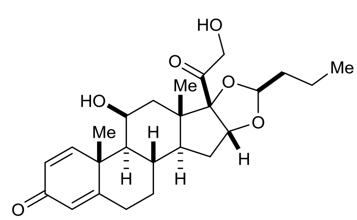
Steroids represent an important and diverse class of terpene-based structures. Steroids are endogenous to both animals and plants and are responsible for a wide range of cellular functions. In humans, steroids act as chemical messengers (hormones) that regulate metabolic, immune, and reproductive functions.[1] Unsurprisingly, steroids are important in drug discovery, medicinal chemistry, and chemical biology. Testament to the structural importance of the steroid core, many FDA-approved drugs are steroid based and are used to treat an assortment of medical ailments such as inflammation, allergic reaction, heart disease, cancer, and metabolic disease and have found importance in other important health-related areas that includes contraception and fitness (Figure 3.1).[2]



mometasone (**109**)
treatment and prevention of allergies



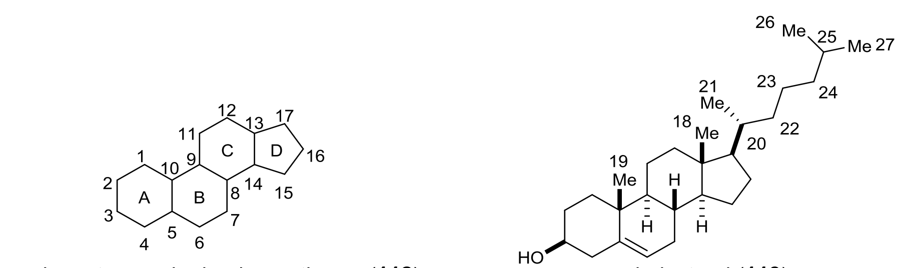
dutasteride (**110**)
treatment of benign prostatic hyperplasia



budesonide (**111**)
treatment of asthma and chronic obstructive pulmonary disease

Figure 3.1. Selected examples of FDA-approved steroid-based drugs.

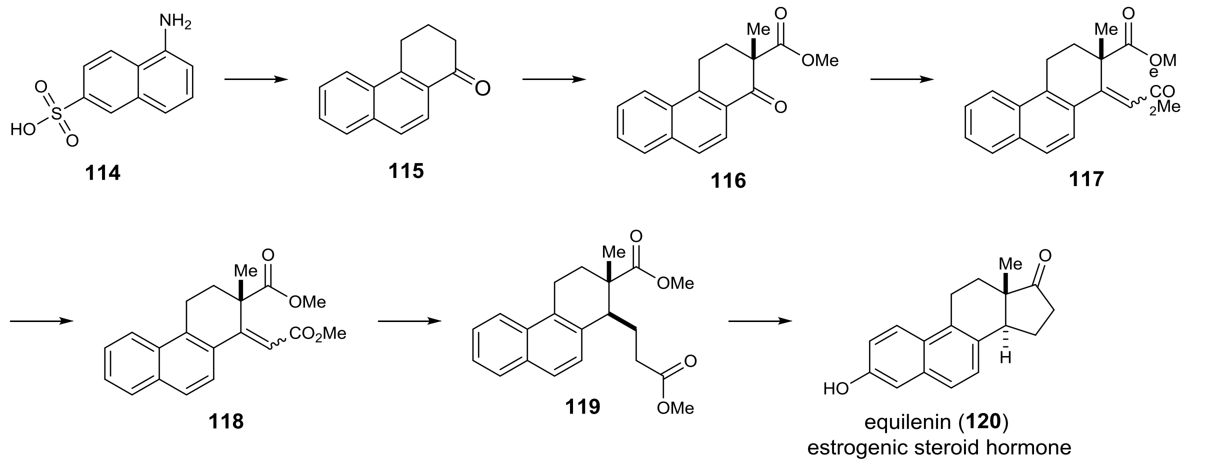
Steroids can be structurally defined by their tetracyclic core, cyclopentanoperhydrophenantrene, which is the basis of all natural and synthetic steroid derivatives (Figure 3.2). Steroids have an established lettering and numbering system for referencing specific rings and carbons, respectively. The three six-membered rings are lettered A, B, and C and the five-membered ring is lettered D. The seventeen carbons constituting the steroid core are numbered in ascending order starting in ring A, continuing onto ring B, onto ring C, and ending in ring D. As exemplified with cholesterol, the carbons of the angular methyl substituents at C13 and C10 are assigned C18 and C19, respectively, and numbering resumes at the C17 side chain. Stereochemistry of substituents are denoted utilizing the wedge-dash notation in which substituents on a wedge indicates β-configuration (e.g. substituents at C3, C8, and C10 in cholesterol) whereas a dash indicates α-configuration (e.g. substituents at C9 and C14).[3]



cyclopentanoperhydrophenanthrene (**112**) cholesterol (**113**)

Figure 3.2. Steroids have an assigned lettering and numbering system.

In 1939, Bachmann and co-workers at the University of Michigan reported the synthesis of equilenin, a steroidal sex hormone (Scheme 3.1).[4] The synthesis was completed in eleven steps from **115**, which was obtained from Cleve's acid (**114**). This marked an important landmark in the field of organic chemistry as the first total synthesis of a natural steroid and is regarded as one of the first syntheses of a complex natural product. Despite advancements in steroid synthesis that have resulted in synthetic strategies for their construction, the majority of steroid-based drugs are obtained using semi-synthesis of feedstock obtained from plant and animal sources.[5]



Scheme 3.1. First total synthesis of a steroid was accomplished by Bachman and co-workers in in 1939.

3.2 Cardiotonic Steroids

An important group of steroids are cardiotonic steroids. As their name suggest, cardiotonic steroids are characterized based on their ability to effect heart physiology. Cardiotonic steroids are proposed to be "the most ingested drugs in medicine."[6] Utilizing cardiotonic steroids (the active principle in plant extracts) to treat heart disease is thought to date as far back as ancient Egyptians. Throughout history, cardiotonic steroids have found a variety of applications in addition to the treatment of heart disease. Squill extracts containing cardiotonic steroids including proscillaridin A (**121**) were used by Romans and Greeks as a diuretic, expectorant, and emetic and by Egyptians as rat poison to prevent the spread of the plague (Figure 3.3).[7] *Strophanthus* extracts containing cardiotonic steroids including ouabain (**122**) were used by African tribes as the active principle in poison arrows.[8] Venom from the toad *Bufo bufo jargarizans*, which is known to be comprised of cardiotonic steroids including β-hydroxybufalin (**123**), has been used in traditional Chinese medicine as an anesthetic and anti-inflammatory agent.[9] Foxglove extracts containing cardiotonic steroids including digoxin (**124**) were used to treat "dropsy," which is the swelling of the body.[8] In the present day, cardiotonic steroids are still widely used in the treatment of heart disease. In fact, digoixin, used to treat atrial fibrillation and atrial flutter, is on the World Health Organization Model List of Essential Medicines.[10]

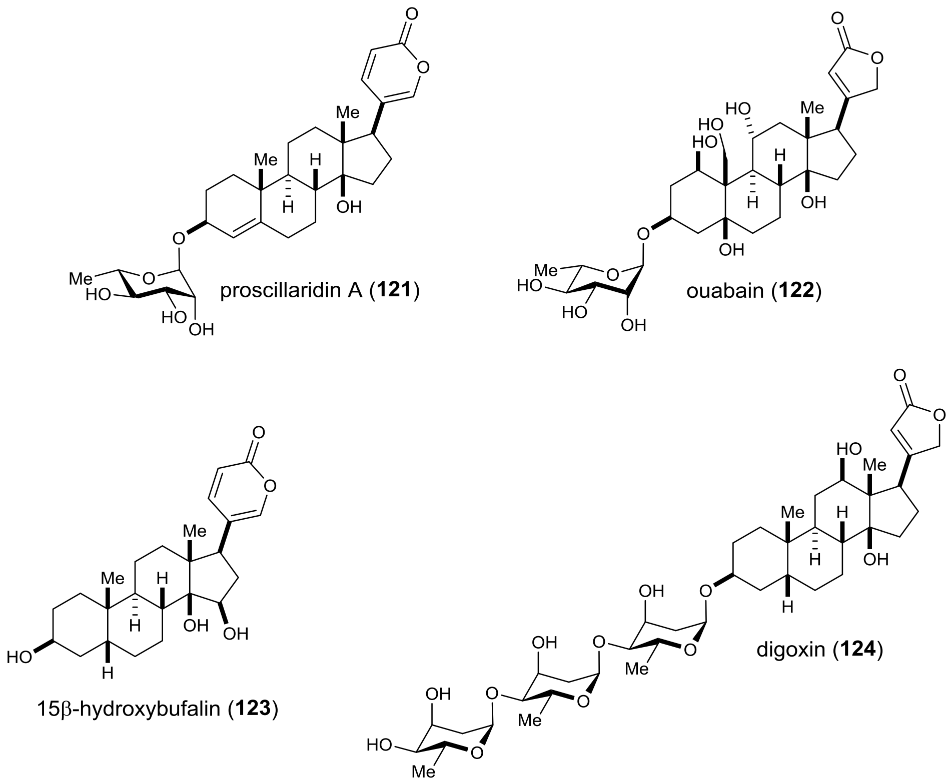


Figure 3.3. Structures of proscillaridin A, oubain, 15β-hydroxybufalin, and digoxin.

Cardiotonic steroids generally exhibit the following structural characteristics: a steroidal framework possessing a *cis* A/B, *trans* B/C, and *cis* C/D ring system, a 14β-hydroxy group, and a 17β-lactone substituent (Figure 3.4). Due to the unique *cis* A/B and C/D fused ring systems, cardiotonic steroids have a characteristic 'U' shape that is very different from the planar all-*trans* ABCD ring systems generally observed. Cardiotonic steroids can be further classified as cardenolides and bufadienolides based on the structure of the 17β-lactone substituents. Cardenolides (e.g. ouabain and digoxin) have a 17β-butenolide substituent and bufadienolides (e.g. proscillaridin A and 15β-hydroxybufalin) have a 17β-(α-pyrone) substituent. Typically, cardenolides are endogenous to plants, while bufadienolides are endogenous to animals.[11]

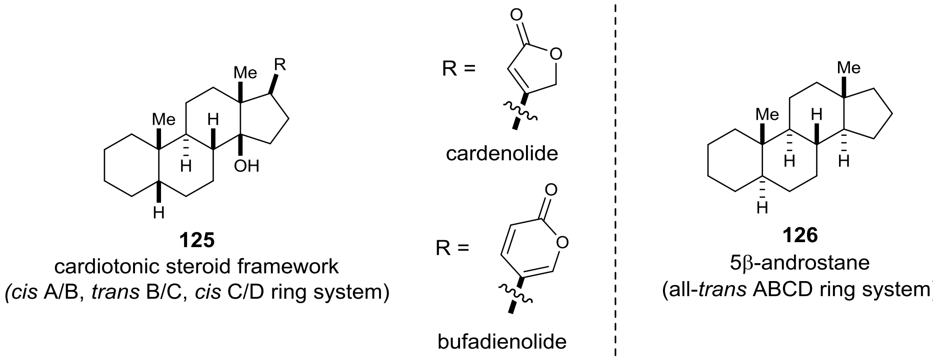


Figure 3.4. Structural framework of cardiotonic steroids.

Cardiotonic steroids have the overall ability to improve heart function by simultaneously slowing the heart rate and acting as an inotropic agent (increasing contractility).[12] The main pharmacological effect of cardiotonic steroids is inhibition of the Na^+/K^+-ATPase (sodium pump). The sodium pump pumps Na^+ out and K^+ into the cytoplasm maintaining a low concentration of Na^+ and high concentration of K^+.[13] The sodium pump is comprised of a catalytic α-subunit, a glycosylated β-subunit, and a γ-subunit. In mammalian cells, cardiotonic steroids are known to bind to the α-subunit and four different isoforms (α1, α2, α3, and α4).[11]

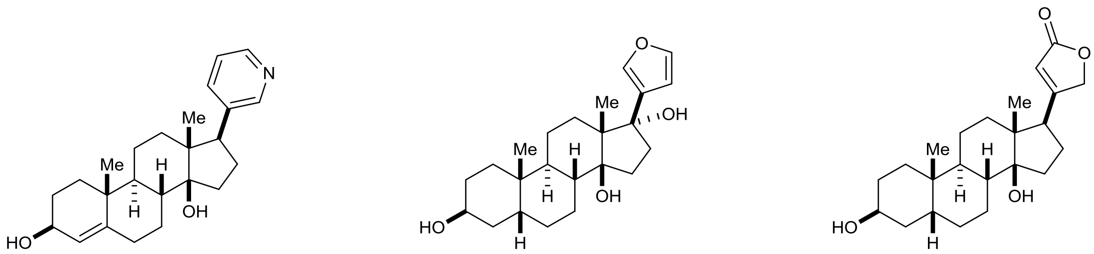
The interaction of cardiotonic steroids with the sodium pump are primarily described by the Na^+ lag hypothesis and the Na^+/K^+-ATPase "sigmalosome" hypothesis. The Na^+ lag hypothesis involves the inhibition of the sodium pump by the binding of cardiotonic steroid that increases the intracellular Na^+ concentration. This leads to an increase in the intracellular Ca^{2+} concentration via the Na^+/Ca^{2+} exchange system ultimately causing the positive inotropic effect.[14] This hypothesis is viewed as incomplete as it does not explain the cellular responses (e.g. cell proliferation and death) that result from the interaction of cardiotonic steroid with the sodium pump and that cardiotonic steroids can affect cells at concentrations lower than the required levels for pump inhibition. The more recent Na^+/K^+-ATPase "sigmalosome" hypothesis suggest the sodium pump is preassembled and the interaction of cardiotonic steroids with the pump leads to conformation changes, which do not necessarily lead to inhibition.[15]

Interestingly, it was hypothesized over sixty years ago that cardiotonic steroid drugs act as a substitute for an endogenous inhibitor of the sodium pump.[16] It was finally realized twenty years ago that this hypothesis is accurate.[17] Remarkably, it was discovered that endogenous cardiotonic steroids are the natural ligands and inhibitors of the sodium pump (notably endogenous ouabain).[18]

In fact, endogenous cardiotonic steroids are viewed as a new class of steroid hormones, since they have been shown to exhibit diverse biological activities *in vivo*. These biological activities include the following: regulating blood pressure, arterial tension, insulin release, and cell proliferation and differentiation.[19]

Although cardiotonic steroids are still widely administered today, they are associated with a high risk. The high risk is due to the high toxicity of cardiotonic steroids and low therapeutic index. In fact, most patients receive a therapeutic dose that is 60% of the lethal dose. As a result, cardiotonic steroids accounted for a significant portion of drug-induced deaths that occurred in hospitals.[12,20] Clearly, cardiotonic steroid analogs with an improved therapeutic index would be highly desirable. Historically, synthesizing cardiotonic steroid drug analogs is challenging due to the inability to prepare appreciable amounts of cardiotonic steroid derivatives (see Sections 3.3 and 3.4) and the misconception that the inotropic effect and toxicity of cardiotonic steroids is a result of the inhibition of the sodium pump. It was discovered, however, that there are two separate receptors in the heart muscle that are responsible for the inotropic effect and toxicity, which suggest the possibility of synthesizing cardiotonic steroid analogs with a higher therapeutic index.[21]

A study of deaths attributed to non-pharmaceutical human exposure to cardiotonic steroids that occurred from 1982-2003 suggested that bufadienolides are significantly more toxic than cardenolides.[22] This suggests that in designing cardiotonic steroid analogs the 17β-butenolide substituent would be favored over the 17β-(α-pyrone) substituent. Interestingly, cardiotonic steroid analogs have been synthesized that replace the 17β-lactone substituent with a heterocycle. Although these 17β-*exo*-heterocyclic steroids generally exhibit lower cardiotonic activity in comparison to the parent cardiotonic steroid, the therapeutic index becomes more favorable. An example of these 17β-*exo*-heterocyclic steroids is steroid **127** (Figure 3.5), which is derived from canarigenin (cardenolide) and scillarenin (bufadienolide). Steroid **127** has actually been shown to possess the same activity of canarigenin and scillarenin and is proposed to act by the same mechanism.[12] An additional cardiotonic steroid analog to note is rostafuroxin (**128**). Rostafuroxin is a cardiotonic steroid analog derived from digitoxigenin (**129**) that possess a 17β-(3-furyl) substituent and a 17α-hydroxy group. Rostafuroxin has been through Phase I and II clinical studies as a treatment for essential hypertension.[23]



127 rostafuroxin (**128**) digitoxigenin (**129**)

treatment of essential hypertension
Phase III-clinical trials, Europe

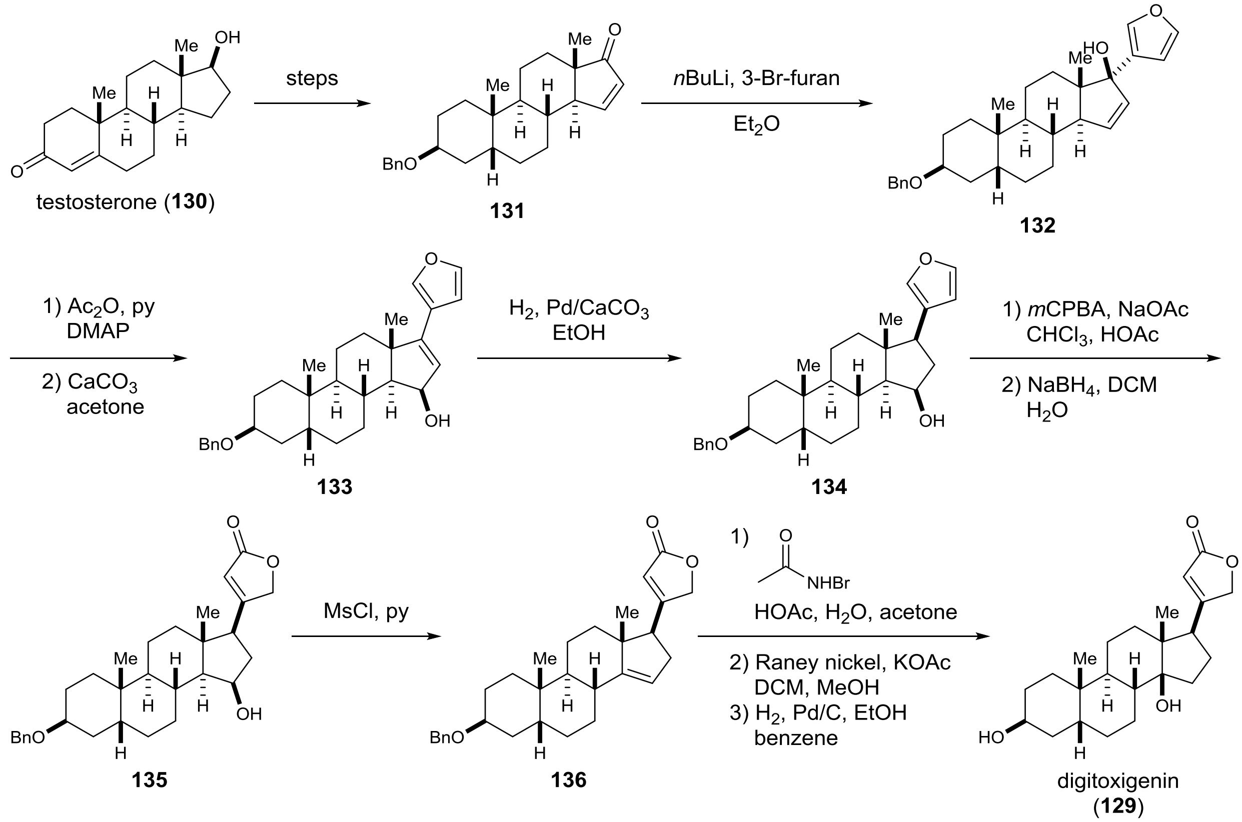
Figure 3.5. Structures of 17β-*exo*-heterocyclic steroid **127**, rostafuroxin, and digitoxigenin.

3.3 Semi-Synthesis of Cardiotonic Steroids

Semi-synthesis of cardiotonic steroids from readily-available steroid precursors have been known since the 1960s.[24] Semi-synthesis of cardiotonic steroids in juxtaposition to synthesis of cardiotonic steroids has the advantage of starting from a preassembled steroid core with set stereocenters. The overall transformations required in the semi-synthesis of a cardiotonic steroid are epimerization of the C14 stereocenter (conversion of *trans* C/D to *cis* C/D) and installation of 17β-lactone substituent. Semi-synthesis of cardiotonic steroids are inherently linear and fairly lengthy.[25] The disadvantages of semi-synthesis is it limits the structural diversity achievable (i.e. limited number of analogs) and enantiomers cannot be synthesized (steroid enantiomers have been shown to possess their own unique biological activity). Nevertheless, several semi-syntheses of cardiotonic steroids should be noted.

3.3.1 Semi-Synthesis of digitoxigenin

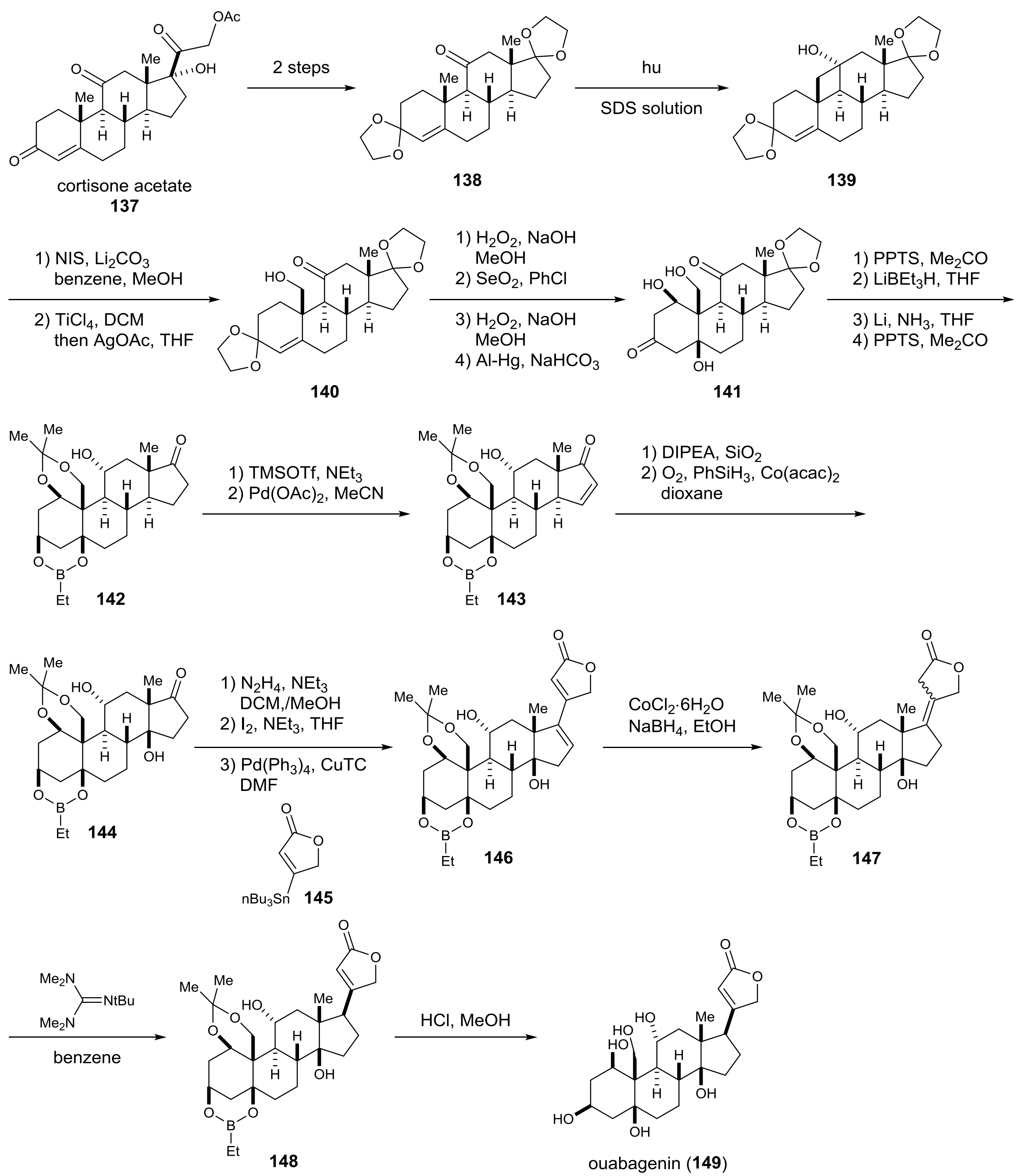
Wiesner and co-workers reported the semi-synthesis of digitoxigenin (**129**) from testosterone (**130**) (Scheme 3.2).[21b,26] This approach is still regarded as one of the most efficient conversions of testosterone to a cardiotonic steroid. Wiesner even comments that "there is practically no room for improvement." The approach relies on installation of a C17 3-furyl group that is oxidized and converted to the 17β-butenolide. The semi-synthesis began from enone **131**, which was obtained from testosterone. Enone **131** was treated with β-furyllitium to afford β-tertiary alcohol **132**. The alcohol was acetylated and then upon treatment with calcium carbonate underwent allylic rearrangement to allylic alcohol **133**. The olefin was then selectively reduced from the α-face to result in formation of β-(3-furyl) **134**. The 3-furyl group was then oxidized to the resulting hydroxylactone, which was reduced to the desired butenolide affording alcohol **135**. The C15 alcohol was then mesylated and eliminated to form $\Delta^{14,15}$ olefin **136**. The 14-hyrdroxy group was installed after bromohydrin formation reaction. The 15α-bromide was removed by Raney nickel and the benzyl group was removed by hydrogenation to provide digitoxigenin.



Scheme 3.2. Semi-synthesis of digitoxigenin from testosterone.

3.3.2 Semi-Synthesis of Ouabagenin

An interesting advancement in the semi-synthesis of cardiotonic steroids was developed by Baran and co-workers (Scheme 3.3).[27] The strategy utilized site-selective C-H oxidations to synthesize the polyoxygenated cardiotonic steroid ouabagenin (the steroid aglycone of ouabain) from cortisone acetate. Cortisone acetate (**137**) was converted in two steps to ketone **138**. At this point the C19-hydroxy group was installed. Ketone **138** was then subjected to Norrish type II conditions to give alcohol **139**. Oxidative fragmentation followed by hydrolysis of the resulting iodide and selective deacetalization resulted in the installation of the C19-hydroxy group and afforded alcohol **140**. The installed C19-hydroxy group was next used to direct expoxidation of the enone from the β-face. Enone was then formed after dehydration with selenium dioxide. The C19-hydroxy group was then again used to direct epoxidation of the enone from the β-face. The diepoxide was then opened with aluminum amalgam resulting in setting the β1- and β5-hydroxy groups to give triol **141**. Acetonide was formed between C1 and C19 and C3 was reduced with LiTEBH resulting in an ethyl boronic ester between C3 and C5. C11 ketone was then converted to α11-hydroxy group by reduction under thermodynamic conditions. Then deacetalization of C17



Scheme 3.3. Semi-synthesis of ouabagenin from cortisone acetate.

provided ketone **142**. Saegusa-Ito oxidation of ketone **142** provided eone **143**. Enone **143** was then deconjugated and after Mukaiyama oxidation the β14-hydroxy group was installed resulting in formation of the *cis* C/D fused ring system. Ketone **144** was then subjected to Barton's hydrazone iodination procedure. The resulting vinyl iodide was then reacted with stannane **145** by Stille cross-coupling to give dienone **146**. Due to difficulties in directly reducing to a17β-butenolide substituent, dienone **146** was converted to β,γ-unsaturated ketone **147**. β,γ-unsaturated ketone **147** was brought back into conjugation with Barton's base to give protected ouabagenin **148**. After deprotection, ouabagenin (**149**) was obtained.

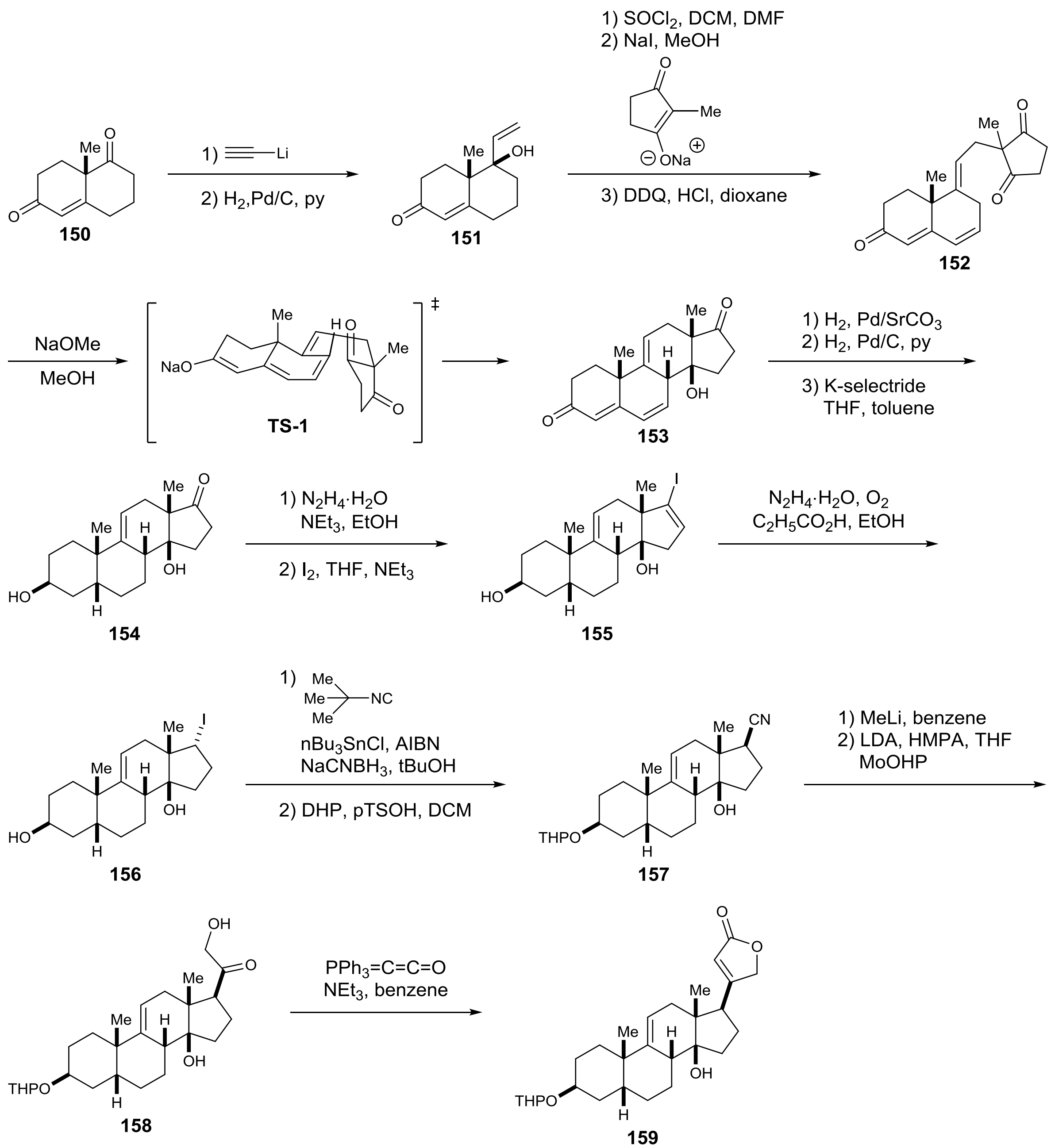
3.4 Synthesis of Cardiotonic Steroids

Over the years many creative and elegant syntheses of natural cardiotonic steroids and cardiotonic steroid cores have emerged.[25] The challenge in the synthesis of cardiotonic steroids is developing an approach that is scalable and would result in appreciable amounts of cardiotonic steroid. As a result, synthetic strategies rely on preassembling ring fragments and coupling the fragments in a divergent manner. Several synthetic methodologies and total syntheses of cardiotonic steroids have been reported that highlight the difficulties associated with the synthesis of cardiotonic steroids.

3.4.1 First Synthesis of Cardiotonic Steroid Core

The first synthetic construction of a cardenolide steroid core was accomplished by Daniewski and co-workers in their racemic synthesis of 9,11-dehydrodigitoxigenin 3-tetrahydropyranyl ether (Scheme 3.4).[28] The synthesis begins with the AB ring system intact by utilizing Wieland-Miescher ketone (**150**), a commonly employed and readily available building block in steroid synthesis, which is elaborated to a tricyclic ABD ring system. The ABCD ring system is formed from a key stereoselective intramolecular vinylogous aldol reaction, which forms the C-ring and consequently establishes three new stereocenters (C8, C13, and C14) and the important *cis* C/D ring junction.

Wieland-Miescher ketone (**150**) was elaborated by reacting with lithium acetylide, which is then partially reduced to allyl alcohol **151**. Unstable allyl chloride is then formed by S_N2' reaction upon treatment with thionyl chloride. The chloride was then substituted with the sodium salt of 2-methyl-cyclopentane-1,3-dione, which installs the D-ring, and after dehydration with DDQ affords ABD tricycle **152**. The next step in the synthesis was the crucial aldol reaction in which ABD tricylce **152** was treated with sodium methoxide to afford steroid core **153**. Daniewski and co-workers rationalize the stereoselectivity based on the angle of attack in **TS-1** being the most favorable out of the eight possible transition states (four transition states arise from attack of C17 ketone). The dienone moiety is then reduced after sequential hydrogenation reactions. In the second hydrogenation reaction, due to its convex shape, the tetracyclic system was reduced from the β-face resulting in a *cis* A/B ring junction. Hydride was then delivered equatorially to C3 to



Scheme 3.4. Synthesis of *rac*-9-11-dehydrodigitoxigenin 3-tetrahydopyranyl ether from Wieland-Miescher ketone.

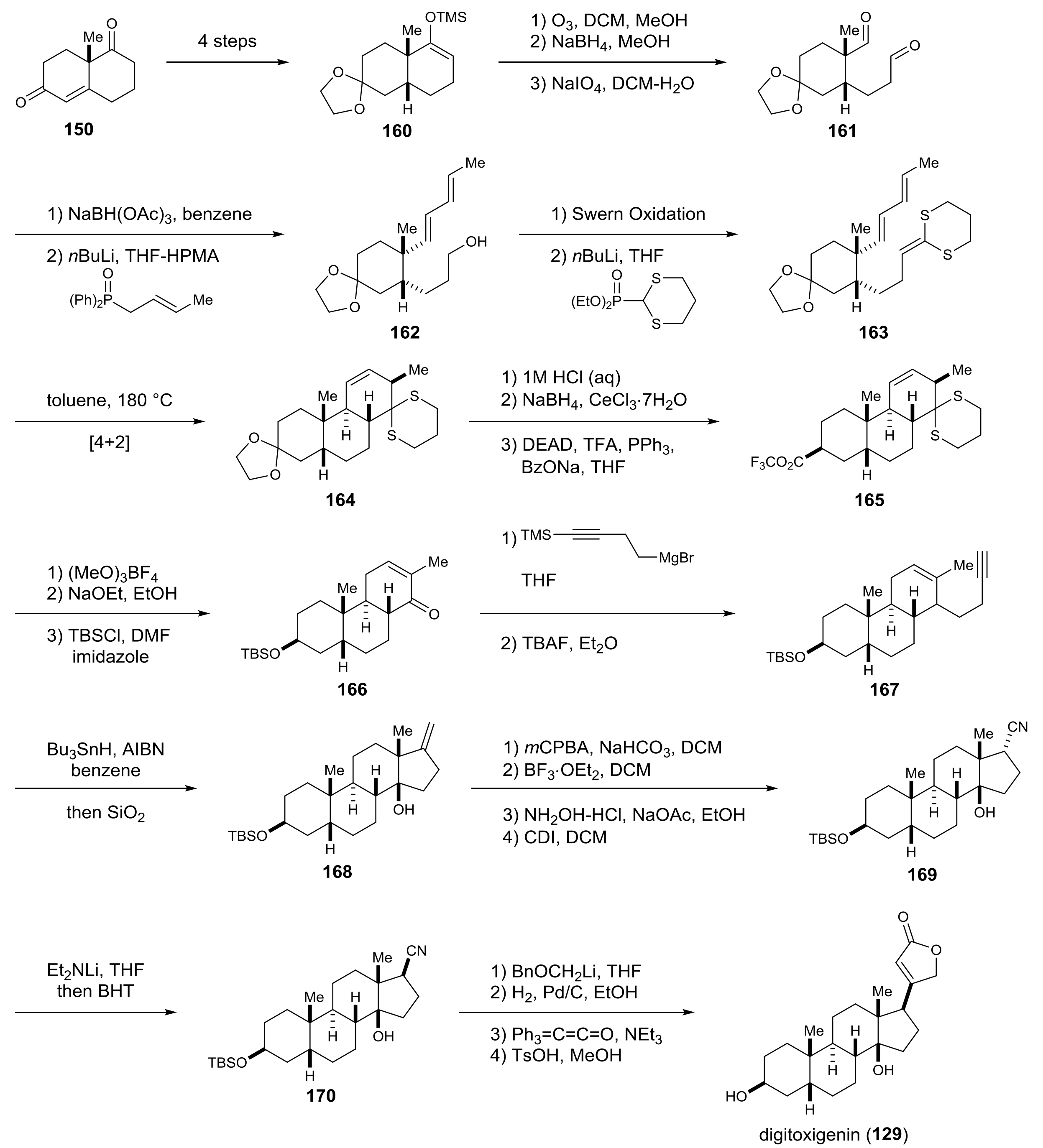
afford alcohol **154**. In the concluding steps, the 17β-lactone ring is installed. Ketone **154** was converted to vinyl iodide **155** through Barton's hydrazone iodination procedure. Vinyl iodide **155** was then reduced from the β-face with diimide to form the thermodynamically favored 17α-iodide **156**. The desired 17β-configuration was then installed through a free-radical reaction in which a 17β-nitrile was formed. The 3β-OH was then protected with THP. Nitrile **157** was then converted to α-hydroxy ketone **158** upon treatment with methyl lithium followed by α-hydroxylation using a slightly modified procedure of Vedejs. 17β-Lactone was then installed upon condensation with the Bestmann phosphoranylidene-ketene to afford steroid **159**.

3.4.2 First Total Synthesis of a Cardiotonic Steroid (Digitoxigenin)

The first total synthesis of a natural cardenolide was accomplished by Stork and co-workers in their synthesis of digitoxigenin (Scheme 3.5).[29] The key step in their approach is an intramolecular [4+2] cycloaddition, which defines the ABC ring system. The ABC ring system is then elaborated to the ABCD ring system and the C17 butenolide is installed. Similar to the Daniewski synthesis, the Stork synthesis began with Wieland-Miescher ketone (**150**); however, only the A-ring of the Wieland-Miescher ketone remained intact.

In four steps, Wieland-Miescher ketone was converted to silyl enol ether **160**. Silyl enol ether **160** was converted to dialdehyde **161** after ozonolysis to α-hydroxy ketone ketone followed by reduction to diol and cleavage to dialdehyde. The sterically less-hindered aldehyde was then selectively reduced and the unreated aldehyde then underwent condensation to form diene **162** under HWE-like conditions developed by Yamamoto. The dienolphile was then installed after oxidation and HWE condensation resulting in dithiane **163**. Next, the key intramolecular [4+2] cycloaddition selectively closes the B and C rings by proceeding through an endo transition state under thermal conditions to give ABC tricycle **164**. The 3β-configuration was established after deacetalization followed by reduction to 3α-alcohol and inversion under Mitsunobu conditions to 3β-trifluoroacetate **165**. Next, dithiane was cleaved with trimethyloxonium fluoborate and after treatment with sodium ethoxide the β,γ-unsaturated ketone of the C-ring was brought into conjugation and the trifluoroacetate was cleaved simultaneously resulting in 3β-hydroxy, which was susbsequently protected to silyl ether **166**. The ABC ring system was then elaborated to include the *cis*-fused D-ring. Selective axial 1,2-addition of Grignard reagent followed by selective desilylation gave alkyne **167**. Exocyclic methylene **168** was then formed after 5-*exo-dig* vinyl radical cyclization of alkyene **167**, which establishes the *cis* A/B, *trans* B/C, and *cis* C/D cardenolide core.

The final challenge was installing the 17β-lactone ring. Exocyclic methylene **168** was epoxidized and rearranged to the thermodynamically favored 17α-aldehyde, which was undesired. The 17β-configuration was ultimately accomplished after conversion of the 17α-aldehyde to 17α-nitrile **169**. 17α-nitrile **169** was epimerized to the desired 17β-nitrile **170** after rationalizing that the anion resulting from deprotonation of 14β-hydroxy group would sterically hinder the β-face resulting in

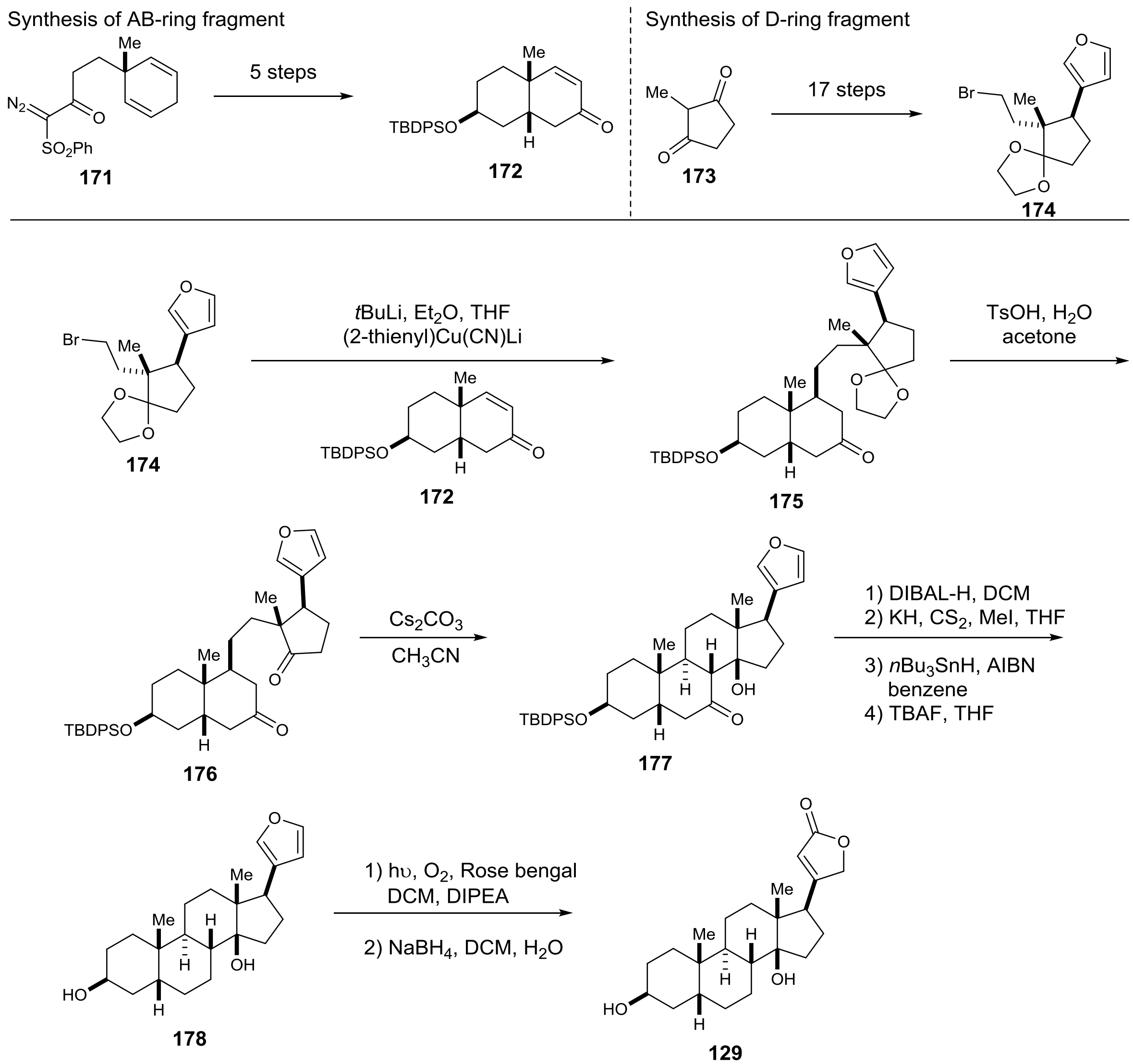


Scheme 3.5. First total synthesis of the natural cardenolide digitoxigenin.

kinetic deprotonation from the concave α-face in the dianion formation. The lactone ring is then formed using a sequence similar to Daniewski wherein 17β-nitrile **170** was converted to α-hydroxy ketone, which was then condensed with the Bestmann phosphoranylidene-ketene. A final deprotection liberating the 3β-hydroxy group completed the synthesis of digitoxigenin.

3.4.3 Second Synthesis of Digitoxigenin

Subsequently, Nakada and Honma reported another total synthesis of digitoxigenin (Scheme 3.6).[30] The synthetic approach couples an AB-fragment and a D-fragment containing a pro-17β-(3-furyl) group to form a tricyclic ABD ring system. The Nakada synthesis is reminiscent of the Daniewski synthesis in that the steroid core is formed after closure of the C-ring via an intramolecular aldol reaction.



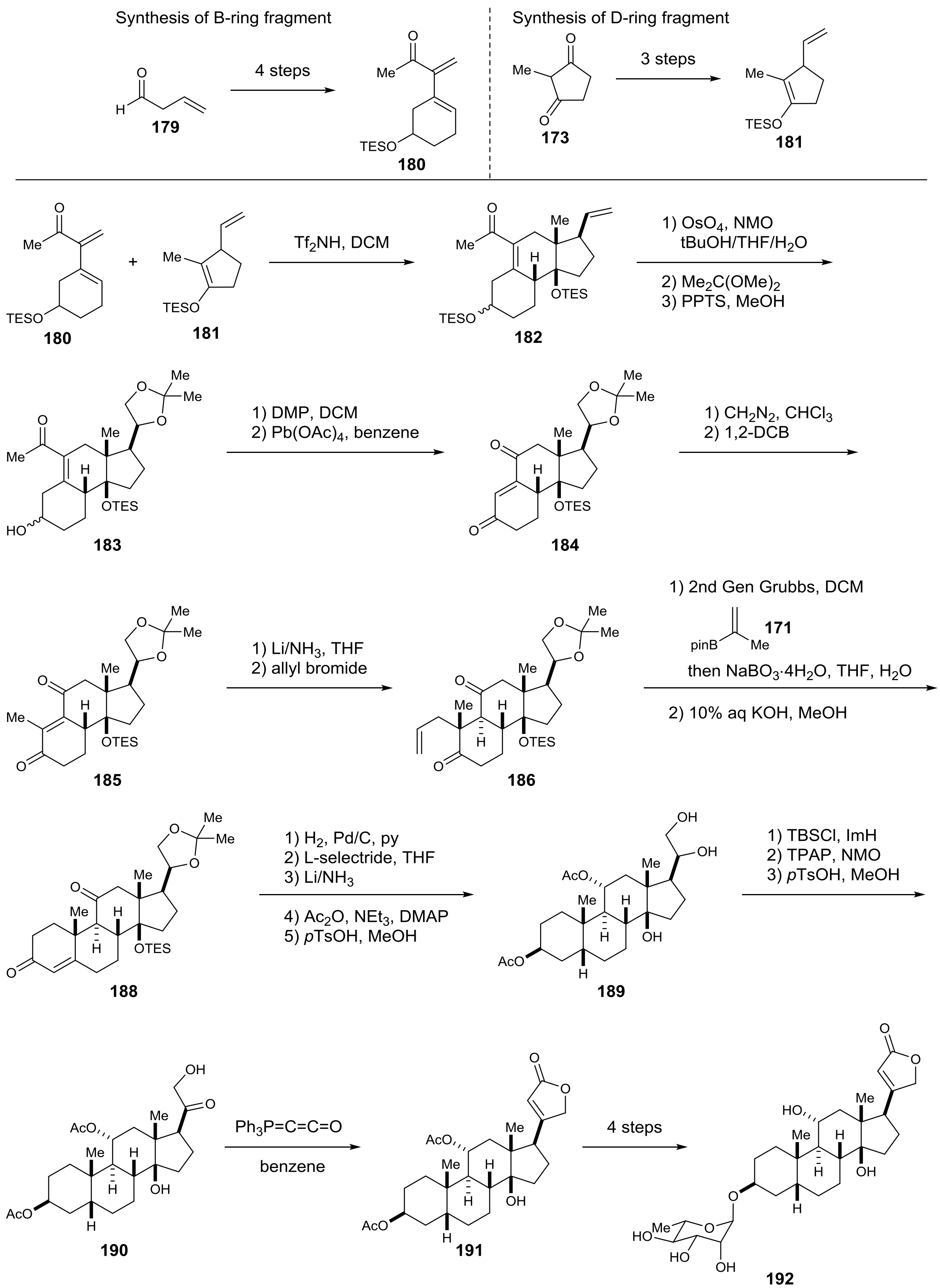
Scheme 3.6. Second reported total synthesis of the natural cardenolide digitoxigenin.

The *cis*-fused AB ring system was assembled as α,β-unsaturated ketone **172** in 5 steps from azide **171**. The D-ring fragment (**174**) was synthesized in 17 steps from diketone **173**. The D-ring fragment (**174**) was then selectively added to the convex β-face of the AB-ring fragment (**172**) via 1,4-addition to afford ketone **175**. Deacetalization of C14 afford diketone **176**. The next transformation was the selective intramolecular aldol reaction resulting in steroid **177**. Interestingly, cesium carbonate was unique in that other bases that were screened resulted in a mixture of aldol and aldol condensation products due to the labile 14β-hydroxy group. The C7 ketone was then removed after reduction to alcohol and subjected to Barton-McCombie deoxygenation conditions. Deprotection liberating the 3β-hydroxy group then afforded steroid **178**. The 17β-(3-furyl) group was then converted to the desired butenolide through a reaction with singlet oxygen resulting in a hemiacetal, which is then reduced to provide digitoxigenin (**129**).

3.4.4 Total Synthesis of Cardiotonic Glycoside Rhodexin A

Jung and Yoo reported the first synthesis of the natural cardiotonic steroid glycoside rhodexin A (Scheme 3.7)[31] and marks only the second total synthesis of a cardiotonic steroid possessing a β3-saccharide and α13-hydroxy group (see Section 3.4.6). The approach of Jung is similar to the synthesis of Stork in that Jung generates a tricyclic system after a [4+2] cycloaddition, which is then elaborated into the tetracyclic steroid system. Unlike Stork's approach, Jung generates a tricyclic BCD ring system instead of an ABC ring system and the [4+2] cycloaddition employed is an intermolecular approach instead of an intramolecular approach.

Jung's racemic synthesis began with assembling B-ring diene **180** from β,γ-unsaturated ketone **179** in 4 steps. The D-ring dienophile was synthesized in 3 steps from diketone **173**. B-ring diene **180** and D-ring dienophile **181** were then cyclized to BCD tricycle **182** in the key inverse-electron-demand Diels-Alder reaction, which proceeds through an exo transition state resulting in a *cis* C/D ring junction with the desired stereochemistry at C8, C13, C14, and C17 set. The β17-vinyl group was then dihydroxylated and the resulting diol was protected as an acetal. After selective desilylation alcohol **183** was obtained. Oxygentation at C11 was installed after a triple oxidation with DMP and lead tetraacetate to afford enedione **184**. The C10-methyl group was next installed after a 1,3-dipolar cycloaddition with diazomethane to pyrazoline, which then after extrusion of nitrogen gave enedione **185**. The BCD ring system was next elaborated to include the A-ring by cross-metathesis followed by aldol condensation. Enedione **185** was subjected to a reductive alkylation procedure to afford tricycle **186**, which after single-electron-transfer and

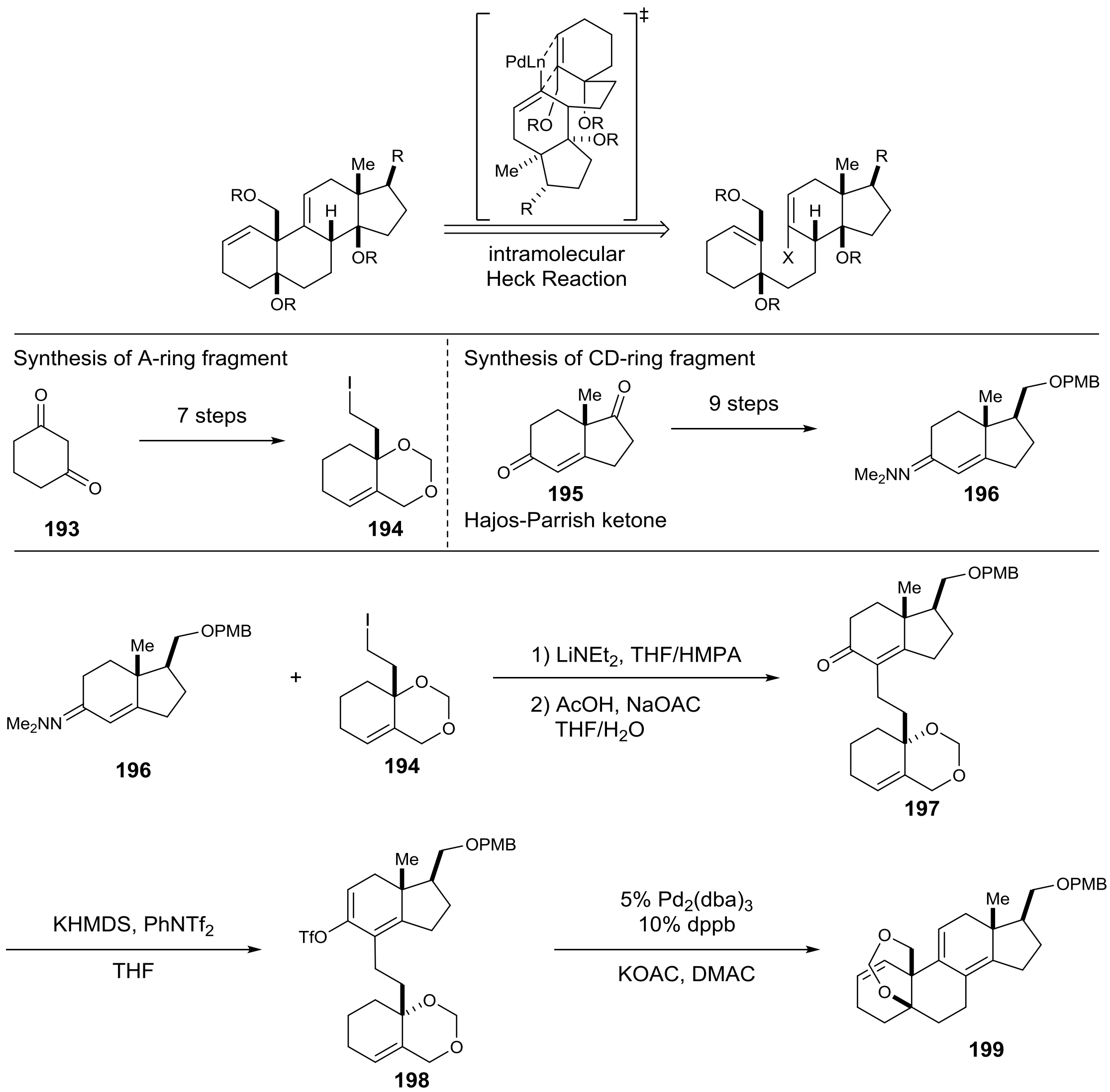


Scheme 3.7. Total synthesis of cardiac glycoside rhodexin A.

equatorial alkylation sets *trans* B/C ring junction and the β10-methyl. Next, cross-metathesis with vinyl boronate **187** followed by oxidation to the methyl ketone. Treatment of the methyl ketone with base results in the formation of steroid core **188** after intramolecular aldol condensation. Next, a series of reductions was performed: C4-olefin was reduced to produce the *cis* A/B ring junction, C3-ketone was reduced by equatorial hydride delivery to 3β-hydroxy group, and C11-ketone was reduced under single-electron-transfer conditions to afford equatorial 11α-hydroy group. The 3β- and 11α-hydroxy groups were protected and the acetal was removed to give steroid **189**. Then after selective protection of the primary alcohol followed by oxidation of the remaining alcohol and then desilylation afforded α-hydroxy ketone **190**. Like the syntheses by Daniewski and Stork, the 17β-lactone ring was constructed after condensation of α-hydroxy ketone with the Bestmann phosphoranylidene-ketene. Cardenolide **191** is then converted to the cardiotonic glycoside rhodexin A (**192**) in 4 steps. Jung recently reported their synthetic efforts towards enantioselective synthesis of rhodexin A using a similar approach, but the key inverse-electron-demand Diels-Alder reaction yielded a C-8 diasteromer.[32]

3.4.5 Construction of Cardiotonic Steroid Core via Intramolecular Heck Raction

Overman and co-workers reported the synthesis of *cis*-fused AB ring systems by an intramolecular Heck reaction to be used in the synthesis of polycyclic systems.[33] Utilizing this methodology, Overman and co-workers later described the formation of the cardiotonic steroid skeleton to serve as a building block for elaboration into complex carditonic steroids (Scheme 3.8).[34] The synthesis begins with the synthesis of protected A-ring fragment **194** and CD ring fragment **196**. The A-ring fragment **194** was synthesized in seven steps from diketone **193** and CD ring fragment was synthesized in nine steps from Hajos-Parrish ketone (**195**). Theses fragments were then coupled and the hydrazone group was cleaved to give enone **197**. Vinyl triflate **198** was formed after treatment with KHMDS and *N*-phenyltriflamide. The pentacyclic protected cardiotonic steroid core **199** was selectively formed after palladium-catalyzed intramolecular Heck reaction.



Scheme 3.8. Synthesis of cardiotonic steroid core via intramolecular Heck reaction.

Overman and co-workers later designed a more concise route.[35] The synthesis includes installation of a vinyl sulfide that could serve as a precursor to an 11α-hydroxy group (Scheme 3.9**).** Similar to their previous synthesis, A-ring and D-ring fragments are synthesized and coupled. A-ring fragment **200** was synthesized in one step from iodide **194** (eight steps from diketone **193**). D-Ring fragment **201** was synthesized in five steps from Hajos-Parrish ketone (**195**). The fragments are coupled after α-deprotonation of the sulfone followed by condensation of the methyl ester to afford sulfone **202**. The C-ring is formed after treatment with samarium iodide triggers the intramolecular aldol reaction. The ring closure formed a mixture of C8 diastereomers. The desired isomer was obtained after epimerization to provide ketone **203**. Next, C11 functionality was installed by protection of the C14-hydroxy group followed by α-sulfenylation. Intramolecular Heck vinyl triflate precursor **204** was formed after enol triflation and deprotection of the silyl ether. The final intramolecular Heck reaction afforded the C11 functionalized pentacyclic protected cardiotonic steroid core **205**.

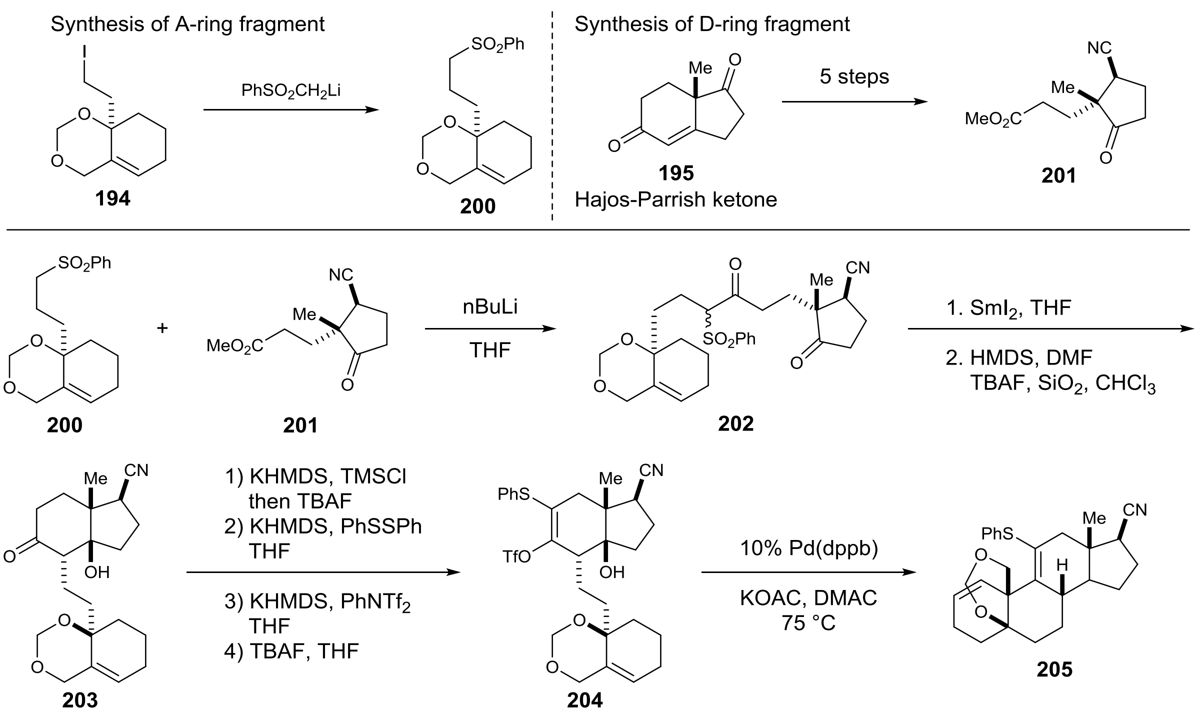
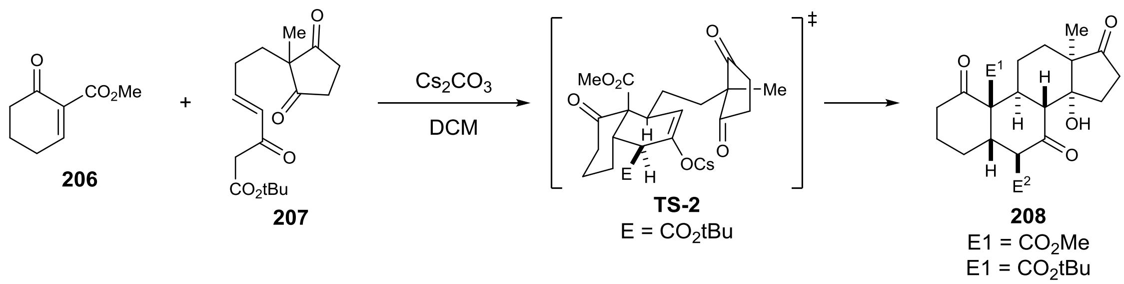


Figure 3.9. Revised synthesis of cardiotonic steroid core via intramolecular Heck reaction.

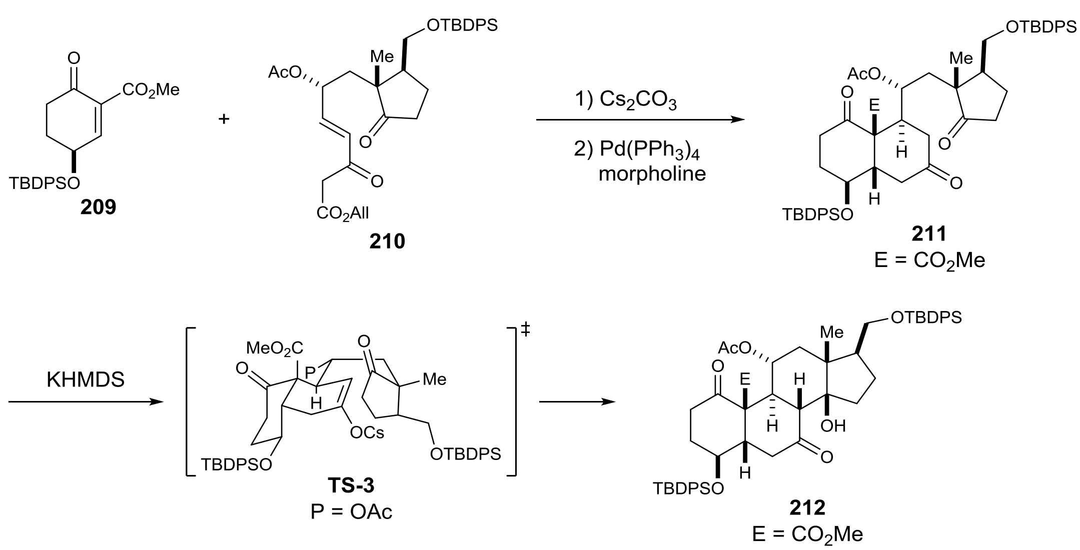
3.4.6 First Total Synthesis of a Cardiotonic Glycoside (Ouabain)

Deslongchamps and co-workers developed a stereoselective method for synthesizing *cis*-decalin systems through an intramolecular Michael reaction of cyclic β-ketoesters on α,β-unsaturated ketones.[36] This methodology ultimately culminated in the development of a one-step stereoselective anionic polycyclization that forms a *cis* A/B, *trans* B/C, and *cis* C/D steroid core and sets six contiguous chiral centers (Scheme 3.10).[37] The polycyclization couples α,β-unsaturated β'-ketoester **206** and Nazarov reagent **207** and was first proposed to proceed through a non-concerted Diels-Alder reaction (later considered a double Michael reaction) followed by intramolecular aldol reaction. The shortcoming of this approach as a viable method in the synthesis of a cardiotonic steroid core suitable for further elaboration into more complex cardiotonic steroids is the stereoselective intramolecular aldol resulted in unnatural α13-methyl and α14-hydroxy groups. The preferential formation of steroid **208** is rationalized by the favorable transition state (**TS-2**) resulting in attack of the C17 ketone. In comparing the transition states of the C-ring aldol cyclizations of the ABD tricycles of the Daniewski synthesis (**TS-1**) and the Deslongchamps approach (**TS-2**), it is interesting to note that the outcomes are different. It is proposed that the C9-C11 olefin (absent in the Deslongchamps cyclization) can be attributed to the difference in outcomes.



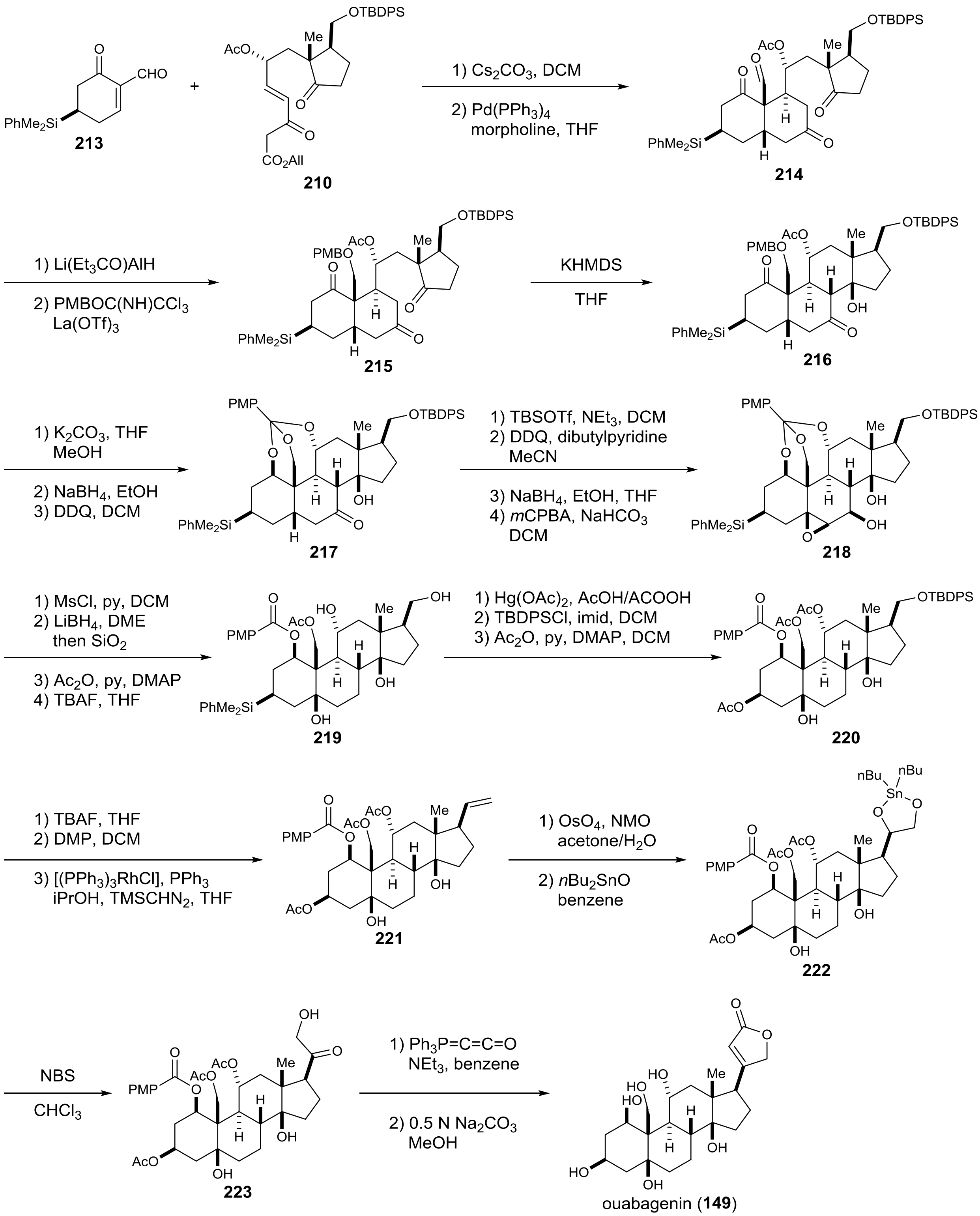
Scheme 3.10. Synthesis of steroid core via anionic polycyclization.

Tailored towards the total synthesis of ouabagenin and ouabain, Deslongchamps and coworkers revised the polycyclization method (Scheme 3.11).[38] The Nazaov reagent now included a pro-α11-hydroxy group and pro-β17-lactone substituent and the one step polycyclization was altered to a three step protocol. α,β-Unsaturated β'-ketoester **209** and Nazarov reagent **210** were coupled through a double Michael reaction and after decarboxylation afforded ABD tricycle **211**. The C-ring is then closed through a selective intramolecular aldol reaction that favors the formation of the *cis*-fused C/D ring system to give cardiotonic steroid framework **212**. The difference in stereochemical outcome of the ring closure can be attributed to the pro-β17-lactone substituent as seen in the Nakada synthesis of digitoxigenin.



Scheme 3.11. Improved synthesis of steroid core via anionic polycyclization.

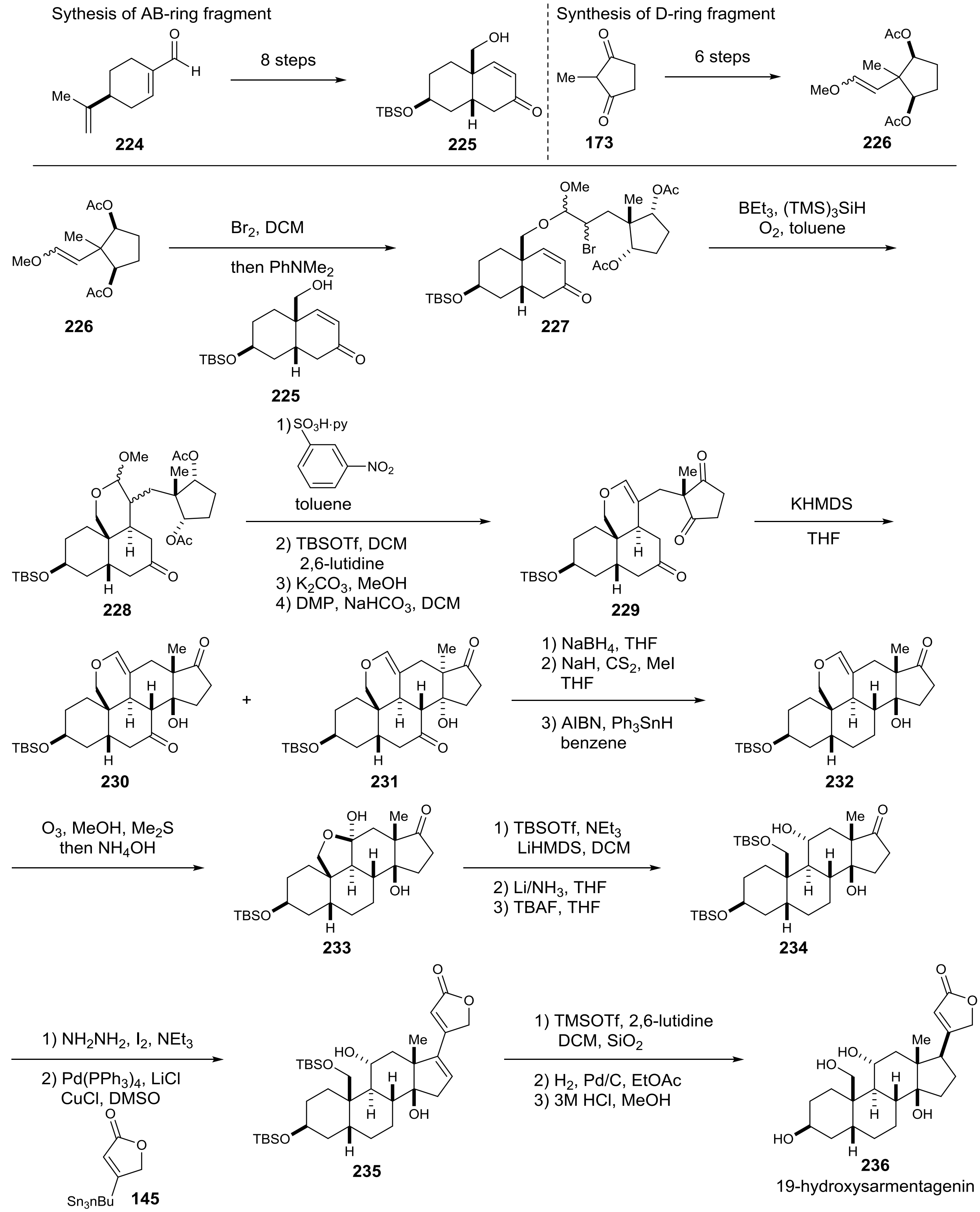
Ultimately, Deslongchamps and co-workers reported the first synthesis of the natural cardiotonic steroid oubagenin and its cardiotonic glycoside ouabain (Scheme 3.12).[39] This triumph in steroid chemistry is the first total synthesis of a cardiotonic steroid possessing an α11-hydroxy group and a cardiotonic steroid possessing a β3-saccharide. α,β-Unsaturated β-ketoaldehyde **213** was synthesized in seven steps from cyclohexenone and Nazarov reagent **210**was synthesized in fourteen steps from Hajos-Parrish ketone. Anionic cyclization of **213** and **210** followed by decarboxylation provided ABD tricycle **214**. Reduction of the C10 aldehyde followed by protection of the resulting alcohol provided ABD tricycle **215**. Closure of the C-ring and formation of the *cis* A/B, *trans* B/C, and *cis* C/D ring system (**216**) was accomplished after intramolecular aldol reaction. Saponification of the C11-acetate allowed for selective reduction of the C1-ketone. Oxidation of the PMB ether with DDQ resulted in the formation of orthoester **217**. β14-Hydroxy group was protected and dehydrogenation with DDQ resulted in α,β-unsaturated ketone. The C7 ketone was then selectively reduced to 7β-allylic alcohol that allowed for hydroxyl-directed β-face epoxidation to afford epoxy alcohol **218**. Next, the 7β-hydroxy group was mesylated and then subjected to reducing conditions that resulted in the simultaneous hydrogenolysis of the 7β-mesylate and reductive opening of the epoxide. The resulting orthoester was then hydrolyzed upon treatment with silica gel. Protection of the C19-hydroxy group and deprotection of the C20-silyl ether gave steroid **219**. Fleming-Tamao oxidation converted the 3β-silane group to the desired 3β-hydroxy group. The primary C20-hydroxy group was protected as a silyl ether and the secondary C3-, C11-, and C19-hydroxy groups were protected as acetates to provide steroid **220**, which contains all the required stereocenters for the synthesis of ouabagenin. The remaining challenge was installing the 17β-lactone. Steroid **220** was converted into β17-vinyl steroid **221** following the three-step procedure of deprotection, followed by DMP oxidation, and then rhodium-catalyzed methylenation. The remaining steps in the construction of the butenolide ring is a very similar approach employed in the Jung synthesis of rhodexin A. β17-vinyl steroid **221** was then oxidized to cyclic tin ether **222**. Selective oxidation with NBS of the secondary hydroxyl group resulted in the formation of α-hydroxy ketone **223**. The α-hydroxy ketone **223** was condensed with the Bestmann phosphoranylidene-ketene and a final deprotection afforded the natural cardiotonic steroid ouabagenin. Deslongchamps and co-workers were successful in further elaborating ouabagenin to the natural cardiotonic glycoside oubain after glycosylation with L-rhamnose. The Deslongchamps synthesis is considered a pinnacle achievement in complex steroid synthesis. Evidence of the challenges and intricacies in steroid synthesis, the Deslongchamps synthesis is forty-one linear steps from Hajos-Parrish ketone and nineteen linear steps to assemble the steroid scaffold (**216**).



Scheme 3.12. Total synthesis of ouabagenin and ouabain.

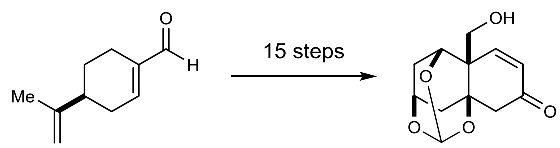
3.4.7 Convergent Synthesis of 19-Hydroxysarmentogenin

Recently, Inoue and co-workers described a convergent synthesis of 19-hydroxysarmentogenin (**236**), which is proposed as a viable cardenolide framework that could be further functionalized into more complex cardiotonic steroids (Scheme 3.13).[40] The synthesis involves assembly of AB-ring fragment **225** in 8 steps from (*S*)-perillaldehyde (**224**) and assembly of D-ring fragment **210** in six steps from diketone **173**. Fragments **225** and **226** were coupled upon bromination of D-ring fragment **226** followed by nucleophilic attack by AB-ring fragment **225** to form ABD tricycle **227**. Homolytic cleavage of the C11-bromide triggers the 6-*exo*-trig radical cylization adding to the β-face of C9 resulting in acetal **228**. The acetal is then converted to a vinyl-ether upon treatment with acid and C3 was then fully protected. Saponification of the acetates to alcohols followed by DMP oxidation provided triketone **229**. Triketone **229** was then treated with KHMDS at elevated temperatures in the key C-ring closure, which resulted in a mixture (8.6:1) of natural (β13-methyl and β14-hydroxy groups from C14 attack) steroid **230** and unnatural (α13-methyl and α14-hydroxy groups from C17 attack) steroid **231**. Resubmitting unnatural steroid **231** to the reaction conditions resulted in formation of natural steroid **230** (via retro-aldol/aldol) suggesting the intramolecular aldol is thermodynamically controlled. Next, the extraneous C7 ketone was removed in three steps. C7 ketone was selectively reduced and the resulting alcohol was converted to xanthate. After deoxygenation, the extraneous C7 was removed to afford pentacycle **232**. The α11-hydroxy group was introduced after ozonolysis of the vinyl-ether followed by deformylation. Treatment of hemiacetal **233** with TBSOTf, NEt_3, and LiHMDS resulted in dehydration of the hemiacetal to the resulting C11 ketone and protection of the C17 ketone and C19 alcohol. The α11-hydroxy group was reintroduced after thermodynamic reduction of the C11 ketone. The C17 ketone was then reintroduced after selective deprotection to give ketone **234**. As in in the Baran semi-synthesis of ouabagenin, the 17-lactone ring was installed after ketone **234** was converted to vinyl iodide and cross-coupled with stannane **145** to afford dienone **235**. The α11-hydroxy group was protected and, contrasting the Baran semi-synthesis, the dienone was directly reduced to the 17β-butenolide substituent and a final deprotection resulted in the desired 19-hydroxysarmentogenin (**236**).



Scheme 3.13. Convergent synthesis of 19-hydroxysarmentogenin.

Inoue and co-workers have applied this approach to the synthesis of ouabagenin.[41] Unlike 19-hydroxysarmentagenin, ouabagenin possesses 1β- and 5β-hydroxy groups. In order to include the hydroxy functionalities, a modified AB-ring fragment was synthesized (Scheme 3.14). The modified AB-ring fragment contains 1β-, 3β-, and 5β-hydroxy groups protected as an orthoester. As in the synthesis of 19-hydroxysarmentagenin, orthoester **237** was coupled with D-ring fragment **226** and the resulting ABD tricyclic system was elaborated in a similar fashion with the orthoester group being removed in the final global deprotection.



Scheme 3.14. Modification of AB-ring fragment to include 1β- and 5β-hydroxy groups.

3.5 Conclusion

Cardiotonic steroids are an important class of steroids that have a well-documented history of being an essential therapy for heart-related ailments. Cardiotonic steroids are still used today, but come with a risk due to their toxicity. Due to this risk and increased knowledge of their pharmacology, cardiotonic steroids and their analogs have become of great interest in pharmaceutical research. The distinctive structural features of cardiotonic steroids still present a synthetic challenge. Cardiotonic steroids possess unique structural characteristics that include a *cis* A/B, *trans* B/C, and *cis* C/D ring system, a 14β-hydroxy group, and a thermodynamically disfavored 17β-lactone substituent. . Semi-synthetic approaches are unable to utilize steroid precursors possessing the *cis* A/B, *trans* B/C, and *cis* C/D ring system and a 14β-hydroxy group. In addition to the challenges in achieving complete stereocontrol of the synthesis of the steroid framework, synthetic strategies must overcome the highly oxygenated nature of cardiotonic steroids that often require redox adjustments and protecting group manipulations. Some creative and elegant strategies have been developed to overcome these inherent challenges. Currently, the lengthy nature of these strategies prevents appreciable quantities of cardiotonic steroids to be synthesized.

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Chapter 4

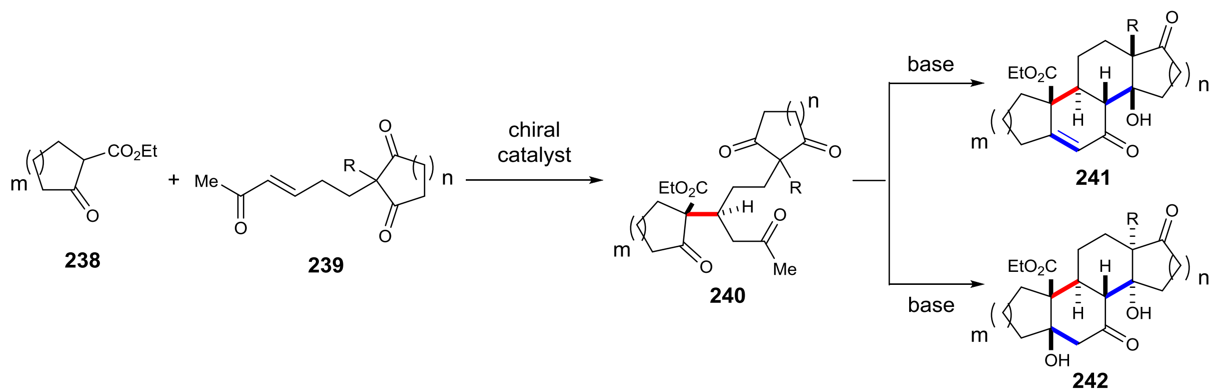
Concise Enantioselective Synthesis of Oxygenated Steroids via Sequential Bis(oxazoline) Copper(II)-Catalyzed Michael Addition/Intramolecular Aldol Cyclization Reactions

4.1 Strategy for Synthesizing Cardiotonic Steroids

Steroids play an important role in drug discovery, medicinal chemistry, and chemical biology. These compounds are responsible for the regulation of vital biological functions in animals and plants, and, not surprisingly, the steroidal scaffold is a privileged motif that is present in many FDA-approved drugs.[1] Developing means to access synthetic and natural steroids was one of the triumphs of the last century chemists, and the first synthesis of a steroidal sex hormone, equilenin by Bachmann dates back to 1939.[2] Despite major advances in the total synthesis of steroids, most steroid-based drugs are obtained by semi-synthesis using feedstock isolated from plant or animal sources.[3] Recent developments in the field of asymmetric catalysis have enabled the efficient preparation of simple enantioenriched steroids such as estrones.[4] However, fewer asymmetric catalytic strategies for the construction of more complex steroids are available. In particular, despite the significant efforts invested in developing scalable synthetic routes to cardiotonic steroids, an asymmetric total synthesis of the steroids of this family still represent a formidable challenge.[5] Considering recent interests in developing safer versions of existing medicines as well as the growing demand for cardenolide-based therapeutics, a concise, scalable and modular synthetic route to the cardenolide skeleton bearing necessary functionalization is highly desired.

To address the aforementioned problems, designed and undertook was a conceptually new asymmetric approach to steroids that enables rapid stereoselective synthesis of various cardiotonic steroid scaffolds (Scheme 4.1). The approach relies on tandem asymmetric diastereoselective Michael addition/intramolecular aldol reactions to achieve expedient assembly of steroids. The benefit of this approach is the utilization of simple and readily available building blocks **238** and **239**, the versatility to synthesize steroidal core **241** and C13, C14-epimeric steroidal core **242**, and the succinctness as steroid cores **241** and **242** could be synthesized in 4-5 steps. Additionally, the method would tolerate modification of **237** and **238**, permitting alteration in the ring size and C13-

substituents of steroid cores **241** and **242**. The ability to quickly generate steroid scaffolds **241** and **242** provides the opportunity to synthesize a variety of natural and unnatural cardiotonic steroids.



Scheme 4.1. Proposed concise and versatile synthesis of natural and unnatural cardiotonic steroid scaffolds via tandem Michael reaction/intramolecular aldol reactions.

4.2 Michael Donors and Michael Acceptors

The conciseness of the proposed method is dependent on the use of simple and readily available building blocks. Cognizant of this factor, Michael donors and acceptors were selected that are commercially available or could be synthesized in a couple steps.

The Michael donor in this method determines the ring size of the A-ring of the steroid core. Michael donors **238a** and **238b** were selected as inexpensive and commercially available building blocks: Michael donor **238a** cost \$1.16/g and Michael donor **238b** cost \$0.67/g (Figure 4.1). Application of Michael donor **238a** would result in natural six-membered A–ring, while Michael donor **238b** would provide unnatural five-membered A-ring.

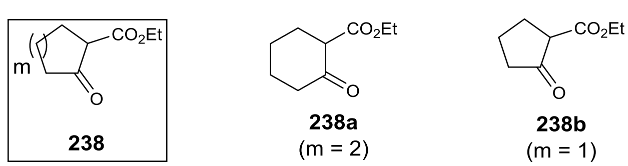
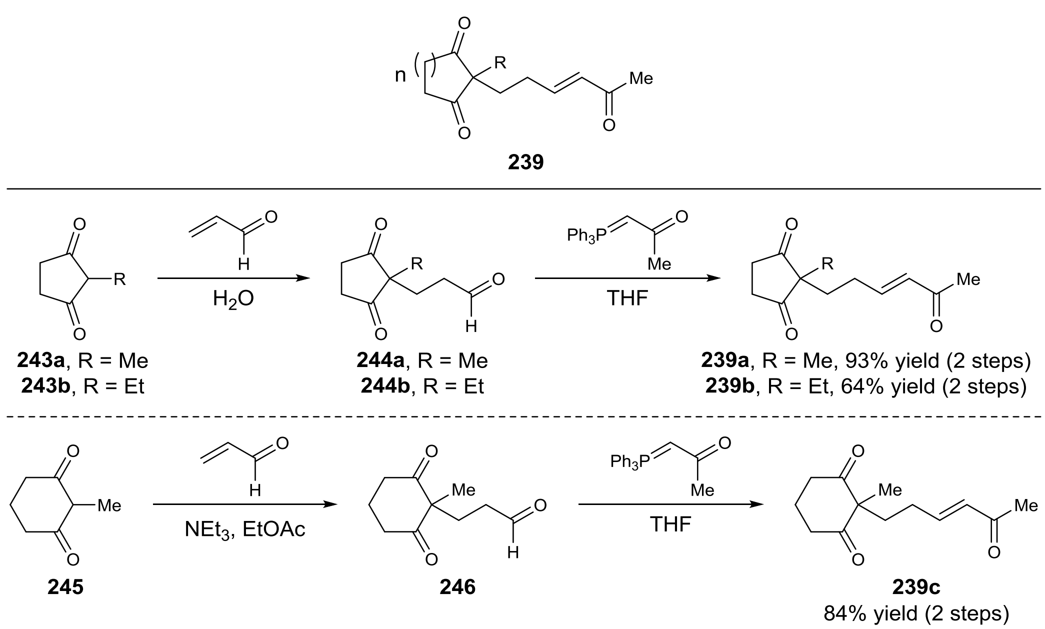


Figure 4.1. Structures of commercially available Michael donors **238a** and **238b**.

The Michael acceptor in this method contains the structural framework of the B, C, and D rings. Three Michael acceptors (**239a**, **239b**, **239c**) were designed and synthesized on multi gram scales in two steps (Scheme 4.2). Michael acceptor **239a** was designed for the synthesis of natural cardiotonic steroid framework as it contains an intact five-membered D-ring and corresponding substituents and functionalities required for the installation of C13, C14, and C17 stereocenters. Michael acceptors **239b** and **239c** were designed to synthesize steroid frameworks with a C13-ethyl substituent and a six-membered D-ring, respectively.

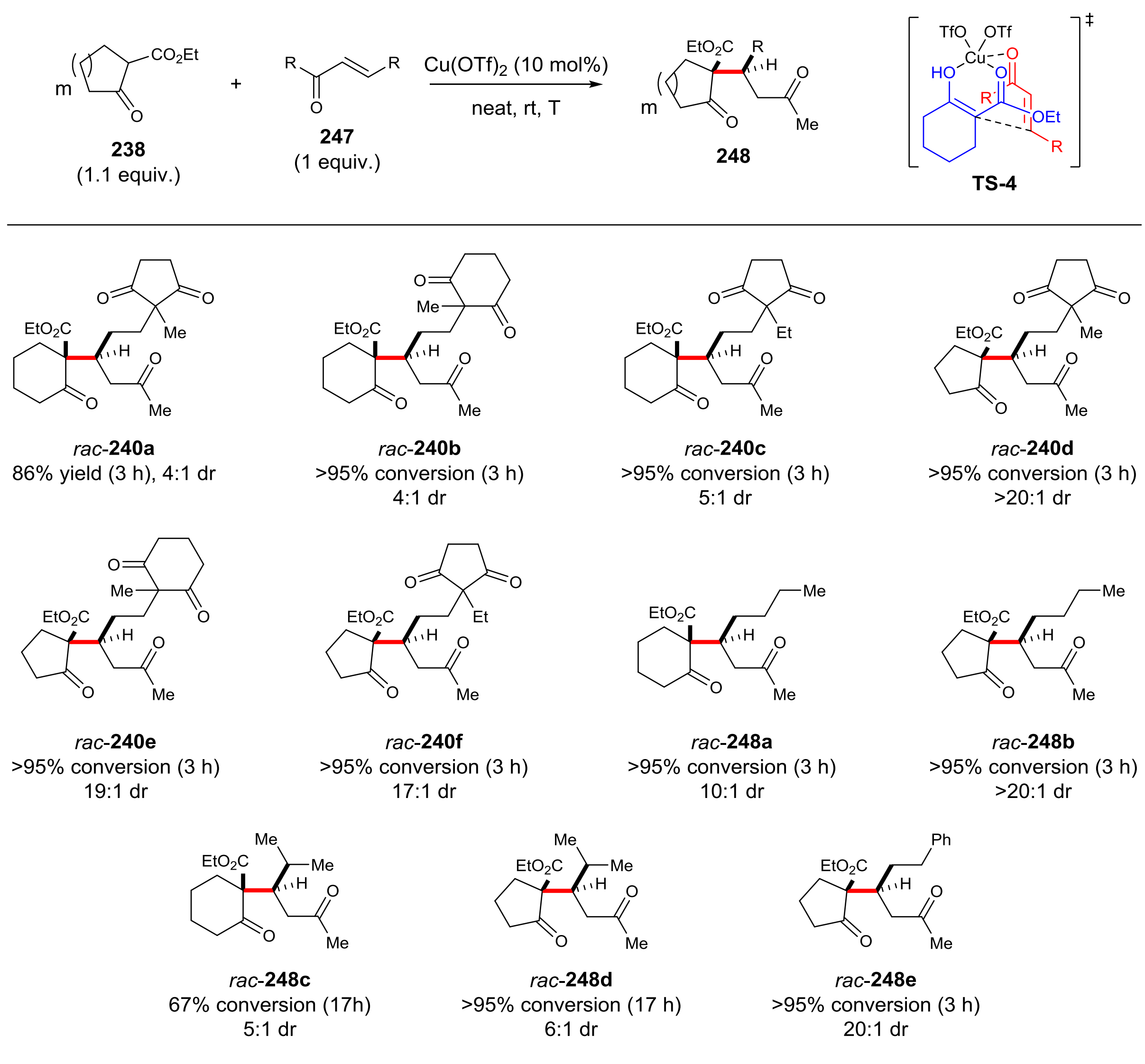
The syntheses started from commercially available diketones (**243a**, **243b**, and **245**), which were converted to known aldehydes (**244a**, **244b**, and **246**) using Michael reaction with acrolein. The aldehydes were then condensed with commercially available Wittig reagent 1-(tri-phenylphosphoranylidene)-2-propanone to afford the desired Michael acceptors (**239a**, **239b**, and **239c**). Although the addition of diketone **245** to acrolein in water to form aldehyde **246** is known, the procedure was altered to include the addition of base (NEt_3), which required the solvent to be aprotic (EtOAc). Base additive was necessary as the enol tautomer content for diketone **245** is not as high for diketone **243a** or **245b**, which affects the rate of addition to acrolein. Additionally, Michael acceptors **239a** and **239c** could be made by condensing aldehydes **244a** and **246** with commercially available diethyl (2-oxopropyl)phosphonate. However, only under mild Masamune-Roush conditions[6] (Hünig's base with LiCl) comparable Wittig condensation yields can be obtained. Traditional HWE conditions (e.g. NaH) or Masamune-Roush conditions with DBU would result in low yields of the desired product as the conditions were basic enough to trigger the desired product to self-cyclize.



Scheme 4.2. Structures and synthesis of Michael acceptors.

4.3 Michael Reaction

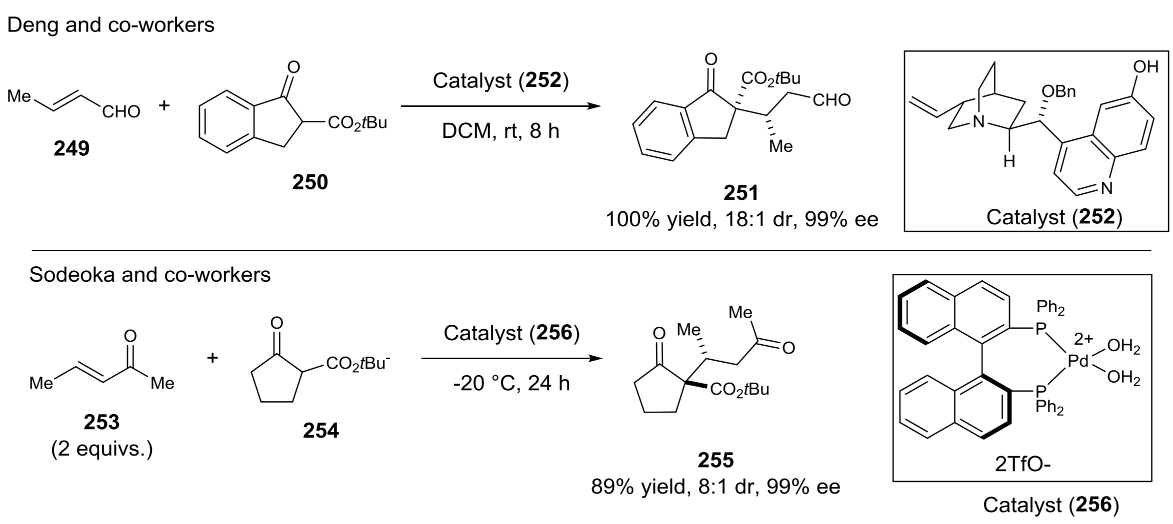
Intermolecular Michael reactions of 2-substituted β-ketoesters and β-substituted enones resulting in vicinal quaternary and tertiary stereocenters are challenging,[7] and only a few asymmetric catalysts for the construction of these motifs are known.[8] Therefore, initially racemic conditions were investigated to understand the intricacies of these reactions. It was discovered that Lewis acid catalysts such as $Cu(OTf)_2$ could promote an efficient Michael reaction between Michael donor **238a** and acceptor **239a** under solvent-free conditions to afford **240a** in 86% yield, 4:1 dr (Scheme 4.3).[9] The diastereoselectivity of this reaction could be increased without affecting the yield if the reaction was run at 0 ºC, and the desired diastereomer was formed as the major



Scheme 4.3. Substrate scope of the enantioselective Michael reactions.

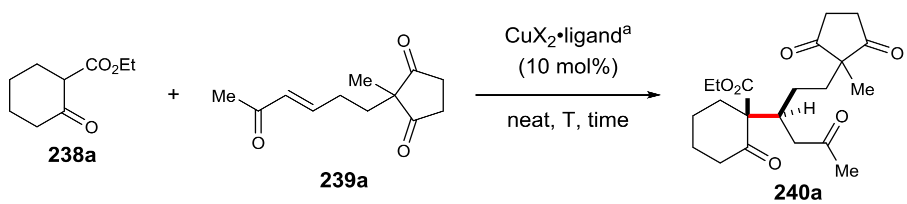
product. Encouraged by these results, the substrate scope of racemic $Cu(OTf)_2$ catalyzed Michael reaction were explored. Pleasantly, it was discovered that the conditions were not only efficient in promoting the couplings of Michael donors **238a** and **238b** with Michael acceptors **239a-c** to provide access to steroid precursors **240a-f**, but also the couplings of additional Michael acceptors as well. Noticeable trends became evident in these studies. In comparison to Michael donor **238a**, reactions with Michael donor **238b** proceeded significantly faster. For both Michael donors **238a** and **238b**, alterations in the β-substituent of the Michael acceptors (α,β-unsaturated keone) were well tolerated. However, slower reaction times were observed with increased sterics near the β-position (e.g. **248c** and **248d**). It is proposed that $Cu(OTf)_2$ catalyzes these Michael reactions by complexing to the Lewis acidic 1,3-dicarbonyl moiety of the Michael donor. This activates the Michael donor for nucleophilic attack of the Michael acceptor (**TS-4**).

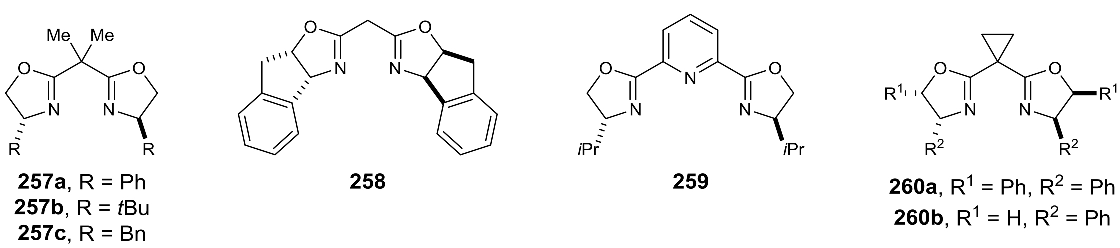
As gaining access to Michael adduct **240** in a highly selective manner is key to the synthetic plan, asymmetric Michael conditions of **238** and **239** were required. Evaluated first were conditions using the few asymmetric catalysts known to construct vicinal quaternary and tertiary stereocenters through intramolecular Michael reactions.[10] Notable examples are the asymmetric catalysts designed by Deng and co-workers and Sodeoka and co-workers. However, evaluation of these asymmetric methods did not result in an efficient enantioselective formation of Michael adduct **240**.



Scheme 4.4. Examples of asymmetric Michael conditions.

Encouraged by the findings that $Cu(OTf)_2$ was efficient in promoting the racemic Michael reaction, an enantioselective variant of this transformation was investigated by employing chiral Cu(II) complexes to catalyze the couplings of **238a** and **239a** (Table 4.1).[11] While $Cu(OTf)_2$ complexes were found to promote the enantioselective reaction (entry 1), with non-coordinating counterions the complexes were found to be more reactive (entry 2). Further evaluation of ligands (entries 3–8), was performed. Copper(II) complexes were synthesized with assistance from Dr. Zhankui Sun and Mr. Will Kaplan and ligands **13** and **14** were evaluated by Mr. Will Kaplan. Ultimatley, 2,2'-(cyclopropane-1,1-diyl)bis(4-phenyl-4,5-dihydrooxazole)-ligand **15b** was identified as the ligand of choice.[12] Thus, the copper(II) hexafluoroantimonate complex of **15b** promoted the formation of **3a** at room temperature in good conversion and selectivity (5:1 dr, 81% ee). The enantioselectivity of this reaction was improved at lower temperatures (entries 9–11), and under the optimal conditions (entry 10) the desired Michael adduct **3a** was obtained in excellent yield and selectivity (89% yield, 5:1 dr, 92% ee).



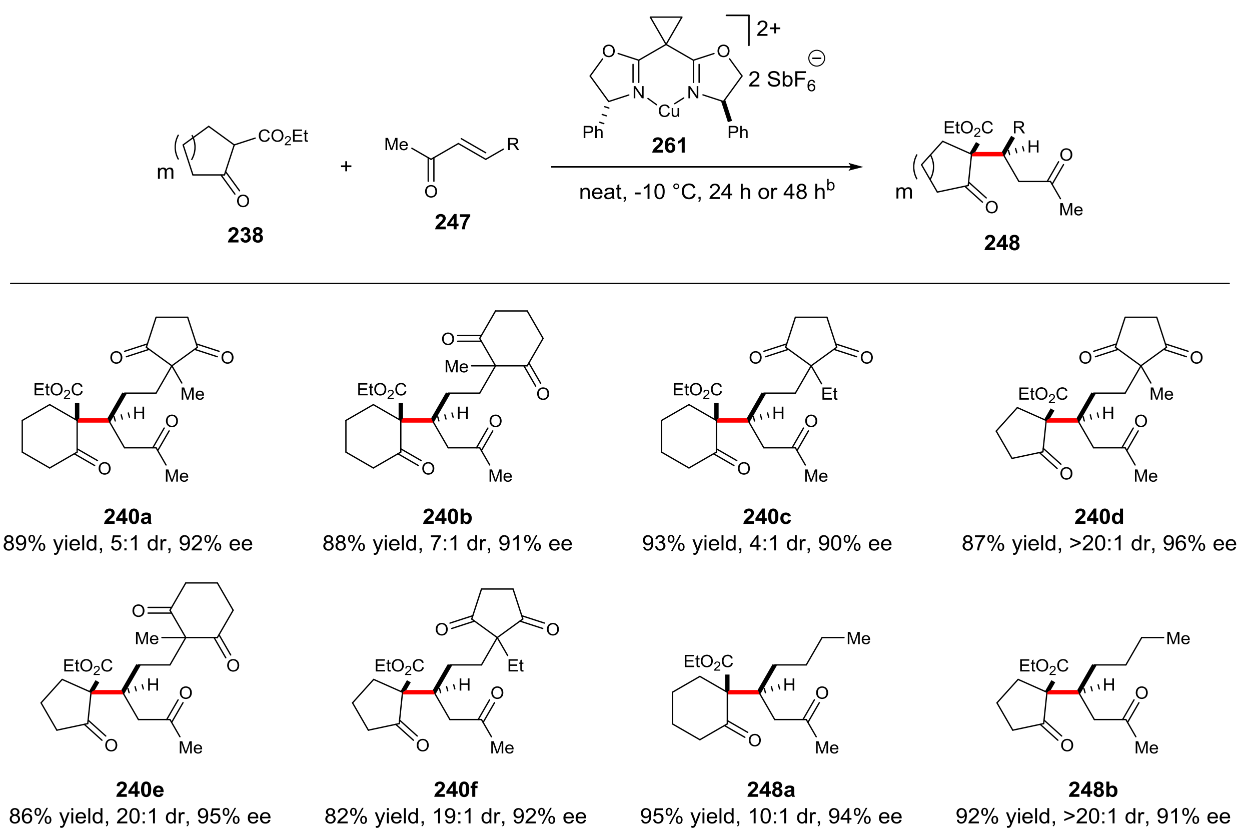


entry	ligand	CuX_2	T, °C	time, h	conversion, %	dr	ee, %
1	**257a**	$Cu(OTf)_2$	23	4	95	2.5:1	73
2	**257a**	$Cu(SbF_6)_2$	23	2.5	>95	2.5:1	65
3	**257b**	$Cu(SbF_6)_2$	23	48	10	n.d.	n.d.
4	**257c**	$Cu(SbF_6)_2$	23	3	0	-	-
5	**258**	$Cu(SbF_6)_2$	23	3	n.d.	n.d.	8
6	**259**	$Cu(SbF_6)_2$	23	3	n.d.	n.d.	10
7	**260a**	$Cu(SbF_6)_2$	23	3	>95	n.d.	71
8	**260b**	$Cu(SbF_6)_2$	23	4	>95	5:1	81
9	**260b**	$Cu(SbF_6)_2$	-5	24	>95	5:1	89
10	**260b**	$Cu(SbF_6)_2$	-10	48	>95	5:1	92
11	**260b**	$Cu(SbF_6)_2$	-20	72	85	6:1	93

[a]These reactions were performed on 1.0 mmol scale with 1 equiv of **238a** and **239a**, and the catalyst of choice (10 mol %).

Table 4.1. Optimization of the conditions for the enantioselective Michael reaction.

The proposed method includes the versatility to alter the A- and/or D-ring size(s) and the C13-substituent. In order to determine if the A-ring size could be contracted, the D-ring size could be expanded, and C13-ethyl substituent could be introduced, the substrate scope of the enantioselective Michael reaction were investigated with Michael donors **238a** and **238b** and Michael acceptors **239a-c** (Figure 4.5). With the assistance of Mr. Will Kaplan, it was discovered that steroid precursors **240a-f** could be obtained in good yields, diastereo- and enantioselectivities. Additionally, the conditions were applied to the synthesis of Michael adducts **248a** and **248b**, which could be cyclized to functionalized Wieland-Miescher and Hajosh-Parrish ketones, with good yields, diastereo- and enantioselectivities being observed. As in the racemic variant, reactions with Michael donor **238b** proceeded significantly faster (24 h) and with higher levels of diastereocontrol (**240d-f** and **248b**). Also, alterations in the β-substituent of the Michael acceptors were well tolerated. The absolute and relative configurations of these adducts were later confirmed by X-ray crystallographic analysis of their cyclized products (Table 4.2 and Scheme 4.8).



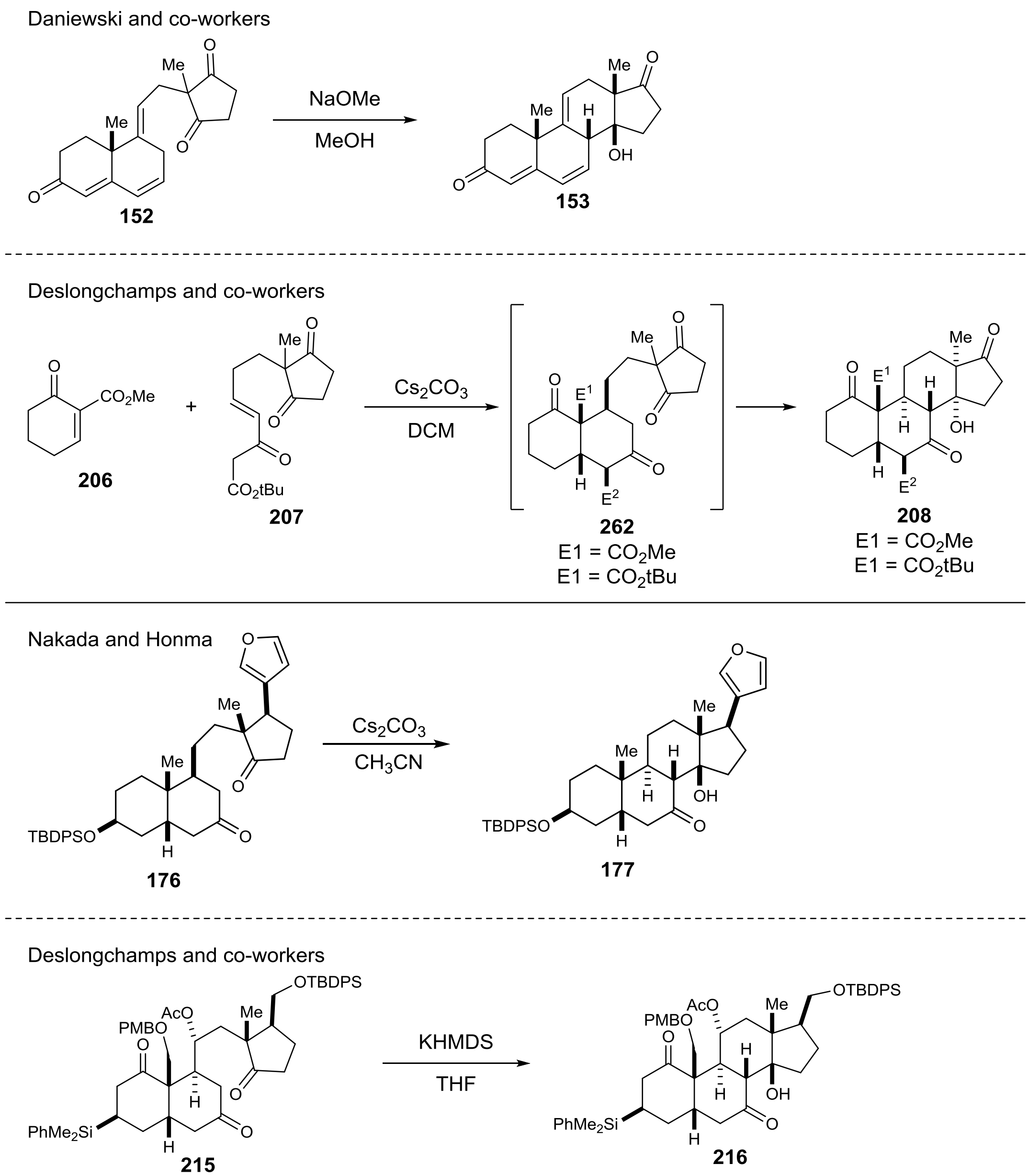
[a]Reactions were performed on 0.82–1.3 mmol scale. The provided absolute stereochemistry of **240a-f** and **248a-b** could be achieved with (*R*,*R*)-**261**; [b] Reaction with **1a** were stirred for 48 h and reactions with **1b** were stirred for 24 h.

Scheme 4.5. Substrate scope of the enantioselective Michael reactions.[a]

4.4 Aldol Reactions

In the synthetic plan, Michael adduct (AD bicycle) **240** undergoes a double aldol sequence, which closes the B and C ring. The aldol reaction that closes the B-ring was expected to proceed first and provide the desired *cis* A/B ring junction with the C10-stereocenter. However, closure of the C-ring possess an inherent challenge. The succinctness of the approach relies on being able to develop conditions that can differentiate the diastereotopic carbonyls of the D-ring.

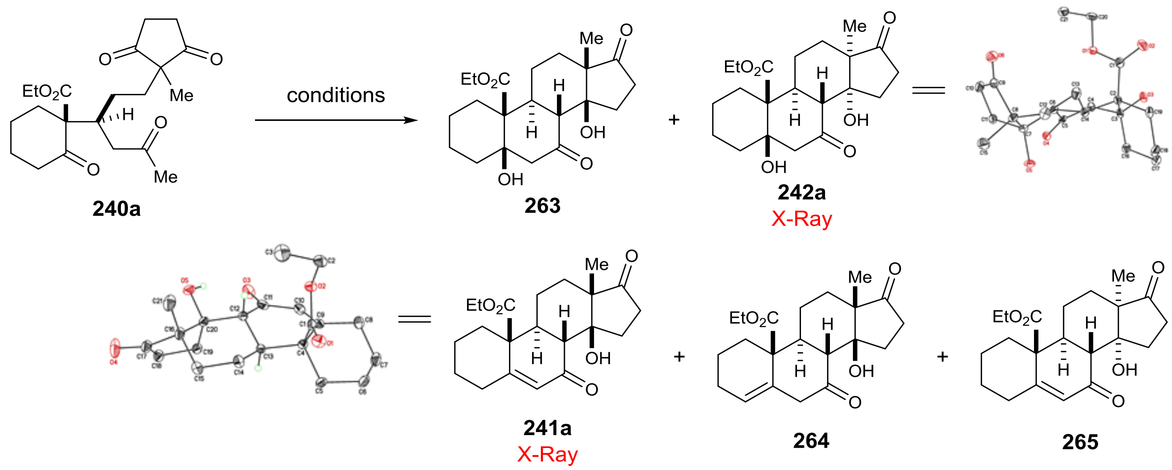
Previous strategies have relied on an aldol reaction to close the C-ring of an ABD tricycle



Scheme 4.6. Examples of ABD tricycles closed by aldol reaction to ABCD tetracycles.

(Scheme 4.6, also see Chapter 3). In comparing the cyclization of ABD tricycle **152** by Daniewski and co-workers to the cyclization of **262** by Deslongchamps and co-workers, it is important to note that the different outcomes, which arise from attacking different carbonyls of the D-ring, can be a result of a subtle structural difference (C9-C11 olefin). A tactic to ensure the desired carbonyl is attack would be to remove the symmetry of the D-ring. This is demonstrated by Nakada and Honma in the synthesis of digitoxigenin and Deslongchamps and co-workers in the synthesis of ouabain. The drawback of this approach is it requires additional steps to remove the symmetry and prevents the flexibility to synthesize natural and unnatural steroid cores from a common synthetic intermediate. Therefore, the objective of the intramolecular studies was to develop conditions for both the synthesis of natural and unnatural steroid cores from Michael adduct **240**.

With the key bond linking **238** and **239** providing **240** in a highly selective manner achieved, the intramolecular double-cyclization of **240a** were next investigated (Table 4.2). The initial attempts to accomplish the cyclization were unsuccessful when proline catalysis (entry 1), soft enolization conditions (entry 2), or tertiary amines (entries 3 and 4) were employed. However, under acidic conditions the cyclizations proceeded to provide unnatural enone **5a** with the α-configuration of the C13- and C14-stereocenters (entry 5). Similarly, DBU-promoted transformation resulted in a clean formation of **5a** at elevated temperatures (entry 6). Piperidine and pyrrolidne – promoted reactions were investigated next (entries 7-11). Interestingly, the use of LiCl as an additive in combination with piperidine or pyrrolidine affected the outcome of the cyclization (entries 10 and 11). In attempts to improve the formation of steroids 2**41a** and **263**, containing the desired natural stereochemistry, KHMDS-promoted cyclizations were investigated (entries 12-14). Remarkably, the temperature was found to be an important parameter, and when conducted in refluxing THF, only the natural diastereomers **241a** and **264** were formed. Interestingly, deconjugation of **241a** to **264** could be avoided by using LiHMDS instead of KHMDS (entry 15). However, a low isolated yield of **241a** was obtained under these conditions due to retro-Michael reaction. To further avoid deconjugation and to prevent the retro-Michael pathway, a milder base, Cs_2CO_3, was employed at elevated temperature. Refluxing in CH_3CN did not provide the desired selectivity for **241a** or **263** (entries 16 and 17). But elevated temperatures in DMF afforded **241a** in high selectivity (entries 18-20), with Cs_2CO_3 at 140 °C being optimal. These conditions resulted in a fast formation of the desired enone **241a** with the β-configuration of the C13- and C14-stereocenters of the CD-ring junction. Additionally, the effect of using Li_2CO_3 in place of Cs_2CO_3 resulted in a preference for **242a** (entry 21).



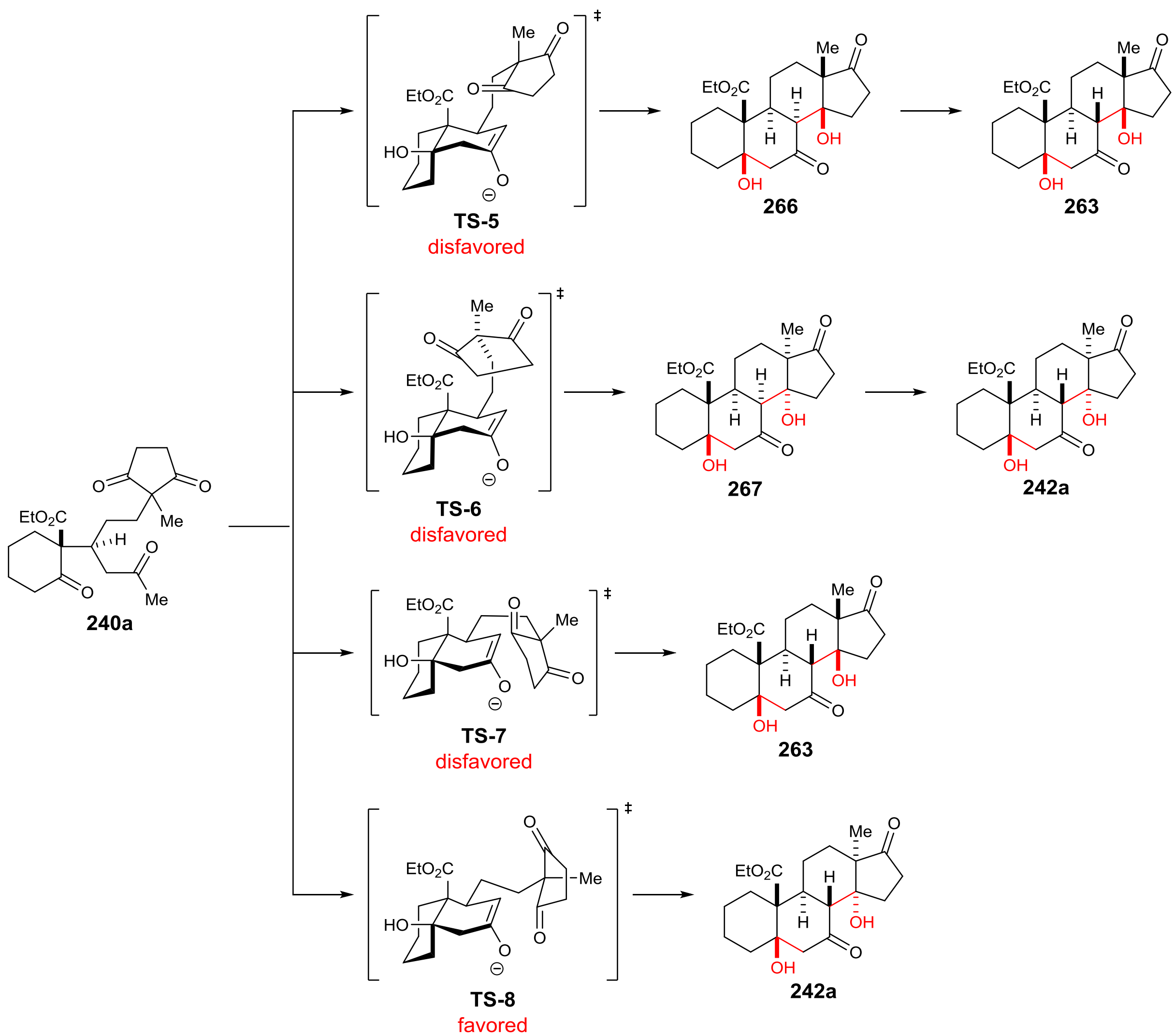
entry	conditions	conversion, % (yield, %)	products	selectivity
1	*D*- or *L*-proline, DMF, rt, 24 h	0	-	-
2	$TiCl_4$, NEt_3, THF, -78 °C to 0 °C	decomposition	-	-
3	DABCO, THF, reflux, 18 h	0	-	-
4	Hünig's base, THF, reflux, 18 h	0	-	-
5[a]	*p*-TSA, toluene, reflux, 18 h	>98	**242a**	only
6	DBU, THF, reflux, 18 h	>98 (94)	**242a**	only
7	pyrroldine, THF, rt, 18 h	0	-	-
8	piperidine, THF, rt, 18 h	0	-	-
9	piperidine, THF, reflux, 18 h	>98	**242a**	only
10	piperidine, LiCl, THF, reflux 18 h	>98	**263**, **242a**, **241a**, **265**	8:10:39:43
11	pyrrolidine, LiCl, THF, reflux, 18 h	>98	**241a**, **265**	52:48
12[b]	KHDMS (1 equiv.), THF, rt, 24 h	>98	**263**, **241a**, **265**	35:15:50
13[b]	KHMDS (1 equiv.), THF, reflux, 24 h	>98	**263**, **242a**, **241a**, **265**	44:44:4:8
14[b]	KHMDS (2 equiv.), THF, reflux, 30 min	>98 (48)	**241a**, **264**	1:2
15[b]	LiHMDS (2 equiv.), THF, reflux, 30 min	>98 (20)	**241a**	only
16	Cs_2CO_3, CH_3CN, reflux, 14 h	>98	**263**, **242a**, **241a**, **265**	53:35:5:7
17	Cs_2CO_3, CH_3CN, reflux, 20 h	>98	**263**, **242a**, **241a**, **265**	17:8:39:36
18	Cs_2CO_3, DMF, 120 °C, 4 h	>98	**241a**, **265**	95:5
19	Cs_2CO_3, DMF, 120 °C, 24 h	>98	**241a**, **265**	>95:5
20	Cs_2CO_3, DMF, 140 °C, 1 h	>98 (89)	**241a**	only
21	Li_2CO_3, DMF, 140 °C, 4 h	>98	**263**, **242a**, **241a**, **265**	10:75:8:7

[a]Unidentified product (c.a. 30%) was formed along with **242a**; [b]Significant amounts of retro-Michael reaction products were observed.

Table 4.2. Double aldol cyclization studies**.**

In comparing **242a** and **263**, these results suggest a clear bias for the unnatural diastereomers (**242a**). While the β-C5-stereocenter formed during closure of the B-ring is expected to be directed by the C10-stereocenter, prior reports by Deslongchamps and co-workers[13] suggest that the unnatural α-configuration of the C13- and C14-stereocenters of the CD-ring junction (i.e. pro-

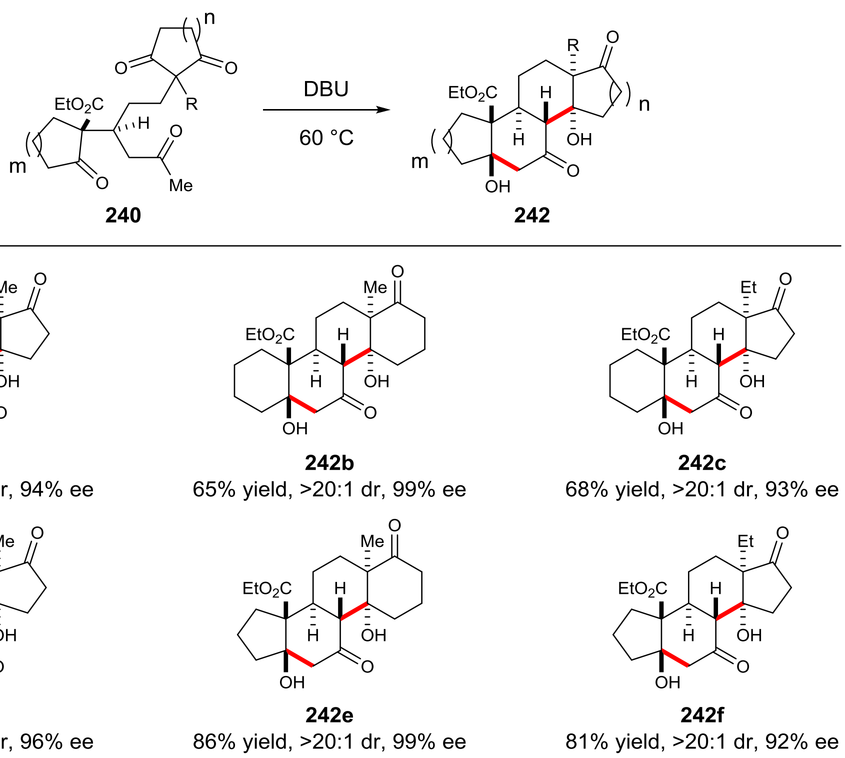
S ketone attack) is preferred. This is consistent with **242a** being favored instead of **263**. A closer inspection of possible transition states of the C-ring closure provides a greater understanding of the preference for the formation of **242a** (Scheme 4.7). With the D-ring possessing diastereotopic carbonyls and with B-ring enolate attacking the D-ring from the α- or β-face, four possible transition states were anticipated (**TS-5-TS-8**). B-Ring enolate attacking the D-ring from the α-face would result in double aldol products **266** and **267**, which could be epimerized to observed steroids **263** and **242a**. However, positioning the D-ring on β-face in this manner would result in unfavorable steric interactions with the C10-ethyl ester (**TS-5** and **TS-6**). B-Ring enolate attacking the D-ring from the β-face, would require the B-ring to be in a boat conformation to achieve the pseudo axial attack.[14] In comparing **TS-7** and **TS-8**, formation of **242a** is favored as steroid **263** involves



Scheme 4.7. Proposed stereoselective formation of unnatural steroid **242a**.

an unfavorable transition state in which the C-ring would have to adopt a boat-like conformation in order to a suitable angle of attack (**TS-7**). Additionally, calculations (DFT, geometry optimization, B3LYP, 6-31+G*) suggest that **242a** is more stable than **263** by 1.8 kcal/mol.

Based on these conclusions, the formation of unnatural steroids **242** from Michael adducts **240** were investigated next (Scheme 4.8). The DBU-promoted cyclizations resulted in the formation of steroids with the epimeric α-CD-ring junction (**242a-e**). In all cases, the epimeric steroids were obtained in excellent yields and selectivities, and the formation of the otherwise challenging to generate by semi-synthesis **242b**, **242d** and **242e** as well as C18-ethyl group containing products **242c** and **242f** was successfully achieved. The structures of steroids **242a** and **242b**, were confirmed by X-ray crystallographic analysis. Attempts to cyclize chiral Michael adducts **248a** and **248b** under these conditions to obtain bicyclic structures resulted in no yield. It was also suggested that unnatural steroids **242** could potentially be synthesized in one-pot from **238** and **239**, as chiral Michael adduct **242a** could be synthesized in one-pot from **238a** and **239a** in 53%

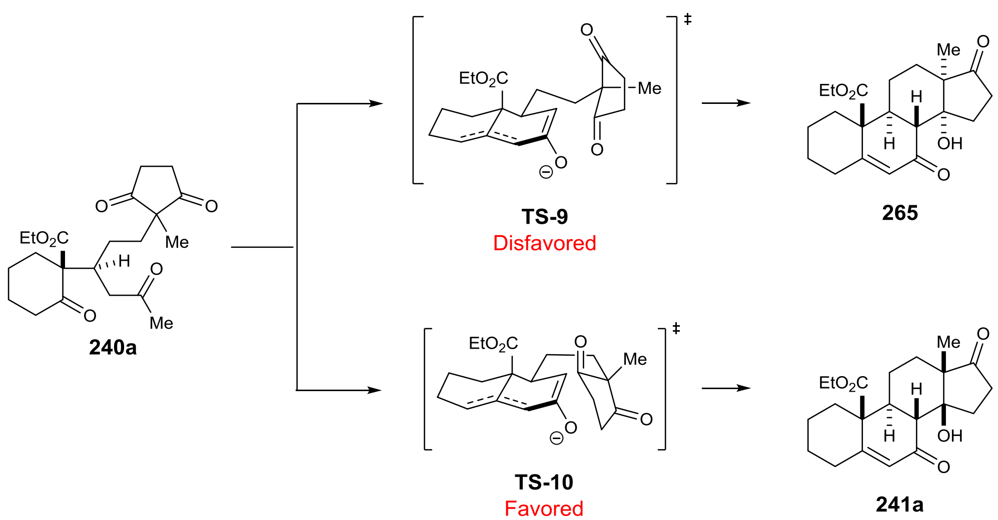


Diastereomeric mixtures of Michael adducts (Scheme 4.5) were treated with base. The yields are reported for the isolated major diastereomer after purification by flash chromatography. *(R,R)*-enantiomer of **261** is required to generate the natural enantiomers of **242**.

Scheme 4.8. Diastereoselective formation of unnatural steroids **242a-f** from chiral Michael adducts **240a-f**.

yield without loss of diastereo- or enantioselectivity. In the one-pot procedure, Michael adduct **240a** was produced by reacting **238a** and **238b** neat with chiral bis(oxazoline) copper(II) complex. THF and excess DBU were added and the reaction was heated overnight. The one-pot procedure has only been applied to the synthesis of unnatural steroid **242a** at the current time.

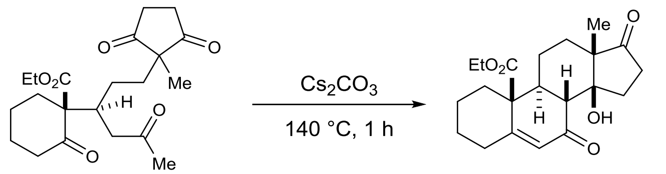
Furthermore, the double cyclization studies (Table 4.2) also indicated a clear preference for natural enone **241a** over unnatural enone **265**. Calculations (DFT, geometry optimization, B3LYP, 6-31+G*) suggest that the energy of the enone **241a** with natural configuration is 2.1 kcal/mol lower than the energy of the unnatural enone **265**. In looking at possible transition states, it is proposed that the formation of natural enone **241a** is favored due to a better angle of attack of attack (Scheme 4.9). The presence of the C5-C6 enone double bond in ring B results in increased torsional strain for the unnatural α-configuration and the natural β-diastereomer **241a** becomes more stable.



Scheme 4.9. Proposed stereoselective formation of natural steroid **241a**.

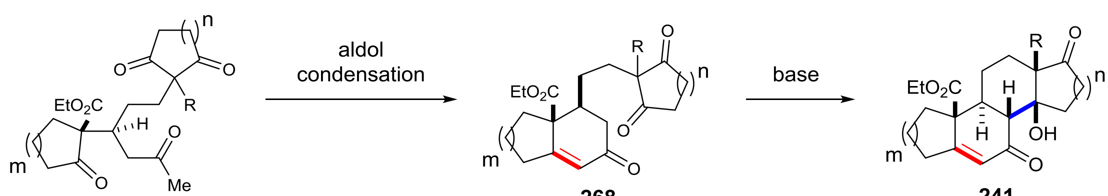
As a control experiment, diastereomerically pure unnatural double aldol steroid **242a** was treated with Cs_2CO_3 at 140 ºC. As expected, **242a** underwent elimination of water, and a 3:1 mixture of **241a**:**265** was observed under the reaction conditions. Natural steroid **241a** is suggested to be formed from **242a** by first condensation to **265**, which under the thermodynamic conditions, undergoes retro-aldol/aldol reaction to form the more thermodynamically favored natural steroid **241a**.

The cyclizations with Cs_2CO_3 at 140 ºC were studied with Michael adducts **240a-e**. The conditions were scalable for the synthesis of **241a**, as 1.5 g of **241a** was generated without significant erosion in yield and enantioselectivity (Scheme 4.10). Unfortunately, the conditions could not be universally applied to Michael adducts **240b-e**. Low yields were observed due to significant amounts of retro-Michael reaction products. Additionally, attempts to cyclize Michael adducts **248a** and **248b** to functionalized Wieland-Miescher and Hajos-Parrish ketones under these conditions were unsuccessful.



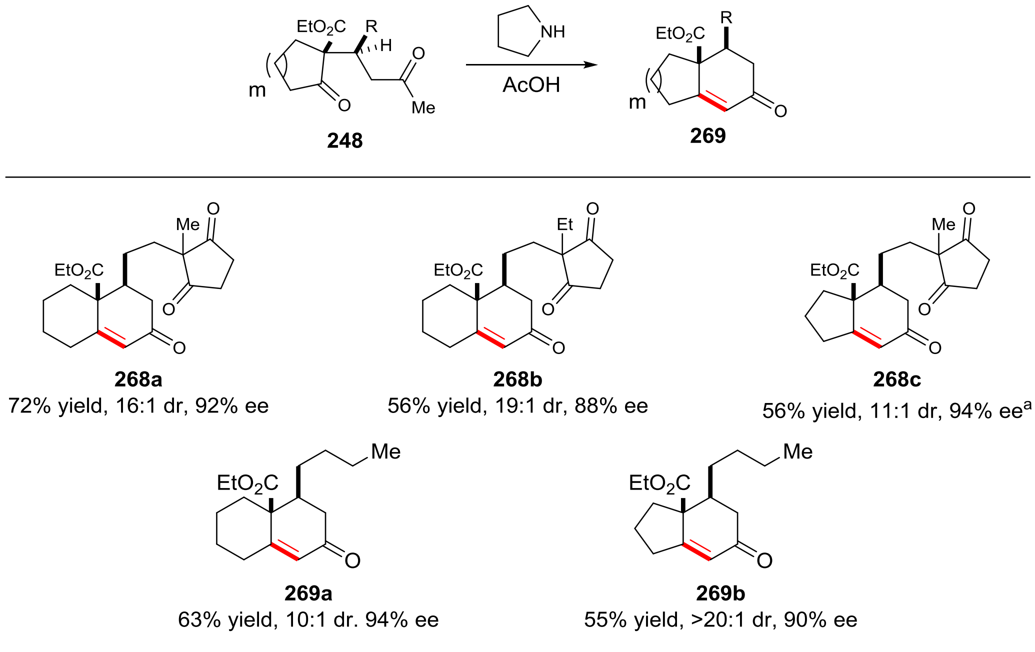
Scheme 4.10. Conversion of Michael adduct **240a** to steroid **241a**.

In parallel, a two-step procedure was being developed that would afford natural steroids **241** through an aldol condensation/aldol approach (Scheme 4.11). The approach would take advantage of the presence of the C5-C6 enone double bond in semicyclized enone **268** to prevent the formation of the unnatural α-C13 and C14 configuration due to in increased torsional strain, but also prevent the undesired retro-Michael reaction pathway.



Scheme 4.11. Two-step synthesis of natural steroid **241** from Michael adduct **240**.

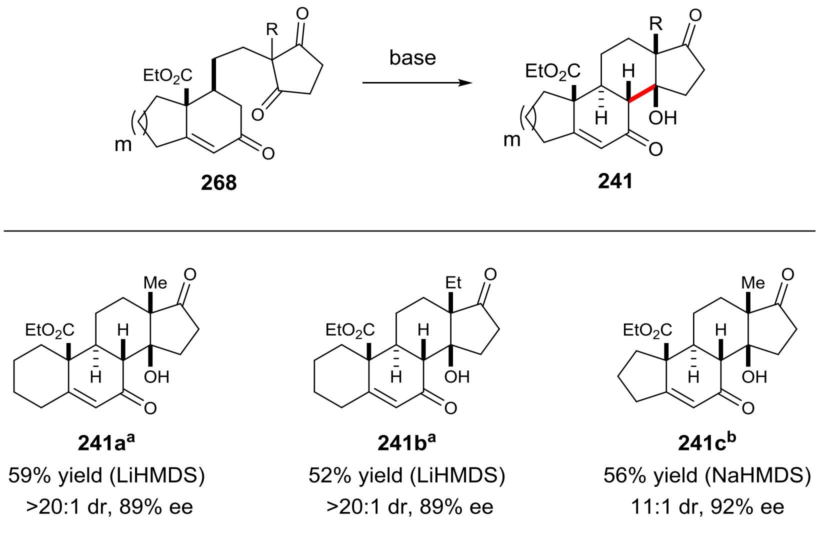
It was determined that pyrrolidine with acetic acid[15] were suitable for the effective semicyclization of chiral Michael adducts **240a**, **240c**, and **240d** (Scheme 4.12) in good yields and no erosion of enantioselectiviy. Additionally, these conditions were used for the generation of substituted Wieland-Miescher and Hajos-Parrish ketones,[16] the cyclization of Michael adducts **248a** and **248b** was performed to provide enones **269a** and **269b**. Such enones contain adjacent quaternary/tertiary stereocenters and to our knowledge have not been generated enantioselectively before.



Diastereomeric mixtures of Michael adducts (Scheme 4.5) were treated with pyrrolidne (1 equiv.) and AcOH (1 equiv.) in EtOAc (0.5 M) for 18 h. The yields are reported after purification by flash chromatography. *(R,R)*-enantiomer of **261** is required to generate the natural enantiomers of **268a-c** and **269a-b**. [a]Enatioselectivity is based on **241c**.

Scheme 4.12. Sythesis of semicyclized enones with pyrrolidine and acetic acid.

Subsequently, to complete the synthesis of natural steroid **241**, the C-ring closure of semicyclized enone **268** was studied. Based on previous results (Table 4.2, entries **12-15**), metal bis(trimethylsilyl)amides in THF at elevated temperatures were investigated. Perhaps as expected, treatment of semicyclized enone **268a** with KHMDS resulted in the formation of the desired steroid (**241a**) and deconjugated steroid **264**. However, using LiHMDS instead resulted in the selective formation of natural steroid **241a** in good yield and selectivity. These conditions were successfully applied to the synthesis of natural steroid **241b** and a similar outcome was observed. Unfortunately, treating semicyclized enone **268c** with the LiHMDS conditions in THF at elevated temperature resulted in no diastereoselectivity. It was proposed that the difference in energies between natural and unnatural eones was not as favorable in the case of **241a** and **265**. To overcome this reduced selectivity, more thermodynamically favorable conditions were investigated. With the assistance of Mr. Bijay Bhattarai, it was determined that NaHMDS refluxed in toluene was effective in affording natural steroid **241c**.



[a]Diastereomeric mixtures of ABD tricyles (Scheme 4.12) were treated with base. The yields are reported after purification by flash chromatography. *(R,R)*-enantiomer of **261** is required to generate the natural enantiomers of **241**. [a]Ran in THF at 60 °C; [b]Ran in toluene at reflux.

Scheme 4.13. Intramolecular aldol cyclization of semicylized enones **268**.

4.6 Enantioenrichment

A known phenomenon,[17] although not often regarded, was observed in the purification of chiral Michael adducts **240a-f**. Michael adducts were synthesized as diastereomeric mixtures that could not be easily separated by column chromatography. This does not present a problem in the synthesis of steroids **241** or **242** as the cyclized diastereomers could be separated by column chromatography. However, initially pure Michael adduct of the major diastereomer were desired to simplify cyclization studies and for analytical purposes. As a result, pure Michael adduct was obtained by separating diastereomeric mixtures of Michael adduct by Prep HPLC using an achiral column backed with bare silica. Although this method provided pure Michael adduct, the diastereomers could not be fully resolved (separated). Interestingly, the pure fractions were observed to be enantioenriched. For example (Table 4.1, entry **2**), pure Michael adduct **240a** could be obtained as a single diastereomer with 99% ee after Prep HPLC purification of a sample of **240a** with 2.5:1 dr and 65% ee. The extent of this factor was realized with Dr. Zhankui Sun. Due to these findings, enantioselectivity of Michael adducts were assigned by assay of diastereomeric mixtures. As an extra precaution, both enantiomers of bis(oxazoline) ligands were employed and the measured enantioselectivities of the enantiomers were in agreement. Additionally, the enantioselectivities observed for the generated cyclized products are in agreement with their chiral precursors.

4.7 Conclusion

A new method for a rapid assembly of natural and unnatural cardenolide skeletons has been developed. This method is enabled by developing a new chiral bis(oxazoline) copper(II) complex-catalyzed enantioselective and diastereoselective Michael reaction of cyclic ketoesters and enones to install vicinal quaternary and tertiary C9- and C10-stereocenters. These products subsequently undergo base-promoted diastereoselective aldol cascade reactions resulting in the natural or unnatural steroid skeletons. The mechanistic studies suggest that the stereodivergence in the cyclization step arises from the torsional effects that favor a thermodynamically more stable natural configuration-containing ring system **241a** at the elevated temperatures. The described method enables expedient generation of polycyclic molecules including modified steroidal scaffolds and substituted Hajos-Parrish and Wieland-Mischer ketones. This protocol has been employed to obtain gram quantities of fully functionalized steroid **241a**.

4.8 Experimentals

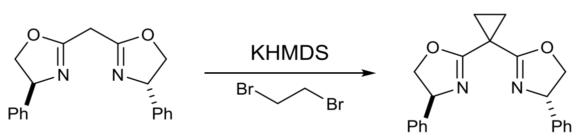
4.8.1 General

All reagents and solvents were purchased from commercial sources and were used as received without further purification unless specified. THF and DMF were purified by Innovative Technology's Pure-Solve System. All reactions were carried out under a positive pressure of nitrogen in flame- or oven-dried glassware with magnetic stirring. Reactions were cooled using cryocool or external cooling baths (sodium chloride/ice water (-10 °C) or dry ice/acetone (-78°C)). Heating was achieved by use of a silicone bath with heating controlled by electronic contact thermometer. Deionized water was used in the preparation of all aqueous solutions and for all aqueous extractions. Solvents used for extraction and chromatography were ACS or HPLC grade. Purification of reactions mixtures was performed by flash chromatography using SiliCycle SiliaFlash P60 (230-400 mesh). Yields indicate the isolated yield of the title compound ≥95% pure as determined by ^{1}H NMR analysis. Whereas the yields in Scheme 1 and Scheme 2 are the average yields of two or more experiments, the yields in the supporting information describe the result of a single experiment. Diastereomeric ratios were determined by ^{1}H NMR analysis. Enantiomeric excess was determined by HPLC analysis using a Waters e2695 Separations Module with a Waters 2998 photodiode array detector.

^{1}H NMR spectra were recorded on Varian vnmrs 700 (700 MHz) spectrometer and chemical shifts (δ) are reported in parts per million (ppm) with solvent resonance as the internal standard ($CDCl_3$

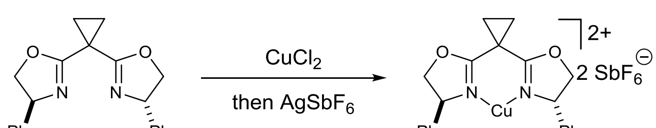
at δ 7.26). Data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, m = multiplet; coupling constant(s) in Hz; integration). Proton-decoupled ^{13}C NMR spectra were recorded on Varian vnmrs 700 (700 MHz) spectrometer and chemical shifts (δ) are reported in ppm with solvent resonance as the internal standard ($CDCl_3$ at δ 77.0). High resolution mass spectra (HRMS) were performed and recorded on Micromass AutoSpec Ultima or VG (Micromass) 70-250-S Magnetic sector mass spectrometers in the University of Michigan mass spectrometry laboratory. Infrared (IR) spectra were recorded as thin films on NaCl plates on a Perkin Elmer Spectrum BX FT-IR spectrometer. Absorption peaks were reported in wavenumbers (cm^{-1}).

4.8.2. Experimental Procedures and Compound Characterizations



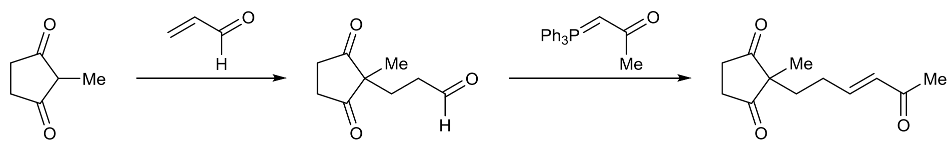
(4*S*,4'*S*)-2,2'-(cyclopropane-1,1-diyl)bis(4-phenyl-4,5-dihydrooxazole)

Bis((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)methane (1.0 g, 3.26 mmol, 1.0 equiv.) was dissolved in THF (30 mL, 0.1 M). 1,2-dibromoethane (562 μl, 6.5 mmol, 2.0 equiv.) and LiHMDS (1.48 g, 8.86 mmol, 2.7 equiv.) were added sequentially. The reaction mixture was allowed to stir for 6 hours. Additional 1,2-dibromoethane (281 μL, 3.26 mmol, 1.0 equiv.) and LiHMDS (1.08 g, 6.47 mmol, 2.0 equiv.) was added. The reaction mixture was allowed to stir for an additional 16 hours. Then, the reaction mixture was quenched with saturated NH_4Cl solution and then saturated $NaHCO_3$ solution was added. The aqueous solution was extracted with EtOAc (3 times). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mixture was purified by column chromatography (silica gel was pretreated with TEA, grad. 50%→100% EtOAc in hexanes) to afford (4*S*,4'*S*)-2,2'-(cyclopropane-1,1-diyl)bis(4-phenyl-4,5-dihydrooxazole) (0.95 g, 2.86 mmol, 88% yield) as an orange oil.



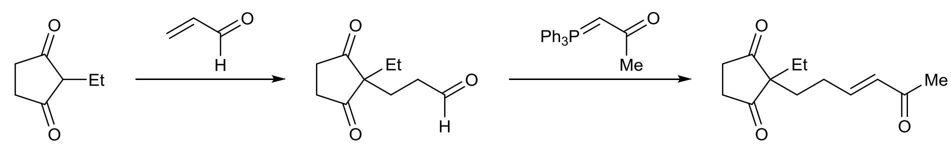
(4*S*,4'*S*)-2,2'-(cyclopropane-1,1-diyl)bis(4-phenyl-4,5-dihydrooxazole) copper(II) hexafluoroantimonate (261)

(4*S*,4'*S*)-2,2'-(cyclopropane-1,1-diyl)bis(4-phenyl-4,5-dihydrooxazole) (950 mg, 2.86 mmol, 1.0 equiv.) and copper(II) chloride (380 mg, 2.86 mmol, 1.0 equiv.) were taken in DCM (14 mL, 0.2 M) and stirred for 3 hours. Silver hexafluoroantimonate(V) (1.97 g, 5.72 mmol, 2.0 equiv.) was added as a solution in DCM (4 mL). The resulting reaction mixture was allowed to stir for 2 hours. The reaction mixture was diluted with THP (25 mL) and filtered through a plug of celite. The catalyst solution was concentrated *in vacuo* and then azeotroped with toluene (3 times). The catalyst was further dried by diluting with DCM (30 mL) and stirred with 4 Å MS (2.0 g) overnight. The green solution was decanted via cannula and the DCM was removed by flow of nitrogen to afford (4*S*,4'*S*)-2,2'-(cyclopropane-1,1-diyl)bis(4-phenyl-4,5-dihydrooxazole) copper(II) hexafluoroantimonate (1.9 g, 2.2 mmol, 85% yield) as a dark green solid.



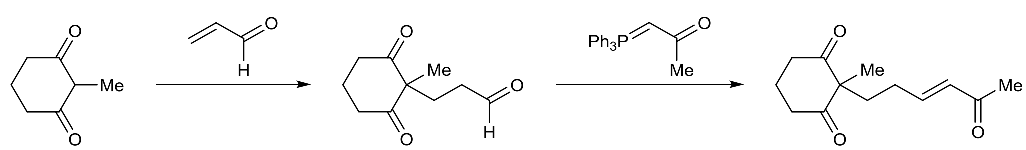
(*E*)-2-methyl-2-(5-oxohex-3-en-1-yl)cyclopentane-1,3-dione (239a)

2-Methylcyclopentane-1,3-dione (5.366 g, 47.9 mmol, 1 equiv.) was taken in H_2O (120 ml, 0.4 M). Acrolein (4.8 mL, 71.9 mmol, 1.5 equiv.) was added. The reaction mixture was allowed to stir overnight and then concentrated *in vacuo*. The reaction mixture was diluted with EtOAc, dried over $MgSO_4$, and concentrated *in vacuo* to afford 3-(1-methyl-2,5-dioxocyclopentyl)propanal[18] (8.05 g, 47.9 mmol, quantitative) as a colorless oil. Unpurified 3-(1-methyl-2,5-dioxocyclopentyl)propanal (8.05 g, 47.9 mmol, 1 equiv.) was then taken in THF (145 mL, 0.33 M). Added 1-(triphenylphosphoranylidene)-2-propanone (21.3 g, 67.1 mmol, 1.4 equiv.) and the reaction mixture was allowed to stir overnight. The reaction mixture was then concentrated *in vacuo* and purified directly by column chromatography (grad. 20%→33% EtOAc in hexanes) to afford (*E*)-2-methyl-2-(5-oxohex-3-en-1-yl)cyclopentane-1,3-dione (9.268 g, 44.6 mmol, 93% yield) as a colorless oil. ^{1}H NMR (700MHz, $CDCl_3$) δ 6.61 (dt, J = 6.8, 16.0 Hz, 1H), 5.98 (d, J = 16.0 Hz, 1H), 2.86-2.79 (m, 2H), 2.73-2.66 (m, 2H), 2.22 (s, 3H), 2.14-2.11 (m, 2H), 1.86-1.83 (m, 2H), 1.15 (s, 3H) ; ^{13}C NMR (175 MHz, $CDCl_3$) δ 215.9, 198.2, 146.2, 131.9, 56.1, 35.0, 32.6, 27.7, 26.8, 20.4; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}O_3$ $[M+Na]^+$ 231.0992, found 231.0998; IR (thin film, cm^{-1}) 2922, 1717, 1671, 1626, 1362, 1255, 980.



(*E*)-2-ethyl-2-(5-oxohex-3-en-1-yl)cyclopentane-1,3-dione (239b)

2-Ethylcyclopentane-1,3-dione (3.498 g, 27.8 mmol, 1 equiv.) was taken in H_2O (70 mL ml, 0.4 M). Acrolein (2.8 mL, 41.6 mmol, 1.5 equiv.) was added. The reaction mixture was allowed to stir overnight and then concentrated *in vacuo*. The reaction mixture was diluted with EtOAc, dried over $MgSO_4$, and concentrated *in vacuo* to afford 3-(1-ethyl-2,5-dioxocyclopentyl)propanal (5.07 g, 27.8 mmol, quantitative) as a colorless oil. Unpurified 3-(1-ethyl-2,5-dioxocyclopentyl)propanal (5.07 g, 27.8 mmol, 1 equiv.) was then taken in THF (84 mL, 0.33 M). Added 1-(triphenylphosphoranylidene)-2-propanone (13.3 g, 41.7 mmol, 1.5 equiv.) and the reaction mixture was allowed to stir overnight. The reaction mixture was then concentrated *in vacuo* and purified directly by column chromatography (grad. 20%→33% EtOAc in hexanes) to afford (*E*)-2-ethyl-2-(5-oxohex-3-en-1-yl)cyclopentane-1,3-dione (3.948 g, 17.8 mmol, 64% yield) as a colorless oil. ^{1}H NMR (700MHz, $CDCl_3$) δ 6.60 (dt, *J* = 7.0, 15.8 Hz, 1H), 5.97 (d, *J* = 16.0 Hz, 1H), 2.79-2.73 (m, 2H), 2.70-2.61 (m, 2H), 2.21 (s, 3H), 2.08 (d, *J* = 6.8 Hz, 2H), 1.85-1.82 (m, 2H), 1.67 (q, *J* = 7.5 Hz, 2H), 0.82 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 216.5, 198.3, 146.4, 131.9, 60.9, 36.0, 31.3, 29.2, 27.8, 26.8, 8.7; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}O_3$ $[M+Na]^+$ 245.1148, found 245.1147; IR (thin film, cm^{-1}) 2922, 1716, 1671, 1626, 1254, 980.

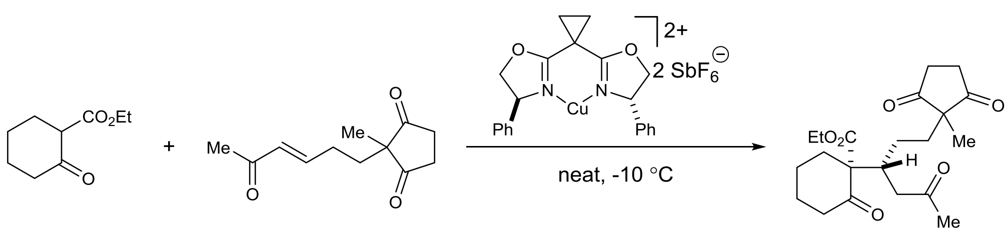


(*E*)-2-methyl-2-(5-oxohex-3-en-1-yl)cyclohexane-1,3-dione (239c)

2-Methylcyclohexane-1,3-dione was taken (2.06 g, 16.4 mmol, 1.0 equiv.) was taken in EtOAc (41 mL, 0.4M). TEA (3.4 mL, 24.6 mmol, 1.5 equiv.) and acrolein (1.7 mL, 24.6 mmol, 1.5 equiv.) were added. The reaction mixture was allowed to stir overnight and then concentrated *in vacuo* to afford 3-(1-methyl-2,6-dioxocyclohexyl)propanal (2.06 g, 16.4 mmol, quantitative) as a colorless oil. Unpurified 3-(1-methyl-2,6-dioxocyclohexyl)propanal (3.0 g, 16.4 mmol, quantitative) was then taken in THF (40 mL, 0.33 M). Added 1-(triphenylphosphoranylidene)-2-propanone (7.3 g, 22.9 mmol, 1.5 equiv.) and the reaction mixture was allowed to stir overnight. The reaction mixture was then concentrated *in vacuo* and purified directly by column chromatography (grad. 20%→33% EtOAc in hexanes) to afford (*E*)-2-methyl-2-(5-oxohex-3-en-1-yl)cyclohexane-1,3-dione (3.1 g, 13.9 mmol, 84% yield) as a colorless oil. ^{1}H NMR (700MHz, $CDCl_3$) δ 6.67 (dt, *J* = 6.8, 16.0 Hz, 1H), 5.99 (d, *J* = 16.0 Hz, 1H), 2.77-2.66 (m, 2H), 2.62-2.58 (m, 2H), 2.20 (s, 3H), 2.05-2.02 (m, 2H), 1.95-1.89 (m, 4H), 1.27 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 209.9, 198.5, 146.9, 131.5, 64.7, 37.9, 33.7, 27.9, 26.8, 22.0, 17.4; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}O_3$ $[M+Na]^+$ 245.1148, found 245.1150; IR (thin film, cm^{-1}) 2956, 1724, 1692, 1672, 1626, 1364, 1246, 980.

General procedure for the synthesis of racemic Michael adducts: Michael acceptor (1.0 equiv.), Michael donor (1.1 equiv.), and copper(II) triflate (0.1 equiv.) were stirred neat at room temperature. After 3 hours, the reaction mixture was purified directly by column chromatography.

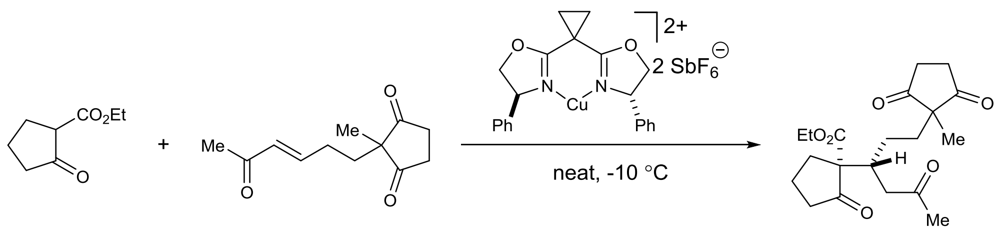
General procedure for the synthesis of chiral Michael adducts: Michael acceptor (1.0 equiv.) and bis(oxazoline)copper(II) complex were cooled to -10 °C. Michael donor (1.1-2.0 equiv.) was then added and the reaction mixture was stirred neat at -10 °C until completion (24-48 h). Copper catalyst can be removed by dissolving the reaction mixture in EtOAc and filtering through a plug of silica gel and washing with Et_2O. Alternatively, the reaction mixture can be purified directly by column chromatography.



ethyl (*R*)-1-((*R*)-1-(1-methyl-2,5-dioxocyclopentyl)-5-oxohexan-3-yl)-2-oxocyclohexane-1-carboxylate (240a)

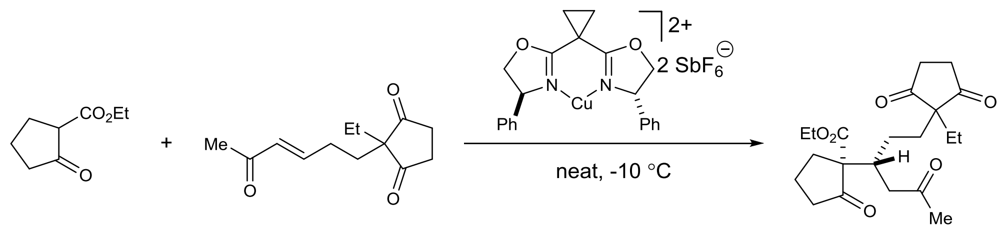
Michael acceptor (238 mg, 1.14 mmol, 1.0 equiv.) and bis(oxazoline)copper(II) complex (95 mg, 0.11 mmol, 0.1 equiv.) were cooled to -10 °C. Michael donor (0.36 mL, 2.29 mmol, 2 equiv.) was then added and the reaction mixture was stirred neat at -10 °C for 48 hours. The reaction mixture was purified directly by column chromatography (grad. 20%→33% EtOAc in hexanes) to afford ethyl (*R*)-1-((*R*)-1-(1-methyl-2,5-dioxocyclopentyl)-5-oxohexan-3-yl)-2-oxocyclohexane-1-carboxylate (404 mg, 1.07 mmol, 93% yield, 5:1 dr, 92% ee) as a colorless oil. $[\alpha]^{26}_{D}$ = +15.7 (*c* 1.0,

$CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$) δ 4.14-4.12 (m, 1H), 4.07-4.05 (m, 1H), 2.73-2.69 (m, 4H), 2.55(dd, *J* = 4.9, 18.2 Hz, 1H), 2.49-2.47 (m, 1H), 2.37-2.31 (m, 3H), 2.18(dd, *J* = 4.9, 18.2 Hz, 1H), 2.09 (s, 3H), 1.91-1.89 (m, 1H), 1.74-1.71 (m, 1H), 1.63-1.39 (m, 5H), 1.21 (t, *J* = 7.0 Hz, 3H) , 1.20-1.18 (m, 1H), 1.01 (s, 3H), 0.93-0.91 (m, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 216.2, 216.0, 207.4, 207.1, 171.4, 64.2, 61.5, 56.8, 45.1, 41.2, 36.1, 35.0, 35.0, 33.7, 32.9, 30.1, 26.9, 26.9, 22.2, 18.8, 14.0; HRMS (ESI) *m/z* calcd for $C_{21}H_{31}O_6$ $[M+H]^+$ 379.2115, found 379.2117; IR (thin film, cm^{-1}) 2937, 1706, 1363, 1206, 1093. Enantiopurity was determined to be 93% ee by chiral HPLC (DAICEL CHIRALPAK AD-H, 25 cm x 4.6 mm, hexanes/2-proponal = 85/15, flow rate = 1 mL/min, λ = 282.0 nm, RT(minor) = 9.5 min, RT(major) = 12.8 min).



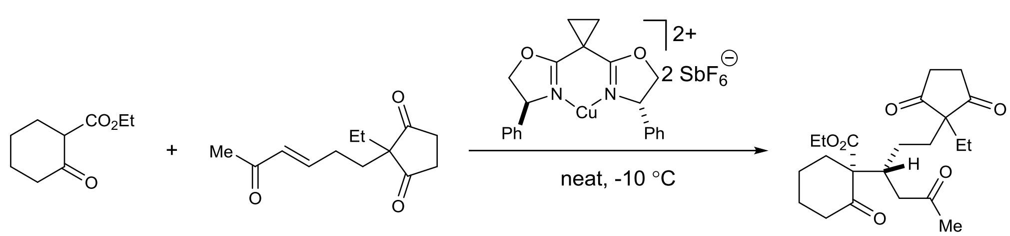
ethyl (*R*)-1-((*R*)-1-(1-methyl-2,5-dioxocyclopentyl)-5-oxohexan-3-yl)-2-oxocyclopentane-1-carboxylate (240d)

Michael acceptor (265 mg, 1.27 mmol, 1.0 equiv.) and bis(oxazoline)copper(II) complex (113 mg, 0.13 mmol, 0.1 equiv.) were cooled to -10 °C. Michael donor (0.38 mL, 2.29 mmol, 2 equiv.) was then added and the reaction mixture was stirred neat at -10 °C for 24 hours. The reaction mixture was purified directly by column chromatography (grad. 20%→33% EtOAc in hexanes) to afford ethyl (*R*)-1-((*R*)-1-(1-methyl-2,5-dioxocyclopentyl)-5-oxohexan-3-yl)-2-oxocyclopentane-1-carboxylate (396 mg, 1.09 mmol, 86% yield, 96% ee) as a colorless oil. $[\alpha]^{26}_D$ = -32.1 (*c* 1.1, $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$) 4.01 (q, *J* = 7.0 Hz, 2H), 2.90 (dd, *J* = 4.9, 18.2 Hz, 1H), 2.73-2.63 (m, 4H), 2.40-2.37 (m, 1H), 2.31-2.30 (m, 1H), 2.24-2.12 (m, 3H), 2.04 (s, 3H), 1.93-1.89 (m, 1H), 1.85-1.77 (m, 2H), 1.48 (t, *J* = 8.4 Hz, 2H) , 1.14 (t, *J* = 7.0 Hz, 3H) ,1.11-1.08 (m, 1H), 1.05-1.01 (m, 1H), 0.97 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 216.0, 216.0, 214.2, 207.6, 170.2, 63.4, 61.3, 56.6, 44.7, 38.3, 36.6, 35.0, 34.9, 33.4, 31.9, 29.9, 26.6, 19.2, 19.0, 13.9; HRMS (ESI) *m/z* calcd for $C_{20}H_{29}O_6$ $[M+H]^+$ 365.1959, found 365.1960; IR (thin film, cm^{-1}) 2966, 1714, 1363, 1223, 1157. Enantiopurity was determined to be 96% ee by chiral HPLC (DAICEL CHIRALPAK AD-H, 25 cm x 4.6 mm, hexanes/2-proponal = 88/12, flow rate = 1 mL/min, λ = 290.0 nm, RT(minor) = 12.5 min, RT(major) = 15.4 min).



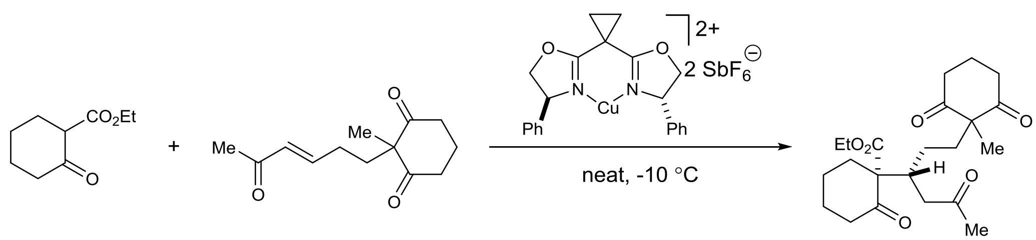
ethyl (*R*)-1-((*R*)-1-(1-ethyl-2,5-dioxocyclopentyl)-5-oxohexan-3-yl)-2-oxocyclopentane-1-carboxylate (240f)

Michael acceptor (181 mg, 0.82 mmol, 1.0 equiv.) and bis(oxazoline)copper(II) complex (71 mg, 0.08 mmol, 0.1 equiv.) were cooled to -10 °C. Michael donor (0.24 mL, 1.63 mmol, 2 equiv.) was then added and the reaction mixture was stirred neat at -10 °C for 24 hours. The reaction mixture was purified directly by column chromatography (grad. 20%→33% EtOAc in hexanes) to afford ethyl (*R*)-1-((*R*)-1-(1-ethyl-2,5-dioxocyclopentyl)-5-oxohexan-3-yl)-2-oxocyclopentane-1-carboxylate (254 mg, 0.67 mmol, 82% yield, 19:1 dr, 92% ee) as a colorless oil. $[\alpha]^{26}_{D}$ = -23.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.10 (q, *J* = 7.2 Hz, 2H), 2.04 (dd, *J* = 6.1, 18.4 Hz, 1H), 2.72-2.65 (m, 4H), 2.47 (qn, *J* = 6.0 Hz, 1H) 2.37-2.21 (m, 4H), 2.12 (s, 3H), 2.01-1.97(m, 1H), 1.93-1.85 (m, 2H), 1.64-1.54 (m, 4H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.19-1.15 (m, 1H), 1.21-1.06 (m, 1H), 0.76 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 216.8, 216.7, 214.4, 207.8, 170.3, 63.4, 61.5, 61.4, 44.6, 38.4, 36.9, 36.1, 36.0, 32.3, 30.1, 28.4, 26.8, 19.3, 14.0, 8.9; HRMS (ESI) *m/z* calcd for $C_{21}H_{30}O_6$ $[M+Na]^+$ 401.1935, found 401.1939; IR (thin film, cm^{-1}) 2968, 1713, 1222, 1157, 1023. Enantiopurity was determined to be 92% ee by chiral HPLC (DAICEL CHIRALPAK AD-H, 25 cm x 4.6 mm, hexanes/2-proponal = 90/10, flow rate = 1 mL/min, λ = 286.0 nm, RT(minor) = 12.0 min, RT(major) = 15.6 min).



ethyl (*R*)-1-((*R*)-1-(1-ethyl-2,5-dioxocyclopentyl)-5-oxohexan-3-yl)-2-oxocyclohexane-1-carboxylate (240c)

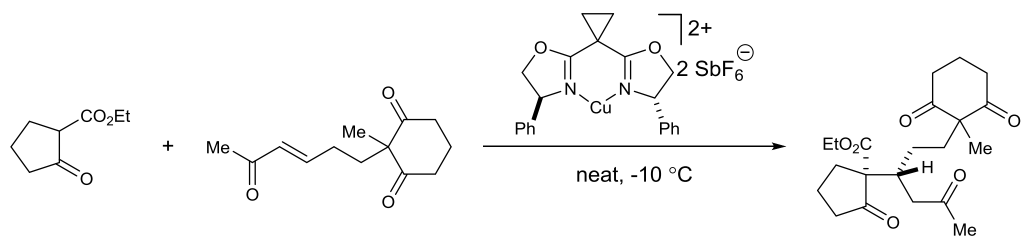
Michael acceptor (241 mg, 1.17 mmol, 1.0 equiv.) and bis(oxazoline)copper(II) complex (104 mg, 0.12 mmol, 0.1 equiv.) were cooled to -10 °C. Michael donor (0.37 mL, 2.33 mmol, 2 equiv.) was then added and the reaction mixture was stirred neat at -10 °C for 48 hours. The reaction mixture was purified directly by column chromatography (grad. 20%→33% EtOAc in hexanes) to afford ethyl (R)-1-((R)-1-(1-ethyl-2,5-dioxocyclopentyl)-5-oxohexan-3-yl)-2-oxocyclohexane-1-carboxylate (384 mg, 0.98 mmol, 90% yield, 4:1 dr, 90% ee) as a colorless oil. $[\alpha]^{25}_{D}$ = +17.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (700MHz, $CDCl_3$) δ 4.19-4.07 (m, 2H), 2.74-2.64 (m, 4H), 2.58 (dd, *J* = 4.9, 18.6 Hz, 1H), 2.51-2.48 (m, 1H), 2.43-2.32 (m, 3H), 2.23 (dd, *J* = 5.5, 18.6 Hz, 1H), 2.12 (s, 3H), 1.94-1.91 (m, 1H), 1.76-1.73 (m, 1H), 1.65-1.40 (m, 7H), 1.27-1.18 (m, 4H), 0.94-0.89 (m, 1H), 0.74 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 217.0, 216.7, 207.4, 207.1, 171.5, 66.2, 61.5, 61.5, 45.1, 41.2, 36.3, 36.1, 36.1, 36.0, 33.0, 32.5, 30.1, 29.1, 26.9, 22.2, 14.0, 9.0; HRMS (ESI) *m/z* calcd for $C_{22}H_{32}O_6$ $[M+Na]^+$ 415.2091, found 415.2098; IR (thin film, cm^{-1}) 2937, 1713, 1234, 1208, 1046. Enantiopurity was determined to be 90% ee by chiral HPLC (DAICEL CHIRALPAK AD-H, 25 cm x 4.6 mm, hexanes/2-proponal = 85/15, flow rate = 1 mL/min, λ = 282.0 nm, RT(minor) = 8.7 min, RT(major) = 12.4 min).



ethyl (*R*)-1-((*R*)-1-(1-methyl-2,6-dioxocyclohexyl)-5-oxohexan-3-yl)-2-oxocyclohexane-1-carboxylate (240b)

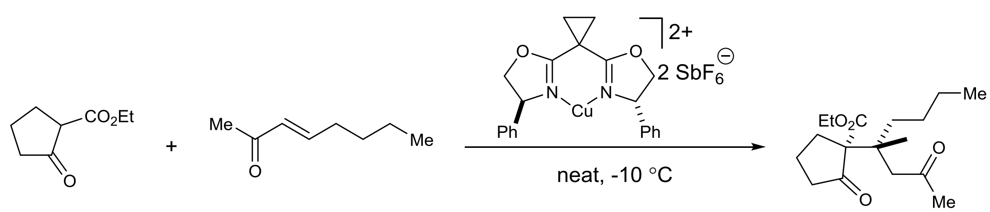
Michael acceptor (200 mg, 0.90 mmol, 1.0 equiv.) and bis(oxazoline)copper(II) complex (78 mg, 0.09 mmol, 0.1 equiv.) were cooled to -10 °C. Michael donor (0.29 mL, 1.80 mmol, 2 equiv.) was then added and the reaction mixture was stirred neat at -10 °C for 48 hours. The reaction mixture was purified directly by column chromatography (grad. 20%→33% EtOAc in hexanes) to afford ethyl (*R*)-1-((*R*)-1-(1-methyl-2,6-dioxocyclohexyl)-5-oxohexan-3-yl)-2-oxocyclohexane-1-carboxylate (310 mg, 0.79 mmol, 88% yield, 7:1 dr, 92% ee) as a colorless oil. $[\alpha]^{26}_{D}$ = +17.8 (*c* 1.2, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.14-4.11 (m, 1H), 4.07-4.04 (m, 1H), 2.73-2.69 (m, 2H), 2.61-2.55 (m, 4H), 2.37-2.33 (m, 3H), 2.20(dd, *J* =4.9, 17.5 Hz, 1H), 2.10 (s, 3H), 2.00-1.97 (m, 1H), 1.92-1.85 (m, 2H), 1.80-1.71 (m, 2H), 1.63 (td, *J* = 4.2, 13.3 Hz, 1H), 1.57-1.53 (m, 2H), 1.44-1.42 (m, 1H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.17-1.13 (m, 1H), 1.13 (s, 3H), 0.89-0.83 (m, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 210.1, 210.0, 207.3, 207.2, 171.4, 65.9, 64.2, 61.5, 45.1, 41.2, 37.7, 37.6, 36.1, 36.1, 32.3, 30.1, 27.3, 26.8, 22.2, 18.5, 17.8, 14.0. HRMS (ESI) *m/z* calcd for $C_{22}H_{33}O_6$

[M+H]$^+$ 393.2272, found 393.2274; IR (thin film, cm^{-1}) 2940, 1692, 1363, 1206. Enantiopurity was determined to be 91% ee by chiral HPLC (DAICEL CHIRALPAK AD-H, 25 cm x 4.6 mm, hexanes/2-proponal = 85/15, flow rate = 1 mL/min, λ = 290.0 nm, RT(minor) = 8.7 min, RT(major) = 11.4 min).



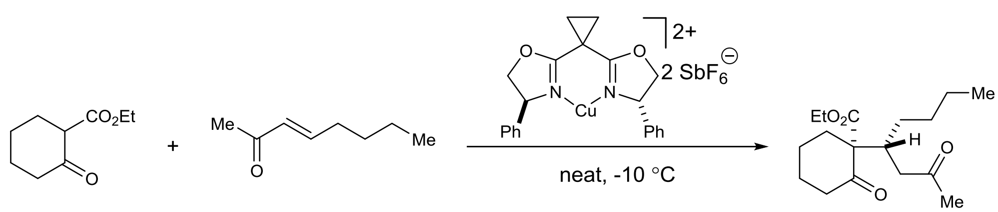
ethyl (*R*)-1-((*R*)-1-(1-methyl-2,6-dioxocyclohexyl)-5-oxohexan-3-yl)-2-oxocyclopentane-1-carboxylate (240e)

Michael acceptor (200 mg, 0.90 mmol, 1.0 equiv.) and bis(oxazoline)copper(II) complex (78 mg, 0.11 mmol, 0.1 equiv.) were cooled to -10 °C. Michael donor (0.27 mL, 1.80 mmol, 2 equiv.) was then added and the reaction mixture was stirred neat at -10 °C for 24 hours. The reaction mixture was purified directly by column chromatography (grad. 20%→33% EtOAc in hexanes) to afford ethyl (*R*)-1-((*R*)-1-(1-methyl-2,6-dioxocyclohexyl)-5-oxohexan-3-yl)-2-oxocyclopentane-1-carboxylate (295 mg, 0.78 mmol, 86% yield, 20:1 dr, 95% ee) as a colorless oil. $[\alpha]^{26}_{D}$ = -30.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 4.07 (q, *J* = 7.2 Hz, 2H), 2.90 (dd, *J* = 5.6, 18.4 Hz, 1H), 2.64-2.58 (m, 4H), 2.46-2.42 (m, 2H), 2.31-2.17 (m, 3H), 2.10 (s, 3H), 1.97-1.82 (m, 5H), 1.74-1.69 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.15 (s, 3H), 1.09-1.02 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 214.4, 210.1, 210.1, 207.9, 170.2, 65.5, 63.8, 61.4, 45.0, 38.4, 37.8, 37.8, 36.9, 35.3, 31.7, 30.1, 27.2, 20.1, 19.3, 17.6, 14.0; HRMS (ESI) *m/z* calcd for $C_{21}H_{31}O_6$ [M+H]$^+$ 379.2115, found 379.2116; IR (thin film, cm^{-1}) 2963, 1713, 1692, 1364, 1224, 1160. Enantiopurity was determined to be 95% ee by chiral HPLC (DAICEL CHIRALPAK AD-H, 25 cm x 4.6 mm, hexanes/2-proponal = 90/10, flow rate = 1 mL/min, λ = 291.0 nm, RT(minor) = 13.0 min, RT(major) = 15.9 min).



ethyl (*R*)-1-((*R*)-4-methyl-2-oxooctan-4-yl)-2-oxocyclopentane-1-carboxylate (248b)

Michael acceptor (150 mg, 1.19 mmol, 1.0 equiv.) and bis(oxazoline)copper(II) complex (100 mg, 0.12 mmol, 0.1 equiv.) were cooled to -10 °C. Michael donor (0.19 mL, 1.31 mmol, 1.1 equiv.) was then added and the reaction mixture was stirred neat at -10 °C for 48 hours. The reaction mixture was purified directly by column chromatography (grad. 0%→10% EtOAc in hexanes) to afford ethyl (*R*)-1-((*R*)-4-methyl-2-oxooctan-4-yl)-2-oxocyclopentane-1-carboxylate (295 mg, 1.05 mmol, 88% yield, 91% ee) as a colorless oil. $[\alpha]^{26}_{D}$ = -58.5 (*c* 1.0, $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$) δ 4.10 (q, *J* = 7.0 Hz, 2H), 2.95 (dd, *J* = 6.3, 18.2 Hz, 1H), 2.62-2.58 (m, 1H), 2.53-2.50 (m, 1H), 2.33-2.22 (m, 3H), 2.11 (s, 3H), 2.02-1.87 (m, 3H), 1.30-1.11(m, 9H), 0.84 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 214.6, 208.0, 170.4, 64.0, 61.3, 45.2, 38.6, 37.1, 31.7, 31.5, 30.2, 29.9, 22.7, 19.3, 14.0, 13.9; HRMS (ESI) *m/z* calcd for $C_{16}H_{27}O_4$ $[M+H]^+$ 283.1904, found 283.1902; IR (thin film, cm^{-1}) 2957, 1714, 1222, 1156. Enantiopurity was determined to be 91% ee by chiral HPLC (DAICEL CHIRALPAK OD-H, 25 cm x 4.6 mm, hexanes/2-proponal = 99/1, flow rate = 1 mL/min, λ = 295.0 nm, RT(major) = 7.5 min, RT(minor) = 9.4 min).

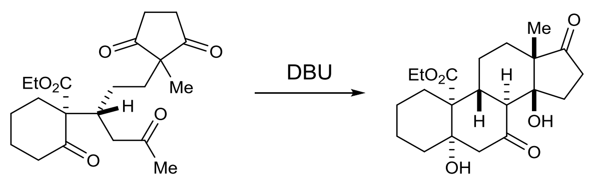


ethyl (*R*)-1-((*R*)-4-methyl-2-oxooctan-4-yl)-2-oxocyclohexane-1-carboxylate (248a)

Michael acceptor (141 mg, 1.12 mmol, 1.0 equiv.) and bis(oxazoline)copper(II) complex (95 mg, 0.11 mmol, 0.1 equiv.) were cooled to -10 °C. Michael donor (0.20 mL, 1.23 mmol, 1.1 equiv.) was then added and the reaction mixture was stirred neat at -10 °C for 48 hours. The reaction mixture was purified directly by column chromatography (grad. 0%→10% EtOAc in hexanes) to afford ethyl (R)-1-((R)-4-methyl-2-oxooctan-4-yl)-2-oxocyclohexane-1-carboxylate (318 mg, 1.07 mmol, 96% yield, 10:1 dr, 92% ee) as a colorless oil. $[\alpha]^{26}_{D}$ = +14.7 (*c* 1.0, $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$) δ 4.17-4.12 (m, 1H), 4.10-4.05 (m, 1H), 2.70-2.67 (m, 1H), 2.55 (dd, *J* = 4.9, 17.5 Hz, 1H), 2.42-2.35 (m, 3H), 2.28 (dd, *J* = 5.6, 18.2 Hz, 1H), 2.09 (s, 3H), 1.92-1.89 (m, 1H), 1.77-1.75 (m, 1H), 1.62-1.58 (m, 3H), 1.34-1.08 (m, 9H), 0.82 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 207.7, 207.4, 171.7, 64.5, 61.2, 45.6, 41.2, 36.1, 32.7, 31.8, 30.3, 29.9, 26.9, 22.8, 22.2, 14.0, 14.0; HRMS (ESI) *m/z* calcd for $C_{17}H_{29}O_4$ $[M+H]^+$ 297.2060, found 297.2063; IR (thin film, cm^{-1}) 2936, 1708, 1363, 1205, 1134. Enantiopurity was determined to be 94% ee by chiral

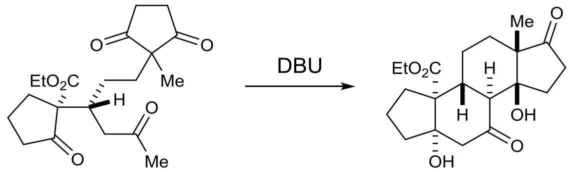
HPLC (DAICEL CHIRALPAK AD-H, 25 cm x 4.6 mm, hexanes/2-proponal = 99.5/0.5, flow rate = 1 mL/min, λ = 285.0 nm, RT(minor) = 17.4 min, RT(major) = 18.6 min).

General procedure for double aldol cyclizations utilizing DBU: Michael adduct (1.0 equiv.) was dissolved in THF (0.1 M). DBU (1.0 equiv.) was added and the reaction mixture was heated overnight at 60 °C. THF was removed by concentrating *in vacuo* and the reaction mixture was purified directly by column chromatography.



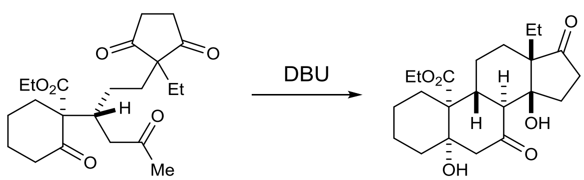
ethyl (5*S*,8*S*,9*R*,10*R*,13*S*,14*S*)-5,14-dihydroxy-13-methyl-7,17-dioxohexadecahydro-10*H*-cyclopenta[a]phenanthrene-10-carboxylate (242a)

Michael adduct (51 mg, 0.13 mmol, 1.0 equiv.) was dissolved in THF (1.3 mL, 0.1 M). DBU (20 µL, 0.13 mmol, 1.0 equiv.) was added and the reaction mixture was heated overnight at 60 °C. THF was removed by concentrating *in vacuo* and the reaction mixture was purified directly by column chromatography (grad. 10%→20% acetone in hexanes) to afford ethyl (5*S*,8*S*,9*R*,10*R*,13*S*,14*S*)-5,14-dihydroxy-13-methyl-7,17-dioxohexadecahydro-10*H*-cyclopenta[a]phenanthrene-10-carboxylate (41 mg, 0.11 mmol, 80% yield, 94% ee) as a white solid. $[\alpha]^{25}_{D}$ = -8.8 (*c* 0.9, $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$) δ 4.29 (s, 1H), 4.21-4.13 (m, 2H), 3.62 (d, *J* = 12.4 Hz, 1H), 2.86 (d, *J* = 11.8 Hz, 1H), 2.56-2.50 (m, 1H), 2.31 (d, *J* = 12.4 Hz, 1H), 2.24-2.14 (m, 5H), 2.09 (td, *J* = 3.9, 14.1 Hz, 1H), 2.01 (dt, *J* = 3.4, 14.0 Hz, 1H), 1.96-1.93 (m, 1H), 1.72 (dq, *J* = 3.1, 13.1 Hz, 1H), 1.58-1.43 (m, 5H), 1.34-1.29 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.01 (s, 3H), 0.86 (qd, *J* = 3.9, 13.5 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 218.2, 212.2, 174.1, 77.6, 74.9, 61.1, 55.1, 54.0, 54.0, 53.9, 53.7, 37.0, 35.5, 34.7, 31.2, 29.0, 25.0, 21.0, 20.2, 19.4, 14.2, 14.1; HRMS (ESI) *m/z* calcd for $C_{21}H_{30}O_6$ $[M+Na]^+$ 401.1935, found 401.1935; IR (thin film, cm^{-1}) 3442 (br), 2939, 1693, 1225, 1041. Enantiopurity was determined to be 94% ee by chiral HPLC (DAICEL CHIRALPAK AD-H, 25 cm x 4.6 mm, hexanes/2-proponal = 85/15, flow rate = 1 mL/min, λ = 216.0 nm, RT(minor) = 10.5 min, RT(major) = 15.7 min).



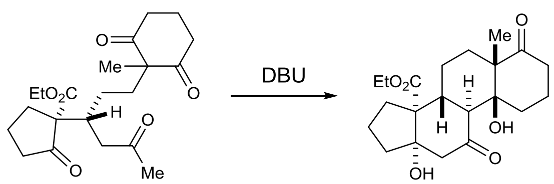
ethyl (3a*R*,3b*R*,5a*S*,8a*S*,8b*S*,10a*S*)-8a,10a-dihydroxy-5a-methyl-6,9-dioxotetradecahydrodi-cyclopenta[a,f]naphthalene-3a(1*H*)-carboxylate (242d)

Michael adduct (69 mg, 0.19 mmol, 1.0 equiv.) was dissolved in THF (1.9 mL, 0.1 M). DBU (28 µL, 0.19 mmol, 1.0 equiv.) was added and the reaction mixture was heated overnight at 60 °C. THF was removed by concentrating *in vacuo* and the reaction mixture was purified directly by column chromatography (grad. 10%→20% acetone in hexanes) to afford ethyl (3a*R*,3b*R*,5a*S*,8a*S*,8b*S*,10a*S*)-8a,10a-dihydroxy-5a-methyl-6,9-dioxotetradecahydrodicyclopenta[a,f]naphthalene-3a(1*H*)-carboxylate (59 mg, 0.16 mmol, 86% yield, 96% ee) as a white solid. $[\alpha]^{26}_{D}$ = -7.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR (700MHz, $CDCl_3$) δ 4.39 (s,1H), 4.29 (dq, *J* = 7.2, 10.9 Hz, 1H), 4.15 (dq, *J* = 7.2, 10.9 Hz, 1H), 3.40 (d, *J* = 12.3 Hz, 1H), 2.68 (d, *J* = 12.1 Hz, 1H), 2.66 (d, *J* = 12.1 Hz, 1H), 2.57-2.51 (m, 2H), 2.20-2.11 (m, 3H), 2.01 (dt, *J* = 3.4, 14.0 Hz, 1H), 1.89-1.82 (m, 2H), 1.81 (s, 1H), 1.76 (dq, *J* = 3.1, 13.5 Hz, 1H), 1.73-1.65 (m, 4H), 1.31 (td, *J* = 4.1, 13.8 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.01 (s, 3H), 0.80 (qd, *J* = 3.6, 13.5 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 217.9, 212.3, 173.1, 84.5, 77.4, 61.0, 60.9, 54.1, 53.3, 51.5, 40.3, 37.0, 34.7, 31.1, 30.5, 28.7, 25.7, 19.4, 18.3, 14.3; HRMS (ES) *m/z* calcd for $C_{20}H_{28}O_6$ $[M+Na]^+$ 387.1778, found 387.1774; IR (thin film, cm^{-1}) 3479 (br), 2935, 1694, 1184, 1068. Enantiopurity was determined to be 96% ee by chiral HPLC (DAICEL CHIRALPAK OD-H, 25 cm x 4.6 mm, hexanes/2-proponal = 90/10, flow rate = 1 mL/min, λ = 295.0 nm, RT(major) = 9.5 min, RT(minor) = 15.3 min).



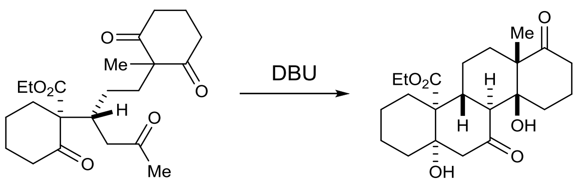
ethyl (5*S*,8*S*,9*R*,10*R*,13*S*,14*S*)-13-ethyl-5,14-dihydroxy-7,17-dioxohexadecahydro-10*H*-cyclopenta[a]phenanthrene-10-carboxylate (242f)

Michael adduct (139 mg, 0.36 mmol, 1.0 equiv.) was dissolved in THF (3.6 mL, 0.1 M). DBU (55 µL, 0.36 mmol, 1.0 equiv.) was added and the reaction mixture was heated overnight at 60 °C. THF was removed by concentrating *in vacuo* and the reaction mixture was purified directly by column chromatography (grad. 10%→20% acetone in hexanes) to afford ethyl (5*S*,8*S*,9*R*,10*R*,13*S*,14*S*)-13-ethyl-5,14-dihydroxy-7,17-dioxohexadecahydro-10*H*-cyclo-penta[a]phenanthrene-10-carboxylate (106 mg, 0.27 mmol, 76% yield, 93% ee) as a white solid. $[\alpha]^{25}_D$ = -37.2 (*c* 0.9, $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$) δ 4.27 (s, 1H), 4.21-4.15 (m, 2H), 3.64-3.62 (m, 1H), 2.83 (d, *J* = 11.9 Hz, 1H), 2.50-2.45 (m, 1H), 2.31 (d, *J* = 12.6 Hz, 1H), 2.25-2.06 (m, 7H), 1.97-1.95(m, 1H), 1.79-1.72 (m, 2H), 1.61-1.45 (m, 2H), 1.34-1.29 (m, 1H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.17 (td, *J* = 4.2, 13.3 Hz, 1H), 0.89-0.83 (m, 1H), 0.73 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 217.0, 216.7, 207.4, 207.1, 171.5, 64.2, 61.5, 61.5, 45.1, 41.2, 36.3, 36.1, 36.1, 36.0, 33.0, 32.0, 30.1, 28.1, 26.9, 22.2, 14.0, 8.9; HRMS (ESI) *m/z* calcd for $C_{22}H_{32}O_6$ $[M+Na]^+$ 415.2091, found 415.2094; IR (thin film, cm^{-1}) 3492 (br), 2939, 1692, 1222, 1070, 1028, 756. Enantiopurity was determined to be 93% ee by chiral HPLC (DAICEL CHIRALPAK OD-H, 25 cm x 4.6 mm, hexanes/2-proponal = 90/10, flow rate = 1 mL/min, λ = 297.5 nm, RT(major) = 8.3 min, RT(minor) = 12.2 min).



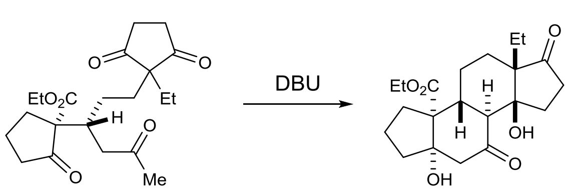
ethyl (5*S*,8*R*,9*S*,10*S*,13*S*,14*R*)-10,13-dihydroxy-5-methyl-4,11-dioxohexadecahydro-14*H*-cyclopenta[a]phenanthrene-14-carboxylate (242e)

Michael adduct (94 mg, 0.25 mmol, 1.0 equiv.) was dissolved in THF (2.5 mL, 0.1 M). DBU (37 μL, 0.25 mmol, 1.0 equiv.) was added and the reaction mixture was heated overnight at 60 °C. THF was removed by concentrating *in vacuo* and the reaction mixture was purified directly by column chromatography (grad. 10%→20% acetone in hexanes) to afford ethyl (5*S*,8*R*,9*S*,10*S*,13*S*,14*R*)-10,13-dihydroxy-5-methyl-4,11-dioxohexadecahydro-14*H*-cyclo-penta[a]phenanthrene-14-carboxylate (86 mg, 0.23 mmol, 91% yield, 99% ee) as a white solid. $[\alpha]^{26}_D$ = -43.9 (*c* 1.0, $CHCl_3$); ^1H NMR (700MHz, $CDCl_3$) δ 4.24 (dq, *J* = 7.2, 10.9 Hz, 1H), 4.19 (dq, *J* = 7.2, 10.9 Hz, 1H), 3.93 (s, 1H), 3.39 (d, *J* = 11.1 Hz, 1H), 3.14 (d, *J* = 11.9 Hz, 1H), 2.59 (d, *J* = 11.1 Hz, 1H), 2.57-2.51 (m, 2H), 2.26-2.21 (m, 1H), 2.11 (td, *J* = 4.4, 14.3 Hz, 1H), 2.01 (dt, *J* = 3.2, 13.5 Hz, 1H), 1.91-1.63 (m, 9H), 1.48 (qt, *J* = 4.4, 14.1 Hz, 1H), 1.44 (td, *J* = 3.6, 13.5 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.20 (qd, *J* = 3.4, 13.5 Hz, 1H, 1.18 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 213.0, 212.8, 173.4, 85.5, 75.1, 61.9, 61.0, 54.0, 52.4, 51.2, 41.4, 36.7, 30.8, 30.7, 28.9, 24.6, 22.3, 19.8, 18.6, 14.2; HRMS (ESI) *m/z* calcd for $C_{21}H_{30}O_6$ $[M+Na]^+$ 401.1935, found 401.1935; IR (thin film, cm^{-1}) 3442 (br), 2955, 1697, 1059. Enantiopurity was determined to be 99% ee by chiral HPLC (DAICEL CHIRALPAK OJ-H, 25 cm x 4.6 mm, hexanes/2-proponal = 90/10, flow rate = 1 mL/min, λ = 295.0 nm, RT(major) = 7.7 min).



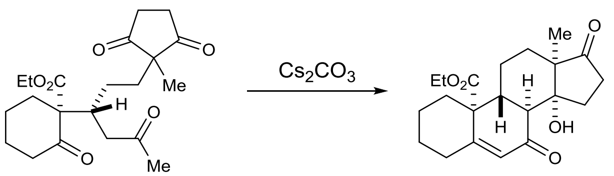
ethyl (4a*R*,4b*R*,6a*S*,10a*S*,10b*S*,12a*S*)-10a,12a-dihydroxy-6a-methyl-7,11-dioxohexadecahydrochrysene-4a(2*H*)-carboxylate (242b)

Michael adduct (60 mg, 0.15 mmol, 1.0 equiv.) was dissolved in THF (1.5 mL, 0.1 M). DBU (23 µL, 0.15 mmol, 1.0 equiv.) was added and the reaction mixture was heated overnight at 60 °C. THF was removed by concentrating *in vacuo* and the reaction mixture was purified directly by column chromatography (grad. 10%→20% acetone in hexanes) to afford ethyl (4a*R*,4b*R*,6a*S*,10a*S*,10b*S*,12a*S*)-10a,12a-dihydroxy-6a-methyl-7,11-dioxohexadecahydrochrysene-4a(2*H*)-carboxylate (39 mg, 0.10 mmol, 65% yield, 99% ee) as a white solid. ^{1}H NMR (700MHz, $CDCl_3$) δ 4.21 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 1H), 3.63-3.61 (m, 1H), 2.26 (d, *J* = 11.9 Hz, 1H), 2.58-2.52 (m, 1H), 2.33-2.20 (m, 4H), 2.11 (td, *J* = 4.4, 14.3 Hz, 1H), 2.06-1.97 (m, 3H), 1.87-1.83 (m, 1H), 1.71-1.67 (m, 1H), 1.57-1.43 (m, 8H), 1.34-1.28 (m, 5H), 1.18 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 213.2, 212.5, 174.6, 75.7, 75.1, 61.1, 55.8, 54.9, 53.9, 51.5, 37.9, 36.5, 35.2, 30.8, 29.0, 26.7, 23.8, 22.3, 21.2, 20.2, 19.8, 14.2; HRMS (ESI) *m/z* calcd for $C_{22}H_{32}O_6$ $[M+Na]^+$ 415.2091, found 415.2092; IR (thin film, cm^{-1}) 3485 (br), 2944, 1695, 1211, 1027, 1002. Enantiopurity was determined to be 99% ee by chiral HPLC (DAICEL CHIRALPAK OJ-H, 25 cm x 4.6 mm, hexanes/2-proponal = 97/3, flow rate = 1 mL/min, λ = 210.2 nm, RT(major) = 16.9 min.



ethyl (3a*R*,3b*R*,5a*S*,8a*S*,8b*S*,10a*S*)-5a-ethyl-8a,10a-dihydroxy-6,9-dioxotetradecahydrodicyclopenta[a,f]naphthalene-3a(1*H*)-carboxylate (242f)

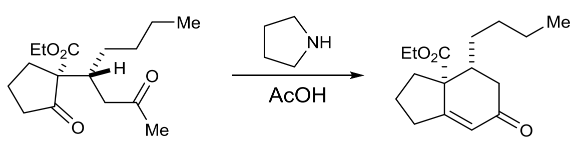
Michael adduct (91 mg, 0.24 mmol, 1.0 equiv.) was dissolved in THF (2.4 mL, 0.1 M). DBU (36 µL, 0.24 mmol, 1.0 equiv.) was added and the reaction mixture was heated overnight at 60 °C. THF was removed by concentrating *in vacuo* and the reaction mixture was purified directly by column chromatography (grad. 10%→20% acetone in hexanes) to afford ethyl (3a*R*,3b*R*,5a*S*,8a*S*,8b*S*,10a*S*)-5a-ethyl-8a,10a-dihydroxy-6,9-dioxotetradecahydrodicyclo-penta[a,f]naphthalene-3a(1*H*)-carboxylate (73 mg, 0.19 mmol, 80% yield, 92% ee) as a white solid. $[\alpha]^{26}_D$ = -31.4 (*c* 1.1, $CHCl_3$); ^1H NMR (700MHz, $CDCl_3$) δ 4.36 (s, 1H), 4.22 (dq, *J* = 7.2, 10.9 Hz, 1H), 4.16 (dq, *J* = 7.2, 10.9 Hz, 1H), 3.40 (d, *J* = 12.3 Hz, 1H), 2.66 (d, *J* = 12.1 Hz, 1H), 2.66 (d, *J* = 12.1 Hz, 1H), 2.56-2.47 (m, 2H), 2.24-2.10 (m, 4H), 1.89-1.79 (m, 4H), 1.76-1.64 (m, 5H), 1.58 (sext, *J* = 7.5 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.16 (td, *J* = 4.1, 13.6 Hz, 1H), 0.79 (qd, *J* = 3.8, 13.5 Hz, 1H), 0.73 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 216.3, 212.4, 173.1, 85.5, 77.9, 61.0, 60.9, 57.2, 53.9, 51.8, 40.2, 37.0, 34.8, 31.0, 30.5, 25.6, 25.2, 24.1, 18.3, 14.2, 7.3; HRMS (ESI) *m/z* calcd for $C_{21}H_{30}O_6$ $[M+Na]^+$ 401.1935, found 401.1932; IR (thin film, cm^{-1}) 3425 (br), 2926, 1726, 1692, 1184, 1065. Enantiopurity was determined to be 92% ee by chiral HPLC (DAICEL CHIRALPAK OD-H, 25 cm x 4.6 mm, hexanes/2-proponal = 90/10, flow rate = 1 mL/min, λ = 210.2 nm, RT(major) = 9.9 min, RT(minor) = 13.9 min).



ethyl (8*S*,9*R*,10*R*,13*R*,14*R*)-14-hydroxy-13-methyl-7,17-dioxo-1,2,3,4,7,8,9,11,12,13,14,15,16,17-tetradecahydro-10*H*-cyclopenta[a]phenanthrene-10-carboxylate (242a)

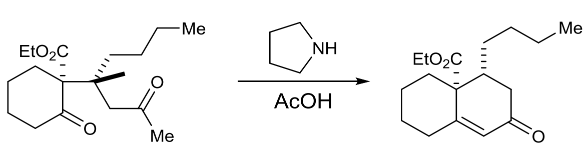
Michael adduct (215 mg, 0.57 mmol, 1.0 equiv.) was dissolved in DMF (5.7 mL, 0.1 M). Cs_2CO_3 (185 mg, 0.57 mmol, 1.0 equiv.) was added and the reaction mixture was immediately heated to 140 °C for 1 hour. The reaction mixture was allowed to cool and then was diluted with EtOAc and washed with a solution of 1:1 brine:H_2O (3 times). The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The reaction mixture was then purified by column chromatography (grad. 5%→15% acetone in hexanes) to afford ethyl (8*S*,9*R*,10*R*,13*R*,14*R*)-14-hydroxy-13-methyl-7,17-dioxo-1,2,3,4,7,8,9,11,12,13,14,15,16,17-tetradecahydro-10*H*-cyclo-penta[a]phenanthrene-10-carboxylate (121 mg, 0.34 mmol, 59% yield, 89% ee) as a white solid.

$[\alpha]^{26}_{D}$ = +211.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (700MHz, $CDCl_3$) δ 5.98 (s, 1H), 4.57 (s, 1H), 4.33-4.28 (m, 1H), 2.75 (d, *J* = 13.6 Hz, 2H), 2.54-2.48 (m, 1H), 2.46-2.43 (m, 1H), 2.40-2.35 (m, 1H), 2.17-2.03 (m, 3H), 1.94-1.84 (m, 3H), 1.80-1.77 (m, 1H), 1.58 (qt, *J* = 3.4, 13.5 Hz, 1H), 1.44 (tt, *J* = 3.8, 13.2 Hz, 1H), 1.39 (dt, *J* = 3.4, 14.0 Hz, 1H), 1.33-1.25 (m, 4H), 1.23-1.12 (m, 2H), 1.04 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 219.9, 201.7, 170.3, 164.3, 126.7, 80.4, 61.6, 52.9, 52.2, 48.6, 45.3, 36.6, 34.9, 32.8, 30.9, 27.7, 26.5, 23.2, 22.1, 14.5, 12.8; HRMS (ESI) *m/z* calcd for $C_{21}H_{28}O_5$ $[M+Na]^+$ 383.1829, found 383.1826; IR (thin film, cm^{-1}) 3482 (br), 2936, 1727, 1667, 1201, 1184. Enantiopurity was determined to be 89% ee by chiral HPLC (DAICEL CHIRALPAK AD-H, 25 cm x 4.6 mm, hexanes/2-proponal = 90/10, flow rate = 1 mL/min, λ = 240.0 nm, RT(minor) = 9.9 min, RT(major) = 12.0 min).



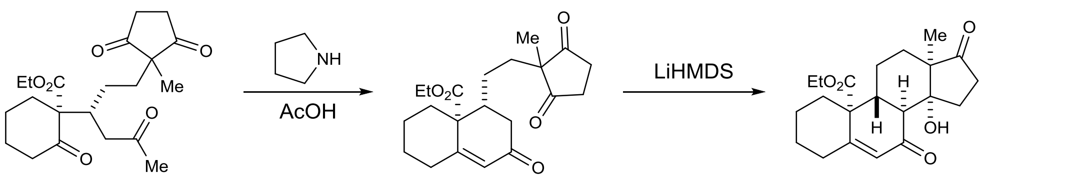
ethyl (3a*R*,4*R*)-4-butyl-6-oxo-1,2,3,4,5,6-hexahydro-3a*H*-indene-3a-carboxylate (269b)[15]

Michael adduct (117 mg, 0.41 mmol, 1.0 equiv.) was dissolved in EtOAc (0.82 mL, 0.5 M). Pyrrolidine (29 µL, 0.41 mmol, 1.0 equiv.) and AcOH (27 µL, 0.41 mmol, 1.0 equiv.) were added and the reaction mixture was stirred overnight. The reaction mixture was concentrated *in vacuo* and purified directly by column chromatography (grad. 0%→10% EtOAc in hexanes) to afford ethyl (3a*R*,4*R*)-4-butyl-6-oxo-1,2,3,4,5,6-hexahydro-3a*H*-indene-3a-carboxylate (59 mg, 0.25 mmol, 62% yield, 90% ee) as a yellow oil. $[\alpha]^{27}_{D}$ = +201.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR (700MHz, $CDCl_3$) δ 5.99 (s, 1H), 4.21-4.11 (m, 2H), 2.77 (dd, *J* = 6.8, 12.4 Hz, 1H), 2.66-2.61 (m, 1H), 2.54-2.49 (m, 1H), 2.46 (dd, *J* = 4.8, 17.5 Hz, 1H), 2.32-2.27 (m, 1H), 1.99-1.95 (m, 1H), 1.86-1.82 (m, 1H), 1.75-1.71 (m, 1H), 1.63-1.59 (m, 1H), 1.42-1.14 (m, 10H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 199.9, 171.2, 170.1, 124.3, 61.4, 59.0, 44.8, 39.4, 36.3, 31.9, 30.9, 29.3, 22.6, 21.5, 14.2, 13.9; HRMS (ESI) *m/z* calcd for $C_{16}H_{24}O_3$ $[M+H]^+$ 265.1798, found 265.1795; IR (thin film, cm^{-1}) 2932, 2871, 1721, 1206, 912, 729. Enantiopurity was determined to be 90% ee by chiral HPLC (DAICEL CHIRALPAK OD-H, 25 cm x 4.6 mm, hexanes/2-proponal = 99/1, flow rate = 1 mL/min, λ = 215.0 nm, RT(minor) = 13.3 min, RT(major) = 15.2 min).



ethyl (4a*R*,5*R*)-5-butyl-7-oxo-1,3,4,5,6,7-hexahydronaphthalene-4a(2*H*)-carboxylate (269a)

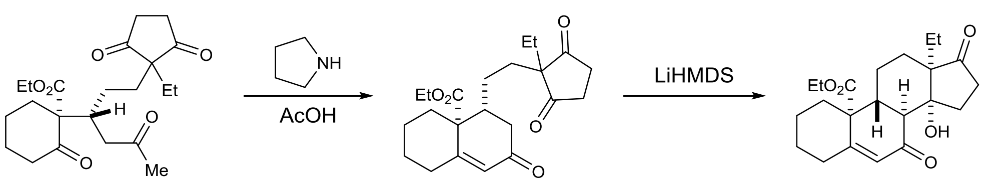
Michael adduct (90 mg, 0.30 mmol, 1.0 equiv.) was dissolved in EtOAc (0.60 mL, 0.5 M). Pyrrolidine (26 µL, 0.30 mmol, 1.0 equiv.) and AcOH (18 µL, 0.30 mmol, 1.0 equiv.) were added and the reaction mixture was stirred overnight. The reaction mixture was concentrated *in vacuo* and purified directly by column chromatography (grad. 0%→10% EtOAc in hexanes) to afford ethyl (4a*R*,5*R*)-5-butyl-7-oxo-1,3,4,5,6,7-hexahydronaphthalene-4a(2*H*)-carboxylate (71 mg, 0.26 mmol, 84% yield, 94% ee) as a yellow oil. $[\alpha]^{27}_{D}$ = +134.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (700MHz, $CDCl_3$) δ 5.94 (s, 1H), 4.24-4.15 (m, 2H), 2.75 (dd, *J* = 2.0, 13.5 Hz, 1H), 2.48-2.41 (m, 2H), 2.31 (dd, *J* = 14.0, 16.3 Hz, 1H), 2.07 (tdd, *J* = 1.7, 5.1, 14.1 Hz, 1H), 1.90-1.85 (m, 2H), 1.77-1.69 (m, 2H), 1.58 (qt, *J* = 3.6, 13.6 Hz, 1H), 1.43-1.31 (m, 3H), 1.30-1.22 (m, 4H), 1.16-1.07 (m, 2H), 0.93-0.85 (m, 4H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 199.5, 171.0, 163.5, 126.4, 61.1, 52.4, 43.9, 39.2, 36.2, 35.1, 29.7, 29.5, 26.7, 23.3, 22.6, 14.3, 13.9; HRMS (ESI) *m/z* calcd for $C_{17}H_{26}O_3$ $[M+H]^+$ 279.1955, found 279.1956; IR (thin film, cm^{-1}) 2934, 1727, 1670, 1195, 1023, 857. Enantiopurity was determined to be 94% ee by chiral HPLC (DAICEL CHIRALPAK AD-H, 25 cm x 4.6 mm, hexanes/2-proponal = 98/2, flow rate = 1 mL/min, λ = 236.0 nm, RT(minor) = 7.8 min, RT(major) = 16.0 min).



ethyl (8*S*,9*R*,10*R*,13*R*,14*R*)-14-hydroxy-13-methyl-7,17-dioxo-1,2,3,4,7,8,9,11,12,13,14,15,16,17-tetradecahydro-10*H*-cyclopenta[a]phenanthrene-10-carboxylate (241a)

Michael adduct (247 mg, 0.65 mmol, 1.0 equiv.) was dissolved in EtOAc (6.5 mL, 0.1 M). Pyrrolidine (54 µL, 0.65 mmol, 1.0 equiv.) and AcOH (40 µL, 0.65 mmol, 1.0 equiv.) were added and the reaction mixture was stirred overnight. The reaction mixture was diluted with EtOAc and washed with aq. $NaHCO_3$ and brine. The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The reaction mixture was then purified by column chromatography (grad. 20%→40% EtOAc in hexanes) to afford ethyl (4a*R*,5*R*)-5-(2-(1-methyl-2,5-dioxocyclopentyl)ethyl)-7-oxo-1,3,4,5,6,7-hexahydronaphthalene-4a(2*H*)-carboxylate (169 mg, 0.47 mmol, 19:1 dr, 72% yield, 16:1 dr, 92% ee). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.93 (s, 1H), 4.18-4.15 (m, 2H), 2.85-2.78 (m, 2H), 2.73-2.62 (m, 3H), 2.42-2.38 (m, 2H), 2.27-2.23 (m, 1H), 2.09-2.04 (m, 1H), 1.85-1.83 (m, 1H), 1.79-1.72 (m, 3H), 1.57-1.45 (m, 3H), 1.38 (qt, , *J* = 3.5, 13.3 Hz, 1H), 1.23 (t, , *J* = 7.0 Hz, 3H), 1.11 (s, 3H), 1.10-1.04 (m, 1H), 0.72 (qd, , *J* = 4.9, 12.6 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 216.2, 216.0, 198.5, 170.7, 163.0, 126.4, 61.3, 56.5, 52.3, 44.4, 38.8, 36.1, 35.2, 35.2, 34.9, 33.0, 26.5, 25.0, 23.2, 19.9, 14.3; HRMS (ESI) *m/z* calcd for $C_{21}H_{28}O_5$ $[M+H]^+$ 361.2010, found 361.2010. Enantiopurity was determined to be 92% ee by chiral HPLC (DAICEL CHIRALPAK AD-H, 25 cm x 4.6 mm, hexanes/2-proponal = 85/15, flow rate = 1 mL/min, λ = 210.2 nm, RT(minor) = 10.4 min, RT(major) = 12.6 min).

ethyl (4a*R*,5*R*)-5-(2-(1-methyl-2,5-dioxocyclopentyl)ethyl)-7-oxo-1,3,4,5,6,7-hexahydronaphthalene-4a(2*H*)-carboxylate (22 mg, 0.061 mmol, 1.0 equiv.) was dissolved in tolune (0.61 mL, 0.1 M) and cooled to -78 ºC. A solution of LiHMDS (10 mg, 0.061 mmol, 1.0 equiv.) in THF was added slowly. The reaction mixture was then stirred for 15 minutes at -78 ºC. The reaction mixture was then immediatedly heated to 60 ºC and stirred for 30 minutes. THF was removed by concentrating *in vacuo* and the reaction mixture was purified directly by column chromatography (grad. 5%→15% acetone in hexanes) to afford ethyl (8*S*,9*R*,10*R*,13*R*,14*R*)-14-hydroxy-13-methyl-7,17-dioxo-1,2,3,4,7,8,9,11,12,13,14,15,16,17-tetradecahydro-10*H*-cyclopenta[a]phenanthrene-10-carboxylate (13 mg, 0.036 mmol, 59% yield, 89% ee) as a white solid.

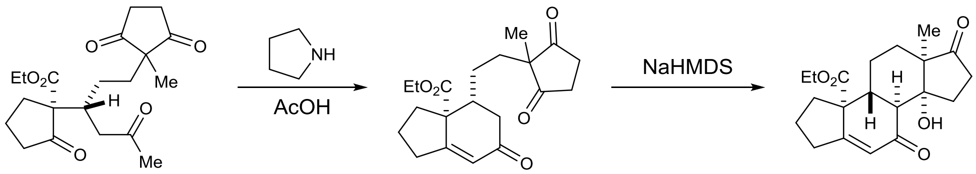


ethyl (8*S*,9*R*,10*R*,13*R*,14*R*)-13-ethyl-14-hydroxy-7,17-dioxo-1,2,3,4,7,8,9,11,12,13,14,15,16,17-tetradecahydro-10*H*-cyclopenta[a]phenanthrene-10-carboxylate (241b)

Michael adduct (518 mg, 1.32 mmol, 1.0 equiv.) was dissolved in EtOAc (13 mL, 0.1 M). Pyrrolidine (110 µL, 1.32 mmol, 1.0 equiv.) and AcOH (82 µL, 1.32 mmol, 1.0 equiv.) were added and the reaction mixture was stirred overnight. The reaction mixture was diluted with EtOAc and washed with aq. $NaHCO_3$ and brine. The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The reaction mixture was then purified by column chromatography (grad. 20%→40% EtOAc in hexanes) to afford ethyl (4a*R*,5*R*)-5-(2-(1-ethyl-2,5-dioxocyclopentyl)ethyl)-7-oxo-1,3,4,5,6,7-hexahydronaphthalene-4a(2*H*)-carboxylate (328 mg, 0.60 mmol, 19:1

dr, 56% yield, 88% ee). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.92 (s, 1H), 4.17-4.13 (m, 2H), 2.76-2.59 (m, 5H), 2.42-2.38 (m, 2H), 2.26-2.21 (m, 1H), 2.08-2.03 (m, 1H), 1.84-1.82 (m, 1H), 1.78-1.71 (m, 3H), 1.63 (q, *J* = 7.0 Hz, 2H), 1.51-1.44 (m, 3H), 1.37 (qt, *J* = 3.5, 12.6 Hz, 1H), 1.27-1.19 (m, 1H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.05 (td, *J* = 4.2, 13.3 Hz, 1H), 0.78 (t, *J* = 7.7 Hz, 3H), 0.67 (qd, *J* = 4.6, 11.2 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 216.9, 216.6, 198.5, 170.7, 163.0, 126.4, 61.3, 61.3, 52.3, 44.5, 38.8, 36.2, 36.1, 34.9, 31.7, 28.9, 26.5, 25.0, 23.1, 14.3, 8.8; HRMS (ESI) *m/z* calcd for $C_{22}H_{30}O_5$ $[M+H]^+$ 375.2166, found 375.2169. Enantiopurity was determined to be 88% ee by chiral HPLC (DAICEL CHIRALPAK AD-H, 25 cm x 4.6 mm, hexanes/2-proponal = 85/15, flow rate = 1 mL/min, λ = 223.0 nm, RT(minor) = 8.5 min, RT(major) = 11.0 min).

ethyl (4a*R*,5*R*)-5-(2-(1-ethyl-2,5-dioxocyclopentyl)ethyl)-7-oxo-1,3,4,5,6,7-hexahydronaphthalene-4a(2*H*)-carboxylate (33 mg, 0.088 mmol, 1.0 equiv.) was dissolved in tolune (0.88 mL, 0.1 M) and cooled to -78 ºC. A solution of LiHMDS (15 mg, 0.88 mmol, 1.0 equiv.) in THF was added slowly. The reaction mixture was then stirred for 15 minutes at -78 ºC. The reaction mixture was then immediatedly heated to 60 ºC and stirred for 45 minutes. THF was removed by concentrating *in vacuo* and the reaction mixture was purified directly by column chromatography (grad. 5%→15% acetone in hexanes) to afford ethyl (8*S*,9*R*,10*R*,13*R*,14*R*)-13-ethyl-14-hydroxy-7,17-dioxo-1,2,3,4,7,8,9,11,12,13,14,15,16,17-tetradecahydro-10*H*-cyclopenta[a]phenanthrene-10-carboxylate (17 mg, 0.045 mmol, 52% yield, 88% ee) as a white solid. ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.97 (s, 1H), 4.52 (s, 1H), 4.29 (dq, *J* = 7.0, 10.5 Hz, 1H), 4.22 (dq, *J* = 7.0, 10.5 Hz, 1H), 2.80 (d, *J* = 13.3 Hz, 1H), 2.75-2.73 (m, 1H), 2.52-2.43 (m, 2H), 2.35-2.30 (m, 1H), 2.12-2.04 (m, 3H), 1.94-1.88 (m, 2H), 1.85-1.77 (m, 3H), 1.73 (dt, *J* = 2.8, 14.0Hz, 1H), 1.58 (dt, *J* = 3.5, 14.0 Hz, 1H), 1.43 (qt, *J* = 3.9, 14.1 Hz, 1H), 1.35 (sext, *J* = 7.4 Hz, 1H), 1.29 (t, *J* = 7.7 Hz, 3H), 1.21-1.13 (m, 2H), 1.11-1.07 (m, 1H), 1.06 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 220.3, 201.9, 170.3, 164.1, 126.8, 81.6, 61.6, 54.3, 52.2, 48.6, 45.3, 36.6, 34.8, 33.3, 28.0, 26.7, 26.5, 23.2, 22.0, 20.3, 14.4, 8.9; HRMS (ESI) *m/z* calcd for $C_{22}H_{30}O_5$ $[M+H]^+$ 375.2166, found 375.2166; IR (thin film, cm^{-1}) 3517 (br), 2938, 1730, 1654, 1185. Enantiopurity was determined to be 88% ee by chiral HPLC (DAICEL CHIRALPAK AD-H, 25 cm x 4.6 mm, hexanes/2-proponal = 90/10, flow rate = 1 mL/min, λ = 225.0 nm, RT(minor) = 8.1 min, RT(major) = 10.2 min).



ethyl (3a*R*,3b*R*,5a*R*,8a*R*,8b*S*)-8a-hydroxy-5a-methyl-6,9-dioxo-2,3,3b,4,5,5a,6,7,8,8a,8b,9-dodecahydrodicyclopenta[a,f]naphthalene-3a(1*H*)-carboxylate (269c)

Michael adduct (390 mg, 1.07 mmol, 1.0 equiv.) was dissolved in EtOAc (10 mL, 0.1 M). Pyrrolidine (90 µL, 1.07 mmol, 1.0 equiv.) and AcOH (66 µL, 1.07 mmol, 1.0 equiv.) were added and the reaction mixture was stirred overnight. The reaction mixture was concentrated *in vacuo* and purified directly by column chromatography (grad. 0%→20% acetone in hexanes) to afford ethyl (3a*R*,4*R*)-4-(2-(1-methyl-2,5-dioxocyclopentyl)ethyl)-6-oxo-1,2,3,4,5,6-hexahydro-3a*H*-indene-3a-carboxylate (208 mg, 0.60 mmol, 56% yield). HRMS (ESI) *m/z* calcd for $C_{22}H_{30}O_5$ $[M+H]^+$ 347.1853, found 347.1857.

(3a*R*,4*R*)-4-(2-(1-methyl-2,5-dioxocyclopentyl)ethyl)-6-oxo-1,2,3,4,5,6-hexahydro-3a*H*-indene-3a-carboxylate (72 mg, 0.21 mmol, 1.0 equiv.) was dissolved in tolune (2 mL, 0.1 M) and cooled to -78 ºC. A solution of NaHMDS (46 mg, 0.25 mmol, 1.2 equiv.) in toluene was added dropwise. The reaction mixture was then stirred for 15 minutes at -78 ºC. The reaction mixture was then immediatedly heated to 110 ºC and stirred for 30 minutes. The reaction mixture was then filtered through a plug of silica gel and washed with EtOAc to afford ethyl (3a*R*,3b*R*,5a*R*,8a*R*,8b*S*)-8a-hydroxy-5a-methyl-6,9-dioxo-2,3,3b,4,5,5a,6,7,8,8a,8b,9-dodecahydrodicyclopenta[a,f]naphthalene-3a(1*H*)-carboxylate (43 mg, 0.34 mmol, 60% yield, 20:1 dr, 92% ee) as a white solid. $[\alpha]^{25}_D$ = +31.8 (*c* 0.4, $CHCl_3$); ^1H NMR (700MHz, $CDCl_3$) δ 6.01 (s, 1H), 4.81 (s, 1H), 4.26 (dq, *J* = 7.2, 10.9 Hz, 1H), 4.19 (dq, *J* = 7.2, 10.9 Hz, 1H), 2.77-2.73 (m, 2H), 2.71-2.67 (m, 1H), 2.58-2.49 (m, 2H), 2.37 (ddd, *J* = 3.4, 7.3, 19.1 Hz, 1H), 2.04-2.01 (m, 2H), 1.96-1.86 (m, 2H), 1.77-1.71 (m, 2H), 1.53 (qd, *J* = 3.8, 13.5 Hz, 1H), 1.45-1.37 (m, 2H), 1.33-1.25 (m, 5H), 1.07 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ219.9, 202.6, 171.2, 170.4, 124.3, 80.2, 61.8, 58.5, 53.2, 48.7, 46.7, 36.4, 32.9, 30.9, 30.8, 27.7, 23.5, 21.4, 14.3, 13.0; HRMS (ESI) *m/z* calcd for $C_{20}H_{26}O_5$ $[M+H]^+$ 347.1853, found 347.1851; IR (thin film, cm^{-1}) 3458 (br), 2936, 1731, 1645, 1391, 1209, 1046, 732. Enantiopurity was determined to be 92% ee by chiral HPLC (DAICEL CHIRALPAK OJ-H, 25 cm x 4.6 mm, hexanes/2-proponal = 95/5, flow rate = 1 mL/min, λ = 245.0 nm, RT(major) = 19.9 min, RT(minor) = 33.2 min).

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