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 sulfonylephosphonate 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 sulfonylephosphonate reagents for the synthesis of unsymmetrical all trans-polyenes. Selective metalation of sulfonylephosphonate 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.

1.2. Brief Overview of Polyenes in Nature

An important class of polyenes are retinoids (Figure 1.1). 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. 9-cis-Retinoic acid (4) is a FDA-approved anti-cancer agent for the treatment of Kaposi’s sarcoma. 13-cis-Retinoic acid (5) is used as an acne drug. It is worth noting that as a result of retinoic acid’s 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.](image-url)
Another important class of polyenes are the polyene macrolide antimycotics (Figure 1.2).\textsuperscript{6} Polyenes in this group are typically obtained from \textit{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.\textsuperscript{7} Natamycin is also an anti-fungal drug, but is also used as a food preservative.\textsuperscript{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.\textsuperscript{9} Polyene macrolide antimycotics have also been widely-studied and synthetically targeted due to their unique properties.

\textbf{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,\textsuperscript{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](image)

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

Scheme 1.5. Brückner and Sorg synthesis of xerulenic acid by successive Negish 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). 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 Suzuki-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.
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 haloalkenylboronic 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

\[
\begin{align*}
\text{alkali} & \quad \text{alkali} \\
\text{base} & \quad \text{base} \\
\text{acid} & \quad \text{acid}
\end{align*}
\]

\[
\begin{align*}
\text{60} & \xrightarrow{\text{alkali}} \text{61} + \text{OPPh}_3 + \text{PPPh}_3 \\
\text{64} & \xrightarrow{\text{base}} \text{65} \xrightarrow{\text{acid}} \text{66} \xrightarrow{\text{acid}} \text{67} \\
\text{67} & + \text{68 (2 equiv.)} \xrightarrow{\text{Wittig}} \text{β-carotene (26)}
\end{align*}
\]

**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 fol-
owed 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.

![Chemical diagram](image)

**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.
References


(8) Food and Drug Administration, HHS (2001). US Regulation 21 CFR s 172.155 Natamycin (pirmaricin) GPO.


(18) Denmark, S. E.; Tymonko, S. A. “Sequential Cross-Coupling of 1,4-Bissilylbutadienes: Synthesis of Unsymmetrical 1,4-Disubstituted 1,3-Butadienes” *J. Am. Chem. Soc.* **2005**, 127, 8004-8005.


Chapter 2

Synthesis of Conjugated Polyenes via Sequential Condensation of Sulfonylphosphonate and Aldehydes

2.1 Strategy to Synthesizing Unsymmetrical Polyenes by Sequential Condensations

Polyenes remain important synthetic targets due to their importance in medicine and materials science. 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. 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.

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. 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.

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(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 halides, boronic acids, stannanes, and silanes.

In 1954, Georg Wittig discovered the synthesis of olefins by a condensation reaction of aldehydes and phosphonium ylides. Since then, additional condensation reactions have been developed that involve direct olefination of aldehydes. An example is the Horner-Wadsworth-Emmons (HWE) reaction. 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 (R¹ = 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.](attachment:image.png)
formation of a (Z)-olefin. β-Alkoxyporphphonate (I-2 and I-4) then cyclizes to oxaphosphetane (I-3 and I-5), which eliminates to the resulting alkenes (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-1H-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.](image)

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 monodeprotonation 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$_{N}$2

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.

**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-sulfone, 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). An improvement from bis-sulfones, bisphosphonates were found to be soluble in common organic solvents and stable to silica gel chromatography.
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 nBuLi. 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 nBuLi 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 Sulfonylphosphonates

Based on the studies with \textit{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 \textit{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 phosphate 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 arylsulfonyl 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 selectivities 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. Evaluation of the optimal base for reactions with allylic phosphonate 89a revealed that the deprotonation of dienyl phosphonates with nBuLi 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). Using sulfonylphosphonate 93a, β-parinaric acid could be assembled from three readily available building blocks: aldehyde 102, sulfonylephosphonate 93a, and aldehyde 103. The synthesis commenced with the condensation of aldehyde 102 with sulfonylphosphonate 93a providing
allylic phosphonate 104 (70% yield, 91:9 9E,11E:9Z,11E). 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. The synthesis included 5 linear steps (6 steps total and is among the shortest approaches to β-parinaric acid. 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 sulfonylephosphonate 93a.

Given that sulfonylephosphonates 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 sulfonylephosphonates. 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 13E-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.\textsuperscript{10,14}

\textbf{Scheme 2.16.} Proposed synthesis of 13\textit{E}-\textit{β}-parinaric acid and \textit{β}-eleostearic acid from sulfonylphosphonate 93\textit{a}.

\textit{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 99\textit{a} and diene 100\textit{a} 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 100\textit{a} it was discovered that the stereochemical outcome could be altered with formation of the \textit{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 tetrazonium 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](attachment:image.png)

**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.
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 sulfonylephosphonates 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 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 (\(\delta\)) are reported in parts per million (ppm) with solvent resonance as the internal standard (CDCl\(_3\) at \(\delta\) 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 (\(\delta\)) are reported in ppm with solvent resonance as the internal standard (CDCl\(_3\) at \(\delta\) 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**

\((E)-1,4\)-bis((1-phenyl-1\(^H\)-tetrazol-5-yI)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\(_2\)CO\(_3\) (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\(_2\)O. 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\(_2\)O (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\(_3\)) \(\delta\) 7.66-7.26 (m, 10H), 6.14-6.11 (m, 2H), 4.48-4.46 (m, 4H).
(E)-1,4-bis((1-phenyl-1H-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
(NH₄)₆Mo₇O₂₄ (0.2 equiv.) in 35% H₂O₂ (0.2 M) was added. The reaction mixture was stirred
overnight and was then diluted with DCM and H₂O. The organic layer was extracted and washed
with brine, dried over MgSO₄, and then concentrated in vacuo. The reaction mixture was recrystallized from methanol/ethanol to afford (E)-1,4-bis((1-phenyl-1H-tetrazol-5-yl)sulfonyl)but-2-ene. ¹H NMR (500 MHz, CDCl₃) 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). K₂CO₃ (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:H₂O. Product crashed out of organic layer so DCM was
added. The DCM organic layer was then washed with a solution of 1:1 brine:H₂O (2 times) and
then brine. The organic layer was dried over MgSO₄, filtered, and then concentrated in vacuo to
afford (E)-1,4-bis(benzo[d]thiazol-2-ylthio)but-2-ene. ¹H NMR (500 MHz, CDCl₃) 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
(NH₄)₆Mo₇O₂₄ (0.2 equiv.) in 35% H₂O₂ (0.2 M) was added. The reaction mixture was stirred
overnight and was then diluted with DCM and H₂O. The organic layer was extracted and washed
with brine, dried over MgSO₄, and then concentrated in vacuo. The reaction mixture was recrystallized from methanol/ethanol to afford (Z)-1,4-bis((1-phenyl-1H-tetrazol-5-yl)sulfonyl)but-2-ene. ¹H NMR (500 MHz, CDCl₃) 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).
(Z)-1,4-bis((1-phenyl-1H-tetrazol-5-yl)thio)but-2-ene (84)
cis-Diol (1 equiv.) was taken in DCM (0.5 M) and cooled to 0 °C. 1-Phenyl-1H-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$_2$SO$_4$, and concentrated \textit{in vacuo}. The reaction mixture was purified by column chromatography (grad. 0%→40% EtOAc in hexanes) to afford (Z)-1,4-bis((1-phenyl-1H-tetrazol-5-yl)thio)but-2-ene. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.58-7.53 (m, 10H), 5.86-5.83 (m, 2H), 4.23-4.21 (m, 4H).

(Z)-1,4-bis((1-phenyl-1H-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$_4$)$_6$Mo$_7$O$_{24}$ (0.2 equiv.) in 35% H$_2$O$_2$ (0.2 M) was added. The reaction mixture was stirred overnight and was then diluted with DCM and H$_2$O. The organic layer was extracted and washed with brine, dried over MgSO$_4$, and then concentrated \textit{in vacuo}. The reaction mixture was recrystallized from methanol/ethanol to afford (Z)-1,4-bis((1-phenyl-1H-tetrazol-5-yl)sulfonyl)but-2-ene. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.72-7.56 (m, 10H), 6.15-6.12 (m, 2H), 5.03-4.95 (m, 4H).

tetraethyl but-2-ene-1,4-diyl(E)-bis(phosphonate) (64)
(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).
\((E)\)-diethyl (4-bromobut-2-en-1-yl)phosphonate (90)\textsuperscript{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. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta 5.86\) (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).

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

1-Phenyl-1H-tetrazole-5-thiol (9.78 g, 54.9 mmol, 1.2 equiv.) was taken in DMF (146 mL, 0.2 M). K\textsubscript{2}CO\textsubscript{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\textsubscript{2}O (2 times) and then brine. The organic layer was dried over MgSO\textsubscript{4} and then concentrated \textit{in vacuo}. The unpurified reaction mixture (~16 g) was then taken in EtOH (416 mL). A solution of (NH\textsubscript{4})\textsubscript{6}Mo\textsubscript{7}O\textsubscript{24} (2.4 g, 2.01 mmol) in 35\% H\textsubscript{2}O\textsubscript{2} (10 mL) was added. The reaction mixture was stirred overnight and was then diluted with DCM and H\textsubscript{2}O. The organic layer was extracted and washed with brine, dried over MgSO\textsubscript{4}, and then concentrated \textit{in vacuo}. The reaction mixture was purified by column chromatography (grad. 50\% EtOAc in hexanes→EtOAc) to afford \((E)\)-diethyl (4-((1-phenyl-1H-tetrazol-5-yl)sulfonyl)but-2-en-1-yl)phosphonate (16.9 g, 42.2 mmol, 92\%) as a white solid. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta 7.70-7.56\) (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); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta 133.5\) (d, \(J = 8.1, 27.1\) Hz, \(J = 147.1, 148.3\) Hz, 2H)
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\(_4\)O\(_5\)PS \([M+H]^+\) 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.

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

2-Mercaptobenzothiazole (5.77 g, 34.5 mmol, 1.2 equiv.) was taken in DMF (92 mL, 0.2 M). K\(_2\)CO\(_3\) (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\(_2\)O (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\(_4\))\(_6\)Mo\(_7\)O\(_{24}\) (1.65 g, 1.42 mmol) in 35% H\(_2\)O\(_2\) (7.5 mL) was added. The reaction was allowed to stir overnight and then was diluted with DCM and H\(_2\)O. 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 \((E)-\text{diethyl } (4-(\text{benzo}[d]\text{thiazol-2-ylsulfonyl})\text{but-2-en-1-yl})\text{phosphonate (11.2 g, 28.8 mmol, quantitative) as a white solid.} \)

\[^1\text{H} \text{NMR (700 MHz, CDCl}_3\) \delta 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); \(^{13}\text{C} \text{NMR (175 MHz, CDCl}_3\) \delta 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\(_5\)PS\(_2\) \([M+H]^+\) 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.
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-1H-tetrazole-5-thiol (6.90 g, 38.7 mmol, 1.2 equiv.) was taken in DMF (102 mL, 0.2 M). K\(_2\)CO\(_3\) (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\(_2\)O (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\(_4\))\(_6\)Mo\(_7\)O\(_{24}\) (1.07g, 0.92 mmol) in 35% H\(_2\)O\(_2\) (4.7 mL) was added. The reaction mixture was allowed to stir overnight and was then diluted with DCM and H\(_2\)O. 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 calcld for C\(_{13}\)H\(_{19}\)N\(_4\)O\(_3\)PS [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 NH₄Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, and then concentrated in vacuo. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes). Isomeric purity was determined by ¹H NMR, based on coupling constants and integration, in conjunction with GC-MS.

diethyl ((2E,4E)-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, 3.18 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 NH₄Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, and then concentrated in vacuo. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford diethyl ((2E,4E)-7-phenylhepta-2,4-dien-1-yl)phosphonate (719 mg, 2.33 mmol, 88%, 90:10 EE:EZ by ¹H NMR) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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), 53.6, 34.4, 30.7 (d, J = 139.5), 16.4 (d, J = 5.8 Hz); HRMS (ES) m/z calcld for C₁₇H₂₅O₃P [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 (2E,4E)-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 NH₄Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, and then concentrated in vacuo. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford diethyl (2E,4E)-octa-2,4-dien-1-ylphosphonate (114 mg, 0.49 mmol, 76%, 91:9 EE:EZ by ¹H NMR) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) 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 (dt, 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); ¹³C NMR (125 MHz, CDCl₃) 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}O₃P [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 (2E,4E)-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 NH₄Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, and then concentrated in vacuo. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford diethyl (2E,4E)-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$_3$) $\delta$ 6.13 (ddd, $J = 5.0, 10.4, 15.2$ Hz, 1H), 6.01 (dd, $J = 10.6, 15.2$ Hz, 1H), 5.64 (ddt, $J = 2.3, 7.0, 14.9$ 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$_3$) $\delta$ 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$_3$P [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 ((2E,4E)-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$_4$Cl 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 ((2E,4E)-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$_3$) $\delta$ 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$_3$) $\delta$ 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$_3$P [M+H]$^+$ 247.1458, found 247.1461; IR (thin film, cm$^{-1}$) 3012, 2961, 2932, 2869, 1465, 1440, 1392, 1366, 1293, 1253, 1212, 1164, 1098, 1027, 989, 960, 841, 810, 782, 711.
**diethyl ((2E,4E)-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 NH₄Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, and then concentrated in vacuo. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford diethyl ((2E,4E)-5-cyclohexylpenta-2,4-dien-1-yl)phosphonate (122 mg, 0.43 mmol, 75%, 91:9 EE:EZ by ¹H NMR) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₅H₂₇O₃P [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.

**diethyl ((2E,4E)-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 NH₄Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, and then concentrated in vacuo. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford diethyl ((2E,4E)-5-cyclopentylpenta-2,4-dien-1-yl)phosphonate (137 mg, 0.50 mmol, 81%, 95:5 EE:EZ by ¹H NMR) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₅H₂₇O₃P [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.
MHz, CDCl$_3$) $\delta$ 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), 1.70 (m, 4H), 1.34-1.24 (m, 8H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 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$_3$P [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.

**diethyl ((2E,4E)-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$_4$Cl 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 ((2E,4E)-6,6-dimethylhepta-2,4-dien-1-yl)phosphonate (104 mg, 0.40 mmol, 70%, >95:5 EE:EZ by $^1$H NMR) as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_3$P [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.
diethyl ((2\textit{E},4\textit{E},6\textit{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\textsubscript{4}Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO\textsubscript{4}, and then concentrated \textit{in vacuo}. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford diethyl ((2\textit{E},4\textit{E},6\textit{E})-7-phenylhepta-2,4,6-trien-1-yl)phosphonate (67 mg, 0.22 mmol, 39%, 62:38 \textit{EE}:\textit{EZ} by \textsuperscript{1}H NMR) as a colorless oil. \textsuperscript{1}H NMR (700 MHz, CDCl\textsubscript{3}) \( \delta \) 7.39 (d, \( J = 7.5 \text{ Hz}, 2\text{H} \)), 7.31 (t, \( J = 7.5 \text{ Hz}, 2\text{H} \)), 7.22 (t, \( J = 7.3 \text{ Hz}, 1\text{H} \)), 6.80 (ddd, \( J = 5.0, 9.6, 15.7 \text{ Hz}, 1\text{H} \)), 6.57 (d, \( J = 15.4 \text{ Hz}, 1\text{H} \)), 6.36-6.33 (m, 2\text{H} ), 6.27 (ddd, \( J = 4.9, 9.9, 14.9 \text{ Hz}, 1\text{H} \)), 5.70 (dt, \( J = 7.7, 15.3 \text{ Hz}, 1\text{H} \)), 4.11 (m, 4\text{H} ), 2.69 (dd, \( J = 7.7, 22.7 \text{ Hz}, 2\text{H} \)), 1.32 (t, \( J = 7.1 \text{ Hz}, 6\text{H} \)); \textsuperscript{13}C NMR (175 MHz, CDCl\textsubscript{3}) \( \delta \) 137.7, 135.1 (d, \( J = 15.3 \text{ Hz} \)), 132.7 (d, \( J = 2.6 \text{ Hz} \)), 132.7 (d, \( J = 4.8 \text{ Hz} \)), 132.5 (d, \( J = 5.3 \text{ Hz} \)), 128.8 (d, \( J = 2.9 \text{ Hz} \)), 128.6, 127.5, 126.3, 122.6 (d, \( J = 13.1 \text{ Hz} \)), 62.0 (d, \( J = 6.8 \text{ Hz} \)), 31.1 (d, \( J = 140.0 \text{ Hz} \)), 16.5 (d, \( J = 5.9 \text{ Hz} \)); HRMS (ES) \( m/z \) calcd for C\textsubscript{17}H\textsubscript{23}O\textsubscript{3}P [M+H]\textsuperscript{+} 307.1458, found 307.1463; IR (thin film, cm\textsuperscript{-1}) 3023, 2985, 2929, 2906, 1597, 1491, 1448, 1392, 1368, 1295, 1243, 1161, 1097, 1027, 965, 864, 838, 814, 785, 752, 695.

\((\textit{E})\)-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\textsubscript{4}Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO\textsubscript{4}, and then concentrated \textit{in vacuo}. The reaction mixture was purified by column chromatography (grad. 15%→30% acetone in hexanes) to afford \((\textit{E})\)-diethyl (5-phenylpent-2-en-1-yl)phosphonate (663 mg, 2.35 mmol, 85%, >95:5 \textit{E}:\textit{Z} by \textsuperscript{1}H NMR) as a colorless oil. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.29 (m, 2\text{H} ), 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); 13C NMR (125 MHz, CDCl3) 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 C15H23O3P [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.

\[ \text{(E)-diethyl hex-2-en-1-ylphosphonate (98b)} \]

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 NH₄Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, 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 ¹H NMR) as a colorless oil. ¹H NMR (500 MHz, CDCl3) 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); ¹³C NMR (125 MHz, CDCl3) 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, J = 139.5 Hz), 25.6 (d, J = 2.4 Hz), 16.4 (d, J = 6.2 Hz), 13.4 (d, J = 3.4 Hz); HRMS (ES) m/z calcd for C9H₁₉O₃P [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.

\[ \text{(E)-diethyl non-2-en-1-ylphosphonate (98c)} \]

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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 NH₄Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, 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 ¹H NMR) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₃H₂₇O₃P [M+H]⁺ 249.1614, found 249.1614; IR (thin film, cm⁻¹) 2980, 2958, 2928, 2858, 1458, 1444, 1392, 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 NH₄Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, 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 ¹H NMR) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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\(_3\)P [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.

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\text{(E)-diethyl (3-cyclohexylallyl)phosphonate (98e)}
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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\(_4\)Cl 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\(_3\)) \( \delta \) 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\(_3\)) \( \delta \) 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\(_3\)P [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.

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\text{(E)-diethyl (3-cyclopentylallyl)phosphonate (98f)}
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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\(_4\)Cl solution and the product was extracted with
EtOAc. The organic layer was washed with brine, dried over MgSO₄, 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 ¹H NMR) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₂H₂₃O₃P [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 NH₄Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, 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 ¹H NMR) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₁H₂₃O₃P [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.
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$_4$Cl 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 ((2E,4E)-5-phenylpenta-2,4-dien-1-yl)phosphonate (98h) (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$_3$P [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$_4$Cl 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.
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. nBuLi (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 NH₄Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, 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 (99a) as a colorless oil. ¹H NMR (700 MHz, CDCl₃) 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); ¹³C NMR (175 MHz, CDCl₃) 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 C₂₀H₂₆ [M⁺] 266.2034, found 266.2039; IR (thin film, cm⁻¹) 3085, 3062, 3015, 2924, 2851, 1496, 1449, 1449, 1030, 994, 966, 754, 698.

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. nBuLi (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 NH₄Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, 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:Σother by 1H NMR) as a colorless oil. 1H NMR (500 MHz, CDCl3) 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); 13C NMR (125 MHz, CDCl3) 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 C18H24 [M]+ 240.1878, found 240.1877; IR (thin film, cm⁻¹) 3085, 3063, 3018, 2959, 2902, 2864, 1496, 1474, 1454, 1362, 1266, 1065, 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 NH₄Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, and then concentrated in vacuo. The reaction mixture was purified by column chromatography (grad. 0%→2% EtOAc in hexanes). Isomeric purity was determined by 1H NMR, based on coupling constants and integration.

![Reaction Diagram](attachment:image.png)

**((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 NH₄Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, 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.

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$_4$Cl 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.
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$_4$Cl 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$_3$) $\delta$ 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$_3$) $\delta$ 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$_5$P [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 equiv.) 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$_2$O: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$_2$SO$_4$, 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: Σ other 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 (El) 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 NH₄Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, and then concentrated in vacuo. The reaction mixture was purified by column chromatography (grad. 0%→2% EtOAc in hexanes). Isomeric purity was determined by ¹H NMR, based on coupling constants and integration.

((3Z,5E)-6-cyclohexylhexa-3,5-dien-1-yl)benzene (107a)
Following the general procedure, ((3Z,5E)-6-cyclohexylhexa-3,5-dien-1-yl)benzene was obtained in 34% yield, 10:1 ZE:EE. ¹H NMR (500 MHz, CDCl₃) 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).

((3E,5Z)-6-cyclohexylhexa-3,5-dien-1-yl)benzene (107b)
Following the general procedure ((3E,5Z)-6-cyclohexylhexa-3,5-dien-1-yl)benzene was obtained in 14% yield, 6:1 ZE:EE. ¹H NMR (500 MHz, CDCl₃) 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. ¹H NMR (500 MHz, CDCl₃) 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).
References


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. 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).

![Chemical structures of FDA-approved steroid-based drugs]

**Figure 3.1.** Selected examples of FDA-approved steroid-based drugs.
Steroids can be structurally defined by their tetracyclic core, cyclopentanopercyclophenanthrene, 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).  

![Cyclopentanopercyclophenanthrene (112) and Cholesterol (113)](image)

**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). 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.  

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Scheme 3.1. First total synthesis of a steroid was accomplished by Bachman and co-workers 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.” 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). Strophanthus extracts containing cardiotonic steroids including ouabain (122) were used by African tribes as the active principle in poison arrows. 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. Foxglove extracts containing cardiotonic steroids including digoxin (124) were used to treat “dropsy,” which is the swelling of the body. In the present day, cardiotonic steroids are still widely used in the treatment of heart disease. In fact, digoxin, used to treat atrial fibrillation and atrial flutter, is on the World Health Organization Model List of Essential Medicines.
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
Cardiotonic steroids have the overall ability to improve heart function by simultaneously slowing the heart rate and acting as an inotropic agent (increasing contractility). The main pharmacological effect of cardiotonic steroids is inhibition of the \( \text{Na}^+$/K^+\)-ATPase (sodium pump). The sodium pump pumps \( \text{Na}^+ \) out and \( \text{K}^+ \) into the cytoplasm maintaining a low concentration of \( \text{Na}^+ \) and high concentration of \( \text{K}^+ \). The sodium pump is comprised of a catalytic \( \alpha \)-subunit, a glycosylated \( \beta \)-subunit, and a \( \gamma \)-subunit. In mammalian cells, cardiotonic steroids are known to bind to the \( \alpha \)-subunit and four different isoforms (\( \alpha_1, \alpha_2, \alpha_3, \) and \( \alpha_4 \)).

The interaction of cardiotonic steroids with the sodium pump are primarily described by the \( \text{Na}^+ \) lag hypothesis and the \( \text{Na}^+$/K^+\)-ATPase “sigmalosome” hypothesis. The \( \text{Na}^+ \) lag hypothesis involves the inhibition of the sodium pump by the binding of cardiotonic steroid that increases the intracellular \( \text{Na}^+ \) concentration. This leads to an increase in the intracellular \( \text{Ca}^{2+} \) concentration via the \( \text{Na}^+$/\text{Ca}^{2+} \) exchange system ultimately causing the positive inotropic effect. 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 \( \text{Na}^+$/K^+\)-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.

Interestingly, it was hypothesized over sixty years ago that cardiotonic steroid drugs act as a substitute for an endogenous inhibitor of the sodium pump. It was finally realized twenty years ago that this hypothesis is accurate. Remarkably, it was discovered that endogenous cardiotonic steroids are the natural ligands and inhibitors of the sodium pump (notably endogenous ouabain).
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{23}
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. 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. 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). 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 Δ14,15 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 \(\alpha\)-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 enone 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 tricycle 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 \textbf{154}. In the concluding steps, the 17β-lactone ring is installed. Ketone \textbf{154} was converted to vinyl iodide \textbf{155} through Barton’s hydrazone iodination procedure. Vinyl iodide \textbf{155} was then reduced from the β-face with diimide to form the thermodynamically favored 17α-iodide \textbf{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 \textbf{157} was then converted to α-hydroxy ketone \textbf{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 \textbf{159}.

\subsection*{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).\textsuperscript{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 (\textbf{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 \textbf{160}. Silyl enol ether \textbf{160} was converted to dialdehyde \textbf{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 untreated aldehyde then underwent condensation to form diene \textbf{162} under HWE-like conditions developed by Yamamoto. The dienophile was then installed after oxidation and HWE condensation resulting in dithiane \textbf{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 \textbf{164}. The 3β-configuration was established after deacetalization followed by reduction to 3α-alcohol and inversion under Mitsunobu conditions to 3β-trifluoroacetate \textbf{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 subsequently protected to silyl ether \textbf{166}. The ABC ring system was then elaborated to include the \textit{cis}-fused D-ring. Selective axial 1,2-addition of Grignard reagent followed by selective desilylation gave alkyne \textbf{167}. Exocyclic methylene \textbf{168} was then formed after 5\textit{-exo-dig} vinyl radical cyclization of alkyne \textbf{167}, which establishes the \textit{cis} A/B, \textit{trans} B/C, and \textit{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). 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) 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 rhodixin 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-hydroxy 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 Reaction**

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. 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.

![Intramolecular Heck Reaction](image)

**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.\(^3\) 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).\(^3\) 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 co-workers revised the polycyclization method (Scheme 3.11). 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). 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. 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 phosphoranylideneketene and a final deprotection afforded the natural cardiotonic steroid ouabagenin. Deslongchamps and co-workers were successful in further elaborating oubagenin to the natural cardiotonic glycoside ouabain 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 cyclization 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).
Inoue and co-workers have applied this approach to the synthesis of ouabagenin. 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.
References


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-((triphenylphosphoranylidene)-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 (NEt₃), 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 (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, and only a few asymmetric catalysts for the construction of these motifs are known. 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). The diastereoselectivity of this reaction could be increased without affecting the yield if the reaction was run at 0 °C, 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). 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. Ultimately, 2,2’-(cyclopropane-1,1-diyl)bis(4-phenyl-4,5-dihydrooxazole)-ligand 15b was identified as the ligand of choice. 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).

![Chemical Structures](image)

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

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>CuX$_2$</th>
<th>T, °C</th>
<th>time, h</th>
<th>conversion, %</th>
<th>dr</th>
<th>ee, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>257a</td>
<td>Cu(OTf)$_2$</td>
<td>23</td>
<td>4</td>
<td>95</td>
<td>2.5:1</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>257a</td>
<td>Cu(SbF$_6$)$_2$</td>
<td>23</td>
<td>2.5</td>
<td>&gt;95</td>
<td>2.5:1</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>257b</td>
<td>Cu(SbF$_6$)$_2$</td>
<td>23</td>
<td>48</td>
<td>10</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>257c</td>
<td>Cu(SbF$_6$)$_2$</td>
<td>23</td>
<td>3</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>258</td>
<td>Cu(SbF$_6$)$_2$</td>
<td>23</td>
<td>3</td>
<td>n.d.</td>
<td>n.d.</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>259</td>
<td>Cu(SbF$_6$)$_2$</td>
<td>23</td>
<td>3</td>
<td>n.d.</td>
<td>n.d.</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>260a</td>
<td>Cu(SbF$_6$)$_2$</td>
<td>23</td>
<td>3</td>
<td>&gt;95</td>
<td>n.d.</td>
<td>71</td>
</tr>
<tr>
<td>8</td>
<td>260b</td>
<td>Cu(SbF$_6$)$_2$</td>
<td>23</td>
<td>4</td>
<td>&gt;95</td>
<td>5:1</td>
<td>81</td>
</tr>
<tr>
<td>9</td>
<td>260b</td>
<td>Cu(SbF$_6$)$_2$</td>
<td>-5</td>
<td>24</td>
<td>&gt;95</td>
<td>5:1</td>
<td>89</td>
</tr>
<tr>
<td>10</td>
<td>260b</td>
<td>Cu(SbF$_6$)$_2$</td>
<td>-10</td>
<td>48</td>
<td>&gt;95</td>
<td>5:1</td>
<td>92</td>
</tr>
<tr>
<td>11</td>
<td>260b</td>
<td>Cu(SbF$_6$)$_2$</td>
<td>-20</td>
<td>72</td>
<td>85</td>
<td>6:1</td>
<td>93</td>
</tr>
</tbody>
</table>

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

Scheme 4.5. Substrate scope of the enantioselective Michael reactions.\(^a\)

\(^a\)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.
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 pyrrolidine – 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 241a 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, Cs₂CO₃, was employed at elevated temperature. Refluxing in CH₃CN 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 Cs₂CO₃ 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 Li₂CO₃ in place of Cs₂CO₃ resulted in a
preference for 242a (entry 21).

![Diagram of chemical reactions and structures](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>conversion, % (yield, %)</th>
<th>products</th>
<th>selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D- or L-proline, DMF, rt, 24 h</td>
<td>0 - -</td>
<td>- -</td>
<td>- -</td>
</tr>
<tr>
<td>2</td>
<td>TiCl₄, NEt₃, THF, -78 °C to 0 °C</td>
<td>decomposition</td>
<td>- -</td>
<td>- -</td>
</tr>
<tr>
<td>3</td>
<td>DABCO, THF, reflux, 18 h</td>
<td>0 -</td>
<td>- -</td>
<td>- -</td>
</tr>
<tr>
<td>4</td>
<td>Hünig’s base, THF, reflux, 18 h</td>
<td>0 -</td>
<td>- -</td>
<td>- -</td>
</tr>
<tr>
<td>5⁺</td>
<td>p-TSA, toluene, reflux, 18 h</td>
<td>&gt;98 242a</td>
<td>only</td>
<td>- -</td>
</tr>
<tr>
<td>6</td>
<td>DBU, THF, reflux, 18 h</td>
<td>&gt;98 (94) 242a</td>
<td>only</td>
<td>- -</td>
</tr>
<tr>
<td>7</td>
<td>piperidine, THF, rt, 18 h</td>
<td>0 -</td>
<td>- -</td>
<td>- -</td>
</tr>
<tr>
<td>8</td>
<td>piperidine, THF, rt, 18 h</td>
<td>0 -</td>
<td>- -</td>
<td>- -</td>
</tr>
<tr>
<td>9</td>
<td>piperidine, THF, reflux, 18 h</td>
<td>&gt;98 242a</td>
<td>only</td>
<td>- -</td>
</tr>
<tr>
<td>10</td>
<td>piperidine, LiCl, THF, reflux 18 h</td>
<td>&gt;98 263, 242a, 241a, 265</td>
<td>8:10:39:43</td>
<td>- -</td>
</tr>
<tr>
<td>11</td>
<td>pyrrolidine, LiCl, THF, reflux, 18 h</td>
<td>&gt;98 241a, 265</td>
<td>52:48</td>
<td>- -</td>
</tr>
<tr>
<td>12ᵇ</td>
<td>KHDMS (1 equiv.), THF, rt, 24 h</td>
<td>&gt;98 263, 242a, 241a, 265</td>
<td>35:15:50</td>
<td>- -</td>
</tr>
<tr>
<td>13ᵇ</td>
<td>KHMDS (1 equiv.), THF, reflux, 24 h</td>
<td>&gt;98 263, 242a, 241a, 265</td>
<td>44:44:4:8</td>
<td>- -</td>
</tr>
<tr>
<td>14ᵇ</td>
<td>KHMDS (2 equiv.), THF, reflux, 30 min</td>
<td>&gt;98 (48) 241a, 264</td>
<td>1:2</td>
<td>- -</td>
</tr>
<tr>
<td>15ᵇ</td>
<td>LiHMDS (2 equiv.), THF, reflux, 30 min</td>
<td>&gt;98 (20) 241a</td>
<td>only</td>
<td>- -</td>
</tr>
<tr>
<td>16</td>
<td>Cs₂CO₃, CH₃CN, reflux, 14 h</td>
<td>&gt;98 263, 242a, 241a, 265</td>
<td>53:35:5:7</td>
<td>- -</td>
</tr>
<tr>
<td>17</td>
<td>Cs₂CO₃, CH₃CN, reflux, 20 h</td>
<td>&gt;98 263, 242a, 241a, 265</td>
<td>17:8:39:36</td>
<td>- -</td>
</tr>
<tr>
<td>18</td>
<td>Cs₂CO₃, DMF, 120 °C, 4 h</td>
<td>&gt;98 241a, 265</td>
<td>95:5</td>
<td>- -</td>
</tr>
<tr>
<td>19</td>
<td>Cs₂CO₃, DMF, 120 °C, 24 h</td>
<td>&gt;98 241a, 265</td>
<td>&gt;95:5</td>
<td>- -</td>
</tr>
<tr>
<td>20</td>
<td>Cs₂CO₃, DMF, 140 °C, 1 h</td>
<td>&gt;98 (89) 241a</td>
<td>only</td>
<td>- -</td>
</tr>
<tr>
<td>21</td>
<td>Li₂CO₃, DMF, 140 °C, 4 h</td>
<td>&gt;98 263, 242a, 241a, 265</td>
<td>10:75:8:7</td>
<td>- -</td>
</tr>
</tbody>
</table>

*Unidentified product (c.a. 30%) was formed along with 242a; bSignificant 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-workers¹³ 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 $\alpha$- or $\beta$-face, four possible transition states were anticipated (TS-5-TS-8). B-Ring enolate attacking the D-ring from the $\alpha$-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 $\beta$-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 $\beta$-face, would require the B-ring to be in a boat conformation to achieve the pseudo axial attack.\textsuperscript{14} In comparing TS-7 and TS-8, formation of 242a is favored as steroid 263 involves

\textbf{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%

![Chemical structures and reaction scheme](image)

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 Cs2CO3 at 140 °C. 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-aldo/aldol reaction to form the more thermodynamically favored natural steroid 241a.

The cyclizations with Cs2CO3 at 140 °C were studied with Michael adducts 240a-e.
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 were suitable for the effective semicyclization of chiral Michael adducts 240a, 240c, and 240d (Scheme 4.12) in good yields and no erosion of enantioselectivity. Additionally, these conditions were used for the generation of substituted Wieland-Miescher and Hajos-Parrish ketones, 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 pyrrolidine (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. Enatioselectivity is based on 241c.


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.
Diastereomeric mixtures of ABD tricycles (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. \(^\text{a} \)Ran in THF at 60 °C; \(^\text{b} \)Ran in toluene at reflux.

**Scheme 4.13.** Intramolecular aldol cyclization of semicyclized 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.

\(^{a}\)Diastereomeric mixtures of ABD tricycles (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. \(^{\text{a}}\)Ran in THF at 60 °C; \(^{\text{b}}\)Ran in toluene at reflux.
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 1H 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 1H NMR analysis. Enantiomeric excess was determined by HPLC analysis using a Waters e2695 Separations Module with a Waters 2998 photodiode array detector.

1H 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 (CDCl3...
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

(4S,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$_4$Cl solution and then saturated Na-HCO$_3$ 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 (4S,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.

(4S,4'S)-2,2'-(cyclopropane-1,1-diyl)bis(4-phenyl-4,5-dihydrooxazole) copper(II) hexafluoroantimonate (261)
(4S,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 (4S,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 H₂O (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 MgSO₄, and concentrated in vacuo to afford 3-(1-methyl-2,5-dioxocyclopentyl)propanal (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. ¹H NMR (700MHz, CDCl₃) 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); ¹³C NMR (175 MHz, CDCl₃) 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 C₁₃H₁₈O₃ [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 H₂O (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 MgSO₄, 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. 

¹H NMR (700MHz, CDCl₃) 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); 
¹³C NMR (175 MHz, CDCl₃) 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 C₁₃H₁₈O₃ [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-oxohexan-3-yl)cyclohexane-1,3-dione (3.1 g, 13.9 mmol, 84% yield) as a colorless oil. 1H NMR (700MHz, CDCl3) 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); 13C NMR (175 MHz, CDCl3) 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 C13H18O3 [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 Et2O. Alternatively, the reaction mixture can be purified directly by column chromatography.

![Chemical structure](image)

**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. [α]²⁶[D] = +15.7 (c 1.0,
**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, CDCl3) 4.01 (q, \(J = 7.0 \text{ Hz, 2H}\), 2.90 (dd, \(J = 4.9, 18.2 \text{ Hz, 1H}\), 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, \(J = 8.4 \text{ Hz, 2H}\), 1.14 (t, \(J = 7.0 \text{ Hz, 3H}\), 1.11-1.08 (m, 1H), 1.05-1.01 (m, 1H), 0.97 (s, 3H); 13C NMR (175 MHz, CDCl3) 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 C21H31O6 [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-propanol = 85/15, flow rate = 1 mL/min, \(\lambda = 282.0 \text{ nm}\), RT(minor) = 9.5 min, RT(major) = 12.8 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. [α]_{D}^{26} = -23.1 (c 1.0, CHCl₃); ¹H NMR (700 MHz, CDCl₃) 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); ¹³C NMR (175 MHz, CDCl₃) 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 C₂₁H₃₀O₆ [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-propanol = 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. [α]_{D}^{25} = +17.9 (c 1.0, CHCl3). ¹H NMR (700MHz, CDCl3) 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); ¹³C NMR (175 MHz, CDCl3) 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 calcld 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. [α]_{D}^{26} = +17.8 (c 1.2, CHCl3); ¹H NMR (700 MHz, CDCl3) δ 4.14-4.11 (m, 1H), 4.07-4.04 (m, 1H), 4.07-4.04 (m, 1H), 2.73-2.69 (m, 2H), 2.61-2.55 (m, 2H), 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); ¹³C NMR (175 MHz, CDCl3) 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 calcld 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-propanol = 85/15, flow rate = 1 mL/min, \(\lambda = 290.0\) nm, RT(minor) = 8.7 min, RT(major) = 11.4 min).

\[
\text{ethyl } (R)-1-((R)-1-(1\text{-methyl-2,6-dioxocyclohexyl})-5\text{-oxohexan-3-yl})-2\text{-oxocyclopentane-1-carboxylate (240e)}
\]

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\text{-methyl-2,6-dioxocyclohexyl})-5\text{-oxohexan-3-yl})-2\text{-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) \(\delta\) 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-propanol = 90/10, flow rate = 1 mL/min, \(\lambda = 291.0\) nm, RT(minor) = 13.0 min, RT(major) = 15.9 min).

\[
\text{ethyl } (R)-1-((R)-4\text{-methyl-2-oxooctan-4-yl})-2\text{-oxocyclopentane-1-carboxylate (248b)}
\]
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. [α]$_{26}^{D}$ = -58.5 (c 1.0, CHCl$_3$); $^1$H 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-propanol = 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. [α]$_{26}^{D}$ = +14.7 (c 1.0, CHCl$_3$); $^1$H 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-propanol = 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.


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 (5S,8S,9R,10R,13S,14S)-5,14-dihydroxy-13-methyl-7,17-dioxohexadecahydro-10H-cyclopenta[a]phenanthrene-10-carboxylate (41 mg, 0.11 mmol, 80% yield, 94% ee) as a white solid. 

\[ \alpha^2D = -8.8 \ (c \ 0.9, \ CHCl_3); \] 

\[ ^1H \text{ NMR (700 MHz, CDCl}_3) \delta 4.29 (s, 1H), 4.21-4.13 (m, 2H), 3.62 (d, J = 12.4 Hz, 1H), 2.86 (d, J = 11.8 Hz, 1H), 2.56-2.50 (m, 1H), 2.31 (d, J = 12.4 Hz, 1H), 2.24-2.14 (m, 5H), 2.09 (td, J = 3.9, 14.1 Hz, 1H), 2.01 (dt, J = 3.4, 14.0 Hz, 1H), 1.96-1.93 (m, 1H), 1.72 (dq, J = 3.1, 13.1 Hz, 1H), 1.58-1.43 (m, 5H), 1.34-1.29 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H), 1.01 (s, 3H), 0.86 (qd, J = 3.9, 13.5 Hz, 1H); \] 

\[ ^{13}C \text{ NMR (175 MHz, CDCl}_3) \delta 218.2, 212.2, 174.1, 77.6, 74.9, 61.1, 55.1, 54.0, 54.0, 53.9, 53.7, 37.0, 35.5, 34.7, 31.2, 29.0, 25.0, 21.0, 20.2, 19.4, 14.2, 14.1; \] 

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-propanol = 85/15, flow rate = 1 mL/min, λ = 216.0 nm, RT(minor) = 10.5 min, RT(major) = 15.7 min).
ethyl (3aR,3bR,5aS,8aS,8bS,10aS)-8a,10a-dihydroxy-5a-methyl-6,9-dioxotetradecahydrodicyclopenta[a,f]naphthalene-3a(1H)-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 (3aR,3bR,5aS,8aS,8bS,10aS)-8a,10a-dihydroxy-5a-methyl-6,9-dioxotetradecahydrodicyclopenta[a,f]naphthalene-3a(1H)-carboxylate (59 mg, 0.16 mmol, 86% yield, 96% ee) as a white solid. \([\alpha]^{26}_D = -7.2 \text{ (c 1.1, CHCl}_3)\); \(^1\)H NMR (700MHz, CDCl\(_3\)) \(\delta 4.39 \text{ (s,1H), 4.29 (dq, } J = 7.2, 10.9 \text{ Hz, 1H), 3.40 (d, } J = 12.3 \text{ Hz, 1H), 2.68 (d, } J = 12.1 \text{ Hz, 1H), 2.66 (d, } J = 12.1 \text{ Hz, 1H), 2.57-2.51 (m, 2H), 2.20-2.11 (m, 3H), 2.01 (dt, } J = 3.4, 14.0 \text{ Hz, 1H), 1.89-1.82 (m, 2H), 1.81 (s, 1H), 1.76 (dq, } J = 3.1, 13.5 \text{ Hz, 1H), 1.73-1.65 (m, 4H), 1.31 (td, } J = 4.1, 13.8 \text{ Hz, 1H), 1.27 (t, } J = 7.2 \text{ Hz, 3H), 1.01 (s, 3H), 0.80 (qd, } J = 3.6, 13.5 \text{ Hz, 1H); } ^{13}\text{C NMR (175 MHz, CDCl}_3\text{) } \delta 217.9, 212.3, 173.1, 84.5, 77.4, 61.0, 60.9, 54.1, 53.3, 51.5, 40.3, 37.0, 34.7, 31.1, 30.5, 28.7, 25.7, 19.4, 18.3, 14.3; \) 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-propanol = 90/10, flow rate = 1 mL/min, \(\lambda = 295.0 \text{ nm, RT(major) = 9.5 min, RT(minor) = 15.3 min).}\


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 (5S,8S,9R,10R,13S,14S)-13-ethyl-5,14-dihydroxy-7,17-dioxohexadecahydro-10H-cyclopenta[a]phenanthrene-10-carboxylate (106 mg, 0.27 mmol, 76% yield, 93% ee) as a white solid. 

\[ [\alpha]^{25}_D = -37.2 \ (c \ 0.9, \ CHCl_3) \]; \(^1\)H NMR (700 MHz, CDCl3) 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, CDCl3) 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, 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 (DAICEC CHIRALPAK OD-H, 25 cm x 4.6 mm, hexanes/2-propanol = 90/10, flow rate = 1 mL/min, \( \lambda = 297.5 \) nm, RT(major) = 8.3 min, RT(minor) = 12.2 min).


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 \textit{in vacuo} and the reaction mixture was purified directly by column chromatography (grad. 10%→20% acetone in hexanes) to afford ethyl (5S,8R,9S,10S,13S,14R)-10,13-dihydroxy-5-methyl-4,11-dioxohexadecahydro-14H-cyclopenta[a]phenanthrene-14-carboxylate (86 mg, 0.23 mmol, 91% yield, 99% ee) as a white solid. 

\[ [\alpha]^{26}_D = -43.9 \ (c \ 1.0, \ CHCl_3) \]; \(^1\)H NMR (700 MHz, CDCl3) 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, CDCl3) 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-propanol = 90/10, flow rate = 1 mL/min, \( \lambda = 295.0 \) nm, RT(major) = 7.7 min).

**ethyl (4aR, 4bR, 6aS, 10aS, 10bS, 12aS)-10a, 12a-dihydroxy-6a-methyl-7, 11-dioxohexadecahydrocrystene-4a(2H)-carboxylate (242b)**

Michael adduct (60 mg, 0.15 mmol, 1.0 equiv.) was dissolved in THF (1.5 mL, 0.1 M). DBU (23 \( \mu L \), 0.15 mmol, 1.0 equiv.) was added and the reaction mixture was heated overnight at 60 °C. THF was removed by concentrating \textit{in vacuo} and the reaction mixture was purified directly by column chromatography (grad. 10%→20% acetone in hexanes) to afford ethyl (4aR, 4bR, 6aS, 10aS, 10bS, 12aS)-10a, 12a-dihydroxy-6a-methyl-7, 11-dioxohexadecahydrocrystene-4a(2H)-carboxylate (39 mg, 0.10 mmol, 65% yield, 99% ee) as a white solid. \(^1\)H NMR (700MHz, CDCl\(_3\)) \( \delta \) 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\(_3\)) \( \delta \) 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-propanol = 97/3, flow rate = 1 mL/min, \( \lambda = 210.2 \) nm, RT(major) = 16.9 min.

**ethyl (3aR, 3bR, 5aS, 8aS, 8bS, 10aS)-5a-ethyl-8a, 10a-dihydroxy-6, 9-dioxotetradecahydrodicyclopenta[a,f]naphthalene-3a(1H)-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 (3aR,3bR,5aS,8aS,8bS,10aS)-5a-ethyl-8a,10a-dihydroxy-6,9-dioxotetradecahydrodicyclopenta[a,f]naphthalene-3a(1H)-carboxylate (73 mg, 0.19 mmol, 80% yield, 92% ee) as a white solid. [α]_{D}^{26} = -31.4 (c 1.1, CHCl₃); ¹H NMR (700MHz, CDCl₃) δ 4.36 (s, 1H), 4.22 (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); ¹³C NMR (175 MHz, CDCl₃) 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 C₂₁H₃₀O₆ [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-propanol = 90/10, flow rate = 1 mL/min, λ = 210.2 nm, RT(major) = 9.9 min, RT(minor) = 13.9 min).

ethyl (8S,9R,10R,13R,14R)-14-hydroxy-13-methyl-7,17-dioxo-1,2,3,4,7,8,9,11,12,13,14,15,16,17-tetradecahydro-10H-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). Cs₂CO₃ (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:H₂O (3 times). The organic layer was then dried over MgSO₄, filtered, and concentrated in vacuo. The reaction mixture was then purified by column chromatography (grad. 5%→15% acetone in hexanes) to afford ethyl (8S,9R,10R,13R,14R)-14-hydroxy-13-methyl-7,17-dioxo-1,2,3,4,7,8,9,11,12,13,14,15,16,17-tetradecahydro-10H-cyclopenta[a]phenanthrene-10-carboxylate (121 mg, 0.34 mmol, 59% yield, 89% ee) as a white solid.
[α]$_{26}^D$ = +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); $^1$H NMR (700MHz, CDCl$_3$) δ 5.98 (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-propanol = 99/1, flow rate = 1 mL/min, $\lambda = 215.0$ nm, RT(minor) = 13.3 min, RT(major) = 15.2 min).

**ethyl (3aR,4R)-4-butyl-6-oxo-1,2,3,4,5,6-hexahydro-3aH-indene-3a-carboxylate (269b)**

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 (3aR,4R)-4-butyl-6-oxo-1,2,3,4,5,6-hexahydro-3aH-indene-3a-carboxylate (59 mg, 0.25 mmol, 62% yield, 90% ee) as a yellow oil. [α]$_{27}^D$ = +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+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-propanol = 90/10, flow rate = 1 mL/min, $\lambda = 240.0$ nm, RT(minor) = 9.9 min, RT(major) = 12.0 min).
ethyl (4aR,5R)-5-butyl-7-oxo-1,3,4,5,6,7-hexahydropyrene-4a(2H)-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 (4aR,5R)-5-butyl-7-oxo-1,3,4,5,6,7-hexahydropyrene-4a(2H)-carboxylate (71 mg, 0.26 mmol, 84% yield, 94% ee) as a yellow oil. [α]$_{27}^D$ = +134.0 (c 1.0, CHCl$_3$); $^1$H NMR (700 MHz, 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-propanol = 98/2, flow rate = 1 mL/min, $\lambda = 236.0$ nm, RT(minor) = 7.8 min, RT(major) = 16.0 min).

ethyl (8S,9R,10R,13R,14R)-14-hydroxy-13-methyl-7,17-dioxo-1,2,3,4,7,8,9,11,12,13,14,15,16,17-tetradecahydro-10H-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 (4aR,5R)-5-(2-(1-methyl-2,5-dioxocyclopentyl)ethyl)-7-oxo-1,3,4,5,6,7-hexahydronaphthalene-4a(2H)-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), 1.09-1.04 (m, 1H), 0.72 (qd, J = 4.9, 12.6 Hz, 1H); \(^{13}\)C NMR (175 MHz, CDCl\(_3\)) \(\delta\) 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-propanol = 85/15, flow rate = 1 mL/min, \(\lambda = 210.2\) 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 toluene (0.61 mL, 0.1 M) and cooled to -78 °C. 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 °C. The reaction mixture was then immediately heated to 60 °C and stirred for 30 minutes. THF was removed by concentrating \textit{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 (13 mg, 0.036 mmol, 59\% yield, 89\% ee) as a white solid.

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 then washed with aq. NaHCO\(_3\) and brine. The organic layer was then dried over MgSO\(_4\), filtered, and concentrated \textit{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
1H 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); 13C 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-propanol = 85/15, flow rate = 1 mL/min, $\lambda = 223.0$ nm, RT(minor) = 8.5 min, RT(major) = 11.0 min).

Ethyl (4aR,5R)-5-(2-(1-ethyl-2,5-dioxocyclopentyl)ethyl)-7-oxo-1,3,4,5,6,7-hexahydonaphthalene-4a(2H)-carboxylate (33 mg, 0.088 mmol, 1.0 equiv.) was dissolved in toluene (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 immediately 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 (8S,9R,10R,13R,14R)-13-ethyl-14-hydroxy-7,17-dioxo-1,2,3,4,7,8,9,11,12,13,14,15,16,17-tetradecahydro-10H-cyclopenta[a]phenanthrene-10-carboxylate (17 mg, 0.045 mmol, 52% yield, 88% ee) as a white solid. 1H 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, $J = 2.8, 14.0$ Hz, 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); 13C 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-propanol = 90/10, flow rate = 1 mL/min, $\lambda = 225.0$ nm, RT(minor) = 8.1 min, RT(major) = 10.2 min).
ethyl (3aR,3bR,5aR,8aR,8bS)-8a-hydroxy-5a-methyl-6,9-dioxo-2,3,3b,4,5,5a,6,7,8,8a,8b,9-dodecahydrodicyclopenta[a,f]naphthalene-3a(1H)-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 (3aR,4R)-4-(2-(1-methyl-2,5-dioxocyclopentyl)ethyl)-6-oxo-1,2,3,4,5,6-hexahydro-3aH-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.

(3aR,4R)-4-(2-(1-methyl-2,5-dioxocyclopentyl)ethyl)-6-oxo-1,2,3,4,5,6-hexahydro-3aH-indene-3a-carboxylate (72 mg, 0.21 mmol, 1.0 equiv.) was dissolved in toluene (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 immediately 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 (3aR,3bR,5aR,8aR,8bS)-8a-hydroxy-5a-methyl-6,9-dioxo-2,3,3b,4,5,5a,6,7,8,8a,8b,9-dodecahydrodicyclopenta[a,f]naphthalene-3a(1H)-carboxylate (43 mg, 0.34 mmol, 60% yield, 20:1 dr, 92% ee) as a white solid. [α]^{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); ^13C 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. Enantipurity was determined to be 92% ee by chiral HPLC (DAICEL CHIRALPAK OJ-H, 25 cm x 4.6 mm, hexanes/2-propanol = 95/5, flow rate = 1 mL/min, λ = 245.0 nm, RT(major) = 19.9 min, RT(minor) = 33.2 min).
References


