C–H OXIDATION REACTIONS IN COMPLEX MOLECULE SYNTHESIS: APPLICATION AND DEVELOPMENT

BY

ERIK M. STANG

DISSERTATION

Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Chemistry
in the Graduate College of the
University of Illinois at Urbana-Champaign, 2011

Urbana, Illinois

Doctoral Committee:

Professor M. Christina White, Chair
Professor Scott E. Denmark
Professor Paul J. Hergenrother
Professor Ralph G. Nuzzo

C–H OXIDATION REACTIONS IN COMPLEX MOLECULE SYNTHESIS: APPLICATION AND DEVELOPMENT

Erik M. Stang *University of Illinois Urbana-Champaign*

Research Advisor: M. Christina White *September 2011*

ABSTRACT

Among the frontier challenges in chemistry in the 21st century are the interconnected goals of increasing synthetic efficiency and diversity in the construction of complex molecules. Oxidation reactions of C–H bonds, particularly when applied at late-stages of complex molecule syntheses, hold special promise for achieving both these goals by minimizing the use of functional group manipulations typically required to synthesize these molecules. Traditionally, C–H oxidation reactions install oxidized functionality onto a preformed molecular skeleton, resulting in a local molecular change. However, the use of C–H activation chemistry to construct complex molecular scaffolds is a new area with tremendous potential in synthesis. This work showcases a late-stage C–H oxidation strategy in the total synthesis of 6-deoxyerythronolide B (6-dEB), the aglycone precursor to the erythromycin antibiotics. An advanced intermediate is cyclized to the 14-membered macrocyclic core of 6-dEB using a late-stage (step 19 of 22) C–H oxidative macrolactonization reaction that proceeds with high regio-, chemo-, and diastereoselectivity (>40:1). A chelate-controlled model for macrolactonization predicted the stereochemical outcome of C–O bond formation and guided the discovery of conditions for synthesizing the first diastereomeric 13-epi-6-dEB precursor. Overall, this

C–H oxidation strategy affords a highly efficient and stereochemically versatile synthesis of the erythromycin core.

Throughout the erythromycin's rich synthetic history, no concept has been entrenched as deeply as the perceived need for biasing elements in order to effect 14-membered macrocyclization. This work showcases the cyclizations of completely unbiased 6-deoxyerythronolide B precursors, using either C–H oxidative or Yamaguchi macrolactonization reactions. Late-stage and stereodivergent C–H oxidation reactions enabled seco acid formation with both configurations at C13. Consequently, it is shown that both the natural and unnatural C13 configurations can be formed in the macrocyclization of the 6-dEB core in the absence of preorganizational elements. Overall these findings require revision of the 30-year-old dogma that preorganization is mandatory for achieving macrocyclization of the erythromycins.

Sequential transformations in a single reaction have the potential to dramatically increase synthetic efficiency by rapidly building molecular complexity while lowering step count and intermediate isolations. Catalytic dehydrogenation reactions of hydrocarbons represent a powerful reaction class capable of activating an otherwise non-reactive substrate through sequential C–H bond activations. As a result, coupling a dehydrogenation transformation to a complexity generating reaction would lead to complex molecular architectures from topologically simple starting materials in a rapid fashion. We report a Pd(II)/bis-sulfoxide catalyzed dehydrogenative Diels-Alder reaction that converts simple terminal olefins into complex cyclohexenyl adducts in good yields and selectivities. Based on the high functional group tolerance, this method enables expedient access to a wide variety of biologically and medicinally relevant heterocycles,

such as hydroisoindolines, *cis*-decalins, hydroisoquinolines, and isoindoloquinolines. Mechanistic studies indicate the reaction proceeds through a sequential allylic C–H cleavage and homoallylic β-hydride elimination to produce a mixture of E and Z terminal 1,3-dienes, which isomerize to the Diels-Alder capable (E)-isomer via Pd(II)-catalysis, followed by a thermal Diels-Alder cycloaddition.

ACKNOWLEDGMENTS

I would like to thank professor M. Christina White for the excellent guidance, constant support, and encouragement she has provided me for the past five years. Her high scientific standards and dedication to excellence was what first drew me to her lab, and something that I will always attempt to imitate. I had the opportunity to work with her on a high risk – high reward research project, and this taught me that the only way to discover something extraordinary is to take a chance. I have been in the unique position to see her as an assistant professor with a small lab, a tenured faculty member with a big lab, and as a professor/new mother. This broad experience has taught me many things about leading a research lab and the many ways one can accomplish a goal, ranging from work harder to work smarter. From my time in her lab, I have a better understanding of how to solve problems from a 'big picture' perspective, and how to convert criticism into fuel for improvement. While we haven't always seen eye-to-eye on how to best solve a particular problem, our "discussions" have helped me grow as a scientist, and I appreciate always being treated as a colleague. I will miss the five-hour midnight group meetings, the forearm "man" tattoo, and the Michael Jordan highlight videos.

I would like to thank professor Kevin Minbiole for his support beginning with my junior year at James Madison University. I am incredibly fortunate to have enrolled in his organic chemistry course, which sparked my interest in organic synthesis. I then had the opportunity to join his research team and learn the very important laboratory techniques that I continue to use to this day. More importantly, I quickly learned the importance of reaction mechanisms under his guidance.

I also want to thank those serving on my committee for their critique and advice: Professor Scott Denmark, Professor Paul Hergenrother, and Professor Ralph Nuzzo. Professor Denmark's asymmetric synthesis course was indispensable for a young organic chemist new to the field and literature. I have repeatedly used his class notes throughout my time here. I am also fortunate to have received unique insights and perspective from Professor Hergenrother, who also did his graduate work on erythromycin synthesis.

I feel privileged that I had the chance to work with the following outstanding chemists upon joining the research lab: Ken Fraunhoffer, Mark Chen, Jared Delcamp, Dustin Covell aka Daren Corpell, and Nicolaas "Niko" Vermeulen. Ken is the co-worker most responsible for my training as a scientist and taught me technique as well as how to best solve problems. Ken was not only my bay-mate and student mentor, but he was also my best friend during my early years. Mark and Jared will always be united in the pirate cove, and are proof that you can be a gnarly dude and an amazing scientist simultaneously. Dustin was my go-to guy throughout my career, and always challenged me to get better, but in the nicest and kindest way possible. Niko served many roles around lab, but I will remember him most as an idea man, followed closely by crazy scientist, grill-master, and mechanic.

I am also blessed to have joined the lab with the following rich and interesting characters: Sean Reed, Andrew "Roo" Young, and Grant Rice. I would like to thank these gentlemen for keeping me sane, whether it was lunch time, movie night with my long-time roommate, Malibu visits, a ZOSO concert or twelve, Sunday night BBQ's, or engaging sports talks. It has been an honor to grow with these fine chemists, to see their

improvement, and to experience the changes our lab has undergone together. I know each will do great research in the future.

I consider myself lucky to have also worked with Marinus Bigi, Chris Taylor, Alex Brucks, Paul Gormisky, Iulia "THE QLAW!" Strambeanu, Shauna Paradine, Tommy Osberger, Greg Snapper, Chao Jiang, and Tobias Thaler. I've had a blast getting to know them all through work, Karaoke, group parties, parties in historic Urbana, Mr. Roboto, "Friday" music, or just saying "what's up brah?" to a familiar face. I have no doubt each will accomplish great things and publish many more papers. A special thanks to Chris Taylor and Tommy Osberger for representing ½ of the 'man cave' and 'centaur cave.' Tommy, in particular, was a godsend lab mate due to his positivity and humor.

I would like to thank my parents, Howard and Jill Stang, for their unwavering support and encouragement. But mostly, I owe them tremendous thanks for teaching me valuable lessons in character and the importance of being a good person. They have always treated people the right way, and I have always tried to emulate that. I want them to know that keeping them in the dark for the past five years was a way to shield them, and it was done out of love.

Lastly, and perhaps most importantly, I owe incredible thanks to an amazing person, Christine Farah. Despite being physically separated by half of the continental United States for a shade over a half-decade, she has always been by my side. I owe her for many weekend visits, many accumulated frequent flier miles, and many mobile minutes. More importantly, I owe her many years of encouragement, love, and support.

TABLE OF CONTENTS

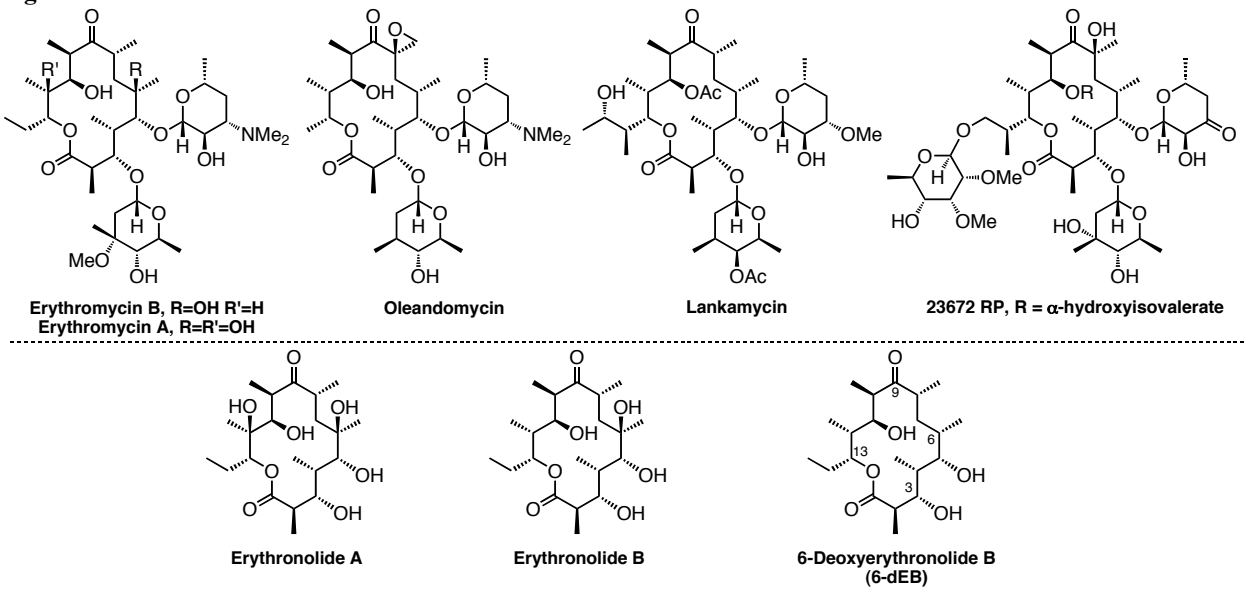
CHAPTER 1

TOTAL SYNTHESIS AND STUDY OF 6-DEOXYERYTHRONOLIDE B BY LATE-STAGE C–H OXIDATION

1.1 INTRODUCTION

Many biologically important small molecules consist of a hydrocarbon skeleton decorated with oxygen functionality. Synthetic chemists have typically synthesized these compounds by incrementally adding oxygenation throughout a synthetic route using a combination of three reaction classes: 1) C–C bond forming reactions between two preoxidized coupling fragments, 2) functional group interconversions (i.e. substitution reactions), and 3) olefin oxidations. While this strategy has enabled the synthesis of seemingly any complex molecule,[1] it often requires the heavy use of functional group manipulations (FGMs), such as protection-deprotection sequences and oxidation state changes. As a consequence, the routes to these polyoxidized molecules often require more synthetic manipulations than the complexity of the target dictates, resulting in lower synthetic efficiencies. Late-stage oxidative tailoring of hydrocarbons, enabled by C–H oxidation methodology, provides an alternative approach to complex molecule synthesis.[2] This late-stage C–H oxidation strategy enables reactive functional groups to be masked as inert C–H bonds until the final stages of a synthesis, and in theory reduces FGMs and improves synthetic efficiencies. However, applications of C–H oxidation reactions in target-oriented synthesis are scarce[3] due to the requirement that oxidation occur at one C–H bond amid scores of others, with predictably high levels of regio-, chemo- and stereoselectivity. Approaches for predicting and influencing the stereochemical course of C–H oxidations, in particular, are not well developed.

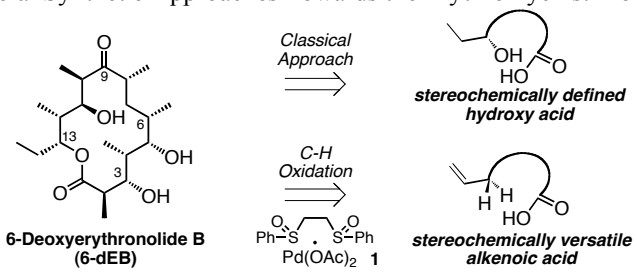
Figure 1. Macrolide Antibiotics



The polyketide macrolide antibiotics are a large family of compounds all possessing a signature macrocyclic lactone (or "macrolide") structure of various sizes (12, 14 or 16 membered lactones), and most possess an amino sugar and/or neutral sugar moieties (Figure 1).[4] These compounds are of great interest due to their antibacterial activity, particularly against gram-positive bacteria and mycoplasmas. The macrolide aglycones found in this class of compounds are nearly structurally homologous and tend to differ only in degree of oxygenation and glycosylation. Furthermore, many of these natural products share a striking stereochemical homology at all comparable stereocenters (Celmer's Rules).[5] Based on their interesting macrocyclic structures and dense array of stereochemistry, the polyketide macrolide antibiotics have inspired tremendous conceptual advances in total synthesis, including novel strategies for acyclic stereocontrol and macrocyclization methodologies. The erythromycins have served as vital members of this antibacterial fleet since their isolation in the 1950's, owing to their broad-spectrum antibacterial activity and lack of activity against eukaryotes.[4] This sub-class of macrolide compounds (including, but not limited to: erythronolide A, erythronolide B, and 6-

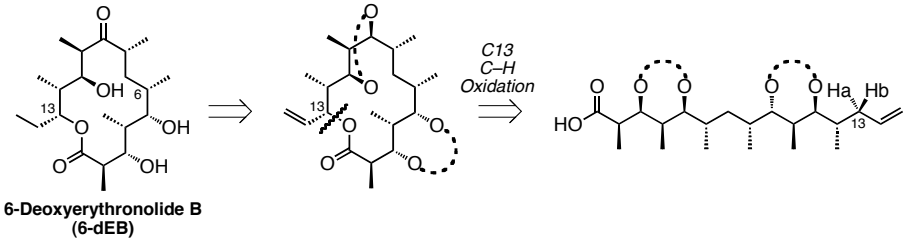
deoxyerythronolide B) all share a 14-membered macrolactone aglycone, an ethyl side chain at C13, as well as 10 asymmetric centers. 6-Deoxyerythronolide B (6-dEB) is the biogenic precursor to the erythromycins, and therefore serves as the archetypical core of these polyketide macrolides.[6]

Figure 2. General Synthetic Approaches Towards the Erythromycins. From reference 14



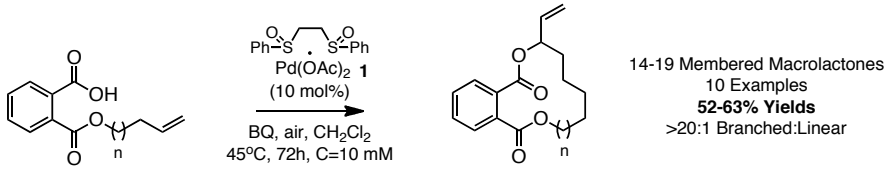
Synthetic studies of the erythromycins, spanning more than a quarter of a century,[7] have relied on internal esterification of a stereochemically defined linear hydroxyacid for macrocycle construction. Of these, 6-dEB has been synthesized three times previously using an acylation-based macrocyclization event.[8,9,10,11] We questioned whether this same core structure could be accessed through a late-stage C–H oxidative macrolactonization reaction where oxygen is installed directly into the hydrocarbon framework late in the synthesis (Figure 2). This C–H oxidation strategy offers several potential advantages. First, the amount of reactive oxygen functionality is minimized, thereby reducing side reactions that erode synthetic yields over the course of multi-step sequences.[1a,12] In addition, installing this 'ester' functionality directly from a C–H bond obviates the need to selectively expose the desired free hydroxyl group needed for acylation-based cyclizations, which often necessitates the use of delicate FGMs.[13] Second, this strategy can furnish diastereomeric macrolactones at the site of oxidation from a stereochemically versatile oxidation precursor.

Figure 3. Retrosynthetic Analysis of 6-deoxyerythronolide B



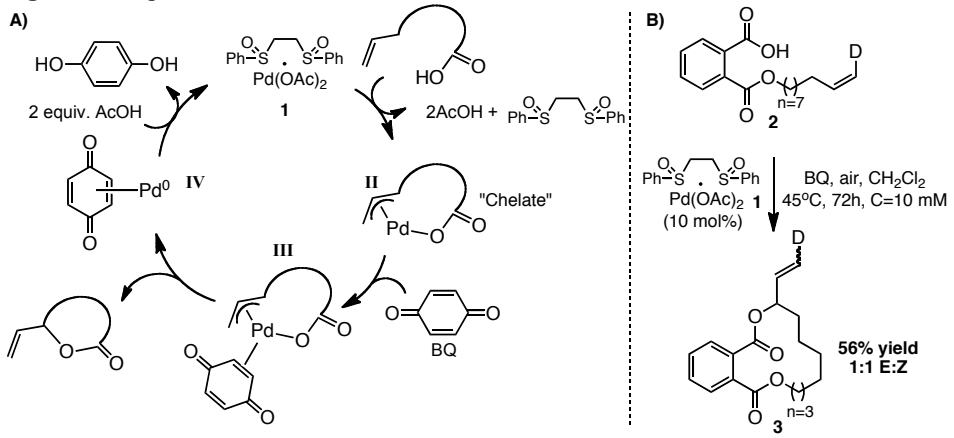
Our retrosynthetic approach to 6-dEB focused on C13 oxidation/macrocyclization to forge the macrolide core, which when fully saturated, presents a formidable chemoselectivity challenge. We therefore envisioned selective oxidation at C13, in preference to multiple tertiary and ethereal C–H bonds, through use of a C14-C15 vinyl moiety (Figure 3).[14] Towards this goal, we recently developed a palladium(II)/bis-sulfoxide catalyzed allylic C–H macrolactonization reaction that converts simple linear alkenoic acids directly into 14- to 19-membered macrolactones with excellent levels of chemo- and regioselectivity (Figure 4).[15] While this C–H oxidative macrolactonization reaction did proceed with high levels of chemo- and regioselectivity on simple alkenoic acid substrates, it led to low levels of diastereocontrol (<3:1 d.r.) at the site of oxidation on all substrates examined. Strategic application of this reaction at a late stage of a target-oriented synthesis hinges on a stereochemically predictive model for C–O bond formation during a global topological change (*i.e.* macrocyclization). Elegant examples of diastereoselective C–H oxidations in complex molecular settings have relied on the local topology of rigid, cyclic architectures to predict and control diastereomeric outcomes.[16] Albeit effective in these contexts, this conceptual framework cannot be used for predicting

Figure 4. C–H Oxidative Macrolactonization Methodology



stereochemical outcomes with flexible, acyclic compounds, thus necessitating an alternative approach.

Figure 5. Proposed Mechanism of C–H Oxidative Macrolactonization



Oxidative C–H macrolactonization is thought to proceed via an initial Pd^{II}/phenylbis-sulfoxide (**1**) promoted allylic C–H cleavage event to generate a π-allylPd(carboxylate) intermediate (**II**, Figure 5A). Based on previous mechanistic studies, the palladium is thought to coordinate both the π-allyl and carboxylate functionality of the same molecule (i.e. chelated).[15,17] Furthermore, deuterium isomerization studies reveal that an alkenoic acid substrate labelled with a (*Z*)-deuterium is isomerized over the course of macrocyclization, giving rise to a 1:1 *E*:*Z* deuterium product ratio (Figure 5B).[14] This isomerization event indicates that the π-allylPd(carboxylate) species rapidly interconverts via a π–σ–π isomerization mechanism, allowing palladium to survey both faces of the π-allyl regardless of which diastereotopic allylic hydrogen is initially cleaved. Subsequent association of the π-acid 1,4-benzoquinone (BQ) promotes a stereodetermining C–O bond-forming event within the coordination sphere of the metal (**III**) to provide the branched allylic macrolide product.[18] BQ then reoxidizes the resulting Pd(0) species (**IV**) back to Pd(II), regenerating the C–H cleavage catalyst and closing the catalytic cycle.

Figure 6. Molecular Modeling Studies

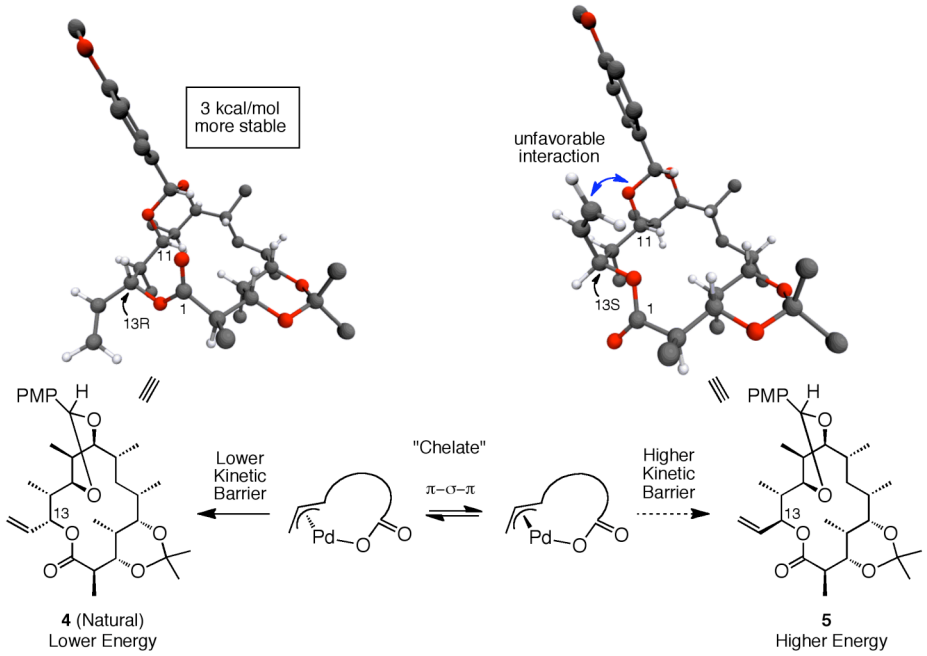


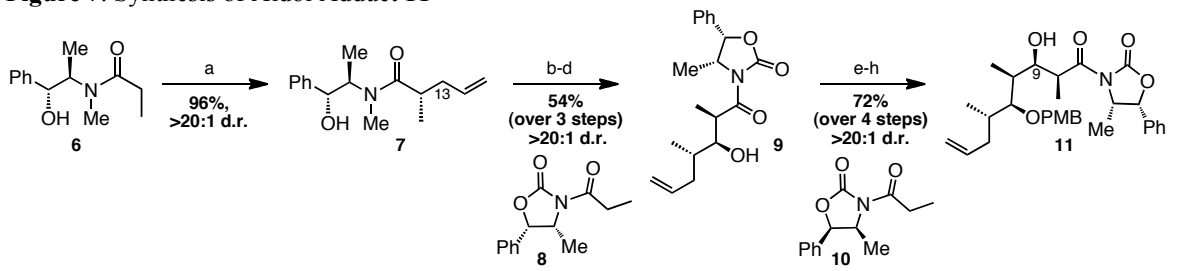
Figure adapted from reference 14

Assuming the π-allylPd(carboxylate) intermediates closely resemble the products, we anticipated that such palladium chelation would lead to transition structures with product-like transannular character, and thus the stereochemical outcome of macrolactonization could be predicted using the relative ground state product energies. Based on molecular modeling studies, macrolide **4** was found to be 3 kcal/mol more stable than **5** (MMFF94 force fields) due, in part, to a pseudo-equatorial disposed exocyclic vinyl moiety (Figure 6).[14] We anticipated that chelate-controlled C–H macrolactonization would therefore strongly favor formation of the natural epimer. Furthermore, disrupting the chelation event could provide a different stereochemical outcome by generating an earlier transition state with very little transannular character.

1.2 RESULTS AND DISCUSSION

1.2.1 Synthesis of the Alkenoic Acid Cyclization Precursor

Figure 7. Synthesis of Aldol Adduct **11**

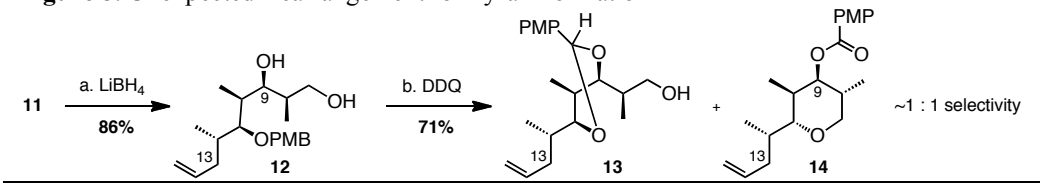


Conditions: (a) LDA (2.1 equiv.), LiCl (6.0 equiv.), allyl iodide (1.5 equiv.), -78°C, >20:1 d.r., 96% (b) NH_3BH_3 (4.0 equiv.), LDA (4.0 equiv.), 0°C, 98% (c) oxalyl chloride (1.3 equiv.), NEt_3 (5.0 equiv.), DMSO (1.6 equiv.), -78°C (d) **8** (1.0 equiv.), Bu_2BOTf (1.2 equiv.), *i*-Pr_2NEt (1.4 equiv.), -78°C, >20:1 d.r., 55% over 2-steps (e) $AlMe_3$ (5.0 equiv.), (MeO)NHMe-HCl (5.0 equiv.), -10°C, 86% (f) PMBBr (1.8 equiv.), NaH (1.8 equiv.), 0°C, 96% (g) Dibal-H (2.0 equiv.), -78°C, 91% (h) **10** (1.0 equiv.), Bu_2BOTf (1.2 equiv.), NEt_3 (1.2 equiv.), -78°C, >20:1 d.r., 96%.

Our study commenced with construction of a versatile, linear C–H oxidation precursor using a series of powerful polyketide synthase (PKS)-inspired, stereoselective aldol- and alkylation reactions in a linear, iterative fashion.[14] Towards the goal of minimizing the total oxygen content, a relatively inert allyl moiety, acting as a latent allylic alcohol, was installed during the first step of the synthetic route via Myers' diastereoselective alkylation[19] (**6** → **7**, >20:1 d.r.), and carried through the entire linear polypropionate synthesis without manipulation (Figure 7). Conversion of the pseudoephedrine-based amide **7** to an aldehyde, followed by a *syn* Evans' aldol reaction[20] with norephedrine-based auxiliary **8** provided aldol product **9** in good yield and selectivity (>20:1 d.r.). A Weinreb amide was next installed so as to prevent a retro-aldol reaction under the basic (NaH) *p*-methoxybenzylidene (PMB) protection conditions. After mono-reduction of the Weinreb amide with DIBAL-H to give an aldehyde, a subsequent *syn* Evans' aldol reaction with auxiliary **10** secured adduct **11** with good yield and >20:1 d.r. With assistance from the C9 hydroxyl group, reductive cleavage of the oxazolidinone auxiliary proceeded smoothly with $LiBH_4$ (**11** → **12**, Figure 8). However, in the presence of the free

primary alcohol, DDQ promoted oxidative cyclization provided a 1:1 mixture of the desired PMB-acetal product (**13**) along with rearranged pyran byproduct (**14**), resulting from displacement of the C11 oxygen with the primary hydroxyl group. After unsuccessful attempts to alter this product selectivity, aldol adduct **11** was first subjected to DDQ promoted ketalization

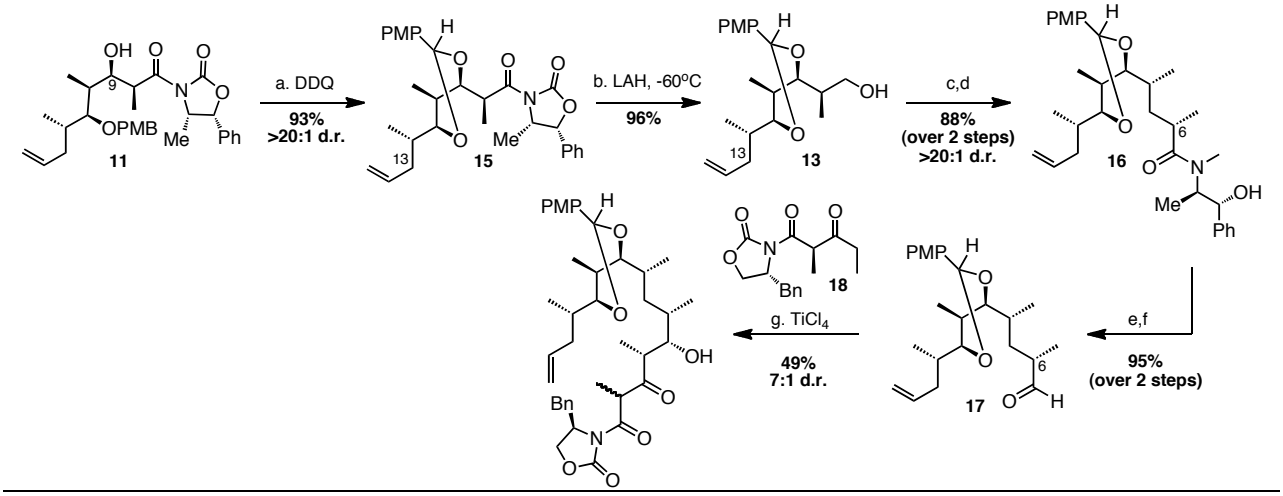
Figure 8. Unexpected Rearrangement for Pyran Formation



Conditions: (a) $LiBH_4$ (1.2 equiv.), r.t., 86% (b) DDQ (1.2 equiv.), $MgSO_4$ (14.0 equiv.), >20:1 d.r., 71% combined.

conditions,[21] securing the PMB acetal product (**15**) cleanly in >20:1 d.r. (Figure 9). Reductive cleavage of the auxiliary could then be effected with LAH at -60°C (**15** → **13**). Without assistance from the free C9 hydroxyl group, the low reaction temperature proved to be critical for selective hydride addition to the desired imide carbonyl over opening of the oxazolidinone. Straightforward conversion to the primary iodide, followed by a Myers' alkylation reaction to set

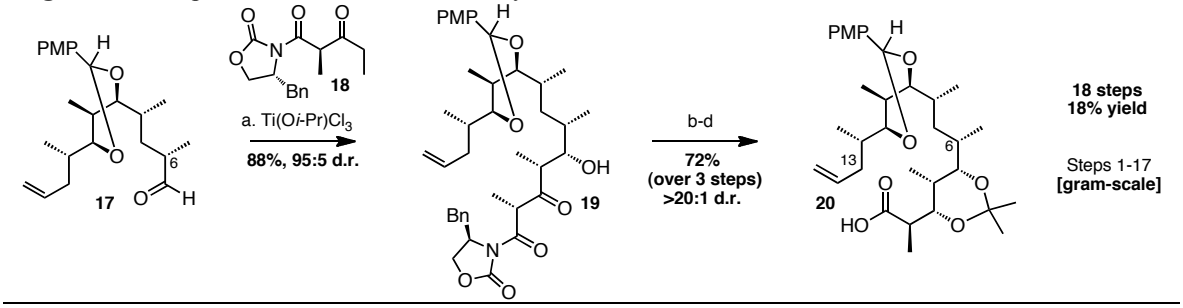
Figure 9. Alkenoic Acid **20** Synthesis: β-Keto Imide Aldol Coupling



Conditions: (a) DDQ (1.2 equiv.), $MgSO_4$ (14.0 equiv.), >20:1 d.r., 93% (b) LAH (3.0 equiv.), -78°C, 96% (c) PPh_3 (1.2 equiv.), I_2 (1.4 equiv.), imidazole (1.5 equiv.), 94% (d) **6** (2.1 equiv.), LDA (4.0 equiv.), LiCl (12.7 equiv.), 0°C, >20:1 d.r., 94% (e) NH_3BH_3 (4.0 equiv.), LDA (4.0 equiv.), 0°C, 99% (f) DMP (1.6 equiv.), 96% (g) **18** (1.5 equiv.), $TiCl_4$ (1.6 equiv.), NEt_3 (1.6 equiv.), -78°C, 7:1 d.r., 49%.

the C6 stereogenic center (**16**), and a reduction-oxidation sequence provided **17** as a sole diastereomer. At this juncture, a *β*-keto imide (**18**) derived enolate would provide the dipropionate unit needed to complete the alkenoic acid synthesis. Standard generation of a titanium(IV) enolate using $TiCl_4$ led to modest coupling yields and selectivities (49%, 7:1 d.r.), with significant epimerization at C2 along with competitive removal of the PMB acetal. Gratifyingly, we found that the use of Ti(O*i*-Pr)Cl_3 Lewis acid, thought to generate a more

Figure 10. Completion of Alkenoic Acid **20** Synthesis



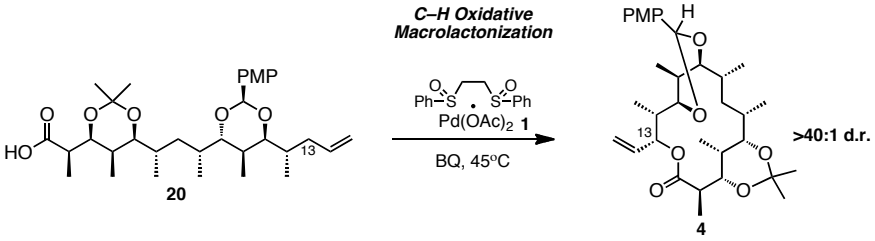
Conditions: (a) **18** (1.5 equiv.), $TiCl_4$ (1.2 equiv.), Ti(O*i*-Pr)$_4$ (0.4 equiv.), NEt_3 (1.6 equiv.), -78°C, 95:5 d.r., 88% (b) $Zn(BH_4)_2$ (1.6 equiv.), -78°C, >20:1 d.r., 75-86% (c) CSA (cat.), 2,2-dimethoxypropane (9.8 equiv.), 84% (d) $LiOOH_{(aq)}$ (2.0 equiv.), 0°C, 99%.

nucleophilic enolate,[22] provided the necessary *syn-syn* aldol adduct **19** in good yield (88%) and selectivity (95:5 d.r.), with no epimerization at C2 and minimal PMB acetal cleavage (Figure 10). Chelate-controlled reduction with $Zn(BH_4)_2$ (>20:1 d.r.), followed by ketalization and chiral auxiliary hydrolysis, completed the synthesis of alkenoic acid **20** in 18 steps and 18% overall yield. Furthermore, all but the last step (steps 1-17) were performed on a gram-scale, providing ample quantities of material to test the C–H oxidative macrolactonization reaction.[14]

1.2.2 C–H Oxidative Macrolactonization Reactions

With the linear oxidation precursor (**20**) in hand, we were poised to investigate whether late-stage C–H macrolactonization would proceed with the predicted levels of selectivity. Initial macrolactonization attempts, under the previously reported conditions, led to sluggish conversion

Table 1. Optimization of the C–H Oxidative Macrolactonization Reaction[a]



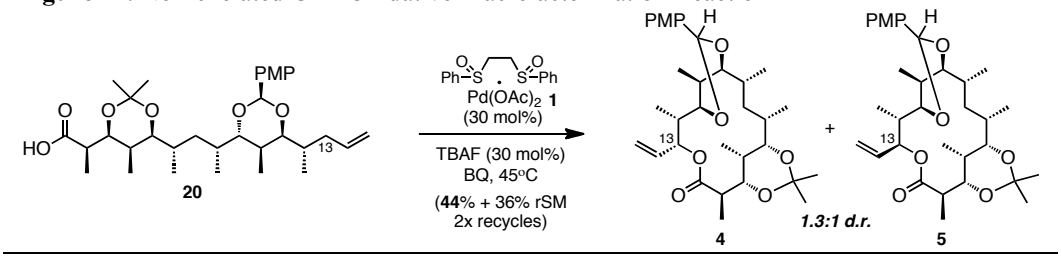
entry	catalyst loading[b] (mol %)	concentration (M)	additive[f]	conversion[c] (%)	yield[d] (%)
1	10	0.01	-----	<10	<5
2	30	0.01	-----	22	11
3	30	0.02	-----	55	34
4[g]	30	0.02	-----	92	56
5	30	0.025	-----	64	21
6	30	0.02	AcOH	35	23
7[e]	100	0.02	-----	100	9
8[e]	100	0.005	-----	100	15

[a] Reaction conditions: **20** (1.0 equiv.), BQ (2.0 equiv.), CH_2Cl_2, 45°C, 72 hr [b] Formed using *in situ* protocol [c] Calculated based on recovered starting material [d] Isolated yield [e] BQ (2.0 equiv.) added after 36 hr and allowed to stir for an additional 24 hr. [f] 80 mol% [g] Recovered starting material recycled through the reaction twice under conditions found in entry 3.

with only trace product formation (entry 1, Table 1). Stoichiometric palladium studies indicated that the C–H cleavage step proceeded to generate the desired π-allylPd complex, albeit at a slow rate, while functionalization occurred as expected. In order to improve the reactivity of the C–H cleavage step, the oxidative lactonization was optimized around catalyst loadings and reaction concentration, as well as adding Brønsted acid additives. Increased catalyst loadings led to higher starting material conversions (entries 2-6), but loadings above 30mol% resulted in significant intermolecular functionalization and thus low product yields (entries 7,8). Similarly, increasing the reaction concentration greatly improved reactivity (entries 3-7), but also diminished product formation above 0.02 M (entries 5,7). Interestingly, the addition of Brønsted acids, such as AcOH, thought to increase the rate of C–H cleavage, actually diminished reactivity (entry 6). In the end, increasing the catalyst loading (10 to 30 mol %) and

concentration (0.01 M to 0.02 M) provided the best results, affording the 14-membered macrolide in 34% yield (45% rSM, entry 3). Consistent with predictions made using the chelate-controlled model, only the desired C13 diastereomer (**4**) was detectable by ^{1}H NMR of the crude reaction mixture (>20:1 d.r.). Furthermore, formation of **5** (*vide infra*) enabled determination of the diastereoselectivity by HPLC analysis (>40:1 d.r.). The mass balance of this reaction indicates that the reaction is highly selective for C13 oxidation. By recycling this valuable starting material through the reaction twice, we obtained diastereomerically pure macrolide **4** in 56% isolated yield (8% rSM, entry 4). The macrocyclization event presented here constitutes a rare example of a highly regio-, chemo-, and stereoselective C–H oxidation at a late-stage of a complex molecule synthesis.[14]

Figure 11. Non-chelated C–H Oxidative Macrolactonization Reaction



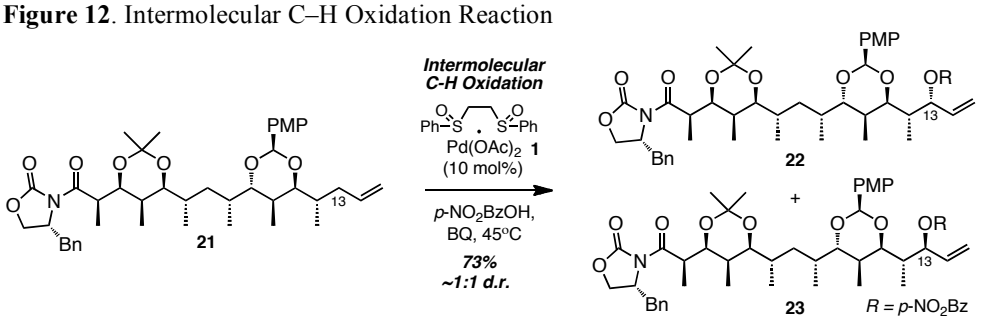
Conditions: **1** (30 mol%), BQ (2.0 equiv.), TBAF (0.3 equiv.), CH_2Cl_2 (0.02 M), 45°C, 72 h, 1.3:1 d.r., 20% + 75% rSM (44% + 36% rSM, 2x recycle).

In attempts to alter the stereochemical outcome of C–H macrolactonization, we aimed to disrupt the palladium chelation event believed to be responsible for the diastereoselectivity.[23] Addition of fluoride anion to π-allylPd complexes has been shown previously to enhance the rate of π-σ-π isomerization, presumably by interacting with a coordination site on palladium.[24] We anticipated that such an additive would disrupt the π-allylPd(carboxylate) chelate to favor an outer-sphere C–O bond forming event. Consistent with this hypothesis, the addition of tetra-*n*-butylammonium fluoride (TBAF)[25] to the oxidative C–H macrolactonization reaction dramatically altered the stereoselectivity to furnish a separable mixture of C13 diastereomers **4**

and **5** in useful quantities (20% + 75% rSM; 44% + 36% rSM, recycled 2X, 1.3:1 d.r., Figure 11). Although the diastereoselectivity was not overturned, we were able to obviate the 3 kcal/mol energy preference for the natural epimer by switching the functionalization mechanism. Despite the potential for stereochemical analogues of erythromycin to display novel chemical and antibacterial properties, this is the first time that a stereochemical modification at the critical macrolide linkage has been reported.[14]

1.2.3 Intermolecular C13 C–H Oxidation and Yamaguchi Macrolactonizations

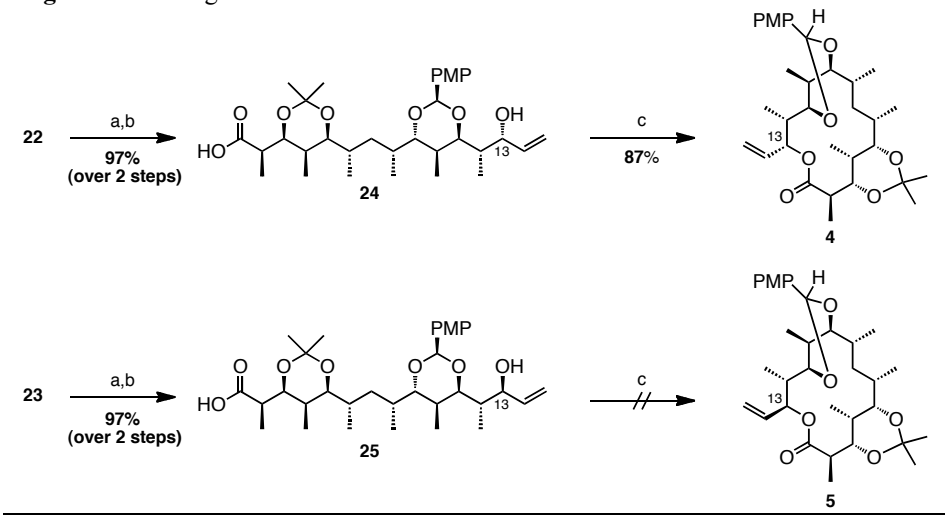
Figure 12. Intermolecular C–H Oxidation Reaction



Conditions: **1** (10 mol%), BQ (2.0 equiv.), *p*-NO_2BzOH (1.5 equiv.), 45°C, 72 h, 1:1 d.r., 73% (combined)

In order to probe the loss of stereocontrol upon addition of fluoride, we aimed to determine the intrinsic diastereoselectivity of C–H oxidation near the allyl moiety in the absence of transannular interactions. Performing our intermolecular (non-chelated) allylic C–H esterification[18] reaction on imide **21** provided C13 *p*-nitrobenzoates **22** and **23** in 73% yield as a 1:1 separable mixture of diastereomers (Figure 12). Notably, in the absence of transannular effects, no chiral information found in the polypropionate backbone was relayed to the site of oxidation. This result supports our hypothesis that C–O bond formation in the fluoride-controlled C–H macrolactonization protocol occurs through a non-chelated process.[14]

Figure 13. Yamaguchi Macrolactonization Studies



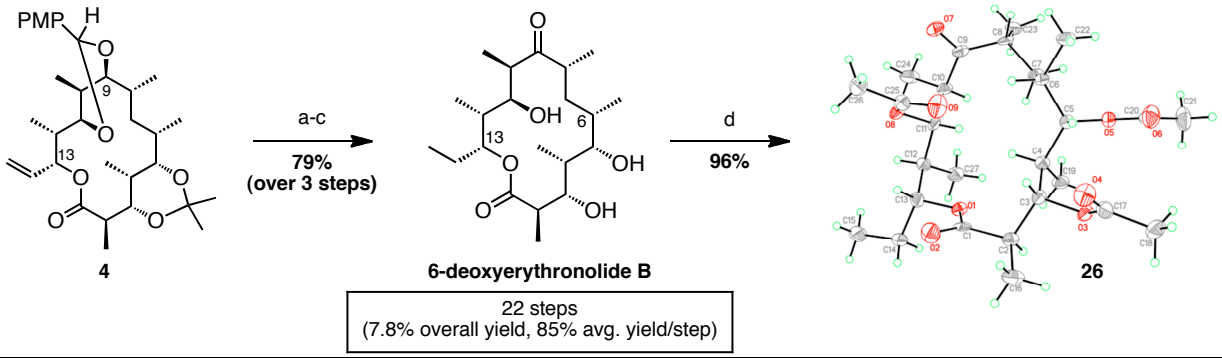
Conditions: (a) $LiOOH_{(aq)}$ (2.0 equiv.), 0°C (b) K_2CO_3 (3.0 equiv.), MeOH, 97% over 2-steps (c) $Cl_3C_6H_2COCl$ (15.0 equiv.), *i*-Pr_2NEt (20.0 equiv.), DMAP (40.0 equiv.), Benzene (0.005 M), r.t., 87% (for **4**). Figure adapted from reference 14.

To further probe the origin of diastereoselectivity in the chelate-controlled C–H macrolactonization, we attempted to synthesize **4** and **5** through a classical acylation-based (Yamaguchi) macrolactonization,[26] that, like the chelate-controlled C–H macrolactonization, is thought to proceed via a product-like transition state. Toward this end, late-stage intermolecular C13 C–H oxidation (*vide supra*) was critical for circumventing lengthy parallel *de novo* syntheses of each epimeric seco acid (**24** and **25**, Figure 13). As anticipated, Yamaguchi macrolactonization of hydroxyacid **24** led to an 87% yield of the natural epimer (macrolide **4**). In contrast, attempted cyclization of **25** yielded oligomer as the exclusive reaction product.[14] These empirical cyclization results support our hypothesis that the origin of diastereoselectivity in the chelate-controlled C–H macrolactonization derives from product-like transition states where a greater kinetic barrier of cyclization prevents formation of the less stable epimer (macrolide **5**).

1.2.4 Completion of 6-Deoxyerythronolide B and Attempted Synthesis of 13-epi-6-Deoxyerythronolide B

With the C13 stereocenter in place, concurrent hydrogenation of the PMB acetal and α-olefin with Pearlman's catalyst ($Pd(OH)_2/C$), site-selective oxidation of the C9 alcohol,[7] and acetonide removal completed the synthesis of 6-deoxyerythronolide B (Figure 14).[14] Following peracetylation of 6-dEB, X-ray quality crystals of triacetate **26** were obtained, which confirmed the relative stereochemical assignments. In total, 6-dEB was synthesized in 22 steps and 7.8% overall yield, representing a highly efficient route to this classic target. This efficiency can be attributed, at least in part, to a C–H oxidative macrolactonization strategy that minimizes the number of reactive functional groups carried through the synthetic sequence. Instead, the final oxygen species was installed at a late-stage from an allylic C–H bond in the proper oxidation state, with the correct stereochemical configuration, all while forming the desired macrolide core.

Figure 14. Completion of 6-deoxyerythronolide B



Conditions: (a) $Pd(OH)_2/C$ (cat.), H_2 (1 atm), *i*-PrOH, 96% (b) TPAP (cat.), NMO (5.0 equiv.), 0°C, 84% (c) 1M $HCl_{(aq)}$ (11.0 equiv.), 98% (d) Ac_2O (93.0 equiv.), DMAP (cat.), Pyridine, 96%. Figure adapted from reference 14.

Efforts to convert **5** into 13-epi-6-deoxyerythronolide B following the same protocol used to construct 6-dEB failed due to acid-catalyzed decomposition during the acetonide removal step involving hemiketal formation at C9 and subsequent dehydration to form an enol ether product.

Interestingly, while the uniform arrangement of catalytic domains in the polyketide synthases (PKSs) accounts for the substitution patterns found in the macrolide antibiotics, the evolutionary basis for "Celmer's Rules" has not yet been elucidated.[27,28] While it is generally considered that evolution of the structure of erythromycin was driven by its shape complementarity to the ribosome,[29] the results presented here, along with the accepted low energy conformational models (*i.e.* "diamond-lattice") for the erythromycin aglycones,[5] raise the interesting question of a contributing chemical basis for the observed stereochemistry that is conserved throughout the polyketide macrolides.

1.3 CONCLUSIONS

In conclusion, C–H oxidative macrolactonization is demonstrated to be a novel approach for complex macrolide synthesis, as well as a rapid means of achieving stereochemical diversity at the key lactone position. Predictably high levels of substrate-based diastereocontrol are possible from advanced linear intermediates under cyclization conditions that proceed via palladium-induced templation. Moreover, conditions that break chelation remove this element of stereocontrol and enable access to an alternate diastereomer. This work highlights that predictably selective C–H oxidation methods can be strategically utilized at late-stages to increase the overall efficiency of target-oriented synthesis. Additionally, methods subject to reagent modulation can rapidly generate stereochemical divergency and may find use in diversity-oriented synthesis.[30]

1.4 EXPERIMENTAL SECTION

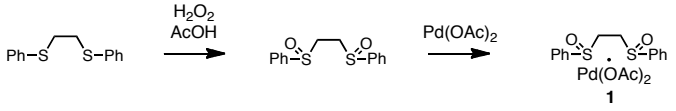
General Information: Unless otherwise noted, all reactions were conducted in flame-dried glassware with magnetic stirring under an inert atmosphere of dry nitrogen. Solvents tetrahydrofuran (THF), diethyl ether (Et_2O), N,N-dimethylformamide (DMF), methanol (MeOH), Dimethyl Sulfoxide (DMSO), 1,4-dioxane, benzene, and methylene chloride (CH_2Cl_2) were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). Deuterochloroform was stored over 3 Å molecular sieves. Diisopropylethylamine (DIPEA), triethylamine (TEA), diisopropylamine (DIPA), and pyridine were distilled from calcium hydride. The following commercially obtained reagents were used as received: propionyl chloride (Sigma-Aldrich), Bu_2BOTf (Fluka, 1M in CH_2Cl_2), Borane-ammonia complex (Sigma-Aldrich, 90%), H_2O_2 (Fisher Scientific, 30% wt solution), 1,4-benzoquinone (Sigma-Aldrich), $Pd(OH)_2/C$ (Sigma-Aldrich, 20 wt %, lot # - PZ 14221JZ).

Propionaldehyde was purified using a Kugelrohr distillation apparatus prior to use. *n*-butyllithium in hexanes (Sigma-Aldrich, 2.5M) was titered using No-D NMR spectroscopy with 1,5-cyclooctadiene (Sigma-Aldrich) as the internal standard.[31] LiCl (Sigma-Aldrich) was stored under an inert atmosphere of Argon and flame dried immediately prior to use. Allyl iodide (Sigma-Aldrich) was passed through a plug of basic alumina prior to use. Oxalyl Chloride (Sigma-Aldrich), titanium tetraisopropoxide (Sigma-Aldrich), and titanium tetrachloride (Sigma-Aldrich) were distilled prior to use. Triphenylphosphine was recrystallized from ethanol and stored under Ar. $Pd(OAc)_2$ (Johnson-Matthey Chemicals) was recrystallized prior to use [see '$Pd(OAc)_2$ Recrystallization' section].

Optical rotations were measured using a 1 mL cell with a 1dm path length on a Perkin-Elmer 341 polarimeter. Optical rotations were obtained with a sodium lamp and are reported as follows: $[\alpha]_{\lambda}^{T\circ C}$ (c = g/100 mL, solvent). Infrared spectra were recorded as thin films on NaCl plates on a Mattson Galaxy Series FTIR 5000 and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained through the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois. Electrospray ioniztion (ESI) spectra were performed on a Waters Q-Tof Ultima spectrometer. ^{1}H NMR spectra were recorded on a Varian Unity-400 (400 MHz) or Varian Unity-500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, oct = octet, m = multiplet, br = broad, app = apparent; coupling constant(s) in Hz; integration. Proton-decoupled 13C-NMR spectra were recorded on a Varian Unity-400 (100 MHz) or Varian Unity-500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). HPLC analysis was performed on an Agilent 1100 Series instrument. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV, potassium permanganate, and ceric ammonium molybdate staining. Flash column chromatography was performed as described by Still et al.[32] using EM reagent silica gel 60 (230-400 mesh).

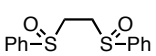
Synthesis of Palladium Catalysts for C–H Oxidation Reactions

Figure 15. Synthesis of Catalyst **1**



$Pd(OAc)_2$ Recrystallization: $Pd(OAc)_2$ (Johnson-Matthey Chemicals) was dissolved in minimal refluxing benzene (~0.5 g $Pd(OAc)_2$/8.0 mL benene). A black precipitate was removed from the refluxing solution by Acrodisc® filtration. The resulting solution was cooled to room temperature. Amber crystals began to form after 15 min. After 1 hr the solution was filtered to give the recrystallized $Pd(OAc)_2$ as gold plates. The recrystallized $Pd(OAc)_2$ was stored for months under an Ar atmosphere with no deleterious effects. A difference in NMR purity was noted between "old" and recrystallized $Pd(OAc)_2$ samples. Reported hydrogen values are normalized ratios of the smallest peak in the acetate region. "Old" $Pd(OAc)_2$: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (s, 1H), 2.10 (s, 3.6H), 2.07 (s, 6.1H), 2.06 (s, 6.1H), 2.03 (m, 15.3H), 2.00 (m, 95.7H), 1.97 (s, 5.7H), 1.95 (s, 6.3), 1.89 (s, 9.4H).

Recrystalized $Pd(OAc)_2$: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.10 (s, 1H), 2.03 (s, 2.8H), 2.00 (s, 40.1H), 1.97 (s, 1.2H), 1.90 (s, 2.3H).



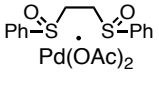
1,2-bis(phenylsulfinyl)ethane: A 50 mL round bottom flask was charged with a stir bar, 2 g (8.12 mmol, 1.0 equiv.) of 1,2-bis(phenylthio)ethane (Oakwood Products Inc.), and 12.2 mL of glacial acetic acid. A solution of H_2O_2 (Sigma-Aldrich, 50 wt%, 31.08 mmol, 2.114 mL, 2.0 equiv.) in acetic acid (6.7 mL) was added dropwise at rt. After approximately 15 min the solution became homogeneous and turned a pale yellow. An additional 8 mL of acetic acid

was then added and the solution allowed to stir for 24 hrs at room temperature. The acetic acid was removed with mild heating (45°C) under high vacuum. The pale yellow solid was emulsified in cold ethanol and cold filtered to yield a mixture of the meso and racemic 1,2-bis(phenylsulfinyl)ethane in 92% yield (2.088 g).

Recrystalization: To a solution of refluxing acetone (~100 ml) was added the crude ligand mixture (~2 g). Acetone was then added slowly to the mixture with reflux until all the powder dissolved. The mixture was then allowed to cool to room temperature. The solution was left at room temperature for an hour then cooled to 4°C overnight. (IMPORTANT: The meso recrystalizes out first as small white clumps and extended time is needed to allow the racemic long white needles to crystallize out. The crystals were filtered off with a buchner funnel and rinsed with cold acetone. For all reactions and catalyst preparations performed during this study, only the *meso*-1,2-bis(phenylsulfinyl)ethane ligand was used.)

Meso-1,2-bis(phenylsulfinyl)ethane: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56-7.52 (m, 10H), 3.05 (s, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 142.29, 131.55, 129.63, 124.10, 47.06. IR (neat) 3048.84, 2970.01, 2922.41, 1442.10, 1036.34, 745.45, 695.70 cm^{-1}

Racemic-1,2-bis(phenylsulfinyl)ethane: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.48 (m, 10H), 3.40 (m, 2H), 2.74 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.55, 131.53, 129.64, 124.08, 47.94. IR (neat, cm^{-1}) 3053.16, 2911.39, 1443.77, 1084.88, 1042.50, 748.52. HRMS (ESI) *m*/*z* calculated for $C_{14}H_{14}O_2S_2Na$ $[M+Na]^+$: 301.0333, found 301.0320.



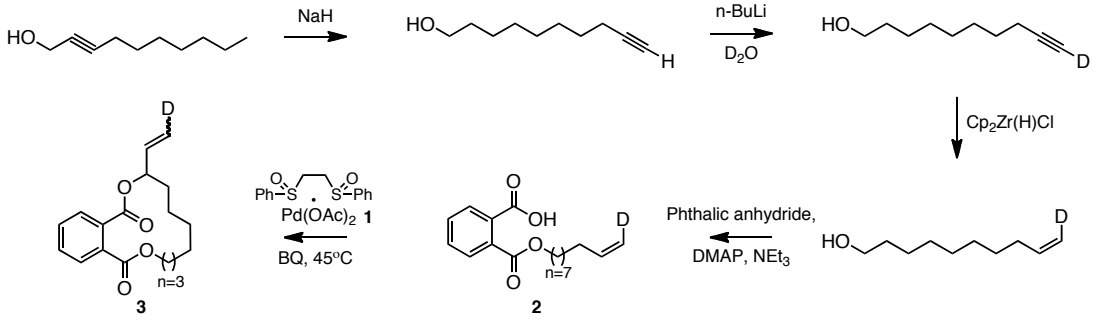
Pd(II)/bis-sulfoxide Catalyst [1]: *In-Situ Pd(II)/bis-sulfoxide Catalyst (1) Preparation for C–H Oxidative Macrolactonization:* An oven dried 1 dram borosilicate vial (topped with a Teflon-lined cap) was charged sequentially with recrystallized

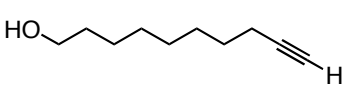
$Pd(OAc)_2$ (2.9 mg, 0.0127 mmol, 0.3 equiv.), *meso*-1,2-bis(phenylsulfinyl)ethane (3.6 mg, 0.0127 mmol, 0.3 equiv.), CH_2Cl_2 (142 μL), and a teflon stir bar. The 1 dram vial was then stirred for 12 hours in 40°C bath, at which time a clear bright red solution resulted. Note: The following precautions were taken to avoid moisture: recrystallized $Pd(OAc)_2$ was stored under an atmosphere of Ar (glove box), and *meso*-1,2-bis(phenylsulfinyl)ethane and the stir bar were stored in a dessicator. The reagents were added quickly to the 1 dram vial on a benchtop balance.

*Pre-complexed Pd(II)/bis-sulfoxide Catalyst (**1**) Preparation for Intermolecular C–H Oxidation*: A flame dried 250 mL flask was charged with *meso*-1,2-bis(phenylsulfinyl)ethane (2.53 g, 9.1 mmol, 1.0 equiv.), CH_2Cl_2 (101 mL, 0.09 M), and recrystallized $Pd(OAc)_2$ (2.04 g, 9.1 mmol, 1.0 equiv.). The mixture was stirred at 40°C for 24h. The reaction becomes a dark red homogenous solution. The solution was concentrated *in vacuo* to incomplete dryness, and then fully dried under a stream of N_2 for 24 hours to give a dark red solid used without further purification. **Note: The catalyst must be stored at below 4°C.** The catalyst very slowly decomposes at ambient temperature; however, may be stored for prolonged periods (months) at reduced temperatures. ^1H NMR and IR data of this catalyst looks like *meso*-1,2-bis(phenylsulfinyl)ethane ligand and $Pd(OAc)_2$.

Deuterium Isomerization Study for Figure 5

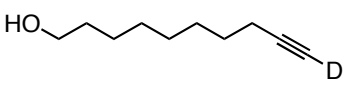
Figure 16. Deuterium Isomerization Study





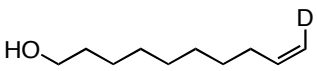
dec-9-yn-1-ol: The title compound was prepared using a known procedure: A flame-dried 100 mL round bottom flask was charged with NaH (0.408 g, 17.0 mmol, 8.0 equiv.) and diaminopropane (15 mL). The solution was topped with a reflux condenser and stirred at 70°C for 1 hr, or until the evolution of gas ceased and a cloudy tan solution resulted. The reaction was cooled to r.t. and a solution of dec-2-yn-1-ol (0.388 mL, 2.15 mmol, 1.0 equiv.) in diaminopropane (8 mL) was added via syringe. The brown reaction mixture was then placed in a 55°C bath and stirred for 17 hrs. At this time the reaction was cooled, diluted with Et_2O (10 mL) and quenched slowly with H_2O (10 mL). The layers were separated, and the aqueous was extracted with Et_2O (4 x 10 mL). The combined organic layers were washed with H_2O (1 x 10 mL), 1 M HCl (1 x 10 mL), and satd brine (1 x 10 mL), then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a clear oil. This crude oil was passed through a short Si plug to remove any residual H_2O with 20% EtOAc/Hex, and concentrated *in vacuo* to afford the clean title compound (0.2985 g, 1.935 mmol, 90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64 (app q, J = 5.7 Hz, 2H), 2.18 (dt, J = 2.5, 7.0 Hz, 2H), 1.94 (t, J = 2.5 Hz, 1H), 1.49-1.59 (m, 4H), 1.31-1.43 (m, 8H), 1.19-1.25 (m, 1H).



10-D-dec-9-yn-1-ol: A flame-dried 25 mL round bottom flask was charged with dec-9-yn-1-ol (0.2985 g, 1.935 mmol, 1.0 equiv.) and THF (3.87 mL, 0.5 M) and cooled to -78°C. At this time, nBuLi (2.5 M, 1.93 mL, 4.84 mmol, 2.5 equiv.) was syringed into reaction dropwise, resulting in an orange solid. The reaction was allowed to warm to 0°C and the heterogenous orange solution was stirred for 1 hr, at which time D_2O (5 mL) was added dropwise. The resulting clear orange solution was stirred for 2 hrs, then poured into a separatory funnel containing satd NH_4Cl (20 mL) and Et_2O (20 mL). The layers were separated, and the aqueous was extracted with Et_2O (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered through a silica plug, and concentrated *in vacuo* to afford a clear oil (0.2922 g, 1.87 mmol, 97%, >20:1 D:H incorporation by ^1H NMR analysis).

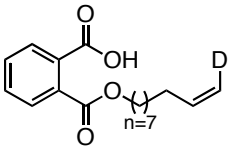
^1H NMR (400 MHz, $CDCl_3$) δ 3.64 (app q, J = 6.0 Hz, 2H), 2.18 (t, J = 7.2 Hz, 2H),1.50-1.58 (m, 4H), 1.33-1.43 (m, 9H).



10-(Z)-D-9-decen-1-ol: A flame-dried 50 mL round bottom flask was charged with $Cp_2Zr(H)Cl$ (0.868 g, 3.366 mmol, 1.8 equiv.) and THF (7.56 mL) to produce a gray slurry. A solution of 10-D-dec-9-yn-1-ol (0.2922 g, 1.870 mmol, 1.0 equiv.) in THF (4.1 mL) was cannulated into the slurry, resulting in a yellow bubbling solution. After 35 min, the brown reaction solution was quenched with satd NH_4Cl (10 mL) and diluted with Et_2O (10 mL). The layers were separated, and the aqueous was extracted with Et_2O (1 x 10 mL). The combined organic layers were washed with satd $NaHCO_3$ (1 x 10 mL), H_2O (1 x 10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil with insoluble white solids. This crude reaction product was passed through a short silica plug with 20%

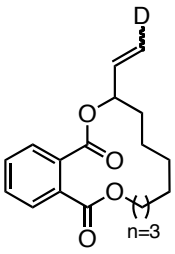
EtOAc/Hex, and concentrated *in vacuo* to afford the clean title compound as a yellow oil (0.2774 g, 1.76 mmol, 94%, >20:1 Z:E by ^{1}H NMR analysis).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (m, 1H), 4.92 (d, J = 10.0 Hz, 1H), 3.64 (app q, J = 6.3 Hz, 2H), 2.04 (m, 2H),1.54-1.59 (m, 2H), 1.26-1.39 (m, 10H).



D-(Z)-alkenoic acid [2]: A 50 mL round bottom flask was charged with 10-(Z)-D-9-decen-1-ol (0.2774 g, 1.76 mmol, 1.0 equiv.), DCM (8.39 mL, 0.21 M), phthalic anhydride (0.274 g, 1.85 mmol, 1.05 equiv.), NEt_3 (0.368 mL, 2.65 mmol, 1.5 equiv.), and DMAP (53.8 mg, 0.44 mmol, 0.25 equiv.) and let stir for 12 hrs. The reaction was then poured into a separatory funnel containing 1 M HCl (10 mL) and DCM (10 mL). The organic layer was washed with 1 M HCl (3 x 10 mL), H_2O (1 x 10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil. Purification by flash chromatography (20% EtOAc/hexanes + 1% AcOH) furnished D-(Z)-alkenoic acid **2** as a yellow oil (0.457 g, 1.497 mmol, 85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (m, 1H), 7.73 (m, 1H), 7.60 (m, 2H), 5.78 (m, 1H), 4.90 (d, J = 10.5 Hz, 1H), 4.33 (t, J = 7.0 Hz, 2H), 2.01 (m, 2H), 1.71-1.77 (m, 2H), 1.23-1.43 (m, 10H).



D-(E+Z)-Macrolides [3]: *In-Situ Pd(II)/bis-sulfoxide Catalyst (**1**) Preparation for C–H Oxidative Macrolactonization:* An oven dried 1 dram borosilicate vial (topped with a Teflon-lined cap) was charged sequentially with recrystallized $Pd(OAc)_2$ (4.48 mg, 0.02 mmol, 0.1 equiv.), *meso*-1,2-bis(phenylsulfinyl)ethane

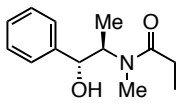
(5.56 mg, 0.02 mmol, 0.1 equiv.), CH_2Cl_2 (0.22 mL), and a teflon stir bar. The 1 dram vial was then stirred for 12 hours in 40°C bath, at which time a clear bright red solution resulted.

C–H Oxidative Macrolactonization: The freshly prepared catalyst (**1**) batch in a 1 dram vial was transferred to a 40 mL scintillation vial via pipette using DCM (5 mL). This vial was charged with 1,4-benzoquinone (43.2 mg, 0.4 mmol, 2.0 equiv.). D-(Z)-alkenoic acid **2** (60.9 mg, 0.2 mmol, 1.0 equiv.) was then dissolved/transferred (via pipette) to the 40 mL scintillation vial using CH_2Cl_2 (14.78 mL) and the reaction was topped with a Teflon-lined cap. This orange solution was stirred in a 45°C bath 72 hrs. The resulting dark brown reaction was cooled to r.t. and transferred to a separatory funnel with CH_2Cl_2, where it was quenched with satd NH_4Cl (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil. ^{1}H NMR analysis of the crude product showed a 1:1 E:Z ratio. Purification by flash chromatography (10% EtOAc/hexanes) furnished D-(E+Z)-macrolides **3** as an inseparable equal mixture of E:Z isomers as a clear oil (33.7 mg, 0.111 mmol, 56%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73-7.75 (m, 4H), 7.51-7.56 (m, 4H), 5.90-5.94 (m, 2H), 5.66-5.69 (m, 2H), 5.33 (d, J = 17.0 Hz, 1H), 5.19 (d, J = 10.5 Hz, 1H), 4.72-4.76 (m, 2H), 3.99-4.03 (m, 2H), 1.70-1.83 (m, 6H), 1.44-1.64 (m, 11H), 1.30-1.39 (m, 7H).

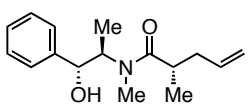
This same procedure was performed using the "*C–H Oxidative Macrolactonization +TBAF*" protocol, where TBAF (9.4 mg, 0.03 mmol, 0.15 equiv.) was also added to the reaction, and gave similar results (27.9 mg, 0.092 mmol, 46%, 1:1 E:Z ratio).

Synthesis of the Linear Macrocyclization Precursor for Figures 7-10



***N*-((1-*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropionamide [6]:** A flame-dried 250 mL round bottom flask was sequentially charged with (1R, 2R)-(-)-Pseudoephedrine (Sigma-Aldrich, 10 g, 60.5 mmol, 1.0 equiv.), CH_2Cl_2 (110 mL, 0.55 M), NEt_3 (9.26 mL, 66.57 mmol, 1.1 equiv.), propionic anhydride (Sigma-Aldrich, 8.34 mL, 64.75 mmol, 1.07 equiv.). The reaction mixture was allowed to stir for 1.5 hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (75 mL). The layers were separated and the organic layer was washed sequentially with saturated $NaHCO_3$ (1 x 50 mL), 1M HCl (2 x 30 mL), brine (1 x 50 mL). Organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude white solid was dissolved in refluxing toluene (18 mL), and allowed to cool overnight in a -20°C refrigerator. Upon recrystallization of a white solid, the supernatant was removed by decantation. The white crystals were dried under vacuum to yield the Myers' auxiliary **6** (12.67 g, 57.25 mmol, 95%).

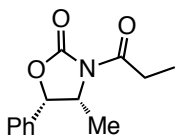
^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$) δ 7.27-7.39 (m, 5H), 4.56-4.61 (m, 1H), 4.43 (m, 1H), 4.31 (br s, 1H), 4.01* (m, 1H), 2.93* (s, 3H), 2.81 (s, 3H), 2.54* (m, 2H), 2.40* (m, 2H), 2.31 (m, 2H), 1.17* (t, J = 7.0 Hz, 3H), 1.13 (t, J = 7.5 Hz, 3H), 1.12 (d, J = 7.5 Hz, 3H), 0.98* (d, J = 6.5 Hz, 3H). $[\alpha]_D^{23}$ = -100^o (c = 0.57, methanol). Note that this spectroscopic data is in full agreement with a previous literature report.[33]



(*S*)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylpent-4-enamide [7]: A flame dried 500 mL round bottom flask under Ar was

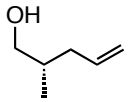
charged with LiCl (11.49 g, 271.12 mmol, 6.0 equiv.) and flame-dried vigorously. The reaction flask was then charged sequentially with THF (54 mL) and diisopropylamine (14.25 mL, 101.67 mmol, 2.25 equiv.). The resulting suspension was cooled to -78°C, and a solution of *n*-butyllithium in hexanes (2.56 M, 36.6 mL, 93.99 mmol, 2.08 equiv.) was added via syringe. The suspension was warmed to 0°C briefly then cooled to -78°C. An ice-cooled solution of Myers' auxiliary **6** (10.0 g, 45.18 mmol, 1.0 equiv.) in THF (141 mL) was added to the reaction flask via cannula. The reaction mixture was stirred at -78°C for 1 h, 0°C for 15 min, room temperature for 5 min, and finally cooled to -78°C, whereupon allyl iodide (98%, 6.3 mL, 67.78 mmol, 1.5 equiv.) was added to reaction via syringe. The reaction was allowed to stir at -78°C for 2 h, 0°C for 30 min, and then quenched by the addition of saturated aqueous ammonium chloride solution (150 mL). The layers were partitioned and the aqueous layer was extracted with ethyl acetate (3 x 200 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford an orange oil. ^{1}H NMR analysis of the crude product showed a d.r. > 20:1. Purification by flash chromatography (35% EtOAc/hexanes) furnished amide **7** as a yellow oil (11.31g, 43.28 mmol, 96%).

^{1}H NMR (4:1 rotamer ratio, asterisk denotes minor rotamer peaks, 400 MHz, $CDCl_3$) δ 7.24-7.38 (m, 5H), 5.78* (m, 1H), 5.69 (dddd, J = 17.2, 14.0, 10.0, 6.8 Hz, 1H), 5.10* (d, J = 17.2 Hz, 1H), 5.02 (d, J = 17.2 Hz, 1H), 4.99 (d, J = 10.4 Hz, 1H), 4.60 (m, 1H), 4.42 (br s, 1H), 4.07* (m, 1H), 2.91* (s, 3H), 2.86 (s, 3H), 2.68 (m, 1H), 2.51* (m, 1H), 2.35 (m, 1H), 2.16* (m, 1H), 2.08 (m, 1H), 1.01-1.12 (m, 6H). Note that this spectroscopic data is in full agreement with a previous literature report.[34]



(4*R*,5*S*)-4-methyl-5-phenyl-3-propionyloxazolidin-2-one [8]: A flame dried 500 mL round bottom flask under Ar was charged with (4R,5S)-(+)-4-Methyl-5-phenyl-2-oxazolidinone (Sigma-Aldrich, 15.183 g, 85.68 mmol, 1.0 equiv.) and THF (248 mL, 0.346 M). The reaction was cooled to -78°C and a solution of *n*-butyllithium in hexanes (2.45 M, 34.97 mL, 85.68 mmol, 1.0 equiv.) was added via syringe over 30 min. The resulting dark red solution was stirred for 15 min at -78°C. The reaction was then charged with propionyl chloride (8.4 mL, 95.96 mmol, 1.12 equiv.) and stirred for 1.5 hr. The reaction was quenched with satd K_2CO_3 (80 mL) and diluted with satd NaCl (40 mL) and EtOAc (100 mL) to achieve a homogenous solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 60 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford an orange oil. Purification by flash chromatography (linear gradient 15-20% EtOAc/hexanes) furnished N-propionyloxazolidinone **8** as a clear oil (18.91 g, 81.05 mmol, 95%).

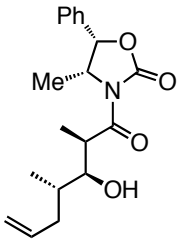
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.44 (m, 5H), 5.67 (d, J = 7.2 Hz, 1H), 4.77 (app pent, J = 6.7 Hz, 1H), 2.96 (m, 2H), 1.18 (t, J = 7.6 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H). $[\alpha]_D^{23}$ = +44.8^o (c = 2.47, CH_2Cl_2). Note that this spectroscopic data is in full agreement with a previous literature report.[35]



(*S*)-2-methylpent-4-en-1-ol: A flame-dried 100 mL round bottom flask under Ar was charged with THF (17 mL) and diisopropylamine (2.82 mL, 20.15 mmol, 4.2 equiv.). The reaction flask was cooled to -78°C and a solution of *n*-butyllithium in hexanes (2.56 M, 7.49 mL, 19.19 mmol, 4.0 equiv.) was added via syringe. The reaction temperature was maintained at -78°C for 10 min and then 0°C for 10 min. Solid Borane-ammonia complex (90%,

0.658 g, 19.19 mmol, 4.0 equiv.) was then added to the reaction mixture, and a vigorous evolution of gas ensued. After stirring for 15 min at 0°C, the reaction was warmed to room temperature for 15 min, then finally recooled to 0°C, where a solution of amide **7** (1.25 g, 4.79 mmol, 1.0 equiv.) in THF (15 mL) was cannulated in the reaction mixture using THF (3 mL) to quantitate the transfer. The reaction was warmed to room temperature, let stir for 1 hr, and then quenched by the cautious addition of 1M HCl (50 mL) and allowed to stir for 30 min. The layers were separated and the aqueous layer was extracted with Et_2O (4 x 20 mL). The combined organic layers were washed successively with 1M HCl (1 x 20 mL), 1M NaOH (1 x 20 mL), and brine (1 x 40 mL). The organic layer was then dried over $MgSO_4$, and concentrated *in vacuo* (cold, under reduced vacuum**)** to afford a clear oil. Purification by flash chromatography (40% Et_2O/pentane) furnished the alcohol product as a clear oil (0.470 g, 4.694 mmol, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, J = 17.2, 10.0, 7.2 Hz, 1H), 5.02 (m, 2H), 3.50 (m, 2H), 2.17 (m, 1H), 1.94 (m, 1H), 1.73 (octet, J = 6.8 Hz, 1H), 1.37 (t, J = 6.0 Hz, 1H), 0.92 (d, J = 6.8 Hz, 3H). $[\alpha]_D^{23}$ = -2.2^o (c = 1.5, $CHCl_3$). Note that this spectroscopic data is in full agreement with a previous literature report.[36]



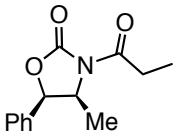
(4*R*,5*S*)-3-((2*R*,3*S*,4*S*)-3-hydroxy-2,4-dimethylhept-6-enoyl)-4-methyl-5-phenyloxazolidin-2-one [9]: A flame-dried 500 mL round bottom flask under Ar was charged with CH_2Cl_2 (48.0 mL) and oxalyl chloride (3.91 mL, 44.80 mmol, 1.27 equiv.) and cooled to -78°C. A solution of DMSO (4.01 mL, 56.50 mmol, 1.60 equiv.) in CH_2Cl_2 (9.7 mL) pre-cooled to -78°C was cannulated into oxalyl chloride solution and evolution of gas occurred. Reaction was stirred stir for 1 hr at -78°C, then a solution of (*S*)-2-methylpent-4-en-1-ol (3.537 g, 35.31 mmol, 1.0 equiv.) in CH_2Cl_2 (8.7 mL) was

cannulated into the reaction flask using CH_2Cl_2 (1 mL) to quantitate the transfer. The reaction was stirred for 2.5 hr at -78°C when NEt_3 (24.6 mL, 176.5 mmol, 5.0 equiv.) was syringed into reaction flask, which was subsequently allowed to warm to room temperature. The reaction was quenched upon the addition of 1M KH_2PO_4 solution (60 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (1 x 15 mL). The combined organic layers were washed with brine (1 x 40 mL) and the organic layer was dried over Na_2SO_4 and filtered into a flame-dried 250 mL round bottom flask containing activated 4Å molecular sieves. The crude aldehyde solution was used directly without further concentration or purification.

A flame-dried 1 L round bottom flask under Ar was charged sequentially with N-propionyloxazolidinone **8** (8.23 g, 35.31 mmol, 1.0 equiv.), CH_2Cl_2 (100 mL), and iPr_2NEt (8.30 mL, 47.7 mmol, 1.35 equiv.) and cooled to 0°C. The reaction flask was then charged with Bu_2BOTf (1 M in CH_2Cl_2, 42.3 mL, 42.3 mmol, 1.2 equiv.) and let stir at 0°C for 1 hr, then cooled to -78°C. The crude aldehyde solution, pre-cooled to -78°C, was cannulated into the reaction flask using CH_2Cl_2 (17 mL) to quantitate the transfer and let stir at -78°C for 1.5 hr, then warmed to room temperature and stirred for 1 hr. The reaction was then quenched with the addition of 1M KH_2PO_4 solution (60 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 60 mL). The combined organic layers were concentrated *in vacuo* to incomplete dryness and the slurry was dissolved in MeOH (65 mL), put in a 0°C bath, and charged cautiously with H_2O_2 (30% wt solution, 98 mL). The product mixture was allowed to stir at room temperature for 1 hr and then diluted with brine (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 60 mL), the organic layers were then combined and dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a clear oil. ^1H NMR analysis of the crude product showed a d.r. > 20:1. Purification by flash chromatography

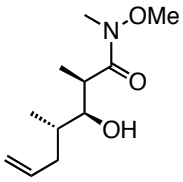
(22% EtOAc/hexanes) followed by recrystallization in refluxing 22% EtOAc/cyclohexane (15 mL) furnished aldol adduct **9** as white needles (6.4835 g, 19.564 mmol, 55% over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.45 (m, 3H), 7.29-7.32 (m, 2H), 5.83 (dddd, *J* = 17.0, 10.0, 8.0, 6.0 Hz, 1H), 5.69 (d, *J* = 7.2 Hz, 1H), 5.07 (d, *J* = 17.0 Hz, 1H), 5.04 (d, *J* = 8.8 Hz, 1H), 4.79 (quint, *J* = 6.8 Hz, 1H), 3.96 (dq, *J* = 7.0, 2.0 Hz, 1H), 3.65 (app dt, *J* = 9.3, 2.6 Hz, 1H), 3.07 (d, *J* = 3.2 Hz, 1H), 2.51-2.57 (m, 1H), 1.93-2.00 (m, 1H), 1.65-1.73 (m, 1H), 1.22 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.4 Hz, 6H). $[\alpha]_D^{23}$ = +47° (c = 0.25, $CHCl_3$). Note that this spectroscopic data is in full agreement with a previous literature report.[37]



(4*S*,5*R*)-4-methyl-5-phenyl-3-propionyloxazolidin-2-one [10]: A flame dried 500 mL round bottom flask under Ar was charged with (4S,5R)-(-)-4-Methyl-5-phenyl-2-oxazolidinone (Sigma-Aldrich, 10.688 g, 60.32 mmol, 1.0 equiv.) and THF (174.3 mL, 0.346 M). The reaction was cooled to -78°C and a solution of *n*-butyllithium in hexanes (2.5 M, 24.13 mL, 60.32 mmol, 1.0 equiv.) was added via syringe over 30 min. The resulting dark red solution was stirred for 15 min at -78°C. The reaction was then charged with propionyl chloride (5.90 mL, 67.55 mmol, 1.12 equiv.) and stirred for 1.5 hr. The reaction was quenched with satd K_2CO_3 (60 mL) and diluted with satd NaCl (30 mL) and EtOAc (80 mL) to achieve a homogenous solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 60 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a clear oil. Purification by flash chromatography (linear gradient 15-20% EtOAc/hexanes) furnished N-propionyloxazolidinone **10** as a clear oil (13.367 g, 57.30 mmol, 95%).

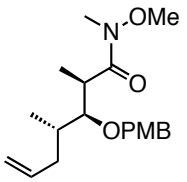
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.43 (m, 5H), 5.67 (d, *J* = 7.5 Hz, 1H), 4.77 (app pent, *J* = 6.8 Hz, 1H), 2.96 (m, 2H), 1.19 (t, *J* = 7.3 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H). $[\alpha]_D^{23}$ = -55.0 ^{o} (c = 2.23, CH_2Cl_2). Note that this spectroscopic data is in full agreement with a previous literature report.[38]



(2*R*,3*S*,4*S*)-3-hydroxy-*N*-methoxy-*N*,2,4-trimethylhept-6-enamide: A flame dried 500 mL round bottom flask was charged with N,O-dimethylhydroxylamine hydrochloride (Sigma-Aldrich, 7.36 g, 73.96 mmol, 5.0 equiv.) and THF (74 mL). The reaction flask was cooled to -10°C, and charged with $AlMe_3$ (Sigma-Aldrich, 2 M in toluene, 37.1 mL, 74.11 mmol, 5.01 equiv.). An evolution of gas ensued and the reaction was stirred at -10°C for 15 min, room temperature 15 min, and then finally cooled to -10°C. Aldol adduct **9** (4.9027 g, 14.79 mmol, 1.0 equiv.) dissolved in THF (74 mL) was cannulated into reaction flask and allowed to warm to room temperature slowly while stirring for 12 hr. The reaction was quenched at -10°C with the cautious addition of saturated Rochelle's salt (100 mL) and the resulting mixture was stirred vigorously for 4 hr. The layers were then separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ (1 x 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil. Purification by flash chromatography (35% EtOAc/hexanes) furnished the 3-hydroxyheptenamide product as a yellow oil (2.732 g, 12.69 mmol, 86%).

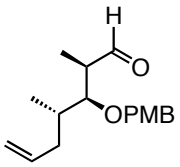
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (dddd, *J* = 16.5, 10.0, 8.4, 6.0 Hz, 1H), 5.03 (d, *J* = 18.3 Hz, 1H), 5.00 (d, *J* = 11.0 Hz, 1H), 4.07 (br, s, 1H), 3.69 (s, 3H), 3.50 (d, *J* = 9.5 Hz, 1H), 3.19 (s, 3H), 3.08 (m, 1H), 2.55 (m, 1H), 1.92 (app dt, *J* = 13.7, 8.6 Hz, 1H), 1.66 (m, 1H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 137.1, 116.2,

74.8, 61.5, 37.1, 35.4, 35.0, 31.8, 15.0, 9.4; IR (film, cm^{-1}): 3453, 3075, 2970, 2936, 1640, 1460, 994; HRMS (ESI) *m/z* calc'd for $C_{11}H_{21}NO_3Na$ $[M + Na]^+$: 238.1419, found 238.1416; $[\alpha]_D^{23}$ = +2.2° (c = 0.56, $CHCl_3$).



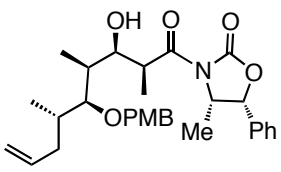
(2*R*,3*S*,4*S*)-3-(4-methoxybenzyloxy)-*N*-methoxy-*N*,2,4-trimethylhept-6-enamide: A flame-dried 25 mL round bottom flask was charged sequentially with the 3-hydroxyheptenamide (0.156 g, 0.725 mmol, 1.0 equiv.), DMF (0.3 M, 2.42 mL), and 4-methoxybenzyl bromide (Sigma-Aldrich, 0.183 mL, 1.27 mmol, 1.75 equiv.). Reaction flask cooled to 0°C and charged with NaH (Sigma-Aldrich, 60 wt% dispersion in mineral oil, 48.1 mg, 1.203 mmol, 1.66 equiv.). The reaction stirred for 1.5 hr and was then poured into a separatory funnel containing H_2O (20 mL) and 50% Et_2O/Pentane (20 mL). The layers were separated and the organic layer was washed with H_2O (1 x 20 mL) and brine (1 x 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil. Purification by flash chromatography (20% EtOAc/hexanes) furnished the 3-(4-methoxybenzoyloxy)heptenamide product as a yellow oil (0.2322 g, 0.6926 mmol, 96%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.75 (dddd, *J* = 16.8, 10.0, 8.0, 6.3 Hz, 1H), 5.00 (d, *J* = 17.0, 1H), 4.98 (d, *J* = 9.0 Hz, 1H) 4.54 (d, *J* = 10.5 Hz, 1H), 4.49 (d, *J* = 11.0 Hz, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 3.60 (dd, *J* = 7.3, 4.3 Hz, 1H), 3.19 (br, s, 4H), 2.37 (m, 1H), 1.87 (m, 1H), 1.67 (m, 1H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.8, 159.1, 137.9, 130.9, 129.5, 115.7, 113.7, 84.5, 74.7, 61.4, 55.2, 38.3, 36.7, 36.0, 32.3, 16.9, 13.8; IR (film, cm^{-1}): 3075, 2964, 2935, 1661, 1613, 1514, 1461, 1248; HRMS (ESI) *m/z* calc'd for $C_{19}H_{30}NO_4$ $[M + H]^+$: 336.2175, found 336.2185; $[\alpha]_D^{23}$ = -9.7° (c = 0.43, $CHCl_3$).



(2*R*,3*S*,4*S*)-3-(4-methoxybenzyloxy)-2,4-dimethylhept-6-enal: A flame-dried 250 mL round bottom flask under Ar was charged with 3-(4-methoxybenzoyloxy)heptenamide (3.6875 g, 10.99 mmol, 1.0 equiv.) and THF (0.26 M, 41.6 mL). The reaction flask was cooled to -78°C and charged with Dibal-H (Sigma-Aldrich, 1 M in hexanes, 22.0 mL, 22.0 mmol, 2.0 equiv.) and let stir at -78°C for 2 hr. The reaction was then cannulated into a solution of 1M HCl and stirred vigorously for 1 hr at which time the layers were separated. The organic layer was washed with H_2O (1 x 50 mL) and brine (1 x 50 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 x 60 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a clear oil. Purification by flash chromatography (10% EtOAc/hexanes) furnished the heptenal product as a clear oil (2.751 g, 9.953 mmol, 91%).

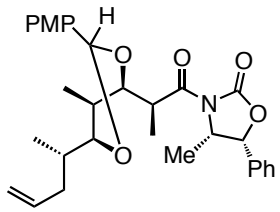
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (d, *J* = <1 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 5.82 (dddd, *J* = 17.5, 10.5, 8.0, 6.0 Hz, 1H), 5.06 (m, 2H), 4.42 (app s, 2H), 3.85 (s, 3H), 3.76 (dd, *J* = 8.0, 3.0 Hz, 1H), 2.65 (dq, J = 7.0, 3.0 Hz, 1H), 2.50 (m, 1H), 2.02 (m, 1H), 1.92 (m, 1H), 1.17 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 159.2, 136.9, 130.2, 129.3, 116.5, 113.8, 81.5, 73.3, 55.3, 49.1, 37.2, 35.9, 15.9, 7.8; IR (film, cm^{-1}): 3074, 2969, 2935, 2878, 2712, 1723, 1613, 1514, 1463, 1249; HRMS (ESI) *m/z* calc'd for $C_{17}H_{24}O_3Na$ $[M + Na]^+$: 299.1623, found 299.1616; $[\alpha]_D^{23}$ = -40.9^o (c = 2.26, $CHCl_3$).



(4*S*,5*R*)-3-((2*S*,3*R*,4*S*,5*S*,6*S*)-5-(4-methoxybenzyloxy)-3-hydroxy-2,4,6-trimethylnon-8-enoyl)-4-methyl-5-phenyloxazolidin-2-one [11]: A flame-dried 100 mL round bottom flask under Ar was charged with N-propionyloxazolidinone **10** (2.208 g, 9.47 mmol, 1.04 equiv.) and CH_2Cl_2 (8.6 mL) and cooled to

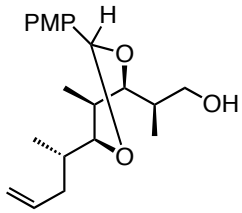
-78°C. The reaction was then charged with Bu_2BOTf (1 M in CH_2Cl_2, 10.7 mL, 10.74 mmol, 1.18 equiv.) and the reaction solution turned dark orange. NEt_3 (1.51 mL, 10.83 mmol, 1.19 equiv.) was added to the reaction, followed by stirring at -78°C for 5 min, 0°C for 10 min, and finally re-cooled to -78°C. A solution of the heptenal (2.516 g, 9.104 mmol, 1.0 equiv.) in CH_2Cl_2 (8.6 mL) was cooled to -78°C, cannulated into reaction flask at -78°C, and stirred for 1.5 hr. The reaction was then warmed to 0°C and stirred for 1.5 hr. The reaction was quenched consecutively with H_2O (9 mL), MeOH (25 mL), and H_2O_2 (30% wt solution, 9 mL), and stirred for 3 hr at room temperature. The reaction was then concentrated *in vacuo* to give a slurry, which was partitioned between H_2O (20 mL) and EtOAc (20 mL). After separating the layers, the aqueous layer was extracted with EtOAc (4 x 20 mL) and the combined organic layers were washed with satd $NaHCO_3$ (1 x 20 mL) and brine (1 x 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil. ^{1}H NMR analysis of the crude product showed a d.r. > 20:1. Purification by flash chromatography (20% EtOAc/hexanes) furnished aldol adduct **11** as a clear oil (4.472 g, 8.774 mmol, 96%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.45 (m, 3H), 7.28-7.32 (m, 4H), 6.87 (d, *J* = 8.0 Hz, 2H), 5.81 (m, 1H), 5.66 (d, *J* = 7.0 Hz, 1H), 5.04 (d, *J* = 16.0 Hz, 1H), 5.02 (d, *J* = 8.5 Hz, 1H), 4.77 (quint, *J* = 6.8 Hz, 1H), 4.63 (app. q, *J* = 11 Hz, 2H), 3.89-3.96 (m, 2H), 3.78 (s, 3H), 3.64 (d, *J* = 9.0 Hz, 1H), 3.52 (d, J = 2.5 Hz, 1H), 2.54-2.56 (m, 1H), 1.83-1.94 (m, 3H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 158.9, 152.4, 137.7, 133.1, 131.5, 128.9 (2 peaks), 128.8, 125.6, 116.0, 113.7, 82.6, 78.9, 74.2, 72.2, 55.3, 54.7, 39.3, 38.0, 37.2, 36.0, 15.9, 14.3, 9.8, 9.2; IR (film, cm^{-1}): 3522, 3073, 2973, 2934, 1783, 1687, 1613, 1514, 1456, 1367; HRMS (ESI) *m/z* calc'd for $C_{30}H_{40}NO_6$ $[M + H]^+$: 510.2856, found 510.2868; $[\alpha]_D^{23} = -3.3^o$ (c = 0.83, $CHCl_3$).



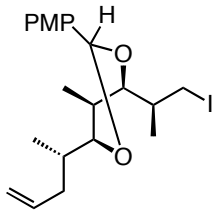
(4*S*,5*R*)-3-((*S*)-2-((2*S*,4*R*,5*R*,6*S*)-2-(4-methoxyphenyl)-5-methyl-6-((*S*)-pent-4-en-2-yl)-1,3-dioxan-4-yl)propanoyl)-4-methyl-5-phenyloxazolidin-2-one [15]: A flame-dried 500 mL round bottom flask was charged with aldol adduct **11** (4.3297 g, 8.49 mmol, 1.0 equiv.), CH_2Cl_2 (100 mL), and $MgSO_4$ (8.0 g). A suspension of DDQ (Sigma-Aldrich, 2.314 g, 10.12 mmol, 1.2 equiv.) and $MgSO_4$ (4.6 g) in CH_2Cl_2 (100 mL) was cannulated in reaction flask, causing an instantaneous color change to green, which then gradually turned brown. The suspension was stirred for 15 min at which time the reaction was quenched with satd $NaHCO_3$ (300 mL). The resulting orange solution was stirred for 5 min at which time the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 80 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a clear oil. ^{1}H NMR analysis of the crude product showed a d.r. > 20:1. Purification by flash chromatography (15% EtOAc/hexanes) furnished PMB acetal **15** as a clear oil (3.9887 g, 7.857 mmol, 93%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.47 (m, 5H), 7.31-7.33 (d, *J* = 7.0 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 5.78 (dddd, *J* = 18.0, 14.8, 9.0, 6.3 Hz, 1H), 5.63 (s, 1H), 5.63 (d, *J* = 8.0 Hz, 1H), 5.03 (app d, *J* = 12.5 Hz, 2H), 4.78- 4.87 (m, 2H), 4.14 (d, *J* = 11.0 Hz, 1H), 3.81 (s, 3H), 3.73 (dd, *J* = 10.0, 2.0 Hz, 1H), 2.53-2.57 (m, 1H), 1.90 (dt, *J* = 13.5, 8.5 Hz, 1H), 1.75-1.79 (m, 1H), 1.48 (dq, *J* = 6.8, 1.0 Hz, 1H), 1.35 (d, *J* = 6.5 Hz, 3H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.79 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 159.9, 152.6, 136.8, 133.0, 131.5, 128.9, 128.8, 127.3, 125.6, 116.4, 113.6, 95.6, 81.1, 78.9 (2 peaks), 55.3, 54.9, 37.0, 36.8, 33.8, 31.6, 14.9, 14.3, 13.7, 13.0; IR (film, cm^{-1}): 3073, 2974, 2936, 2879, 1783, 1698, 1615, 1517, 1455, 1347; HRMS (ESI) *m/z* calc'd for $C_{30}H_{38}NO_6$ $[M + H]^+$: 508.2699, found 508.2705; $[\alpha]_D^{23} = -5.8^o$ (c = 1.05, $CHCl_3$).



(*R*)-2-((2*S*,4*S*,5*R*,6*S*)-2-(4-methoxyphenyl)-5-methyl-6-((*S*)-pent-4-en-2-yl)-1,3-dioxan-4-yl)propan-1-ol [13]: A flame-dried 250 mL round bottom flask under Ar was charged with PMB acetal **15** (3.9887 g, 7.857 mmol, 1.0 equiv.) and THF (0.25 M, 31.4 mL) and cooled to -78°C. The reaction flask was then charged with LAH (Sigma-Aldrich, 1 M in THF, 23.6 mL, 23.6 mmol, 3.0 equiv.) via syringe over the course of 10 min, and the reaction flask was allowed to warm up to room temperature on its own accord over 12 hrs. The reaction was then cooled to 0°C and quenched with the cautious addition of 1 M NaOH (15 mL), followed by celite and $MgSO_4$ and allowed to stir vigorously at room temperature for 1.5 hr. The reaction mixture was filtered through a celite plug washing with THF (400 mL) and concentrated *in vacuo* to afford a clear oil. Purification by flash chromatography (30% EtOAc/hexanes) furnished alcohol **13** as a white solid (2.522 g, 7.541 mmol, 96%).

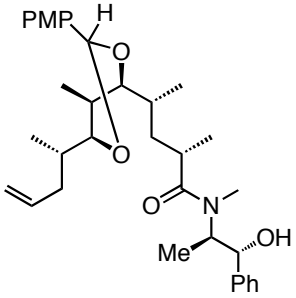
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.79 (dddd, *J* = 18, 15.2, 8.8, 6.4 Hz, 1H), 5.63 (s, 1H), 5.03 (m, 2H), 3.80 (s, 3H), 3.54-3.68 (m, 4H), 2.47-2.54 (m, 2H), 1.88-1.97 (m, 2H), 1.80 (m, 1H), 1.43 (br s, 1H), 1.19 (d, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 136.8, 131.9, 127.2, 116.4, 113.6, 95.4, 81.9, 78.5, 65.9, 55.3, 37.2, 34.3, 33.8, 30.1, 13.8 (2 peaks), 13.1; IR (film, cm^{-1}): 3317, 3074, 2968, 2933, 2877, 1615, 1515, 1248; HRMS (ESI) *m/z* calc'd for $C_{20}H_{31}O_4$ $[M + H]^+$: 335.2222, found 335.2215; $[\alpha]_D^{23}$ = -41.8° (c = 0.35, $CHCl_3$).



(2*S*,4*R*,5*R*,6*S*)-4-((*S*)-1-iodopropan-2-yl)-2-(4-methoxyphenyl)-5-methyl-6-((*S*)-pent-4-en-2-yl)-1,3-dioxane: A flame dried 25 mL round bottom flask was charged sequentially with PPh_3 (0.513 g, 1.961 mmol, 1.2 equiv.), CH_2Cl_2 (5.5 mL), imidazole (Sigma-Aldrich, 0.166 g, 2.452 mmol, 1.5 equiv.), and I_2 (Sigma-Aldrich,

0.560 g, 2.207 mmol, 1.35 equiv.). An exotherm ensued upon the addition of I_2 and resulted in a brown suspension. The reaction flask was charged with alcohol **13** (0.5468 g, 1.635 mmol, 1 equiv.) in CH_2Cl_2 (1.1 mL) via cannula and let stir for 3 hr, at which time the reaction was concentrated *in vacuo* and purified by flash chromatography (5% EtOAc/hexanes) to furnish the iodide product as a white solid (0.6837 g, 1.538 mmol, 94%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.78 (dddd, *J* = 17.5, 14.5, 8.5, 6.0 Hz, 1H), 5.57 (s, 1H), 5.03 (m, 2H), 3.80 (s, 3H), 3.55 (dd, *J* = 10.0, 2.5 Hz, 2H), 3.32 (dd, *J* = 10.3, 2.8 Hz, 1H), 3.12 (dd, *J* = 10.0, 5.5 Hz, 1H), 2.51 (m, 1H), 2.21 (m, 1H), 1.92 (dt, *J* = 14.0, 8.5 Hz, 1H), 1.80 (m, 1H), 1.74 (q, *J* = 6.5 Hz, 1H), 1.22 (d, *J* = 7.0 Hz, 3H), 1.13 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 136.7, 131.6, 127.2, 116.5, 113.6, 96.0, 84.0, 78.5, 55.3, 37.1, 33.8, 31.8, 29.2, 17.7, 13.9, 13.0, -7.9; IR (film, cm^{-1}): 3073, 2968, 2932, 2876, 2836, 1615, 1516, 1460, 1378, 1301, 1249; HRMS (ESI) *m/z* calc'd for $C_{20}H_{30}O_3I$ $[M + H]^+$: 445.1240, found 445.1221; $[\alpha]_D^{23}$ = -37.0° (c = 0.21, $CHCl_3$).

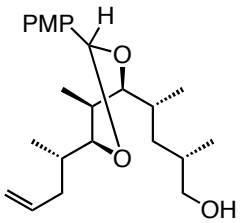


(2*S*,4*R*)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-4-((2*S*,4*S*,5*R*,6*S*)-2-(4-methoxyphenyl)-5-methyl-6-((*S*)-pent-4-en-2-yl)-1,3-dioxan-4-yl)-*N*,2-dimethylpentanamide [16]: A 250 mL round bottom flask under Ar was charged with LiCl (3.13 g, 73.98 mmol, 12.7 equiv.) and flame-dried vigorously 5 times. The reaction flask was then charged sequentially with THF (16.7 mL) and diisopropylamine (3.51 mL, 25.1 mmol, 4.31 equiv.). The resulting suspension was cooled to -78°C, and a solution of *n*-butyllithium in hexanes (2.48 M, 9.39 mL, 23.3 mmol, 4.0 equiv.) was added via syringe. The suspension was

warmed to 0°C briefly then cooled to -78°C. An ice-cooled solution of Myers' auxiliary **6** (2.707 g, 12.23 mmol, 2.1 equiv.) in THF (38 mL) was added to the reaction flask via cannula. The reaction mixture was stirred at -78°C for 1 h, 0°C for 15 min, room temperature for 5 min, and finally cooled to 0°C, whereupon a 0°C solution of freshly prepared iodide compound (2.5885 g, 5.825 mmol, 1.0 equiv.) in THF (12 mL) was added to the reaction via cannula. The reaction was allowed to warm up to room temperature on it's own accord over 12 hr. The reaction was then quenched by the addition of saturated aqueous ammonium chloride solution (100 mL). The layers were partitioned and the aqueous layer was extracted with ethyl acetate (4 x 80 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a clear oil. ^{1}H NMR analysis of the crude product showed a d.r. > 20:1. Purification by flash chromatography (linear gradient 25% to 30% EtOAc/hexanes) furnished amide **16** as a white amorphous solid (2.937 g, 5.462 mmol, 94%).

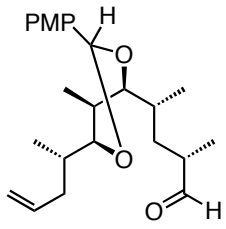
^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, 500 MHz, $CDCl_3$) δ 7.25-7.39 (m, 6H), 7.17-7.20 (m, 1H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.80* (d, *J* = 8.5 Hz, 2H), 5.70-5.81 (m, 1H), 5.47 (s, 1H), 5.44* (s, 1H), 4.88-4.98 (m, 2H), 4.61 (app t, *J* = 7.3 Hz, 1H), 4.54* (dd, *J* = 9.0, 1.5 Hz, 1H), 4.24 (br, s, 1H), 4.07* (app quint, *J* = 7.4 Hz, 1H), 3.73 (s, 3H), 3.71* (s, 3H), 3.56 (m, 1H), 3.53* (m, 1H), 3.26* (d, *J* = 9.0 Hz, 1H), 3.23 (d, *J* = 10.5 Hz, 1H), 3.06* (m, 1H), 2.87* (s, 3H), 2.80 (s, 3H), 2.69 (m, 1H), 2.47 (m, 1H), 1.98 (m, 2H), 1.82-1.92 (m, 2H), 1.71-1.76 (m, 1H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.97 (dd, *J* = 11.5, 7.0 Hz, 1H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 6.5 Hz, 3H), 0.80-0.85 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 176.6*, 159.7, 142.7, 141.4*, 137.5*, 137.0, 132.3*, 132.1, 128.8, 128.5*, 128.2, 127.5, 127.1, 126.8*, 126.0, 116.2, 115.9*, 113.6, 113.5*, 95.2, 94.9*, 84.9*, 84.7, 78.9, 78.7*, 76.3, 75.4*, 57.7*, 55.3, 38.9*, 38.4, 37.4*, 37.2, 34.4,

34.0*, 34.0, 33.7*, 30.0*, 29.8, 28.7, 28.4*, 27.1, 19.4*, 18.4, 16.7*, 15.9, 15.6*, 14.4, 13.8, 13.7*, 13.3; IR (film, cm^{-1}): 3401, 3072, 2969, 2932, 2873, 1621, 1516, 1463, 1377, 1301, 1249; HRMS (ESI) *m/z* calc'd for $C_{33}H_{48}NO_5$ $[M + H]^+$: 538.3532, found 538.3521; $[\alpha]_D^{23} = -31.7^o$ (c = 0.62, $CHCl_3$).



(2*S*,4*R*)-4-((2*S*,4*S*,5*R*,6*S*)-2-(4-methoxyphenyl)-5-methyl-6-((*S*)-pent-4-en-2-yl)-1,3-dioxan-4-yl)-2-methylpentan-1-ol: A flame-dried 25 mL round bottom flask under Ar was charged with THF (1.58 mL) and diisopropylamine (0.25 mL, 1.814 mmol, 4.2 equiv.). The reaction flask was cooled to -78°C and a solution of *n*-butyllithium in hexanes (2.45 M, 0.71 mL, 1.728 mmol, 4.0 equiv.) was added via syringe. The reaction temperature was maintained at -78°C for 10 min and then 0°C for 10 min. Solid Borane-ammonia complex (90%, 59.2 mg, 1.728 mmol, 4.0 equiv.) was then added to the reaction mixture, and a vigorous evolution of gas ensued. After stirring for 15 min at 0°C, the reaction was warmed to room temperature for 15 min, then finally recooled to 0°C, where a solution of amide **16** (0.2322 g, 0.4319 mmol, 1.0 equiv.) in THF (1.0 mL) was cannulated in the reaction mixture using THF (0.5 mL) to quantitate the transfer. The reaction was warmed to room temperature, let stir for 1 hr 45 min, and then quenched by the precautious addition of H_2O (3 mL) followed by satd NH_4Cl (5 mL) and Et_2O (5 mL). The layers were separated and the organic layers were washed successively with satd NH_4Cl (1 x 10 mL) and 1M NaOH (1 x 10 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil. Purification by flash chromatography (20% EtOAc/hexanes) furnished the primary alcohol product as a yellow oil (160.9 mg, 0.4273 mmol, 99%).

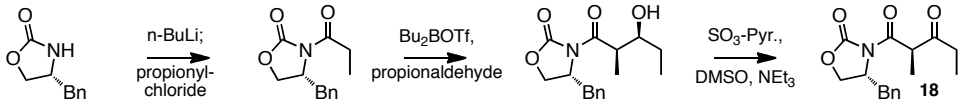
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 5.78 (dddd, *J* = 17.8, 14.8, 8.6, 6.0 Hz, 1H), 5.60 (s, 1H), 5.04 (m, 2H), 3.79 (s, 3H), 3.60 (dd, *J* = 10.0, 2.2 Hz, 1H), 3.56 (dd, *J* = 10.4, 4.4 Hz, 1H), 3.39 (dd, *J* = 10.6, 6.6 Hz, 1H), 3.33 (d, *J* = 10.8 Hz, 1H), 2.53-2.57 (m, 1H), 2.28-2.52 (m, 1H), 1.71-1.94 (m, 4H), 1.61 (br s, 1H), 1.35 (ddd, *J* = 14.0, 9.2, 2.8 Hz, 1H), 1.19 (d, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 6.4 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.92 (ddd, *J* = 14.0, 9.4, 5.0 Hz, 1H), 0.82 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 136.9, 131.8, 127.1, 116.3, 113.5, 95.2, 84.7, 78.6, 67.1, 55.2, 37.7, 37.1, 33.7, 33.3, 29.3, 29.1, 18.4, 16.6, 13.7, 13.2; IR (film, cm^{-1}): 3453 (br), 2966, 2929, 2879, 1617, 1518, 1462, 1379, 1302, 1249; HRMS (ESI) *m/z* calc'd for $C_{23}H_{37}O_4$ $[M + H]^+$: 377.2692, found 377.2709; $[\alpha]_D^{23} = -11.6^o$ (c = 0.44, CH_2Cl_2).

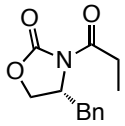


(2*S*,4*R*)-4-((2*S*,4*S*,5*R*,6*S*)-2-(4-methoxyphenyl)-5-methyl-6-((*S*)-pent-4-en-2-yl)-1,3-dioxan-4-yl)-2-methylpentanal [17]: A 50 mL round bottom flask was charged sequentially with primary alcohol (294.8 mg, 0.7829 mmol, 1.0 equiv.), CH_2Cl_2 (0.063 M, 12.4 mL), H_2O (3 drops), and Dess-Martin periodinane (Sigma-Aldrich, 0.531 g, 1.253 mmol, 1.6 equiv.). The white suspension was stirred at room temperature for 1 hr, at which time it was quenched with the addition of a 5:1 solution of $Na_2S_2O_3$: $NaHCO_3$ (33 mL). The resulting solution was stirred until homogeneity was reached, at which time the layers were separated, and the aqueous layer was washed with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a white solid. Purification by flash chromatography (10% EtOAc/hexanes) furnished aldehyde **17** as a white amorphous solid (281.1 mg, 0.7506 mmol, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, *J* = 2.0 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.79 (dddd, *J* = 16.8, 14.4, 8.4, 5.6 Hz, 1H), 5.53 (s, 1H), 5.04 (m, 2H), 3.79 (s, 3H), 3.60 (dd, *J* = 9.8, 2.0 Hz, 1H), 3.34 (d, *J* = 10.8 Hz, 1H), 2.52-2.61 (m, 2H), 2.24-2.31 (m, 1H), 1.86-1.96 (m, 2H), 1.74-1.82 (m, 2H), 1.21 (d, *J* = 7.2 Hz, 3H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 6.4 Hz, 3H), 1.02 (m, 1H), 0.88 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 159.7, 136.9, 131.8, 127.1, 116.2, 113.5, 95.3, 84.3, 78.7, 55.2, 44.2, 37.2, 35.1, 33.8, 29.7, 29.1, 16.0, 15.0, 13.7, 13.2; IR (film, cm^{-1}): 3073, 2973, 2937, 2839, 2711, 1724, 1617, 1518, 1460, 1249; HRMS (ESI) *m/z* calc'd for $C_{23}H_{35}O_4$ $[M + H]^+$: 375.2535, found 375.2540; $[\alpha]_D^{23}$ = -42.1° (c = 0.38, CH_2Cl_2).

Figure 17. Synthesis of β-keto imide **18**

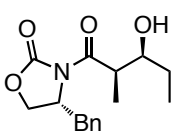




(*R*)-4-benzyl-3-propionyloxazolidin-2-one: A flame dried 250 mL round bottom flask under Ar was charged with (R)-4-Benzyl-2-oxazolidinone (TCI, 5.226 g, 29.49 mmol, 1.0 equiv.) and THF (85.2 mL, 0.346 M). The reaction was cooled to -78°C and a solution of *n*-butyllithium in hexanes (2.45 M, 12.0 mL, 29.49 mmol, 1.0 equiv.) was added via syringe over 30 min. The resulting dark red solution was stirred for 15 min at -78°C. The reaction was then charged with propionyl chloride (2.88 mL, 33.0 mmol, 1.12 equiv.) and stirred for 1.5 hr. The reaction was quenched with satd K_2CO_3 (30 mL) and diluted with satd NaCl (15 mL) and EtOAc (20 mL) to achieve a homogenous solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a clear oil. Purification by flash

chromatography (15% EtOAc/hexanes) furnished (*R*)-4-benzyl-3-propionyloxazolidin-2-one as a clear oil (6.647 g, 28.49 mmol, 97%).

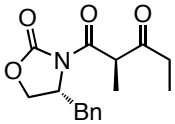
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.36 (m, 5H), 4.67 (m, 1H), 4.16-4.23 (m, 2H), 3.31 (dd, *J* = 16.5, 4.0 Hz, 1H), 2.96 (m, 2H), 2.77 (dd, *J* = 16.5, 12.0 Hz, 1H), 1.20 (t, *J* = 9.3 Hz, 3H). Note that this spectroscopic data is in full agreement with a previous literature report.[39]



(*R*)-4-benzyl-3-((2*R*,3*S*)-3-hydroxy-2-methylpentanoyl)oxazolidin-2-one: A flame dried 100 mL round bottom flask under Ar was charged with (*R*)-4-benzyl-3-propionyloxazolidin-2-one (3.39 g, 14.53 mmol, 1.0 equiv.) and CH_2Cl_2 (27.4 mL, 0.53 M). The reaction was cooled to -78°C and a solution of Bu_2BOTf (1 M in CH_2Cl_2, 17.15 mL, 17.15 mmol, 1.18 equiv.) was added via syringe over 5 min. The resulting orange solution was charged with NEt_3 (2.63 mL, 18.89 mmol, 1.3 equiv.) dropwise, and the resulting light yellow solution was stirred at -78°C for 15 min, warmed to r.t. briefly, then cooled down to 0°C. Once 0°C achieved, propionaldehyde (1.37 mL, 18.89 mmol, 1.3 equiv.) was syringed into rxn dropwise and stirred for 3.5 hr at 0°C. The reaction was quenched consecutively with H_2O (13 mL), MeOH (40 mL), and H_2O_2 (30% wt solution, 13 mL), and stirred for 2.5 hr at room temperature. The reaction was then concentrated *in vacuo* to give a slurry, which was partitioned between H_2O (20 mL) and EtOAc (20 mL). After separating the layers, the aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with satd $NaHCO_3$ (1 x 20 mL) and brine (1 x 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil. ^{1}H NMR analysis of the crude product showed a d.r. > 20:1. Purification by flash chromatography (30% EtOAc/hexanes) furnished aldol adduct (*R*)-

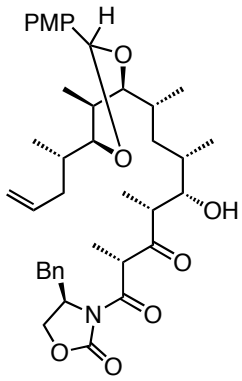
4-benzyl-3-((2*R*,3*S*)-3-hydroxy-2-methylpentanoyl)oxazolidin-2-one as a white solid (3.294 g, 11.31 mmol, 78%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20-7.35 (m, 5H), 4.71 (m, 1H), 4.18-4.25 (m, 2H), 3.87 (m, 1H), 3.79 (dq, *J* = 2.5, 7.0 Hz, 1H), 3.25 (dd, *J* = 13.5, 3.5 Hz, 1H), 2.88 (d, *J* = 2.5 Hz, 1H), 2.79 (dd, *J* = 13.5, 9.5 Hz, 1H), 1.58 (m, 1H), 1.47 (m, 1H), 1.25 (d, *J* = 7.5 Hz, 3H), 0.98 (t, *J* = 7.5 Hz, 3H). $[\alpha]_D^{23}$ = -39.9 ^{o} (c = 1.07, $CHCl_3$). Note that this spectroscopic data is in full agreement with a previous literature report.[40]



(*R*)-1-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-2-methylpentane-1,3-dione [18]: A flame dried 500 mL round bottom flask was charged with aldol adduct (*R*)-4-benzyl-3-((2*R*,3*S*)-3-hydroxy-2-methylpentanoyl)oxazolidin-2-one (3.274 g, 11.24 mmol, 1.0 equiv.), CH_2Cl_2 (56 mL, 0.20 M), and DMSO (56 mL). The reaction was cooled to -10°C and NEt_3 (4.74 mL, 34.1 mmol, 3.03 equiv.) was added via syringe. A separate flame-dried 100 mL round bottom flask was charged with SO_3-Pyr. complex (Sigma-Aldrich, 5.42 g, 34.05 mmol, 3.03 equiv.) and DMSO (56 mL). The SO_3-pyr solution was cannulated into the reaction vessel, taking precautions to keep the temperature below 0 °C, and let stir for 2 hr. The reaction was diluted with Et_2O (100 mL) and quenched with satd $KHSO_4$ (60 mL). The layers were separated and the aqueous layer was extracted with Et_2O (1 x 50 mL). The combined organic layers were washed consecutively with satd $NaHCO_3$ (1 x 60 mL) and brine (1 x 60 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a white solid. The crude solid was dissolved in refluxing Et_2O/hexanes (20/80) and let cool to r.t. overnight. The mother liquor was decanted and discarded to afford *β*-keto imide **18** as clear crystalline solid (2.691 g, 9.301 mmol, 83%).

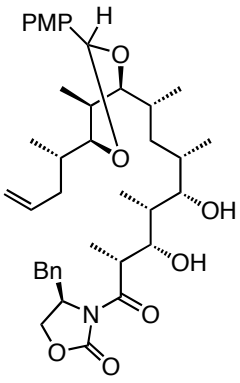
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.36 (m, 5H), 4.74 (m, 1H), 4.60 (q, *J* = 7.2 Hz, 1H), 4.24 (dd, *J* = 9.2, 8.0 Hz, 1H), 4.17 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.31 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.76 (dd, *J* = 13.6, 10.0 Hz, 1H), 2.66 (m, 2H), 1.44 (d, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H). $[\alpha]_D^{23}$ = -141.4 ^{o} (c = 0.99, CH_2Cl_2). Note that this spectroscopic data is in full agreement with a previous literature report.[41]



(*R*)-4-benzyl-3-((2*R*,4*R*,5*S*,6*S*,8*R*)-5-hydroxy-8-((2*S*,4*S*,5*R*,6*S*)-2-(4-methoxyphenyl)-5-methyl-6-((*S*)-pent-4-en-2-yl)-1,3-dioxan-4-yl)-2,4,6-trimethyl-3-oxononanoyl)oxazolidin-2-one [19]: A flame-dried 100 mL round bottom flask under Ar at 0°C was charged sequentially with CH_2Cl_2 (15.1 mL), $TiCl_4$ (263 μL, 2.396 mmol, 1.16 equiv.), and $Ti(O\text{-}iPr)_4$ (234 μL, 0.7975 mmol, 0.386 equiv.). The mixture was stirred for 15 min, at which time a solution of *β*-keto imide **18** (0.8907 g, 3.078 mmol, 1.49 equiv.) in CH_2Cl_2 (7.5 mL) was cannulated into reaction flask. To the resulting dark yellow solution was added NEt_3 (0.461 mL, 3.30 mmol, 1.6 equiv.) drop wise, eventually turning the solution dark red. The dark red solution was stirred for 1 hr at 0°C, then cooled to -78°C. A solution of aldehyde **17** (0.7737 g, 2.066 mmol, 1.0 equiv.) in CH_2Cl_2 (8.0 mL) at -78°C was cannulated drop wise into reaction, using 2 mL of CH_2Cl_2 to quantitate the transfer. The reaction was stirred at -78°C for 2 hr at which time it was quenched with satd NH_4Cl (30 mL), diluted with CH_2Cl_2 (10 mL), and let warm to room temperature. The layers were then separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with satd $NaHCO_3$ (1 x 30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil. ^{1}H NMR analysis of the crude product showed a d.r. > 20:1. Purification by flash chromatography (25%

EtOAc/hexanes) furnished *syn-syn* aldol adduct **19** as a white foam (1.209 g, 1.822 mmol, 88%). Note: Epimerization of C-2 (erythronolide numbering) occurred on silica gel, lowering the d.r. to ~12:1. This epimerization was avoided by running short silica gel columns.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.5 Hz, 2H), 7.27-7.35 (m, 3H), 7.19 (d, *J* = 5.6 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 5.78 (dddd, *J* = 16.5, 10.5, 8.0, 5.8 Hz, 1H), 5.60 (s, 1H), 5.02 (m, 2H), 4.85 (q, *J* = 7.3 Hz, 1H), 4.79 (m, 1H), 4.28 (app. t, *J* = 8.5 Hz, 1H), 4.20 (app. dd, *J* = 9.0, 3.0 Hz, 1H), 3.80 (m, 1H), 3.79 (s, 3H), 3.65 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.32 (d, *J* = 10.5 Hz, 1H), 3.30 (dd, *J* = 13.0, 3.0 Hz, 1H), 3.01 (dq, *J* = 7.5, 1.5 Hz, 1H), 2.78 (m, 2H), 2.52 (m, 2H), 1.98 (q, *J* = 7.0 Hz, 1H), 1.73-1.89 (m, 3H), 1.59 (m, 1H), 1.49 (d, *J* = 7.5 Hz, 3H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.05 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H) 0.87 (m, 1H), 0.80 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 170.2, 159.6, 154.2, 137.3, 134.8, 132.2, 129.4, 129.0, 127.5, 127.2, 116.1, 113.5, 95.0, 85.5, 78.8, 77.8, 76.0, 66.7, 55.3, 51.7, 46.3, 39.9, 37.9, 37.2, 34.7, 33.9, 30.8, 28.8, 18.1, 17.8, 13.8, 13.3, 13.2, 8.1; IR (film, cm^{-1}): 3548, 3070, 2967, 2933, 2878, 1775, 1720, 1618, 1518, 1456, 1247; HRMS (ESI) *m/z* calc'd for $C_{39}H_{54}NO_8$ $[M + H]^+$: 664.3849, found 664.3879; $[\alpha]_D^{23} = -71.9^o$ (c = 0.30, CH_2Cl_2).



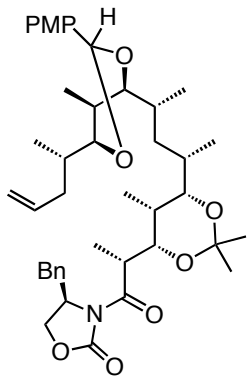
(*R*)-4-benzyl-3-((2*R*,3*S*,4*R*,5*S*,6*S*,8*R*)-3,5-dihydroxy-8-((2*S*,4*S*,5*R*,6*S*)-2-(4-methoxyphenyl)-5-methyl-6-((*S*)-pent-4-en-2-yl)-1,3-dioxan-4-yl)-2,4,6-trimethylnonanoyl)oxazolidin-2-one: $Zn(BH_4)_2$ solution[42] was prepared according to the following procedure: A flame dried 50 mL round bottom flask was charged (in glove box) with $ZnCl_2$ (Strem, ultradry, 1 g, 7.19 mmol, 1.0 equiv.), removed from the glove box, and suspended in Et_2O (12.4 mL, 0.57 M). The reaction was topped with a reflux condenser, put under Ar, and refluxed

at 80°C for 2 hr, resulting in complete solvation of the $ZnCl_2$. The $ZnCl_2$ solution was then removed from stirring and let cool, during which time a flame dried 100 mL round bottom flask was charged with $NaBH_4$ (Sigma-Aldrich, 0.657 g, 17.10 mmol, 2.37 equiv.) and suspended in Et_2O (37.0 mL, 0.46 M). Upon cooling, the $ZnCl_2$ solution was cannulated into the $NaBH_4$ suspension under Ar, being careful to leave behind residual amounts of solid $ZnCl_2$. This white suspension was allowed to stir for 12 hr as it gradually turned grey. The grey suspension was then allowed to settle, and the clear solution was transferred to a flame dried 100 mL round bottom flask under Ar via syringe, being careful to leave behind solids. The resulting clear $Zn(BH_4)_2$ solution (0.145M) under Ar was then used immediately in the next reaction.

A flame dried 25 mL round bottom flask under Ar was charged with *syn-syn* aldol adduct **19** (99.1 mg, 0.149 mmol, 1.0 equiv.) and CH_2Cl_2 (3.04 mL, 0.049 M). The reaction flask was cooled to -78°C and a freshly prepared solution of $Zn(BH_4)_2$ (0.145 M, 1.64 mL, 0.2384 mmol, 1.6 equiv.) was added dropwise via syringe. The reaction was allowed to stir at -78°C for 2.5 hrs, at which time it was quenched with H_2O (5 mL) and warmed to r.t. AcOH added dropwise until bubbling ceased (~10 drops) and diluted with satd NH_4Cl (5 mL). This solution was stirred for 5 min. and then partitioned between satd $NaHCO_3$ and CH_2Cl_2. After separation, the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a clear oil. ^{1}H NMR analysis of the crude product showed a d.r. > 20:1. Purification by flash chromatography (35% EtOAc/hexanes) furnished the *syn*-diol product as a white foam (83 mg, 0.125 mmol, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.8 Hz, 2H), 7.29-7.36 (m, 3H), 7.20 (m, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.79 (dddd, J = 16.6, 10.8, 8.6, 6.0 Hz, 1H), 5.63 (s, 1H), 5.02 (m, 2H), 4.69 (m, 1H), 4.22 (m, 2H), 4.00 (m, 2H), 3.79 (s, 3H), 3.64 (dd, J = 10.2, 1.8 Hz, 1H), 3.39 (d, J

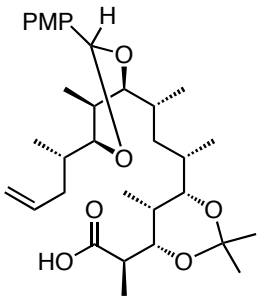
= 9.2 Hz, 1H), 3.34 (d, *J* = 10.4 Hz, 1H), 3.27 (dd, *J* = 13.6, 3.2 Hz, 1H), 2.78 (dd, *J* = 13.6, 9.6 Hz, 1H), 2.65 (bs, 2H), 2.53-2.57 (m, 1H), 2.41 (m, 1H), 1.97 (q, *J* = 6.9 Hz, 1H), 1.88 (dt, *J* = 13.6, 8.8 Hz, 1H), 1.74-1.82 (m, 3H), 1.52-1.58 (m, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.87 (m, 1H), 0.82 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 159.6, 153.3, 137.2, 134.9, 132.1, 129.4, 129.0, 127.4, 127.2, 116.1, 113.5, 95.2, 84.9, 79.4, 78.7, 75.5, 66.3, 55.3 (2 peaks), 40.7, 39.3, 37.7, 37.4, 37.2, 35.5, 33.9, 30.6, 29.2, 18.0, 17.5, 13.8, 13.3, 11.5, 6.7; IR (film, cm^{-1}): 3556, 2973, 2934, 2877, 1781, 1694, 1517, 1455, 1382; HRMS (ESI) *m/z* calc'd for $C_{39}H_{56}NO_8$ $[M + H]^+$: 666.4006, found 666.4009; $[\alpha]_D^{23}$ = -47.2° (c = 0.36, CH_2Cl_2).



(*R*)-4-benzyl-3-((*R*)-2-((4*S*,5*R*,6*S*)-6-((2*S*,4*R*)-4-((2*S*,4*S*,5*R*,6*S*)-2-(4-methoxyphenyl)-5-methyl-6-((*S*)-pent-4-en-2-yl)-1,3-dioxan-4-yl)pentan-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propanoyl)oxazolidin-2-one [21]: A flame dried 100 mL round bottom flask was charged sequentially with *syn*-diol (0.4443 g, 0.6672 mmol, 1.0 equiv.), CH_2Cl_2 (37.1 mL, 0.018 M), and 2,2-dimethoxypropane (Sigma-Aldrich, 0.80 mL, 6.54 mmol, 9.8 equiv.). CSA (Sigma-Aldrich, 36.6 mg, 0.157 mmol, 0.236 equiv.) was added to the reaction and the conversion was carefully monitored by TLC (Upon complete conversion of diol, some PMB hydrolysis occurred). After 30 min., the reaction was quenched with satd $NaHCO_3$ (30 mL) and stirred for 5 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a clear oil. Purification by flash chromatography

(12% EtOAc/hexanes) furnished acetonide **21** as a white foam that could be stored for long periods at 4°C without decomposition of the PMB group (0.3968 g, 0.562 mmol, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.8 Hz, 2H), 7.28-7.36 (m, 3H), 7.22 (m, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.79 (dddd, *J* = 16.2, 10.2, 8.2, 5.8 Hz, 1H), 5.60 (s, 1H), 5.03 (m, 2H), 4.70 (m, 1H), 4.20 (m, 2H), 4.09 (dd, *J* = 9.6, 2.0 Hz, 1H), 3.94 (dq, *J* = 10.8, 6.8 Hz, 1H), 3.80 (s, 3H), 3.60 (dd, *J* = 10.2, 1.4 Hz, 1H), 3.42 (dd, *J* = 9.6, 2.0 Hz, 1H), 3.32 (d, *J* = 10.8 Hz, 1H), 3.24 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.76 (dd, *J* = 14.0, 9.6 Hz, 1H), 2.51-2.55 (m, 1H), 2.37 (m, 1H), 1.87-1.99 (m, 2H), 1.76-1.83 (m, 1H), 1.62-1.70 (m, 2H), 1.47-1.54 (m, 1H), 1.43 (s, 3H), 1.38 (s, 3H), 1.32 (d, *J* = 6.8 Hz, 3H), 1.18 (d, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 7.6 Hz, 3H), 0.83 (d, *J* = 6.8, 3H), 0.78 (d, *J* = 6.8, 3H), 0.72-0.78 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 159.6, 152.5, 136.9, 135.0, 132.1, 129.4, 128.9, 127.4, 127.1, 116.3, 113.5, 98.8, 94.8, 86.2, 78.6, 77.9, 74.5, 66.0, 55.2, 55.0, 39.8, 39.1, 37.7, 37.2, 34.2, 33.9, 30.7, 30.4, 29.9, 28.6, 19.6, 18.3, 16.1, 15.8, 13.9, 13.4, 5.5; IR (film, cm^{-1}): 2968, 2933, 2880, 1784, 1693, 1517, 1455, 1380; HRMS (ESI) *m/z* calc'd for $C_{42}H_{60}NO_8$ $[M + H]^+$: 706.4319, found 706.4329; $[\alpha]_D^{23}$ = -71.4° (c = 0.21, CH_2Cl_2).

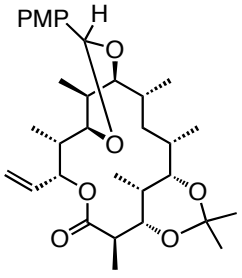


(*R*)-2-((4*S*,5*R*,6*S*)-6-((2*S*,4*R*)-4-((2*S*,4*S*,5*R*,6*S*)-2-(4-methoxyphenyl)-5-methyl-6-((*S*)-pent-4-en-2-yl)-1,3-dioxan-4-yl)pentan-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propanoic acid [20]: A 25 mL round bottom flask was charged sequentially with acetonide **21** (51.4 mg, 0.0728 mmol, 1.0 equiv.), THF (3.81 mL, 0.0191 M), and H_2O (0.76 mL, 0.0956 M). The reaction was placed in a 0°C bath and charged sequentially with H_2O_2 (30% wt solution, 60.0 μL, 0.583 mmol, 8.0 equiv.) and a 0.2 M $LiOH_{(aq)}$ solution (0.73 mL, 0.145 mmol, 2.0

equiv.). The reaction was gradually warmed to r.t. over 12 hours, at which point it was filtered through a silica plug with 100% EtOAc + 1% AcOH, and concentrated *in vacuo*. The crude yellow oil was loaded directly onto a silica column (25/75 EtOAc/Hex + 1% AcOH) to furnish alkenoic acid **20** as a yellow oil (39.5 mg, 0.0722 mmol, 99%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 6.8 Hz, 2H), 5.78 (ddt, *J* = 17.2, 10.0, 7.2 Hz, 1H), 5.60 (s, 1H), 5.03 (m, 2H), 3.87 (dd, *J* = 9.5, < 1.0 Hz, 1H), 3.80 (s, 3H), 3.59 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.37 (dd, *J* = 9.8, 1.3 Hz, 1H), 3.32 (d, *J* = 11.0 Hz, 1H), 2.66-2.69 (m, 1H), 2.53 (m, 1H), 2.36 (m, 1H), 1.88-1.97 (m, 2H), 1.80 (m, 1H), 1.60-1.68 (m, 2H), 1.53 (m, 1H), 1.41 (s, 3H), 1.39 (s, 3H), 1.26 (d, *J* = 6.5 Hz, 3H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 7.0, 3H), 0.83 (d, *J* = 7.0, 3H), 0.75 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.6, 159.6, 136.9, 132.1, 127.2, 116.3, 113.6, 99.2, 94.9, 86.2, 78.6, 78.2, 74.9, 55.3, 41.9, 39.1, 37.2, 34.2, 34.0, 31.5, 30.4, 29.9, 28.7, 19.6, 18.3, 16.0, 14.7, 13.9, 13.4, 5.0; IR (film, cm^{-1}): 2968, 2933, 2880, 1784, 1693, 1517, 1455, 1380; HRMS (ESI) *m/z* calc'd for $C_{32}H_{50}O_7Na$ $[M + Na]^+$: 569.3454, found 569.3448; $[\alpha]_D^{23}$ = -27.5^o (c = 1.12, $CHCl_3$).

C–H Oxidative Macrocyclization Reactions for Table 1 and Figure 11



Macrolide [4]: *In-Situ Pd(II)/bis-sulfoxide Catalyst (**1**) Preparation for C–H Oxidative Macrolactonization:* An oven dried 1 dram borosilicate vial (topped with a Teflon-lined cap) was charged sequentially with recrystallized $Pd(OAc)_2$ (2.9 mg, 0.0127 mmol, 0.3 equiv.), *meso*-1,2-bis(phenylsulfinyl)ethane (3.6 mg, 0.0127 mmol, 0.3 equiv.), CH_2Cl_2 (142 μL), and a teflon stir

bar. The 1 dram vial was then stirred for 12 hours in 40°C bath, at which time a clear bright red solution resulted. Note: The following precautions were taken to avoid moisture: recrystallized $Pd(OAc)_2$ was stored under an atmosphere of Ar (glove box), and *meso*-1,2-bis(phenylsulfinyl)ethane and the stir bar were stored in a dessicator. The reagents were added quickly to the 1 dram vial on a benchtop balance.

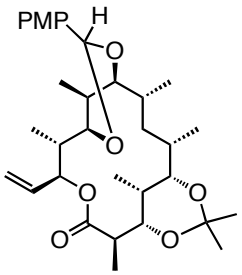
C–H Oxidative Macrolactonization: (Note: The *in-situ* catalyst (**1**) preparation was the only portion of this reaction found to be sensitive to moisture. No precautions were taken to avoid moisture during the macrolactonization setup, as all transfers were performed in an air atmosphere, on the benchtop.) To a freshly prepared catalyst (**1**) batch in a 1 dram vial, 1,4-benzoquinone (9.2 mg, 0.0852 mmol, 2.0 equiv.) was added via wax paper. Alkenoic acid **20** (23.3 mg, 0.0426 mmol, 1.0 equiv.) was then dissolved/transferred (via pipette) to the 1 dram vial using CH_2Cl_2 (1.99 mL, total molarity-0.02 M) and the reaction was topped with a Teflon-lined cap. This bright red solution was stirred in a 45°C bath 72 hrs. The resulting dark green reaction was cooled to r.t. and transferred to a separatory funnel with CH_2Cl_2, where it was quenched with satd NH_4Cl (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a clear oil. ^{1}H NMR analysis of the crude product showed a d.r. >20:1, and a product:SM ratio of 0.75:1. Purification by flash chromatography (10% EtOAc/hexanes to 25% EtOAc/hexanes + 1% AcOH) furnished macrolide **4** as a clear oil (7.8 mg, 0.0143 mmol, 34%) and recovered alkenoic acid **20** (10.5 mg, 0.0192 mmol, 45%).

Recycling Experiment (the alkenoic acid **20** collected at the end of a reaction was re-exposed to two further C–H oxidative macrolactonizations): Starting with alkenoic acid **20** (41.2 mg, 0.0753 mmol), macrolide **4** was obtained in 56% overall yield (22.9 mg, 0.0420 mmol)

along with recovered alkenoic acid **20** (3.3 mg, 0.00606 mmol, 8%). *Run 1* - macrolide **4** (13.2 mg, 0.0242 mmol, 32% yield) and recovered alkenoic acid **20** (22.0 mg, 0.0402 mmol, 53%). *Run 2* - macrolide **4** (6.4 mg, 0.0117 mmol, 29% yield) and recovered alkenoic acid **20** (11.9 mg, 0.0218 mmol, 54%). *Run 3* - macrolide **4** (3.3 mg, 0.00606 mmol, 28% yield) and recovered alkenoic acid **20** (3.3 mg, 0.00603 mmol, 28%).

Determination of diastereomeric ratio: Authentic (and purified) samples of macrolides **4** and **5** allowed the diastereomeric ratio of the crude C–H oxidative macrolactonization mixture to be obtained (Agilent Zorbax SB-CN, 40%H_2O/60%CH_3CN, 2mL/min, 30°C, t_R = 3.27, 3.67 min). Macrolide **4**, t_R = 3.67. Macrolide **5**, t_R = 3.27. The d.r. for the reaction was measured to be 41.7:1 **4**:**5**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.03 (m, 1H), 5.78 (ddd, *J* = 17.0, 10.8, 4.5 Hz, 1H), 5.73 (s, 1H), 5.21 (dt, *J* = 17.0, 1.5 Hz, 1H), 5.17 (dt, *J* = 10.5, 1.5 Hz, 1H), 3.97 (d, *J* = 6.5 Hz, 1H), 3.84 (d, *J* = 10.5 Hz, 1H), 3.80 (s, 3H), 3.70 (d, *J* = 9.0 Hz, 1H), 3.41 (d, *J* = 10.5 Hz, 1H), 2.82 (dq, *J* = 11.0, 6.5 Hz, 1H), 2.38 (m, 1H), 2.21 (m, 1H), 1.93 (q, *J* = 6.5 Hz, 1H), 1.74-1.82 (m, 2H), 1.49 (s, 3H), 1.47 (s, 3H), 1.40 (app t, *J* = 13.3 Hz, 2H), 1.22 (d, *J* = 6.5 Hz, 3H), 1.20 (d, *J* = 6.5 Hz, 3H), 1.07 (d, *J* = 6.0 Hz, 3H), 1.05 (d, *J* = 6.0 Hz, 3H), 1.01 (d, *J* = 7.0, 3H), 0.87 (d, *J* = 7.0, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 159.9, 135.5, 131.6, 127.5, 115.8, 113.6, 100.6, 95.2, 85.5, 77.6, 74.8, 73.5 (2 peaks), 55.3, 41.6, 39.6, 35.9, 32.6, 31.9, 29.7, 28.3, 26.8, 20.1, 16.3, 16.0, 13.5, 12.3, 8.0, 7.4; IR (film, cm^{-1}): 2961, 2937, 2856, 1729, 1616, 1517, 1456, 1382; HRMS (ESI) *m/z* calc'd for $C_{32}H_{49}O_7$ $[M + H]^+$: 545.3478, found 545.3500; $[\alpha]_D^{23} = -6.4^o$ (c = 0.34, CH_2Cl_2).



Macrolide [5]: *In-Situ Pd(II)/bis-sulfoxide Catalyst (**1**) Preparation for C–H Oxidative Macrolactonization:* An oven dried 2 dram borosilicate vial (topped with a Teflon-lined cap) was charged sequentially with recrystallized $Pd(OAc)_2$ (5.24 mg, 0.0233 mmol, 0.3 equiv.), *meso*-1,2-bis(phenylsulfinyl)ethane (6.49 mg, 0.0233 mmol, 0.3 equiv.), CH_2Cl_2 (250 μL), and a teflon stir bar. The 2 dram vial was then stirred for 12 hours in 40°C bath, at which time a clear bright red solution resulted. Note: The following precautions were taken to avoid moisture: recrystallized $Pd(OAc)_2$ was stored under an atmosphere of Ar (glove box), and *meso*-1,2-bis(phenylsulfinyl)ethane and the stir bar were stored in a dessicator.. The reagents were added quickly to the 2 dram vial on a benchtop balance.

C–H Oxidative Macrolactonization + TBAF: (Note: The *in-situ* catalyst (**1**) preparation was the only portion of this reaction found to be sensitive to moisture. No precautions were taken to avoid moisture during the macrolactonization setup, as all transfers were performed in an air atmosphere, on the benchtop.) To a freshly prepared catalyst (**1**) batch in a 2 dram vial, 1,4-benzoquinone (16.8 mg, 0.155 mmol, 2.0 equiv.) was added via wax paper. Alkenoic acid **20** (42.5 mg, 0.0777 mmol, 1.0 equiv.) was then dissolved/transferred (via pipette) to the 2 dram vial using CH_2Cl_2 (3.62 mL, total molarity-0.02 M). Solid tetrabutyl ammonium fluoride trihydrate (Fluka, 7.34 mg, 0.0233 mmol, 0.30 equiv.) was then added to reaction vial and the reaction was topped with a Teflon-lined cap. This bright red solution was stirred in a 45°C bath 72 hrs. The resulting dark brown reaction was cooled to r.t. and transferred to a separatory funnel with CH_2Cl_2, where it was quenched with satd NH_4Cl (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a clear oil. ^1H NMR analysis of

the crude product showed a d.r. 1.3:1 (**4**:**5**), and a products:SM ratio of 0.25:1. Purification by flash chromatography (10% EtOAc/hexanes to 25% EtOAc/hexanes + 1% AcOH) furnished a 1.3:1 mixture of macrolides **4:5** as a clear oil (8.3 mg, 0.0152 mmol, 20%) and recovered alkenoic acid **20** (32.0 mg, 0.0585 mmol, 75%). Separation of **4** and **5** was then accomplished using MPLC (2 stacked 12 g SiO_2 columns, 2.5% Acetone/hex) to afford clean macrolide **4** and the title compound **5**.

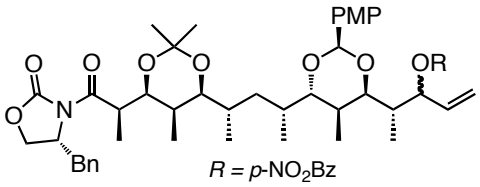
Recycling Experiment (the alkenoic acid **20** collected at the end of a reaction was re-exposed to two further C–H oxidative macrolactonizations): Starting with alkenoic acid **20** (42.5 mg, 0.0777 mmol), macrolides **4** and **5** were obtained in 44% overall yield (18.6 mg, 0.0341 mmol) as a 1.3:1 mixture, along with recovered alkenoic acid **20** (15.5 mg, 0.0284 mmol, 36%). *Run 1* - macrolides **4** and **5** (8.3 mg, 0.0152 mmol, 20% yield) and recovered alkenoic acid **20** (32.0 mg, 0.0585 mmol, 75%). *Run 2* - macrolides **4** and **5** (6.4 mg, 0.0117 mmol, 20% yield) and recovered alkenoic acid **20** (23.3 mg, 0.0426 mmol, 73%). *Run 3* - macrolides **4** and **5** (3.9 mg, 0.00716 mmol, 17% yield) and recovered alkenoic acid **20** (15.5 mg, 0.0284 mmol, 67%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.95 (ddd, *J* = 17.0, 11.0, 6.5 Hz, 1H), 5.73 (s, 1H), 5.52 (br s, 1H), 5.19 (d, *J* = 17.0 Hz, 1H), 5.07 (d, *J* = 10.5 Hz, 1H), 4.27 (d, *J* = 8.0 Hz, 1H), 4.09 (d, *J* = 5.5 Hz, 1H), 3.90 (d, *J* = 10.0 Hz, 1H), 3.81 (s, 3H), 3.36 (d, *J* = 11.0 Hz, 1H), 2.66 (dq, *J* = 9.5, 7.0 Hz, 1H), 2.53 (m, 1H), 2.15-2.21 (m, 2H), 1.80 (m, 2H), 1.51 (s, 3H), 1.46 (s, 3H), 1.38 (m, 1H), 1.31 (d, *J* = 6.5 Hz, 3H), 1.30-1.38 (m, 1H), 1.26 (d, *J* = 7.0 Hz, 3H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 7.5 Hz, 3H), 0.97 (d, *J* = 7.0, 3H), 0.96 (d, *J* = 7.0, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 159.8, 136.9, 131.7, 127.2, 114.5 (broad), 113.6, 99.6, 94.6, 85.2, 77.5, 76.2, 72.9, 72.6, 55.3, 43.8, 40.3, 36.3, 33.0, 31.9, 29.9, 28.9, 27.1, 19.8, 16.5, 16.4, 15.8, 13.8, 7.8, 5.0; IR (film, cm^{-1}): 3071.5, 2969, 2938,

2889, 1736, 1616, 1516, 1461, 1381, 1248; HRMS (ESI) *m/z* calc'd for $C_{32}H_{49}O_7$ $[M + H]^+$: 545.3478, found 545.3495; $[\alpha]_D^{23} = -15.7^o$ (c = 1.30, CH_2Cl_2).

Note: The broad carbon signal at 114.5 ppm, corresponding to the terminal olefin carbon, was verified by 2D HMQC experiments, where the diastereotopic terminal olefin hydrogens were clearly coupled with the terminal olefin carbon.

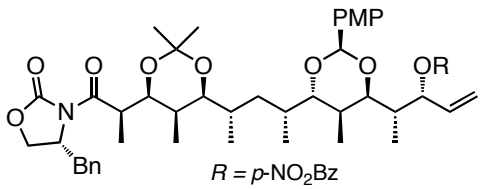
Intermolecular C–H Oxidation Reaction and Seco Acid Syntheses for Figure 12 and 13



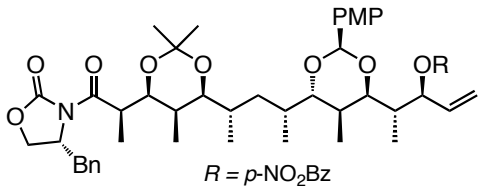
Allylic *p*-nitrobenzoates [22 and 23]: *Intermolecular C–H Oxidation Stock Solution:* A stock solution was prepared by charging a 1 dram borosilicate vial (topped with a Teflon-lined cap) sequentially with Pd(II)/bis-sulfoxide catalyst **1** (28.2 mg, 0.0559 mmol, 1.0 equiv.), 1,4-benzoquinone (120.8 mg, 1.119 mmol, 20.0 equiv.), *p*-nitrobenzoic acid (140 mg, 0.839 mmol, 15.0 equiv.), 1,4-dioxane (1.89 mL), and a Teflon stir bar. The stock solution was stirred vigorously for 30 min to dissolve all of the *p*-nitrobenzoic acid. Note: No precautions were taken to avoid moisure during the setup, as all transfers were performed in an open atmosphere on the benchtop.

Intermolecular C–H Oxidation: 0.189 ml of the stock solution [Pd(II)/bis-sulfoxide catalyst **1** (2.82 mg, 0.00559 mmol, 0.1 equiv.), 1,4-benzoquinone (12.08 mg, 0.1119 mmol, 2.0 equiv.), *p*-nitrobenzoic acid (14 mg, 0.0839 mmol, 1.5 equiv.), 1,4-dioxane (0.189 mL, 0.296 M)] was then syringed into a ½ dram vial containing acetonide **21** (39.5 mg, 0.0559 mmol, 1.0 equiv.). The resulting dark brown solution was then capped with a teflon top, and stirred at 45°C for 72 hrs. At this time, the black solution was cooled to r.t. and pippetted into a separatory

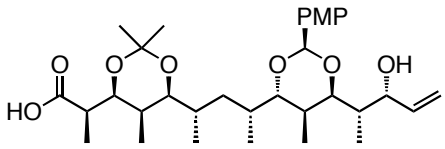
funnel washing with CH_2Cl_2. A 5% K_2CO_3 solution (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with a 5% K_2CO_3 solution (2 x10 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil. ^{1}H NMR analysis of the crude product showed a d.r. of 1.11:1 (**22** to **23**). Purification by flash chromatography (20% EtOAc/hexanes) furnished *p*-nitrobenzoate **22** (18.7 mg, 0.0215 mmol, 38.5%, rf = 0.28) and *p*-nitrobenzoate **23** (16.8 mg, 0.0193 mmol, 34.5%, rf = 0.22) as yellow oils (73% combined yield).



***p*-nitrobenzoate 22**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 9.0 Hz, 2H), 8.18 (d, *J* = 9.0 Hz, 2H), 7.45 (d, *J* = 9.0 Hz, 2H), 7.27-7.36 (m, 3H), 7.22 (d, *J* = 7.0 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.07 (m, 1H), 5.89 (ddd, *J* = 15.5, 10.5, 5.0 Hz, 1H), 5.53 (s, 1H), 5.24 (m, 2H), 4.75 (m, 1H), 4.29 (t, *J* = 8.0 Hz, 1H), 4.22 (dd, *J* = 9.0, 2.5 Hz, 1H), 4.06 (dd, *J* = 9.5, 1.5 Hz, 1H), 3.94 (m, 1H), 3.81 (s, 3H), 3.77 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.36 (m, 2H), 3.25 (dd, *J* = 13.5, 3.0 Hz, 1H), 2.76 (dd, *J* = 13.0, 10.0 Hz, 1H), 2.16 (m, 1H), 2.03 (m, 2H), 1.67 (m, 1H), 1.61 (m, 1H), 1.41 (m, 1H), 1.38 (s, 3H), 1.32 (s, 3H), 1.30 (d, *J* = 6.5 Hz, 3H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.75 (d, *J* = 7.0, 3H), 0.72 (d, *J* = 7.0 Hz, 3H), 0.72 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 163.5, 159.7, 152.7, 150.5, 136.0, 135.0, 134.9, 131.7, 130.6, 129.4, 129.0, 127.4, 127.2, 123.5, 116.5, 113.6, 98.9, 94.7, 86.1, 77.4, 75.2, 74.9, 74.5, 66.1, 55.3, 55.0, 39.9, 38.9, 38.6, 37.8, 35.2, 30.6, 30.1, 29.9, 28.3, 19.6, 19.1, 15.9, 15.3, 13.2, 8.6, 5.7; IR (film, cm^{-1}): 3060, 2968, 2936, 2882, 1784, 1729, 1695, 1609, 1530, 1456, 1382; HRMS (ESI) *m/z* calc'd for $C_{49}H_{63}N_2O_{12}$ $[M + H]^+$: 871.4381, found 871.4351; $[\alpha]_D^{23}$ = -67.8^o (c = 1.73, CH_2Cl_2). Note: **22** was inseparable from *p*-anisaldehyde (an acid decomposition product), which did not effect the following reactions.



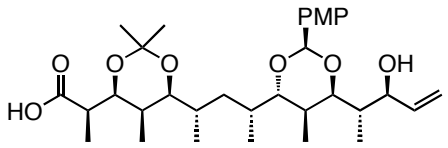
***p*-nitrobenzoate 23**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 9.0 Hz, 2H), 8.14 (d, *J* = 9.0 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.29-7.36 (m, 3H), 7.22 (d, *J* = 6.5 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 5.89 (m, 2H), 5.54 (s, 1H), 5.35 (m, 2H), 4.71 (m, 1H), 4.21 (m, 2H), 4.09 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.94 (m, 1H), 3.80 (m, 1H), 3.78 (s, 3H), 3.42 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.33 (d, *J* = 11.0 Hz, 1H), 3.24 (dd, *J* = 13.5, 3.0 Hz, 1H), 2.76 (dd, *J* = 13.5, 9.5 Hz, 1H), 2.33 (m, 2H), 1.98 (m, 1H), 1.65 (m, 2H), 1.47 (m, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 1.31 (d, *J* = 6.5 Hz, 3H), 1.22 (d, *J* = 7.0 Hz, 3H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 6.5, 3H), 0.77 (d, *J* = 6.5 Hz, 3H), 0.76 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 163.5, 159.8, 152.6, 150.3, 136.1, 135.0, 132.4, 131.6, 130.6, 129.4, 129.0, 127.4, 127.2, 123.4, 119.4, 113.6, 98.9, 95.0, 86.2, 77.9, 77.2 (under $CHCl_3$), 76.4, 74.6, 66.0, 55.3, 55.1, 39.9, 39.1, 38.0, 37.8, 34.4, 30.7, 30.4, 30.0, 28.3, 19.7, 18.4, 16.0, 15.9, 13.4, 9.4, 5.5; IR (film, cm^{-1}): 3065, 2971, 2927, 2878, 1784, 1727, 1695, 1615, 1529, 1456, 1387; HRMS (ESI) *m/z* calc'd for $C_{49}H_{63}N_2O_{12}$ $[M + H]^+$: 871.4381, found 871.4361; $[\alpha]_D^{23} = -38.2^o$ (c = 1.22, CH_2Cl_2).



Seco Acid [24]: A 10 mL round bottom flask was charged sequentially with *p*-nitrobenzoate **22** (18.7 mg, 0.0214 mmol, 1.0 equiv.), THF (1.12 mL, 0.0191 M), and H_2O (0.224 mL, 0.0956 M). The reaction was placed in a 0°C bath and charged sequentially with H_2O_2 (30% wt solution, 17.7 μL, 0.172 mmol, 8.0 equiv.) and a 0.2 M $LiOH_{(aq)}$ solution (0.215 mL, 0.043 mmol, 2.0 equiv.). The reaction was gradually warmed to r.t. over 9 hours at which point it was filtered through a silica plug with 100% EtOAc + 1% AcOH, and concentrated *in vacuo*. The crude yellow oil was taken directly onto next step without further purification.

A 25 mL round bottom flask containing the crude benzoate ester was dissolved in MeOH (1.48 mL, 0.0145 M) and charged with $K_2CO_{3(s)}$ (8.9 mg, 0.0644 mmol, 3.0 equiv.) and stirred for 1 hr at room temperature. The reaction was then quenched with satd $NH_4Cl_{(aq)}$ (5 mL) and filtered through a ½ celite/silica plug with 100% EtOAc + 1% AcOH, and concentrated *in vacuo*. Purification by flash chromatography (30% EtOAc/hexanes + 1% AcOH) furnished seco acid **24** as a clear oil (11.4 mg, 0.0203 mmol, 95% over 2-steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.92 (ddd, *J* = 16.8, 10.4, 4.4 Hz, 1H), 5.61 (s, 1H), 5.29 (d, *J* = 17.2, 1H), 5.21 (d, *J* = 10.8, 1H), 4.38 (br s, 1H), 3.97 (d, *J* = 9.6, 1H), 3.87 (d, *J* = 8.8 Hz, 1H), 3.80 (s, 3H), 3.47 (d, *J* = 7.6 Hz, 1H), 3.33 (d, *J* = 10.4 Hz, 1H), 2.67 (m, 1H), 2.37 (m, 1H), 2.00-2.18 (m, 2H), 1.89 (q, *J* = 6.8 Hz, 1H), 1.61 (m, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.26 (d, *J* = 6.4 Hz, 3H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.87 (m, 6H), 0.80 (d, *J* = 6.8, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 138.4, 131.4, 127.2, 123.7, 115.1, 113.7, 99.3, 95.0, 86.2, 76.8, 75.2, 74.2, 55.3, 41.7, 39.0, 38.7, 33.9, 31.6, 29.9 (2 peaks), 29.7, 28.6, 19.6, 17.8, 16.0, 14.5, 13.4, 10.1, 5.5; IR (film, cm^{-1}): 3498 (br), 3117, 3064, 2972, 2932, 2875, 2612, 1733, 1704, 1607, 1520, 1456, 1431; HRMS (ESI) *m/z* calc'd for $C_{32}H_{51}O_8$ $[M + H]^+$: 563.3584, found 563.3574.



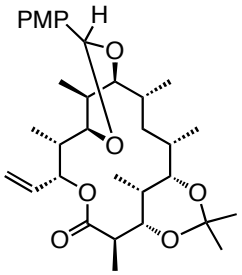
Seco Acid [25]: A 10 mL round bottom flask was charged sequentially with *p*-nitrobenzoate **23** (16.8 mg, 0.0193 mmol, 1.0 equiv.), THF (1.01 mL, 0.0191 M), and H_2O (0.202 mL, 0.0956 M). The reaction was placed in a 0°C bath and charged sequentially with H_2O_2, 30% wt solution, 15.9 μL, 0.154 mmol, 8.0 equiv.) and a 0.2 M $LiOH_{(aq)}$ solution (0.193 mL, 0.039 mmol, 2.0 equiv.). The reaction was gradually warmed to r.t. over 9 hours at which

point it was filtered through a silica plug with 100% EtOAc + 1% AcOH, and concentrated *in vacuo*. The crude yellow oil was taken directly onto next step without further purification.

A 25 mL round bottom flask containing the crude benzoate ester was dissolved in MeOH (1.33 mL, 0.0145 M) and charged with $K_2CO_{3(s)}$ (8.0 mg, 0.0579 mmol, 3.0 equiv.) and stirred for 1 hr at room temperature. The reaction was then quenched with satd $NH_4Cl_{(aq)}$ (5 mL) and filtered through a ½ celite/silica plug with 100% EtOAc + 1% AcOH, and concentrated *in vacuo*. Purification by flash chromatography (35% EtOAc/hexanes + 1% AcOH) furnished seco acid **25** as a clear oil (10.6 mg, 0.0188 mmol, 97% over 2-steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.82 (ddd, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.66 (s, 1H), 5.23 (d, *J* = 17.0, 1H), 5.16 (d, *J* = 10.0, 1H), 4.21 (app t, *J* = 7.0, 1H), 3.92 (d, *J* = 10.5, 1H), 3.88 (d, *J* = 8.5 Hz, 1H), 3.79 (s, 3H), 3.39 (d, *J* = 9.5 Hz, 1H), 3.34 (d, *J* = 10.5 Hz, 1H), 2.69 (m, 1H), 2.36 (m, 1H), 1.91-2.05 (m, 3H), 1.63 (m, 3H), 1.51 (m, 1H), 1.41 (s, 3H), 1.39 (s, 3H), 1.26 (m, 3H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.05 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 6H), 0.79 (d, *J* = 7.0, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 138.5, 131.2, 127.2, 116.6, 113.7, 109.8, 99.3, 95.1, 86.1, 80.2, 77.9, 75.0, 55.3, 48.6, 39.5, 38.8, 34.4, 31.4, 30.3, 29.9, 29.7, 28.8, 19.6, 18.4, 15.9, 14.1, 13.4, 10.9, 5.1; IR (film, cm^{-1}): 3427, 3189, 3081, 2972, 2930, 2862, 1730, 1717, 1616, 1517, 1458, 1379, 1249; HRMS (ESI) *m/z* calc'd for $C_{32}H_{51}O_8$ $[M + H]^+$: 563.3584, found 563.3591.

Yamaguchi Macrolactonization Studies for Figure 13



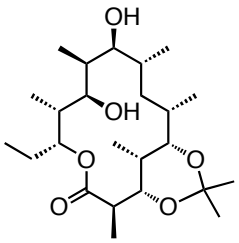
Macrolide [4]: *Yamaguchi Macrolactonization:* A flame-dried 25 mL round bottom flask under Ar was charged with seco acid **24** (11.4 mg, 0.0197 mmol, 1.0 equiv.). The substrate was then azeotroped with benzene (3 x 1 mL) under high vacuum. The reaction flask was then charged sequentially with benzene (1.97 mL), DIPEA (34.4 μL, 0.1976 mmol, 10.0 equiv.), and 2,4,6-trichlorobenzoyl chloride (Sigma-Aldrich, 15.4 μL, 0.0988 mmol, 5.0 equiv.) and stirred for 1 hr. At this time, an additional portion of DIPEA (34.4 μL, 0.1976 mmol, 10.0 equiv.) and 2,4,6-trichlorobenzoyl chloride (Sigma-Aldrich, 30.8 μL, 0.1976 mmol, 10.0 equiv.) was added to the reaction and it was stirred for 4 hr. The reaction was then charged with DMAP (Sigma-Aldrich, 96.9 mg, 0.794 mmol, 40.1 equiv.) in one portion and immediately diluted with benzene (1.91 mL – 0.005 M total). The resulting white slurry was stirred for 45 min before it was quenched with 1 M $NaHSO_4$ (10 mL) and diluted with CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then washed with satd $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a clear oil. Purification by flash chromatography (10% EtOAc/hexanes) furnished macrolide **4** as a clear oil (9.4 mg, 0.0172 mmol, 87%).

For spectroscopic data, see **4** in the C–H oxidative macrolactonization section.

Oligomer: *Yamaguchi Macrolactonization:* A flame-dried 25 mL round bottom flask under Ar was charged with seco acid **25** (10.4 mg, 0.01803 mmol, 1.0 equiv.). The substrate was then azeotroped with benzene (3 x 1 mL) under high vacuum. The reaction flask was then charged

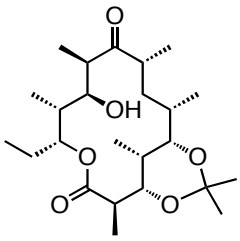
sequentially with benzene (1.80 mL), DIPEA (31.4 μL, 0.1803 mmol, 10.0 equiv.), and 2,4,6-trichlorobenzoyl chloride (Sigma-Aldrich, 14.5 μL, 0.091 mmol, 5.0 equiv.) and stirred for 1 hr. At this time, an additional portion of DIPEA (31.4 μL, 0.1803 mmol, 10.0 equiv.) and 2,4,6-trichlorobenzoyl chloride (Sigma-Aldrich, 29.0 μL, 0.1803 mmol, 10.0 equiv.) was added to the reaction and it was stirred for 4 hr. The reaction was then charged with DMAP (Sigma-Aldrich, 88.3 mg, 0.723 mmol, 40.1 equiv.) in one portion and immediately diluted with benzene (1.81 mL – 0.005 M total). The resulting white slurry was stirred for 45 min before it was quenched with 1 M $NaHSO_4$ (10 mL) and diluted with CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then washed with satd $NaHCO_3$ and concentrated *in vacuo* (not dried or filtered) to afford the oligomeric material (confirmed by ^1H NMR and GPC analysis).

Completion of 6-deoxyerythronolide B Synthesis for Figure 14



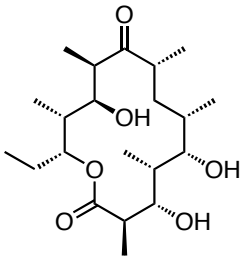
(1*S*,2*R*,5*R*,6*R*,7*R*,8*S*,9*S*,10*R*,12*S*,13*S*,17*R*)-5-ethyl-7,9-dihydroxy-2,6,8,10,12,15,15,17-octamethyl-4,14,16-trioxabicyclo[11.3.1]heptadecan-3-one: A 10 mL round bottom flask was charged with macrolide **4** (15.2 mg, 0.0279 mmol, 1.0 equiv.) and H_2 purged *i*-PrOH (0.74 mL, 0.0375M) at ambient temperature. The reaction was then charged with $Pd(OH)_2/C$ (20 wt%, 2.8 mg), topped with H_2 balloon, and let stir at r.t. for 6 hr. At this time, the reaction was diluted with EtOAc (3 mL) and filtered through celite plug (washing with EtOAc), and concentrated *in vacuo* to afford a clear oil. Purification by flash chromatography (25% EtOAc/hexanes) furnished the diol product as a clear oil (11.5 mg, 0.0268 mmol, 96%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.23 (ddd, *J* = 9.5, 4.5, <1.0 Hz, 1H), 3.87 (d, *J* = 6.0 Hz, 1H), 3.73 (d, *J* = 10.0 Hz, 1H), 3.66 (d, *J* = 10.5 Hz, 1H), 3.60 (d, *J* = 3.5 Hz, 1H), 3.34 (d, *J* = 9.0 Hz, 1H), 3.07 (app td, *J* = 10.5, 3.0 Hz, 1H), 2.77 (dq, *J* = 11.0, 7.0 Hz, 1H), 2.16 (m, 1H), 1.98 (q, *J* = 7.5 Hz, 1H), 1.68-1.83 (m, 3H), 1.51 (m, 2H), 1.46 (s, 6H), 1.20-1.25 (m, 2H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 7.5 Hz, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 7.0, 3H), 0.90 (t, *J* = 7.5 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 101.0, 82.0, 78.0, 75.7, 73.4, 71.1, 42.0, 40.8, 36.3, 34.3, 32.5, 32.4, 32.0, 29.7, 25.5, 19.9, 16.2, 15.9, 13.5, 10.6, 9.9, 8.8, 7.8; IR (film, cm^{-1}): 3446, 2966, 2928, 2857, 1728, 1455, 1381, 1267; HRMS (ESI) *m/z* calc'd for $C_{24}H_{45}O_6$ $[M + H]^+$: 429.3216, found 429.3214; $[\alpha]_D^{23}$ = +25.0° (c = 0.12, CH_2Cl_2). Note that this spectroscopic data is in full agreement with a previous literature report.[10]



(1*S*,2*R*,5*R*,6*R*,7*S*,8*R*,10*R*,12*S*,13*S*,17*R*)-5-ethyl-7-hydroxy-2,6,8,10,12,15,15,17-octamethyl-4,14,16-trioxabicyclo[11.3.1]heptadecane-3,9-dione: A flame-dried 10 mL round bottom flask was charged with diol (9.2 mg, 0.021465 mmol, 1.0 equiv.), powdered 4Å mol sieves (60 mg), and CH_2Cl_2 (2.15 mL, 0.01M). The reaction was then placed in a 0°C bath and charged sequentially with NMO (Sigma-Aldrich, 12.6 mg, 0.1073 mmol, 5.0 equiv.) and TPAP (Sigma-Aldrich, 97%, 2.3 mg, 0.0064 mmol, 0.3 equiv.) and let stir at 0°C for 20 min. The reaction was then diluted with EtOAc (3 mL) and filtered through a short silica plug (washing with EtOAc), and concentrated *in vacuo* to afford a clear oil. Purification by flash chromatography (20% EtOAc/hexanes) furnished the β-hydroxyketone product as a clear oil (7.7 mg, 0.0181 mmol, 84%) and recovered diol SM (1.2 mg, 0.002799 mmol, 13% rSM).

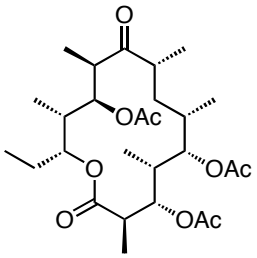
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.30 (ddd, *J* = 9.5, 4.5, 1.0 Hz, 1H), 3.97 (m, 1H), 3.93 (d, *J* = 6.0 Hz, 1H), 3.79 (d, *J* = 10.5 Hz, 1H), 3.05 (d, *J* = 4.5 Hz, 1H), 2.80 (m, *2*H), 2.66 (m, 1H), 2.15 (m, 1H), 1.89 (q, *J* = 6.5 Hz, 1H), 1.65-1.84 (m, 3H), 1.53 (m, 1H), 1.47 (s, 6H), 1.25 (m, 1H), 1.20 (d, *J* = 6.5 Hz, 3H), 1.08 (d, *J* = 6.5 Hz, 3H), 1.05 (d, *J* = 6.5 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.0, 3H), 0.92 (d, *J* = 7.0, 3H), 0.91 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.2, 177.8, 101.1, 77.9, 76.1, 73.2, 71.2, 44.2, 42.1, 41.0, 39.0, 37.5, 32.9, 32.3, 29.7, 25.6, 20.0, 15.9, 13.5, 13.2, 10.6, 9.3, 7.8, 6.1; IR (film, cm^{-1}): 3479 (br), 2975, 2941, 2879, 1709, 1456, 1381, 1271; HRMS (ESI) *m/z* calc'd for $C_{24}H_{42}O_6Na$ $[M + Na]^+$: 449.2903, found 449.2889; $[\alpha]_D^{23}$ = -50.1° (c = 0.64, CH_2Cl_2). Note that this experimental data is in full agreement with a previous literature report.[9]



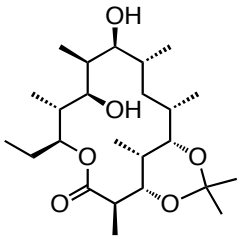
6-deoxyerythronolide B: A 10 mL round bottom flask was charged with β-hydroxyketone (3.97 mg, 0.0093 mmol, 1.0 equiv.), THF (0.21 mL, 0.044M), and 1M HCl_{aq} (100 μL, 0.1 mmol, 10.8 equiv.). After stirring for 8 hrs, the reaction was diluted with Et_2O (5 mL) and partitioned between Et_2O and H_2O (5 mL). After separating the phases, the organic layer was washed with satd $NaHCO_3$ (1 x 10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a clear oil. Purification by flash chromatography (35% EtOAc/hexanes) furnished **6-deoxyerythronolide B** as a clear oil (3.53 mg, 0.0091 mmol, 98%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.15 (ddd, *J* = 9.5, 4.0, 1.0 Hz, 1H), 4.00 (m, 1H), 3.92 (d, *J* = 10.5 Hz, 1H), 3.87 (d, *J* = 4.0 Hz, 1H), 3.68 (ddd, *J* = 10.0, 4.5, 2.0 Hz, 1H), 2.87 (d, *J* = 1.5 Hz, 1H), 2.78 (m, 2H), 2.63 (m, 1H), 2.00-2.05 (m, 2H), 1.79-1.89 (m, 2H), 1.64-1.75 (m, 2H), 1.53 (m, 1H), 1.30 (d, *J* = 7.0 Hz, 3H), 1.25 (m, 1H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.06 (d, *J* = 7.0

Hz, 3H), 1.05 (d, J = 7.0 Hz, 3H), 1.02 (d, J = 6.5, 3H), 0.93 (t, J = 7.5, 3H), 0.89 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.5, 178.4, 79.5, 76.5, 76.3, 70.9, 43.9, 43.4, 40.6, 39.2, 37.7, 37.5, 35.6, 25.4, 16.6, 14.8, 13.2, 10.6, 9.2, 6.9, 6.2; IR (film, cm^{-1}): 3489, 2974, 2931, 1708, 1460, 1381, 1381; HRMS (ESI) *m/z* calc'd for $C_{21}H_{38}O_6Na$ $[M + Na]^+$: 409.2566, found 409.2555; $[\alpha]_D^{23}$ = -39.4^o (c = 0.64, CH_2Cl_2). Note that this experimental data is in full agreement with previous literature reports.[8,9,10]



(3*R*,4*S*,5*R*,6*S*,7*S*,9*R*,11*R*,12*S*,13*S*,14*R*)-14-ethyl-3,5,7,9,11,13-hexamethyl-2,10-dioxooxacyclotetradecane-4,6,12-triyl triacetate [26]: A 10 mL round bottom flask was charged with 6-deoxyerythronolide B (3.53 mg, 0.0091 mmol, 1.0 equiv.), pyridine (0.70 mL, 0.013 M), Ac_2O (80.0 μL, 0.846 mmol, 93.0 equiv.), and 1 crystal of DMAP. The reaction was stirred for 40 hr, at which time the reaction was concentrated *in vacuo* and purified by flash chromatography (50% Et_2O/pentane) to furnish triacetate **26** as a white solid (4.5 mg, 0.00878 mmol, 96%). This white solid was dissolved in refluxing CH_2Cl_2/hexanes (100 μL/ 500 μL) and placed in -40°C freezer overnight. The mother liquor was decanted and discarded to afford clear X-ray quality crystals (See X-ray crystal structure data). Note that this compound has been synthesized previously.[43]

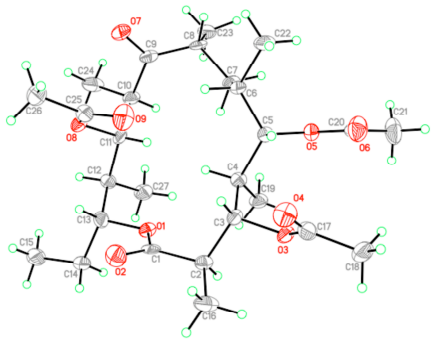


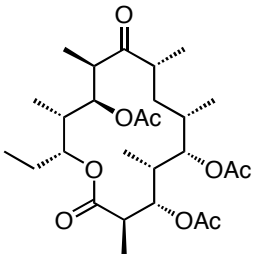
(1*S*,2*R*,5*S*,6*R*,7*R*,8*S*,9*S*,10*R*,12*S*,13*S*,17*R*)-5-ethyl-7,9-dihydroxy-2,6,8,10,12,15,15,17-octamethyl-4,14,16-trioxabicyclo[11.3.1]heptadecan-3-one: A 10 mL round bottom flask was charged with macrolide **5** (10.6 mg, 0.0195 mmol, 1.0 equiv.) and H_2 purged *i*-PrOH (0.52 mL, 0.0375M) at ambient temperature. The reaction was then charged with

$Pd(OH)_2/C$ (20 wt%, 2.4 mg), topped with H_2 balloon, and let stir at r.t. for 6 hr. At this time, the reaction was diluted with EtOAc (3 mL) and filtered through celite plug (washing with EtOAc), and concentrated *in vacuo* to afford a clear oil. Purification by flash chromatography (25% EtOAc/hexanes) furnished the title compound as a clear oil (6.91 mg, 0.0161 mmol, 83%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.13 (dd, J = 10.0, 3.0, 1H), 4.22 (d, J = 9.0 Hz, 1H), 4.01 (d, J = 4.0 Hz, 1H), 3.87 (dd, J = 10.0, 2.0 Hz, 1H), 3.28 (br s, 1H), 3.25 (d, J = 10.5 Hz, 1H), 2.61 (dq, J = 10.0, 7.0 Hz, 1H), 2.37 (br s, 1H), 2.14 (m, 1H), 2.04 (m, 1H), 1.80-1.96 (m, 4H), 1.71 (m, 1H), 1.47 (s, 3H), 1.44 (s, 3H), 1.35-1.40 (m, 2H), 1.32 (d, J = 7.0 Hz, 3H), 1.08 (d, J = 7.5 Hz, 6H), 0.98 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.86 (t, J = 7.0 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 99.5, 83.1, 81.0, 76.3, 72.3, 69.6, 44.0, 41.2, 36.0, 33.4, 33.2, 32.8, 31.6, 29.9, 27.8, 19.8, 16.8 (2 peaks), 16.3, 15.9, 11.2, 10.7, 7.8; IR (film, cm^{-1}): 3454, 2971, 2933, 2881, 2855, 1731, 1461, 1381, 1257; HRMS (ESI) *m/z* calc'd for $C_{24}H_{45}O_6$ $[M + H]^+$: 429.3216, found 429.3232; $[\alpha]_D^{23} = -3.9^o$ (c = 0.69, CH_2Cl_2).

X-ray Crystal Structural Data for Figure 14





(3*R*,4*S*,5*R*,6*S*,7*S*,9*R*,11*R*,12*S*,13*S*,14*R*)-14-ethyl-3,5,7,9,11,13-hexamethyl-2,10-dioxooxacyclotetradecane-4,6,12-triyl triacetate [26]:

Table. Crystal data and structure refinement for b91cas.

Identification code	b91cas	
Empirical formula	C28 H46 Cl2 O9	
Formula weight	597.55	
Temperature	193(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 8.353(2) Å	a= 90°.
	b = 23.757(6) Å	b= 108.566(4)°.
	c = 8.573(2) Å	g = 90°.
Volume	1612.7(7) $Å^3$	
Z	2	
Density (calculated)	1.231 Mg/m^3	
Absorption coefficient	0.248 mm^{-1}	
F(000)	640	
Crystal size	0.20 x 0.16 x 0.08 mm^3	
Theta range for data collection	1.71 to 25.40°.	
Index ranges	-10<=h<=10, -28<=k<=28, -10<=l<=10	
Reflections collected	12585	

Independent reflections	5782 [R(int) = 0.0777]
Completeness to theta = 25.40°	99.8 %
Absorption correction	Integration
Max. and min. transmission	0.9799 and 0.9474
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5782 / 91 / 362
Goodness-of-fit on F^2	0.867
Final R indices [I>2sigma(I)]	R1 = 0.0571, wR2 = 0.1126
R indices (all data)	R1 = 0.1317, wR2 = 0.1298
Absolute structure parameter	0.21(9)
Largest diff. peak and hole	0.368 and -0.353 e.$Å^{-3}$

Crystallographic data have been deposited at the Cambridge Crystallographic Centre, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 726952.

Molecular Modeling Studies for Figure 6

Monte Carlo conformational searches were performed for both macrolide **4** and **5** using the Molecular Operating Environment program (MOE), Version 2006.08[44], with the empirical MMFF94s force field with no distance cutoffs for non-bonded interactions. 3500 random conformations were generated and minimized with Gaussian distribution of dihedrals biased towards multiples of 30°, dihedral minimization (RMS = 100), 0.001 Cartesian minimization RMS gradient, 0.0001 Cartesian perturbation, 0.1 RMS tolerance, a maximum of 2000 energy minimization steps for each minimization, a failure limit of 5000, no chiral inversion, no rotation about π-bonds or amide bonds, and an energy cutoff of 5 kcal/mol. Without further energy minimizations, macrolide **4** was found to be 2.16 kcal/mol more stable than macrolide **5**.

The lowest energy structures obtained from the Monte Carlo conformational searches were then energy-minimized using the MMFF94s force field (1) implemented in the Program MOE (2), version 2009.2, to a root mean square energy gradient inferior to 10^{-5} kcal/mol/angstrom. No non-bonded cutoff functions were used and the dielectric constant was set to 1 (i.e. in vacuo calculations). No additional parameterization of the MMFF94s potential energy function was necessary. In addition, the heat of formation of both macrolides (**4** and **5**) were calculated at the semi-empirical PM3 level using the program MOPAC (3) as implemented in MOE.

Macrolide **4**:

MMFF94s potential energy: 49.8 kcal/mol

PM3 heat of formation: -275.1 kcal/mol

Macrolide **5**:

MMFF94s potential energy: 52.8 kcal/mol

PM3 heat of formation: -273.7 kcal/mol

Energy difference Delta E (**4** – **5**)

MMFF94s potential energy: -3.0 kcal/mol

PM3 heat of formation: -1.4 kcal/mol

These results were confirmed with DFT/ B3LYP/6-31G*//HF/3-21G single points calculations i.e. HF/3-21G energy minimized structures were used to calculate single-point DFT B3LYP/6-31G* energies, without additional minimization.

1.5 REFERENCES

[1] (a) Corey, E. J.; Cheng, X. –M. *The Logic of Chemical Synthesis*; Wiley: New York, 1995 (b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH Verlag: Weinheim, Germany, 1996.

[2] For a recent C–H oxidation review, see: Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439.

[3] (a) Nicolaou, K.C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Clalborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K. Sorensen, E. J. *Nature* **1994**, *367*, 630. (b) Wender, P.A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976. (c) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510. (d) Davies, H. M. L.; Dai, X.; Long, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2485. (e) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824.

[4] *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press, Orlando FL, 1984.

[5] Celmer, W. D. *Pure & Appl. Chem*. **1971**, *28*, 413.

[6] Staunton, J.; Wilkinson, B. *Chem. Rev.* **1997**, *97*, 2611.

[7] For the first synthesis of an erythromycin compound, see: Corey, E. J.; Trybulski, E. J.; Melvin, L. S.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Falck, J. R.; Brunelle, D. J.; Haslanger, M. F.; Kim, S.; Yoo, S. *J. Am. Chem. Soc.* **1978**, *100*, 4620.

[8] Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568.

[9] Myles, D. C.; Danishefsky, S. J.; Schulte, G. *J. Org. Chem.* **1990**, *55*, 1636.

[10] Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921.

[11] For a formal synthesis of 6-dEB, see: Crimmons, M. T.; Slade, D. J. *Org. Lett.* **2006**, *8*, 2191.

[12] Fraunhoffer, K. J.; Bachovchin, D. A.; White, M. C. *Org. Lett.* **2005**, *7*, 223.

[13] For one example of a difficult alcohol deprotection, see the synthesis of oleandolide B, a macrolide antibiotic natural product closely related to 6-dEB: ref. 10.

[14] Stang, E. M.; White, M. C. *Nat. Chem.* **2009**, *1*, 547.

[15] Fraunhoffer, K. J.; Prabagaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 9032.

[16] For a recent example, see: O'Malley, D. P.; Yamaguchi, J.; Young, I. S.; Seiple, I. B.; Baran, P. S. *Angew. Chem. Int. Ed.* **2008**, *47*, 3581.

[17] Other metal-templated macrocyclization examples: (a) Yamamoto, H.; Maruoka, E. *J. Am. Chem. Soc.* **1981**, *103*, 6133. (b) Eschenmoser, A. *Pure Appl. Chem.* **1969**, *20*, 1. (c) Namba, K.; Kishi, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15382. (d) Fürstner, A.; Albert, M; Mlynarski, J.; Matheu, M. *J. Am. Chem. Soc.* **2002**, *124*, 1168.

[18] Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970.

[19] Myers, A.G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

[20] Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

[21] Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1565.

[22] Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750.

[23] Bäckvall, J. -E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619.

[24] Burckhardt, U.; Baumann, M.; Togni, A. *Tetrahedron: Asymmetry* **1997**, *8*, 155.

[25] For other examples of fluoride anion modulating the reactivity of a palladium-catalyzed macrocyclization event, see: Denmark, S. E.; Muhuhi, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 11768.

[26] Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

[27] Fischbach, M. A.; Walsh, C. T. *Chem. Rev.* **2006**, *106*, 3468.

[28] Castonguay, R.; He, W.; Chen, A. Y.; Khosla, C.; Cane, D. E. *J. Am. Chem. Soc.* **2007**, *129*, 13758.

[29] Katz, L.; Ashley, G. W. *Chem. Rev.* **2005**, *105*, 499.

[30] (a) Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46. (b) Balskus, E. P.; Jacobsen, E. N. *Science* **2007**, *317*, 1736. (c) Lewis, C. A.; Miller, S. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 5616.

[31] Hoye, T. R.; Eklov, B. M.; Voloshin, M. *Org. Lett.* **2004**, *6*, 2567-2570.

[32] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[33] Larsson, M. L.; Nguyen, B. V.; Hogberg, H. E.; Hedenstrom, E. *Eur. J. Org. Chem.* **2001**, 353-364.

[34] Bode, J. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 3611-3612.

[35] a) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290-5313. b) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.

[36] (a) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506-2526. (b) Bode, J. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 3611-3612.

[37] Bialy, L.; Lopez-Canet, M.; Waldmann, H. *Synthesis* **2002**, *14*, 2096-2104.

[38] Aissa, C.; Riveiros, R. ; Furstner, A. *J. Am. Chem. Soc.* **2003**, *125*, 15512-15520.

[39] a) Tyrrell, E.; Tsang, M. W. H.; Skinner, G. A.; Fawcett, J. *Tetrahedron* **1996**, *52* (29) 9841-9852. b) Chan, P. C. M.; Chong, M.; Kousha, K. *Tetrahedron* **1994**, *50* (9), 2703-2714.

[40] Chan, P. C. M.; Chong, M.; Kousha, K. *Tetrahedron* **1994**, *50* (9), 2703-2714.

[41] Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48* (11), 2127-2142.

[42] a) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338-344. b) Gensler, W. J.; Johnson, F.; Sloan, A. D. B. *J. Am. Chem. Soc.* **1960**, *82*, 6074-6081.

[43] Egan, R. S.; Martin, J. R.; Perun, T. J.; Mitscher, L. A. *J. Am. Chem. Soc.* **1975**, *97*, 4578-4583.

[44] *Molecular Operating Environment*, version 2006.08; Chemical Computing Group: Montreal, Quebec, Canada.

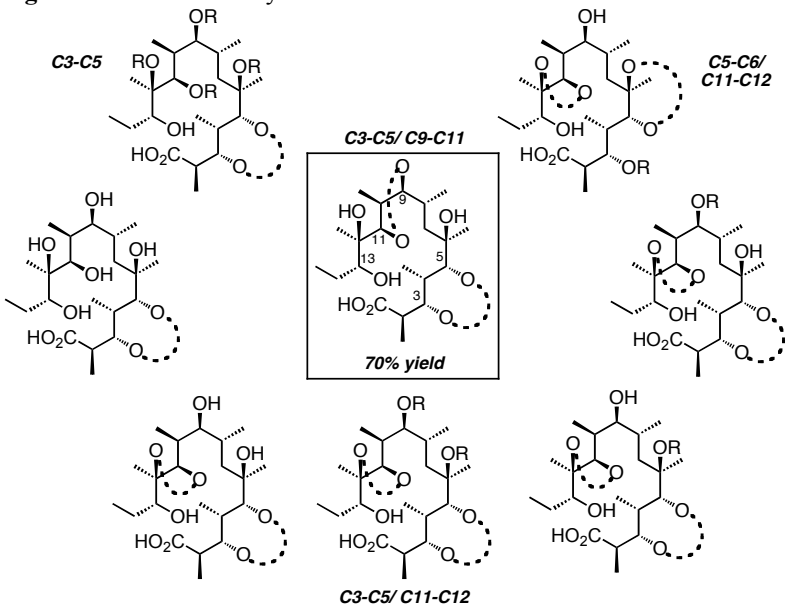
CHAPTER 2

ON THE MACROCYCLIZATION OF THE ERYTHROMYCIN CORE: PREORGANIZATION IS NOT REQUIRED

2.1 INTRODUCTION

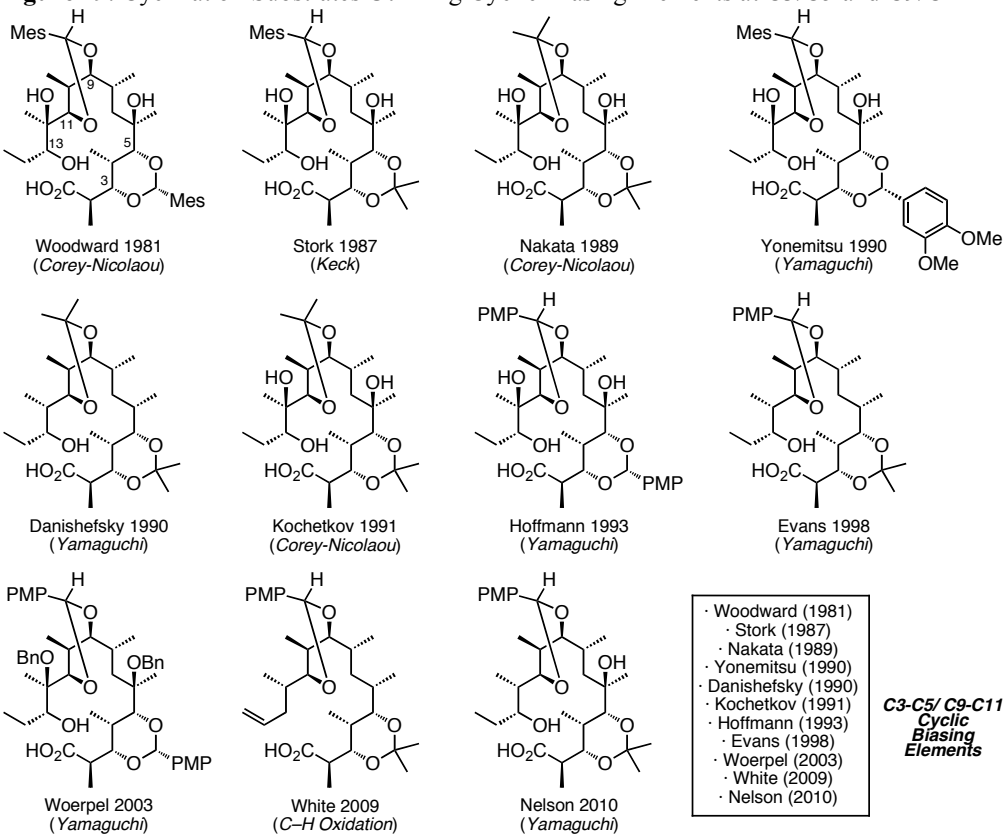
The erythromycins, discovered and isolated in the early 1950's, are the best-known members of the clinically important macrolide class of antibiotics.[45] The 14-membered macrolactone core imbedded in these natural products has inspired new synthetic methodology for the construction of large ring lactones, beginning with the landmark synthesis of erythronolide B by the Corey group in 1978.[46] During these studies, a single acetonide protecting group was utilized at the C3/C5 position. Similarly, this protecting group was used by the Masamune group years later for the synthesis of 6-deoxyerythronolide B (6-dEB).[47] While no rationale was given for the use of this acetonide at the time, its function was revealed during the

Figure 18. Woodward Cyclization Studies



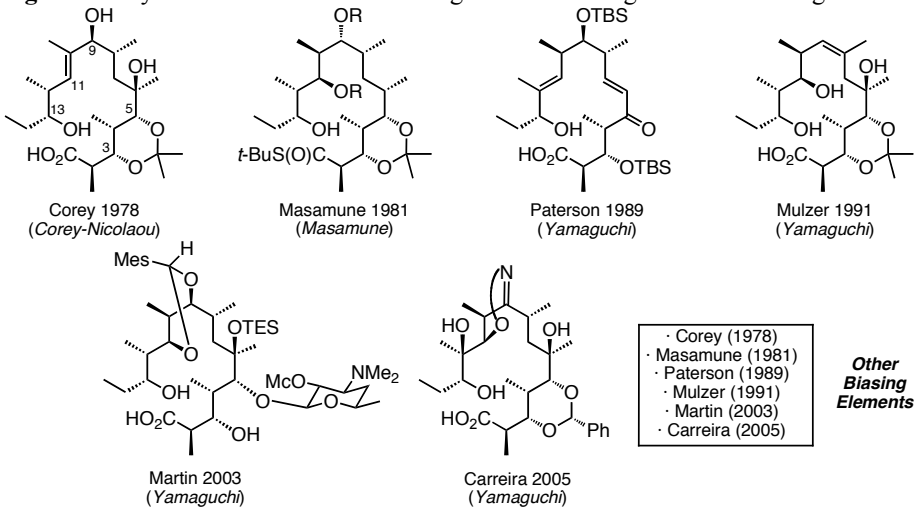
Woodward group's historic synthesis of erythromycin A in 1981.[48] In three consecutive communications, the Woodward group extensively explored the conformational requirements for efficient acylation-based macrolactonization of erythromycin A seco acid derivatives (Figure 18). In particular, cyclic protecting groups were placed at varying positions in order to serve as biasing elements,[49] *i.e.* artificial structural features intended to aid macrocyclic ring closure through substrate preorganization. The results from this study led the Woodward group to conclude that "certain structural features such as… cyclic protecting groups at C3/C5 and C9/C11 are *required for efficient lactonization*" and that "these structural requirements probably arise from conformation requirements for lactonization." This conclusion – that preorganization is required for efficient cyclization – has become a well-accepted doctrine that has influenced the planning of all ensuing erythromycin syntheses (*vide infra*).

Figure 19. Cyclization Substrates Utilizing Cyclic Biasing Elements at C3/C5 and C9/C11



Inspired by the Woodward report, synthetic endeavors by Stork, Nakata, Yonemitsu, Danishefsky, Kochetkov, Hoffmann, Evans, Woerpel, Nelson, and our labs have reduced conformational space available to the seco acid backbones of the erythronolide series (*i.e.* 6-dEB, erythronolide B, and erythronolide A) through the use of six-membered ring protecting groups on C3/C5 and C9/C11 (Figure 19).[50,51] In addition to cyclic protecting group scaffolds, other types of biasing elements (e.g. heterocycles, olefins, etc.) have been employed in similar positions to rigidify the hydroxy acid backbone (Figure 20).[52,53] In a particularly notable example, Paterson validated this approach using two olefinic rigidifying elements in place of cyclic protecting groups.[54] Furthermore, the Martin group demonstrated that steric bulk at C5 coupled to a C9/C11 cyclic acetal could enable cyclization.[55] In this case, the use of a sterically bulky desosamine sugar residue at the C5, or a C3 cladinose and C5 desosamine sugar residue together, were thought to reduce the conformational mobility along the C1-C8 subunit of the polypropionate backbone and facilitate cyclization of erythromycin B precursors.

Figure 20. Cyclization Substrates Utilizing 'Other' Biasing Elements Strategies

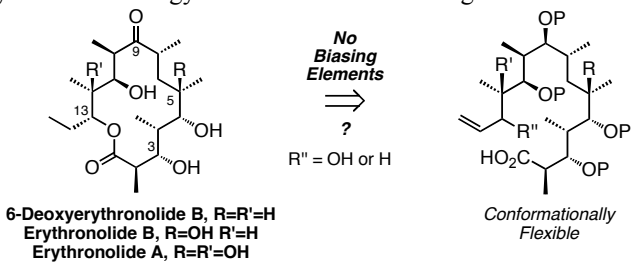


Since the original Corey erythronolide B synthesis, which utilized the newly developed Corey-Nicoloau macrocyclization[56] technique, a wide variety of lactonization methods have been

employed for macrolide construction of the erythromycins including the Masamune,[57] Keck,[58] Yamaguchi,[59] Yonemitsu-Yamaguchi,[60] and the Shiina[61] macrolactonization reactions. Despite these significant advances in macrocyclization methods and dilution techniques,[62] the use of biasing elements has been universal for the cyclization of erythromycin substrates. The steadfast application of one or more structural biasing elements in erythromycin's synthetic history demonstrates the resonating impact of Woodward's cyclization studies.

We previously reported a late-stage C–H oxidation strategy for the total synthesis of 6-deoxyerythronolide B (6-dEB), using a palladium(II)/bis-sulfoxide(**1**)-catalyzed C–H oxidative macrolactonization reaction developed in our labs.[51,63] As a part of our synthetic planning, we also chose to employ traditional cyclic protecting groups at C9/C11 and C3/C5 (**20)** in order to facilitate macrocyclic ring closure (*vide supra*, Table 1). In the presence of these biasing elements, the 14-membered macrolide product was formed in 34% yield (45% recovered starting material, rSM; 56% yield recycled 2x) and with *>40:1 d.r. in favor of the natural C13 diastereomer **4***. Based on the Hammond postulate, we attributed the inability to form the unnatural C13 diastereomer under the chelate-controlled C–H oxidative macrolactonization conditions[64] to the large difference in ground-state product energies between the C13 diastereomers (the natural C13 diastereomer was calculated to be 3 kcal/mol more stable than the C13 epimer). Similarly, while acylation-based Yamaguchi cyclization of **24** provided the natural macrolide **4** in high yield, the unnatural C13 diastereomer (**5**) *could not be formed* (Figure 13).

Figure 21. Cyclization Strategy Without Substrate Preorganization. From reference 69



6-Deoxyerythronolide B, R=R'=H
Erythronolide B, R=OH R'=H
Erythronolide A, R=R'=OH

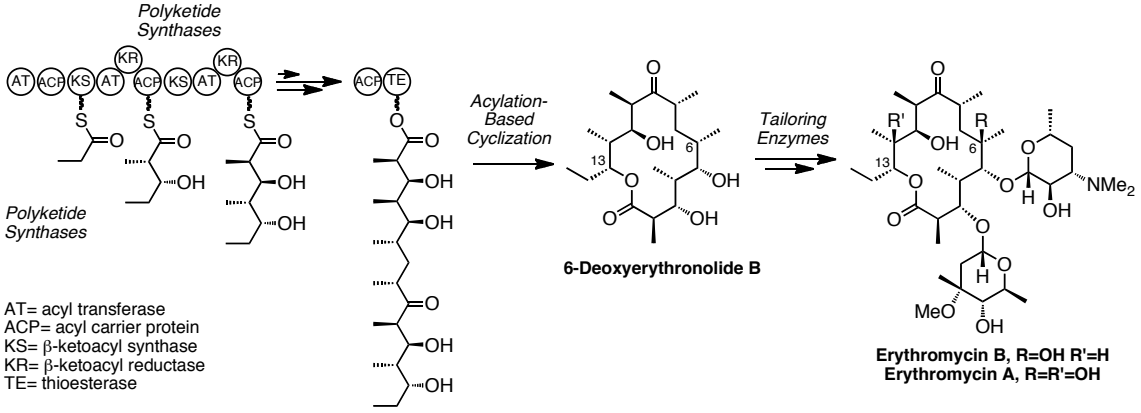
Upon revisiting the Woodward studies, in which the positioning of cyclic protecting groups had been optimized for the natural erythromycin structure, we questioned whether the biasing elements were in fact hampering the cyclization of stereochemical analogues. In this vein, we recognized the absence of a *key control experiment*: attempted cyclization of a substrate completely devoid of biasing elements. Surprisingly, this experiment has remained unreported in the literature despite over 30 years of erythromycin syntheses. We therefore set out to test the well-accepted idea that preorganization is necessary for cyclization of the erythromycin structure (Figure 21).

2.2 RESULTS AND DISCUSSION

2.2.1 Synthesis of the Unbiased Alkenoic Acid and Yamaguchi Cyclization Precursors

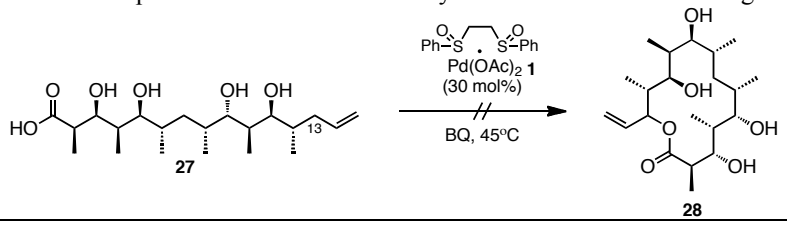
6-Deoxyerythronolide B, the aglycone precursor to the erythromycins, serves as the archetypical core of the polyketide macrolide antibiotics. In Nature, a seco acid bearing unadorned hydroxyl groups at C3, C5, and C11 and ketone functionality at C9 is cyclized to form 6-dEB, which is then hydroxylated at the C6 and C12 positions through enzymatic C–H functionalization to form erythronolides B and A, respectively (Figure 22).[65] To mimic the biosynthesis of 6-dEB, cyclization was first attempted on a substrate (**27**) with unprotected hydroxyl groups at C3, C5, C9, and C11 under C–H oxidative macrolactonization conditions (Figure 23). Unfortunately, these attempts were met with failure, due to facile olefin oxidation

Figure 22. Biosynthesis of the Erythromycins and Macrocyclization to form 6-dEB



processes. In addition to preventing such competing olefin oxidation pathways, protecting groups were deemed necessary to preclude the formation of unwanted ring sizes[66] and to inhibit preorganization via 1,3-hydrogen bonding (hydrogen bonding in acyclic 1,3-diols may induce a solution conformation analogous to that of acetonide protecting groups).[67] Polypropionate molecules typically adopt conformations that minimize *syn*-pentane interactions, and thus will have inherent preorganization that may aid cyclization.[68] However, in attempts to minimize

Figure 23. Attempted C–H Oxidative Macrocyclization Without Protecting Groups

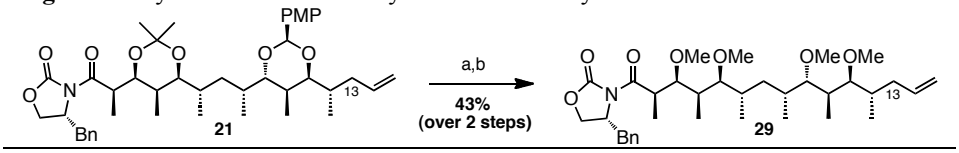


Conditions: **27** (1.0 equiv.), **1** (30 mol%), BQ (2.0 equiv.), CH_2Cl_2 (0.02 M), 45°C, 72 h.

artificial bias (bias not present in the native polypropionate structure), we selected methyl ether protecting groups for these cyclization studies because of their inability to induce electrostatic preorganization while maintaining similar steric properties to the natural substrate's free hydroxyls. We reasoned that the use of any other protecting group, albeit potentially more synthetically useful, might inadvertently enable cyclization through either steric[55] or electronic

preorganization of the substrate. Accordingly, we synthesized a tetramethyl ether protected hydroxy acid and alkenoic acid as the unbiased cyclization precursors.[69]

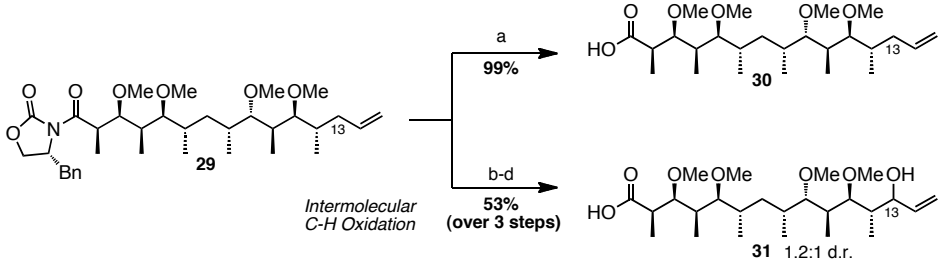
Figure 24. Synthesis of Tetramethylated Common Synthetic Intermediate **29**



Conditions: (a) 1M $HCl_{(aq)}$ (2.0 equiv.), 45°C, 70% (b) Me_3OBF_4 (50.0 equiv.), proton sponge™ (75.0 equiv.), 62%.

The syntheses of both unbiased cyclization precursors **30** and **31** proceeded conveniently via a common intermediate, terminal olefin **29.** Global deprotection of a previously synthesized bis-acetal intermediate (**21**) under aqueous HCl conditions, followed by permethylation with Me_3OBF_4 and proton sponge furnished tetramethylated terminal olefin **29** (Figure 24). Straightforward chiral auxiliary removal with LiOOH provided the C–H oxidative cyclization substrate **30** in 99% yield (Figure 25). Intermolecular palladium(II)/bis-sulfoxide(**1**)-catalyzed C–H oxidation provided the C13 oxidized products as diastereomeric allylic *p*-nitrobenzoates in 59% yield (1.2:1 d.r.). Chiral auxiliary hydrolysis with LiOOH and methanolysis of the *p*-nitrobenzoates furnished the unbiased seco acids **31** in 89% yield (over 2-steps, 1.2:1 d.r.).[69] Notably, C–H oxidation greatly aided these studies by circumventing *de novo* syntheses of both epimeric Yamaguchi precursors **31**.[51,70]

Figure 25. Synthesis of Unbiased Alkenoic Acid **30** and Epimeric Seco Acids **31**

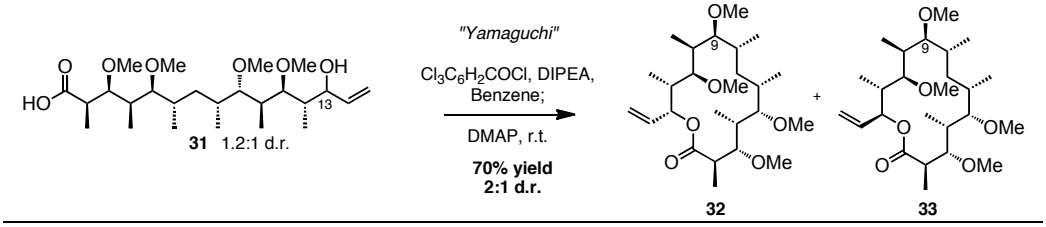


Conditions: (a) $LiOOH_{(aq)}$ (2.0 equiv.), 0°C, 99% (b) **1** (10 mol%), BQ (2.0 equiv.), *p*-NO_2BzOH (1.5 equiv.), 45°C, 72 h, 1.2:1 d.r., 59% combined (c) $LiOOH_{(aq)}$ (2.0 equiv.), 0°C (d) K_2CO_3 (3.0 equiv.), MeOH, 89% over 2-steps. Adapted from reference 69.

2.2.2 Yamaguchi Macrolactonization Reaction Without Substrate Preorganization

In order to evaluate if preorganization is needed for efficient macrolactonization of erythromycin precursors, we attempted a traditional acylation-based macrolactonization with unbiased hydroxy acids **31** (1.2:1 d.r.). Although in the original Woodward studies, acylation-based macrolactonization was effected via the Corey-Nicolaou method, most subsequent studies utilized the Yamaguchi protocol. Therefore, we again decided to employ the Yamaguchi cyclization method for these studies.[59] Strikingly, both the natural and unnatural C13 diastereomeric hydroxy acids cyclized efficiently under standard Yamaguchi macrolactonization conditions, to afford the 14-membered macrolide products **32** and **33** in *70% yield* (2:1 d.r., Figure 26). The ease with which these hydroxy acids cyclized in the absence of biasing elements is remarkable; matching the best yield obtained from Woodward's original preorganization studies. Despite decades of erythromycin syntheses, this is the first reported case where precursors to any member of the erythromycins have been cyclized successfully without the use of biasing elements to aid in 14-membered macrolide formation.[69]

Figure 26. Yamaguchi Macrolactonization of Unbiased 6-dEB Precursor **31**



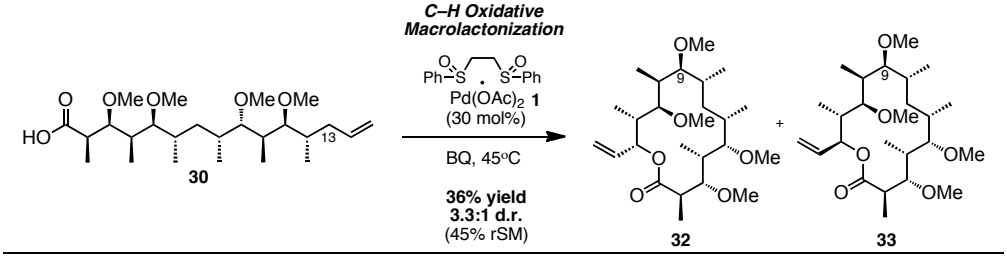
Conditions: $Cl_3C_6H_2COCl$ (15.0 equiv.), *i*-Pr_2NEt (20.0 equiv.), DMAP (40.0 equiv.), Benzene (0.005 M), r.t., 2:1 d.r., 70% combined. Adapted from reference 69.

2.2.3 C–H Oxidative Macrolactonization Reaction Without Substrate Preorganization

The C–H oxidative macrolactonization of unbiased alkenoic acid (**30** → **32**/**33**) also proceeded in the absence of biasing elements (Figure 27), providing *comparable yields* (36% yield, 44% recovered SM) to the analogue containing biasing elements (**20** → **4**, Table 1). More

importantly, in contrast to previous results with cyclic protecting groups at C9/C11 and C3/C5, the unnatural C13-diastereomer **33** could be now be accessed from this unbiased precursor (1:3.3 d.r. from **30** vs. 1:>40 d.r. from **20**).[69] Based on these results, we may conclude that Pd/bis-sulfoxide-catalyzed C–H oxidative macrolactonizaton of erythromycin precursors also does not require biasing elements, although such elements can significantly improve the diastereomeric outcome of the cyclization.

Figure 27. C–H Oxidative Macrolactonization of Unbiased 6-dEB Precursor **30**



Conditions: **1** (30 mol%), BQ (2.0 equiv.), CH_2Cl_2 (0.02 M), 45°C, 72 h, 3.3:1 d.r., 36% + 45% rSM. Adapted from reference 69.

2.3 CONCLUSIONS

We demonstrate for the first time that a linear seco acid and alkenoic acid substrate, both precursors to the erythromycin core structure (6-dEB), can be efficiently lactonized when devoid of preorganizational elements. These results definitively demonstrate that artificial preorganization is not a requirement for the efficient cyclization of erythromycin's polypropionate core (6-dEB). While we cannot exclude the possibility that erythronolide B or A would still require preorganization due to the presence of a C6 and/or C12 hydroxyl(s), this study suggests that the inherent conformation of the linear biosynthetic polypropionate structure is sufficient for facile macrolactonization. Significantly, we show that designed preorganization dramatically impacts the cyclization outcome of stereochemical analogues of the erythromycins. Removal of artificial biasing elements allows for increased stereochemical flexibility in the macrocyclization process. Overall these findings require the revision of the thirty-year-old

dogma that preorganization is mandatory for achieving macrocyclization of the erythromycins. We anticipate that empowered with the knowledge that preorganization is not a requirement for cyclization, a broader evaluation of protecting groups will lead to the syntheses of stereochemically modified and/or functional group deficient analogues of erythromycin that may have been difficult and/or impossible to generate under the former perceived constraints.

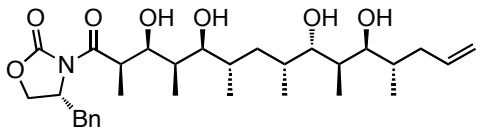
2.4 EXPERIMENTAL SECTION

General Information: Unless otherwise noted, all reactions were conducted in flame-dried glassware with magnetic stirring under an inert atmosphere of dry nitrogen. Solvents tetrahydrofuran (THF), diethyl ether (Et_2O), methanol (MeOH), 1,4-dioxane, benzene, and methylene chloride (CH_2Cl_2) were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). Deuterochloroform was stored over 3 Å molecular sieves. Diisopropylethylamine (DIPEA) was distilled from calcium hydride. The following commercially obtained reagents were used as received: Pd(II)/bis-sulfoxide catalyst (Sigma-Aldrich, lot #68482-1), proton-sponge^{TM} (Sigma-Aldrich), Me_3OBF_4 (Sigma-Aldrich), H_2O_2 (Fisher Scientific, 30% wt solution), 1,4-benzoquinone (Sigma-Aldrich), 2,4,6-trichlorobenzoyl chloride (Sigma-Aldrich).

Optical rotations were measured using a 1 mL cell with a 0.5 dm path length on a Perkin-Elmer 341 polarimeter. Optical rotations were obtained with a sodium lamp and are reported as follows: $[\alpha]_{\lambda}^{T^{\circ}C}$ (c = g/100 mL, solvent). Infrared spectra were recorded as thin films on NaCl plates on a Mattson Galaxy Series FTIR 5000 and are reported in frequency of absorption (cm^{-1}). High- and low-resolution mass spectra were obtained through the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois. Electrospray ionization (ESI) spectra were performed on a Waters Q-Tof Ultima spectrometer. Field desorption (FD) spectra were performed on a Micromass 70-VSE spectrometer. ^{1}H NMR spectra were recorded on a Varian Unity-500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent; coupling constant(s) in Hz; integration. Proton-decoupled 13C-NMR spectra were recorded on a Varian Unity-500 (125 MHz) or Varian Unity-

600 (150 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV, potassium permanganate, and ceric ammonium molybdate staining. Flash column chromatography was performed as described by Still et al.[71] using EM reagent silica gel 60 (230-400 mesh).

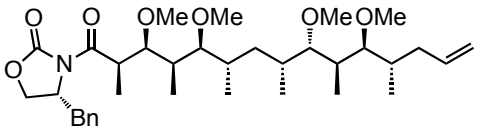
Synthesis of Unbiased Alkenoic Acid and Epimeric Seco Acids for Figures 24 and 25



(*R*)-4-benzyl-3-((2*R*,3*S*,4*R*,5*S*,6*S*,8*R*,9*S*,10*R*,11*S*,12*S*)-3,5,9,11-tetrahydroxy-2,4,6,8,10,12-hexamethylpentadec-14-enoyl)oxazolidin-2-one: A 1 dram borosilicate vial was charged sequentially with bis-acetal **21**[51] (50.0 mg, 0.0708 mmol, 1.0 equiv.) THF (1.77 mL, 0.04 M) and $1M_{(aq)}$ HCl (0.14 ml, 0.142 mmol, 2.0 equiv.). The reaction vial was topped with a teflon-lined cap and was heated at 45°C for 12 hrs. Upon completion, the reaction was partitioned between H_2O (10 mL) and Et_2O (10 mL). After separation, the organic layer was washed with satd. $NaHCO_3$ (1 x 15 mL). The combined aqueous layers were then extracted with Et_2O (2 x 20 mL) and EtOAc (2 x 20 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a clear oil. Purification by flash chromatography (60% EtOAc/hexanes to 100% EtOAc) furnished the tetraol product as a white foam (27 mg, 0.0498 mmol, 70%).

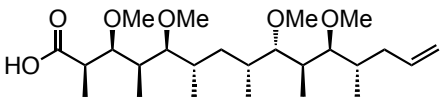
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, 7.3 Hz, 2H), 7.29 (d, J = 7.0 Hz, 1H), 7.20 (d, J = 7.0 Hz, 2H), 5.84 (dddd, J = 16.5, 10.0, 8.0, 6.0 Hz, 1H), 5.05 (d, J = 17.0 Hz, 1H), 5.01 (d, J = 10.0 Hz, 1H), 4.66-4.71 (m, 1H), 4.18-4.26 (m, 2H), 4.04 (app t, J = 5.0 Hz, 1H), 3.98 (dq, J =

6.5, 6.5 Hz, 1H), 3.98 (m, 1H), 3.74 (d, *J* = 10.0 Hz, 1H), 3.56 (d, *J* = 8.5 Hz, 1H), 3.46 (bs, 2H), 3.41 (d, *J* = 8.5 Hz, 1H), 3.25 (dd, *J* = 13.5, 3.0 Hz, 1H), 2.77 (dd, *J* = 13.5, 9.5 Hz, 1H), 2.51-2.54 (m, 1H), 1.90-1.96 (m, 2H), 1.76-1.80 (m, 3H), 1.60-1.68 (m, 2H), 1.30 (d, *J* = 7.0 Hz, 3H), 1.25 (m, 1H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.88-0.91 (m, 1H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.81 (d, *J* = 6.0 Hz, 3H), 0.80 (d, *J* = 6.0 Hz, 3H), 0.79 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 153.1, 137.7, 134.9, 129.4, 129.0, 127.4, 116.0, 80.4, 76.1, 74.6, 71.6, 66.2, 55.2, 41.0, 38.4, 37.8, 37.7, 36.9, 36.8, 36.0, 32.8, 31.9, 16.3, 15.5, 14.2, 12.9, 8.9, 6.2; IR (film, cm^{-1}): 3406, 3068, 3030, 2970, 2929, 2881, 1780, 1695, 1456, 1383, 1354, 1211; HRMS (ESI) *m/z* calc'd for $C_{31}H_{50}NO_7$ $[M + H]^+$: 548.3587, found 548.3586; $[\alpha]_D^{23}$ = -56.4° (c = 1.43, CH_2Cl_2).



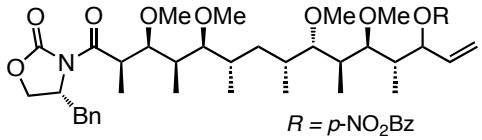
(*R*)-4-benzyl-3-((2*R*,3*S*,4*R*,5*S*,6*S*,8*R*,9*S*,10*R*,11*S*,12*S*)-3,5,9,11-tetramethoxy-2,4,6,8,10,12-hexamethylpentadec-14-enoyl)oxazolidin-2-one [29]: A 10 mL round bottom flask was charged with tetraol (18.1 mg, 0.0330 mmol, 1.0 equiv.) and dissolved in CH_2Cl_2 (2.4 mL, 0.014 M). Proton-sponge^{TM} (531 mg, 2.47 mmol, 75.0 equiv.) and Me_3OBF_4 (244 mg, 1.65 mmol, 50.0 equiv.) were then added to the reaction and allowed to stir for 18 hrs at room temperature in the dark. The reaction was quenched with satd NH_4Cl (5 mL), transferred to a separatory funnel and diluted with EtOAc (15 mL), and the layers were separated. The organic layer was washed with 1M HCl (1 x 10 mL) and H_2O (1 x 15 mL). The combined aqueous layers were extracted with EtOAc (2 x 15 mL) and the combined organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil. Purification by flash chromatography (20% EtOAc/hexanes) furnished tetramethyl ether **29** as a clear oil (12.3 mg, 0.0204 mmol, 62%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.3 Hz, 2H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 2H), 5.81 (dddd, *J* = 17.0, 10.0, 8.0, 6.5 Hz, 1H), 5.04 (d, *J* = 18.0 Hz, 1H), 5.01 (d, *J* = 11.5 Hz, 1H), 4.58-4.63 (m, 1H), 4.18 (m, 2H), 4.02 (dq, *J* = 7.0, 7.0 Hz, 1H), 3.54 (s, 3H), 3.49 (m, 1H), 3.48 (s, 3H), 3.46 (s, 3H), 3.39 (s, 3H), 3.26 (dd, *J* = 13.5, 3.0 Hz, 1H), 3.22 (d, *J* = 8.5 Hz, 1H), 3.11 (d, *J* = 9.5 Hz, 1H), 3.04 (dd, *J* = 4.5, 4.0 Hz, 1H), 2.77 (dd, *J* = 13.5, 10.0 Hz, 1H), 2.43 (m, 1H), 2.00 (m, 1H), 1.73-1.92 (m, 5H), 1.68 (m, 1H), 1.30 (d, *J* = 7.0 Hz, 3H), 1.11 (m, 1H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 7.5 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 6.5, 3H), 0.80 (d, *J* = 7.0, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 152.8, 137.8, 135.2, 129.4, 128.9, 127.4, 115.8, 85.7, 85.0, 84.8, 84.6, 66.0, 60.8, 60.5, 60.4, 59.4, 55.6, 40.7, 38.1, 38.0, 37.9, 37.8, 37.7, 36.2, 33.1, 32.5, 16.8, 16.0, 14.2 (2 peaks), 10.5, 10.4; IR (film, cm^{-1}): 3070, 2968, 2931, 2829, 1784, 1695, 1639, 1456, 1381, 1352; HRMS (ESI) *m/z* calc'd for $C_{35}H_{58}NO_7$ $[M + H]^+$: 604.4213, found 604.4216; $[\alpha]_D^{23} = -1.7^o$ (c = 0.6, CH_2Cl_2).



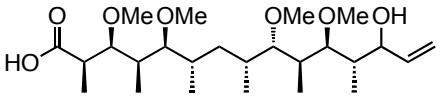
(2*R*,3*S*,4*R*,5*S*,6*S*,8*R*,9*S*,10*R*,11*S*,12*S*)-3,5,9,11-tetramethoxy-2,4,6,8,10,12-hexamethylpentadec-14-enoic acid [30]: A 10 mL round bottom flask was charged sequentially with tetramethyl ether **29** (16.8 mg, 0.0278 mmol, 1.0 equiv.), THF (1.45 mL, 0.0191 M), and H_2O (0.29 mL, 0.0956 M). The reaction was placed in a 0°C bath and charged sequentially with H_2O_2 (30% wt solution, 22.9 μL, 0.2227 mmol, 8.0 equiv.) and a 0.2 M $LiOH_{(aq)}$ solution (0.28 mL, 0.0556 mmol, 2.0 equiv.). The reaction was gradually warmed to r.t. over 12 hours, at which point it was concentrated *in vacuo*, and loaded directly onto a silica column (25/75 EtOAc/Hex + 1% AcOH) to furnish tetramethyl alkenoic acid **30** as a yellow oil (12.3 mg, 0.0277 mmol, 99%). This material was then used immediately in the C–H oxidative macrolactonization reaction.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (dddd, *J* = 17.0, 10.0, 7.5, 5.5 Hz, 1H), 5.04 (d, *J* = 17.5 Hz, 1H), 5.01 (d, *J* = 11.0 Hz, 1H), 3.51 (s, 3H), 3.50 (m, 1H), 3.50 (s, 3H), 3.46 (s, 3H), 3.45 (s, 3H), 3.27 (dd, *J* = 7.5, 1.0 Hz, 1H), 3.06 (d, *J* = 10.0 Hz, 1H), 2.85 (dd, *J* = 5.5, 4.0 Hz, 1H), 2.79 (m, 1H), 2.42 (m, 1H), 1.73-1.91 (m, 7H), 1.21 (d, *J* = 7.0 Hz, 3H), 1.03 (app t, *J* = 9.0 Hz, 1H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 6.0 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.78 (d, *J* = 6.5 Hz, 3H).



(4*R*,5*S*,6*S*,7*S*,8*R*,10*S*,11*S*,12*R*,13*S*,14*R*)-15-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-5,7,11,13-tetramethoxy-4,6,8,10,12,14-hexamethyl-15-oxopentadec-1-en-3-yl 4-nitrobenzoate: A stock solution was made of Pd(II)/bis-sulfoxide catalyst **1** (11.8 mg, 0.0235 mmol, 10.0 equiv.) in dioxane (0.789 mL, 0.0296 M) in a 1 dram vial. A ½ dram vial was charged sequentially with tetramethyl ether **29** (14.1 mg, 0.0234 mmol, 1.0 equiv.), BQ (5.04 mg, 0.0467 mmol, 2.0 equiv.), and *p*-NO_2BzOH (5.86 mg, 0.35 mmol, 1.5 equiv.). The ½ dram reaction vial was then charged with 78.9 μL of Pd(II)/dioxane stock solution (10 mol% Pd, 0.296M dioxane), and topped with a Teflon-lined cap, and stirred in a 45°C bath for 72 hrs. The resulting black solution was cooled to r.t. and transferred to a separatory funnel with CH_2Cl_2, where it was quenched with 5% K_2CO_3 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a clear oil. ^{1}H NMR analysis of the crude product showed a d.r. of 1.2:1. Purification by flash chromatography (25% EtOAc/hexanes) furnished the *p*-nitrobenzoate ester products as a clear oil (10.6 mg, 0.01379 mmol, 59%, 1.2:1 d.r.).

^{1}H NMR (500 MHz, $CDCl_3$) *Major diastereomer:* δ 8.30 (app. t, *J* = 9.0 Hz, 2H), 8.23 (m, 2H), 7.28-7.34 (m, 3H), 7.19 (app. t, *J* = 7.5 Hz, 2H), 5.87-5.99 (m, 1H), 5.78 (app. t, *J* = 6.0 Hz, 1H), 5.41 (d, *J* = 17.0 Hz, 1H), 5.35 (d, *J* = 9.0 Hz, 1H), 4.56-4.62 (m, 1H), 4.14-4.21 (m, 2H), 3.98-4.04 (m, 1H), 3.50-3.52 (m, 1H), 3.47-3.49 (m, 1H), 3.37-3.51 (m, 12H), 3.22-3.27 (m, 1H), 3.11-3.15 (m, 1H), 3.02-3.03 (m, 1H), 2.73-2.79 (m, 1H), 2.28 (m, 1H), 1.74-1.97 (m, 4H), 1.63-1.70 (m, 1H), 1.28-1.30 (m, 3H), 1.07-1.15 (m, 1H), 0.98-1.03 (m, 3H), 0.81-0.94 (m, 12H). *Minor Diastereomer (Diagnostic):* δ 5.88 (m, 1H), 5.25 (d, *J* = 9.0 Hz, 1H), 5.23 (d, *J* = 17.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.7 (2 peaks), 163.9, 163.6, 152.8, 150.6, 150.4, 136.2, 135.8, 135.5, 135.2 (2 peaks), 133.1, 130.7, 130.6, 129.4 (2 peaks), 128.9 (2 peaks), 127.4, 123.7, 123.5, 119.2, 116.3, 85.7, 85.6, 84.9, 84.5 (2 peaks), 81.7, 80.8, 77.6, 76.2, 66.0, 61.2 (2 peaks), 60.7 (4 peaks), 60.5 (2 peaks), 60.4, 59.9 (2 peaks), 59.4 (2 peaks), 55.6, 40.7 (2 peaks), 40.6, 40.1, 38.2, 38.1 (2 peaks), 37.9, 37.8 (2 peaks), 37.7, 33.3, 33.2, 32.8, 32.6, 16.9, 16.8, 14.2 (2 peaks), 14.0 (2 peaks), 11.7, 10.5 (3 peaks), 10.4, 9.9; IR (film, cm^{-1}): 3111, 3086, 3057, 3028, 2972, 2933, 2829, 1782, 1726, 1693, 1608, 1529, 1456, 1381, 1350, 1273, 1211, 1196, 1101; HRMS (ESI) *m/z* calc'd for $C_{42}H_{61}N_2O_{11}$ $[M + H]^+$: 769.4275, found 769.4269.



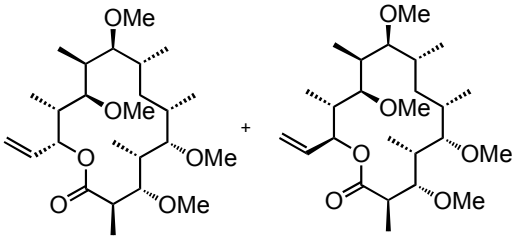
(2*R*,3*S*,4*R*,5*S*,6*S*,8*R*,9*S*,10*S*,11*S*,12*S*)-13-hydroxy-3,5,9,11-tetramethoxy-2,4,6,8,10,12-hexamethylpentadec-14-enoic acid [31]: A 10 mL round bottom flask was charged sequentially with the *p*-nitrobenzoate esters (8.8 mg, 0.01144 mmol, 1.0 equiv.), THF (0.59 mL, 0.0191 M), and H_2O (0.12 mL, 0.0956 M). The reaction was placed in a 0°C bath and charged sequentially with H_2O_2 (30% wt solution, 9.4 μL, 0.0915 mmol, 8.0 equiv.) and a 0.2 M $LiOH_{(aq)}$ solution (0.114 mL, 0.0229 mmol, 2.0 equiv.). The reaction was gradually warmed to r.t. over 12 hours, at which

point it was filtered through a short silica plug with 100% EtOAc + 1% AcOH, and concentrated *in vacuo*. The crude *p*-nitrobenzoate esters/carboxylic acid compounds were then taken onto the next step without any further purification.

A 10 mL round bottom flask was charged sequentially with *p*-nitrobenzoate esters/carboxylic acids (0.01144 mmol, 1.0 equiv.), MeOH (0.79 mL, 0.0145M), and K_2CO_3 (4.7 mg, 0.0343 mmol, 3.0 equiv.). The reaction was stirred at r.t. for 2 hr, then filtered through short silica plug with 100% EtOAc + 1% AcOH and concentrated *in vacuo* to afford a clear oil. Purification by flash chromatography (40% EtOAc/hexanes + 1% AcOH) furnished tetramethyl hydroxy acid **31** as a clear oil (4.7 mg, 0.0102 mmol, 89% over 2 steps, 1.2:1 d.r.). This purified material was used immediately in the following Yamaguchi reaction.

^{1}H NMR (500 MHz, $CDCl_3$) *Major diastereomer:* δ 5.86 (ddd, *J* = 17.0, 10.5, 7.0, 1H), 5.31 (d, *J* = 12.5 Hz, 1H), 5.28 (d, *J* = 17.0 Hz, 1H), 4.04 (app t, *J* = 7.5 Hz, 1H), 3.54-3.56 (m, 1H), 3.45-3.53 (m, 12H), 3.06 (d, *J* = 10.5 Hz, 1H), 2.85 (m, 1H), 2.79 (m, 1H), 1.79-1.92 (m, 6H), 1.25-1.33 (m, 1H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.03 (m, 1H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.80-0.91 (m, 12H). *Minor Diastereomer (Diagnostic):* δ 5.92 (ddd, *J* = 15.5, 10.5, 5.0 Hz, 1H), 5.19 (d, *J* = 16.0 Hz, 1H), 5.18 (d, *J* = 10.5 Hz, 1H), 4.41 (m, 1H), 3.08 (d, *J* = 9.0 Hz, 1H).

Unbiased Yamaguchi Macrolactonization Study for Figure 26



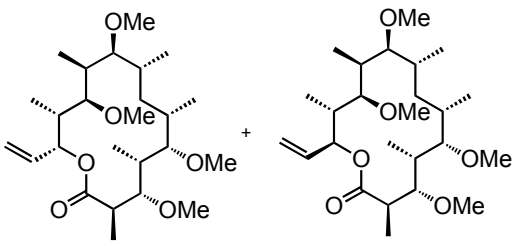
(3*R*,4*S*,5*R*,6*S*,7*S*,9*R*,10*S*,11*S*,12*S*,13*R*)-4,6,10,12-tetramethoxy-3,5,7,9,11,13-hexamethyl-14-vinyloxacyclotetradecan-2-one [32 and 33]: This reaction was run according to literature precedent.[50,51]

A 25 mL round bottom flask was charged with tetramethyl hydroxyacid **31** (4.6 mg, 0.00998 mmol, 1.0 equiv.), and this material was azeotropically dried with benzene (3 x 1 mL) under high vacuum. The reaction flask was then charged sequentially with benzene (1.0 mL), DIPEA (17.4 μL, 0.0998 mmol, 10.0 equiv.), and 2,4,6-trichlorobenzoyl chloride (7.8 μL, 0.0499 mmol, 5.0 equiv.) and stirred for 1 hr. At this time, an additional portion of DIPEA (17.4 μL, 0.0998 mmol, 10.0 equiv.) and 2,4,6-trichlorobenzoyl chloride (15.6 μL, 0.0998 mmol, 10.0 equiv.) was added to the reaction and it was stirred for 4 hr. The reaction was then charged with DMAP (48.9 mg, 0.400 mmol, 40.1 equiv.) in one portion and immediately diluted with benzene (1.0 mL – 0.005 M total). The resulting white slurry was stirred for 45 min before it was quenched with 1 M $NaHSO_4$ (10 mL) and diluted with CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then washed with satd. $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a clear oil. ^{1}H NMR analysis of the crude product showed a d.r. of 2:1 (**32** : **33**). Purification by flash chromatography (10% EtOAc/hexanes) furnished a 2:1 mixture of tetramethyl macrolides **32** and **33** as a clear oil (3.1 mg, 0.0070 mmol, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) *Major diastereomer:* δ 5.80 (ddd, *J* = 14.5, 10.0, 4.0 Hz, 1H), 5.72 (m, 1H), 5.17 (dd, *J* = 16.5, 2.0 Hz, 1H), 5.17 (dd, *J* = 12.0, 2.0 Hz, 1H), 3.49 (s, 3H), 3.45 (s, 3H), 3.45 (s, 3H), 3.41 (s, 3H), 3.25 (dd, *J* = 7.0, 2.5 Hz, 1H), 3.12 (d, *J* = 9.0 Hz, 1H), 3.05 (dd, *J* = 5.0, 2.0 Hz, 1H), 2.80 (dq *J* = 7.0, 7.0 Hz, 1H), 2.65 (dd, *J* = 9.0, 3.5 Hz, 1H), 1.89-2.02 (m, 2H), 1.78-1.88 (m, 1H), 1.69-1.76 (m, 2H), 1.29-1.34 (m, 1H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 7.5, 3H), 0.82 (d, *J* = 7.0, 3H), 0.72-0.78 (m, 1H). *Minor Diastereomer (Diagnostic):* δ 5.15-5.26 (m, 3H), 3.44 (s, 3H), 3.43 (s, 3H), 3.36 (s, 3H), 3.34 (s, 3H), 2.94 (d, *J* = 8.5 Hz, 1H), 2.73 (dq, *J* = 7.0,

7.0 Hz, 1H), 2.72-2.74 (m, 1H), 2.20 (m, 1H), 2.02-2.07 (m, 1H), 1.53-1.62 (m, 1H), 1.27 (d, J = 7.0 Hz, 3H), 1.24 (d, J = 6.5 Hz, 3H), 1.09 (d, J = 6.5 Hz, 3H), 1.02 (m, 3H), 0.95 (d, J = 7.5 Hz, 3H), 0.93 (d, J = 8.5 Hz, 3H). ^{13}C NMR (asterisk denotes minor diastereomer peaks, 125 MHz, $CDCl_3$) δ 175.7, 173.4*, 136.4, 136.0*, 117.4*, 115.3, 91.3, 87.6*, 85.4, 85.4*, 85.1, 79.4, 74.2, 62.0, 61.4*, 61.3, 59.5*, 59.2, 58.7*, 45.1*, 43.6, 42.4, 40.7, 39.2*, 36.6*, 36.2*, 35.3, 34.7, 34.6, 33.9, 32.3*, 29.7, 24.7*, 23.3*, 22.7*, 19.9*, 19.3*, 17.9, 17.1, 13.4*, 12.6, 12.0*, 11.2, 9.5, 9.4*, 8.5; IR (film, cm^{-1}): 3089, 2970, 2929, 2829, 1732, 1458, 1371, 1171, 1099. HRMS (ESI) *m/z* calc'd for $C_{25}H_{47}O_6$ $[M + H]^+$: 443.3373, found 443.3372; LRMS (FD) *m/z* found 443.6.

Unbiased C–H Oxidative Macrolactonization Study for Figure 27



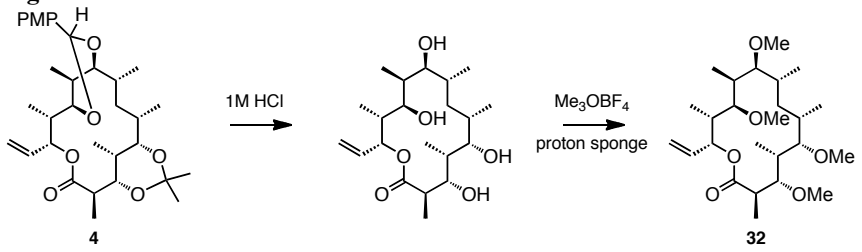
(3*R*,4*S*,5*R*,6*S*,7*S*,9*R*,10*S*,11*S*,12*S*,13*R*)-4,6,10,12-tetramethoxy-3,5,7,9,11,13-hexamethyl-14-vinyloxacyclotetradecan-2-one [32 and 33]: An oven-dried 1 dram vial was charged sequentially with Pd(II)/bis-sulfoxide catalyst **1** (4.2 mg, 0.00834 mmol, 0.30 equiv.) and BQ (6.0 mg, 0.0556 mmol, 2.0 equiv.). Tetramethyl alkenoic acid **30** (12.3 mg, 0.0278 mmol, 1.0 equiv.) was then dissolved/transferred (via pipette) to the 1 dram vial using CH_2Cl_2 (1.45 mL, 0.02 M) and the reaction was topped with a Teflon-lined cap. This bright red solution was stirred vigorously in a 45°C bath for 72 hrs. The resulting dark green reaction was cooled to r.t. and transferred to a separatory funnel with CH_2Cl_2, where it was quenched with satd. NH_4Cl (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic

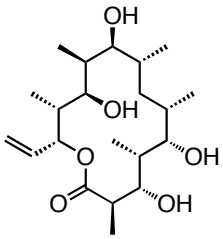
layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a clear oil. ^{1}H NMR analysis of the crude product showed a d.r. of 3.3:1 (**32** : **33**), and a product:SM ratio of 0.8:1. Purification by flash chromatography (10% EtOAc/hexanes to 25% EtOAc/hexanes + 1% AcOH) furnished a mixture of tetramethyl macrolides **32** and **33** as a clear oil (4.4 mg, 0.0099 mmol, 36%) and recovered tetramethyl alkenoic acid **30** (5.5 mg, 0.0124 mmol, 45%).

^{1}H NMR (500 MHz, $CDCl_3$) *Major diastereomer:* δ 5.80 (ddd, *J* = 15.0, 10.5, 4.5 Hz, 1H), 5.72 (m, 1H), 5.17 (dd, *J* = 16.0, 2.0 Hz, 1H), 5.17 (dd, *J* = 12.5, 2.0 Hz, 1H), 3.49 (s, 3H), 3.45 (s, 3H), 3.45 (s, 3H), 3.40 (s, 3H), 3.25 (dd, *J* = 7.0, 2.5 Hz, 1H), 3.12 (d, *J* = 9.5 Hz, 1H), 3.05 (dd, *J* = 5.5, 2.5 Hz, 1H), 2.80 (dq *J* = 7.0, 7.0 Hz, 1H), 2.64 (dd, *J* = 9.0, 3.5 Hz, 1H), 1.89-2.02 (m, 2H), 1.79-1.88 (m, 1H), 1.69-1.78 (m, 2H), 1.28-1.33 (m, 1H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 7.5 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.72-0.78 (m, 1H). *Minor Diastereomer (Diagnostic):* δ 5.15-5.26 (m, 3H), 3.44 (s, 3H), 3.43 (s, 3H), 3.36 (s, 3H), 3.34 (s, 3H), 2.94 (d, *J* = 8.5 Hz, 1H), 2.73 (dq, *J* = 7.5, 7.5 Hz, 1H), 2.72-2.74 (m, 1H), 2.20 (m, 1H), 2.02-2.06 (m, 1H), 1.53-1.62 (m, 1H), 1.27 (d, *J* = 7.5 Hz, 3H), 1.24 (d, *J* = 7.0 Hz, 3H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.02 (m, 3H), 0.95 (d, *J* = 7.5 Hz, 3H), 0.93 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (asterisk denotes minor diastereomer peaks, 125 MHz, $CDCl_3$) δ 175.7, 173.4*, 136.4, 136.0*, 117.4*, 115.3, 91.3, 87.6*, 85.4, 85.4*, 85.1, 79.4, 74.2, 62.0, 61.4*, 61.3, 59.5*, 59.2, 58.7*, 45.1*, 43.6, 42.4, 40.7, 39.2*, 36.6*, 36.2*, 35.3, 34.7, 34.6, 33.9, 32.3*, 29.7, 24.7*, 23.3*, 22.7*, 19.9*, 19.3*, 17.9, 17.1, 13.4*, 12.6, 12.0*, 11.2, 9.5, 9.4*, 8.5; IR (film, cm^{-1}): 3089, 2970, 2929, 2829, 1732, 1458, 1371, 1171, 1099; HRMS (ESI) *m/z* calc'd for $C_{25}H_{47}O_6$ $[M + H]^+$: 443.3373, found 443.3375; LRMS (FD) *m/z* found 443.3.

Synthesis of Authentic Tetramethoxy Macrolide Standard

Figure 28. Structural Confirmation of Macrolide **32**

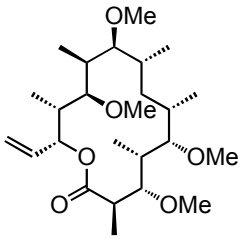




(3*R*,4*S*,5*R*,6*S*,7*S*,9*R*,10*S*,11*S*,12*R*,13*R*,14*R*)-4,6,10,12-tetrahydroxy-3,5,7,9,11,13-hexamethyl-14-vinyloxacyclotetradecan-2-one: Compound **4** is a previously synthesized intermediate.[51] A 1 dram borosilicate vial was charged sequentially with macrolide **4** (7.7 mg, 0.0141 mmol, 1.0 equiv.) THF (0.35 mL, 0.04 M) and $1M_{(aq)}$ HCl (28.2 μL, 0.0282 mmol, 2.0 equiv.). The reaction vial was topped with a teflon-lined cap and was heated at 45°C for 12 hrs. Upon completion, the reaction was partitioned between H_2O (10 mL) and Et_2O (10 mL). After separation, the organic layer was washed with satd $NaHCO_3$ (1 x 15 mL). The combined aqueous layers were then extracted with Et_2O (2 x 20 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a clear oil. Purification by flash chromatography (50% EtOAc/hexanes) furnished the tetrahydroxy macrolide product as a clear oil (4.1 mg, 0.0106 mmol, 75%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (dddd, *J* = 15.5, 11.0, 4.5 Hz, 1H), 5.69 (m, 1H), 5.31 (d, *J* = 17.5 Hz, 1H), 5.27 (d, *J* = 10.5 Hz, 1H), 4.22 (d, *J* = 4.0 Hz, 1H), 4.00 (bs, 1H), 3.87 (d, *J* = 10.5 Hz, 1H), 3.58 (d, *J* = 10.0 Hz, 1H), 3.41 (m, 1H), 3.16 (s, 1H), 3.00 (dt, *J* = 3.0, 9.5 Hz, 1H), 2.80 (dq, *J* = 10.0, 6.5 Hz, 1H), 2.10 (m, 1H), 2.04 (m, 1H), 1.96 (m, 1H), 1.83 (m, 1H), 1.75 (q, *J* = 7.0 Hz, 1H), 1.41 (m, 1H), 1.29 (d, *J* = 6.5 Hz, 3H), 1.17 (m, 1H), 1.10 (d, *J* = 6.5

Hz, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.86-0.89 (m, 1H), 0.79 (d, *J* = 6.5 Hz, 3H).



(3*R*,4*S*,5*R*,6*S*,7*S*,9*R*,10*S*,11*S*,12*S*,13*R*,14*R*)-4,6,10,12-tetramethoxy-3,5,7,9,11,13-hexamethyl-14-vinyloxacyclotetradecan-2-one [32]: A 10 mL round bottom flask was charged with tetrahydroxy macrolide (4.1 mg, 0.0106 mmol, 1.0 equiv.) and dissolved in CH_2Cl_2 (0.76 mL, 0.014 M). Proton-sponge™ (113.5 mg, 0.53 mmol, 50.0 equiv.) and Me_3OBF_4 (52.2 mg, 0.353 mmol, 33.3 equiv.) were then added to the reaction and allowed to stir for 18 hrs at room temperature in the dark. The reaction was quenched with satd. NH_4Cl (5 mL), transferred to a separatory funnel and diluted with EtOAc (15 mL), and the layers were separated. The organic layer was washed with 1M HCl (1 x 10 mL) and H_2O (1 x 15 mL). The combined aqueous layers were extracted with EtOAc (2 x 15 mL) and the combined organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow oil. Purification by flash chromatography (10% EtOAc/hexanes) furnished tetramethyl macrolide **32** as a clear oil (2.6 mg, 0.00587 mmol, 55%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddd, *J* = 15.0, 10.5, 4.5 Hz, 1H), 5.72 (m, 1H), 5.17 (dd, *J* = 15.5, 1.5 Hz, 1H), 5.17 (dd, *J* = 12.5, 1.5 Hz, 1H), 3.49 (s, 3H), 3.45 (s, 3H), 3.45 (s, 3H), 3.41 (s, 3H), 3.25 (dd, *J* = 6.5, 2.0 Hz, 1H), 3.12 (d, *J* = 9.0 Hz, 1H), 3.05 (dd, *J* = 5.0, 2.0 Hz, 1H), 2.80 (dq *J* = 7.0, 7.0 Hz, 1H), 2.65 (dd, *J* = 9.0, 3.5 Hz, 1H), 1.89-2.02 (m, 2H), 1.80-1.87 (m, 1H), 1.69-1.78 (m, 2H), 1.27-1.32 (m, 1H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 7.5 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.72-0.78 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 136.4, 115.3, 91.3, 85.4, 85.1, 79.4, 74.2, 62.0, 61.3, 59.2, 43.6, 42.4, 40.7, 35.3, 34.7, 34.6, 33.9, 29.7, 18.0, 17.1, 12.6, 11.3,

9.5, 8.5; IR (film, cm^{-1}): 2958, 2927, 2854, 2831, 1732, 1458, 1369, 1171, 1099; HRMS (ESI) *m/z* calc'd for $C_{25}H_{47}O_6$ $[M + H]^+$: 443.3373, found 443.3373; $[\alpha]_D^{23} = +20.7^o$ (c = 0.22, CH_2Cl_2).

2.5 REFERENCES

[45] *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press, Orlando FL, 1984.

[46] Corey, E. J.; Trybulski, E. J.; Melvin, L. S.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Falck, J. R.; Brunelle, D. J.; Haslanger, M. F.; Kim, S.; Yoo, S. *J. Am. Chem. Soc.* **1978**, *100*, 4620.

[47] Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568.

[48] Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chênevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3213.

[49] For a review on conformation-directed macrocyclization reactions, see: Blankenstein, J.; Zhu, J. *Eur. J. Org. Chem.* **2005**, 1949.

[50] (a) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1565. (b) Nakata, M.; Arai, M.; Tomooka, K.; Ohsawa, N.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2618. (c) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7 (d) Myles, D. C.; Danishefsky, S. J.; Schulte, G. *J. Org. Chem.* **1990**, *55*, 1636. (e) Sviridov, A. F.; Borodkin, V. S.; Ermolenko, M. S.; Yashunsky, D. V.; Kochetkov, N. K. *Tetrahedron* **1991**, *47*, 2317 (f) Stürmer, R.; Ritter, K.; Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 101. (g) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921. (h) Peng, Z. –H.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 6018. (i) Chandra, B.; Fu, D.; Nelson, S. G. *Angew. Chem. Int. Ed.* **2010**, *49*, 2591. For a formal total synthesis of 6-dEB using cyclic biasing elements see: (j) Crimmons, M. T.; Slade, D. J. *Org. Lett.* **2006**, *8*, 2191.

[51] Stang, E. M.; White, M. C. *Nat. Chem.* **2009**, *1*, 547.

[52] Muri, D.; Lohse-Fraefel, N.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4036.

[53] Mulzer, J.; Kirstein, H. M.; Buschmann, J.; Lehmann, C.; Luger, P. *J. Am. Chem. Soc.* **1991**, *113*, 910.

[54] Paterson, I.; Rawson, D. J. *Tetrahedron Lett.* **1989**, *30*, 7463.

[55] (a) Hergenrother, P. J.; Hodgson, A.; Judd, A. S.; Lee, W. –L.; Martin, S. F. *Angew. Chem. Int. Ed.* **2003**, *42*, 3278. (b) Breton, P.; Hergenrother, P. J.; Dida, T.; Hodgson, A.; Judd, A. S.; Kraynack, E.; Kym, P. R.; Lee, W.-C.; Loft, M. S.; Yamashita, M.; Martin, S. F. *Tetrahedron*, **2007**, *63*, 5709.

[56] Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614.

[57] Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756.

[58] Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

[59] Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

[60] (a) Tone, H.; Nishi, T.; Oikawa, Y. Hikota, M.; Yonemitsu, O. *Tetrahedron Lett.* **1987**, *28*, 4569. (b) Tone, H.; Nishi, T.; Oikawa, Y. Hikota, M.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1167.

[61] Shiina, I.; Katoh, T.; Nagai, S.; Hashizume, M. *Chem. Rec.* **2009**, *9*, 305.

[62] Macrolactonization reactions used in the context of total synthesis: Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* **2006**, *106*, 911.

[63] Fraunhoffer, K. J.; Prabagaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 9032.

[64] Other metal-templated macrocyclization examples: (a) Yamamoto, H.; Maruoka, E. *J. Am. Chem. Soc.* **1981**, *103*, 6133. (b) Eschenmoser, A. *Pure Appl. Chem.* **1969**, *20*, 1. (c) Namba, K.; Kishi, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15382. (d) Fürstner, A.; Albert, M; Mlynarski, J.; Matheu, M. *J. Am. Chem. Soc.* **2002**, *124*, 1168.

[65] (a) Staunton, J.; Wilkinson, B. *Chem. Rev.* **1997**, *97*, 2611. (b) Khosla, C. *Chem. Rev.* **1997**, *97*, 2577.

[66] Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH Verlag: Weinheim, Germany, 1996.

[67] Anderson, C. E.; Britt, D. K.; Sangji, S.; O'Leary, D. J.; Anderson, C. D.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 5721.

[68] Hoffmann, R. W. *Angew. Chem. Int. Ed.* **2000**, *39*, 2054.

[69] Stang, E. M.; White, M. C. *Angew. Chem. Int. Ed.* **2011**, *50*, 2094.

[70] Streamlining synthesis via late-stage C–H oxidation: (a) For first explicit demonstration of this concept see: Fraunhoffer, K. J.; Bachovchin, D. A.; White, M. C. *Org. Lett.* **2005**, *7*, 223. (b) Covell, D. J.; Vermeulen, N. A.; White, M. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 8217 c) ref. 51. d) Hoffman, R. W. *Synthesis* **2006**, *21*, 3531. f) Hoffman, R. W. in *Elements of Synthesis Planning*, Springer, Heidelberg, 2009.

[71] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

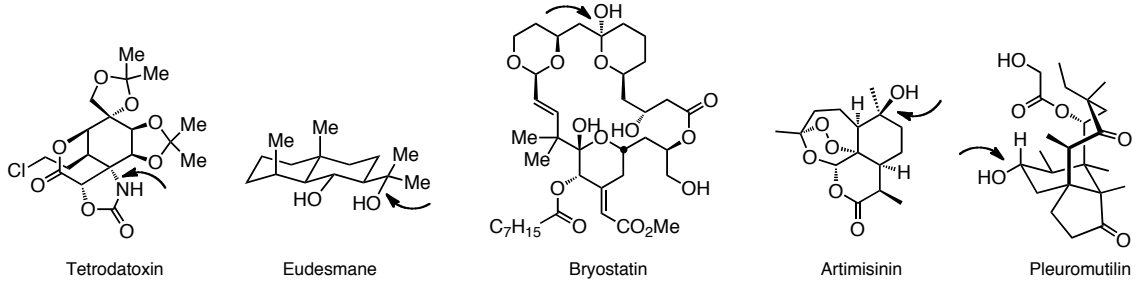
CHAPTER 3

MOLECULAR COMPLEXITY VIA C–H OXIDATION: A DEHYDROGENATIVE DIELS-ALDER REACTION

3.1 INTRODUCTION

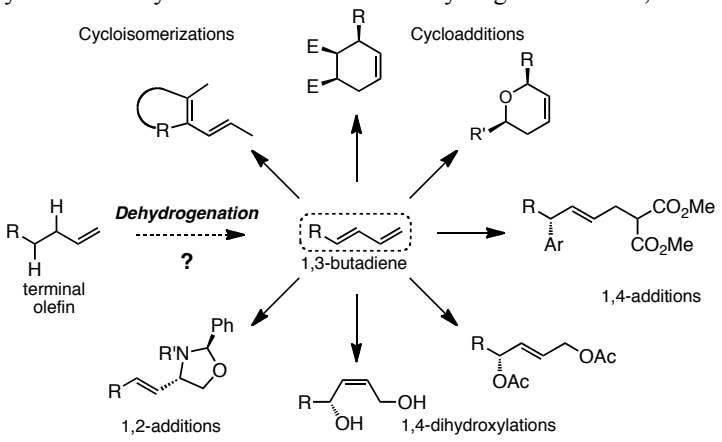
The selective transformation of inert C–H bonds into more reactive functionality is a challenging problem given the vast number of C–H bonds present in any organic molecule, but one that also presents great opportunities for streamlining complex molecule synthesis.[72,73] Akin to Nature,[74] synthetic chemists traditionally utilize C–H oxidation reactions to install oxidized functionality onto a preformed molecular skeleton, resulting in a local molecular change. Recent examples are Du Bois nitrene insertion strategy for the synthesis of tetrodatoxin,[75] Baran's hydroxylation of the Eudesmane terpenes,[76] oxyfunctionalization of Bryostatin analogues by Wender,[77] and iron-catalyzed hydroxylation of artemisinin[78] and pleuromutilin[79] derivatives performed in our labs (Figure 29). Although C–H oxidation reactions have been primarily used to install functional groups onto established carbon frameworks, this reaction class also holds tremendous promise for directly accessing reactive intermediates that can be coupled to productive secondary reactions to forge new carbon frameworks. The use of C–H activation as a

Figure 29. Examples of C–H Oxidation Reactions for Installing Functionality



"substrate-activating" strategy is exemplified by catalytic dehydrogenative oxidation of alkanes to form alkenes.[80] This activation step is typically followed by a bond construction step, such as an alkene metathesis reaction, which proceeds under 'one-pot' conditions.[81] Although extremely rare, preparatively useful processes have utilized such a secondary reaction to generate valuable, stable products while avoiding undesired side reactions and reactive intermediate isolations. The ability to perform this inert substrate activation and bond construction step in tandem makes transition metal-catalyzed dehydrogenation reactions a particularly powerful C–H activation strategy.[82] In this regard, we questioned whether a dehydrogenation reaction could be developed that would convert simple terminal olefins into reactive 1,3-diene intermediates[83] capable of participating in a wide range of complexity generating transformations[84] (e.g. cycloadditions,[85] 1,2- and 1,4-additions,[86] cycloisomerizations[87]). Performing such a sequence in tandem would enable the rapid construction of diverse molecular skeletons from topologically simple starting materials (Figure 30).[88]

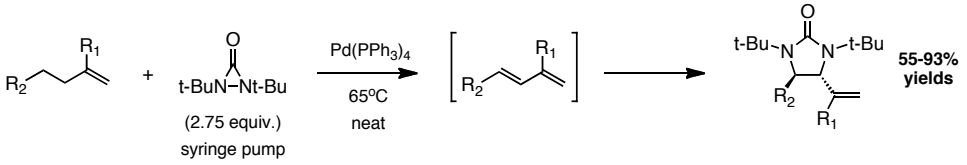
Figure 30. Synthetic Utility of a Terminal Olefin Dehydrogenation for 1,3-Diene Formation



One terminal olefin dehydrogenation system has been reported previously, which utilizes a palladium-(0) catalyst and is thought to proceed through a 1,3-diene intermediate. This reactive intermediate is then trapped with a diamine ligand to provide convenient access to vicinal

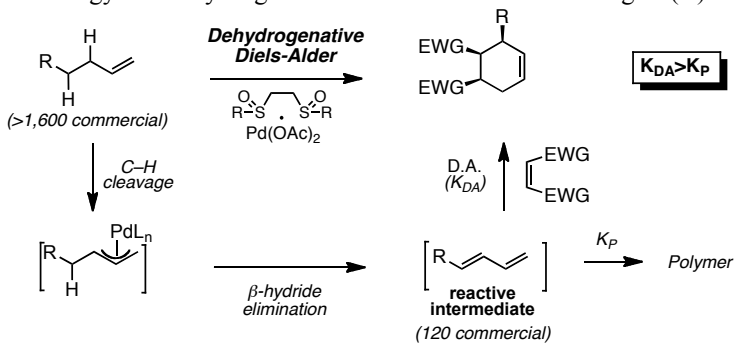
diamine products (Figure 31).[89] However, the source of nitrogen for the diamination (di-*tert*-butyldiaziridinone) is also the palladium oxidant and ligand, and 2.5 equivalents are required. Because the palladium ligand is also the source of nucleophilic nitrogen, and is used in superstoichiometric amounts, it is unlikely that this reaction manifold would allow for a secondary process other than diamination. We therefore desired a truly general olefin dehydrogenation reaction for the synthesis of 1,3-dienes, which could be coupled to a variety of secondary reactions. In order to accomplish this, we required a ligand that wouldn't functionalize the newly formed diene.

Figure 31. Yian Shi Diamination of Terminal Olefins



Within recent years, our laboratory has introduced electrophilic Pd(II)/sulfoxide catalysis as a general platform for allylic C–H activation that enables direct allylic esterification,[90] amination,[91] and alkylation[92] of terminal olefins through the intermediacy of a π-allylPd species. We hypothesized that a dehydrogenation reaction of terminal olefins could also be developed using this reaction manifold by promoting β-hydride elimination from the π-allylPd intermediate, in the absence of nucleophile (Figure 32). Given the abundance of bulk commodity terminal olefins (>1,600 commercial) versus the relative scarcity of commercial 1,3-dienes (120 commercial) along with the inefficient synthetic routes required for their construction, we anticipated that such a dehydrogenation transformation would provide a significant synthetic advantage. Moreover, because 1,3-dienes are typically used as synthetic building blocks, ideally this dehydrogenation reaction could be coupled to a desirable secondary reaction. While diene products arising from dehydrogenation reactions have not been previously observed in our

Figure 32. General Strategy for Dehydrogenation of Terminal Olefins Using Pd(II)/sulfoxide Catalysis.



Adapted from reference 95

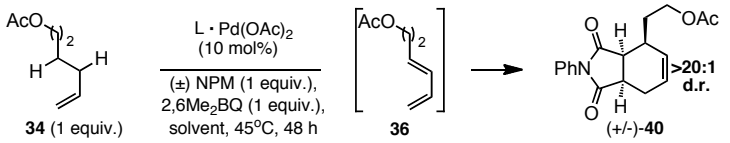
Pd(II)/sulfoxide systems, diene formation has been achieved using Pd(0) catalysis with oxidized substrates (i.e. allylic oxygenates) via β-hydride elimination from π-allylPd intermediates.[93] However, in addition to general difficulties associated with dehydrogenation chemistry (e.g. thermodynamically uphill), generating 1,3-butadienes from terminal olefin substrates poses several unique challenges: 1) dienes are reactive intermediates prone to isomerizations and olefin oxidations and 2) the electrophilic catalysts needed for the C–H activation step often catalyze diene oligomer- and polymerization processes.[94] Performing dehydrogenation chemistry in tandem with a useful secondary reaction has proven to be an effective strategy for circumventing such issues.[81] We therefore sought to generate low concentrations of the reactive 1,3-butadiene intermediate in the presence of high concentrations of a reactive component capable of furnishing a stable product. Of the possible secondary transformations, the Diels-Alder reaction would be particularly enabling, as it remains one of the most powerful complexity-generating reactions in organic chemistry.[85]

3.2 RESULTS AND DISCUSSION

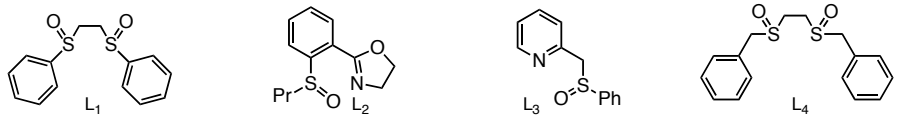
3.2.1 Optimization of the Dehydrogenative Diels-Alder Reaction

We began our study by examining the viability of the dehydrogenation step in the absence of dienophile, using limiting amounts of α-olefin **34** under standard allylic C–H activation conditions (Table 2).[95] Although 1,4-benzoquinone is typically used as an oxidant for such allylic C–H functionalization processes, bulky 2,6-dimethyl-1,4-benzoquinone (2,6-Me_2BQ) was used here, both to prevent a possible quinone Diels-Alder with the diene products (While BQ reacts readily with 1,3-butadienes, 2,6-dimethylbenzoquinone typically requires prolonged reaction times at temperatures >100°C)[96] and to prevent functionalization of the intermediate π-allylPd species with the acetate counterion (BQ promotes the functionalization of π-allyl complexes with carboxylates, a process slowed with increasing steric bulk around the quinone ligand).[90a] While the use of $Pd(OAc)_2$ resulted in only recovered starting material (entry 1), commercially available Pd(II)/phenylbis-sulfoxide catalyst **35** provided initial dehydrogenation reactivity, albeit in low yield (6% yield of **36**, entry 2). We hypothesized that the electron poor phenylbis-sulfoxide ligand generated an aggregated/dimeric π-allylPd species after C–H cleavage, which was unable to decompose through β-hydride elimination due to insufficient palladium coordination sites. Mono-heterocyclic catalysts were then evaluated in attempts to disrupt such aggregated/dimeric intermediates, however, these highly electron rich ligands were not compatible with the C–H cleavage event (entry 3,4). Alkylbis-sulfoxide ligands proved to be ideal for this dehydrogenation chemistry by promoting C–H cleavage and destabilizing the resulting π-allylPd intermediates, enabling a more facile β-hydride elimination step. It was found that 10 mol% of the Pd(II)/benzylbis-sulfoxide catalyst **39**[90,92b] resulted in the highest catalytic turnover, leading to 28% diene product (4:1 E:Z selectivity, entry 5). Longer reaction times led

Table 2. Development of a Dehydrogenative Diels-Alder Reaction



entry	catalyst[a]	solvent	additive[f]	dienophile[e]	yield diene[b]	yield cycloadduct[c]
1	$Pd(OAc)_2$	dioxane	-----	-----	<1[d]	-----
2	L_1 **35**	dioxane	-----	-----	6	-----
3	L_2 **37**	dioxane	-----	-----	<1[d]	-----
4	L_3 **38**	dioxane	-----	-----	<1[d]	-----
5	L_4 **39**	dioxane	-----	-----	28	-----
6	L_4 **39**	dioxane	-----	NPM	<1[d]	33
7	L_4 **39**	DCE	-----	NPM	<1[d]	52
8	L_4 **39**	DCE	*p*-NO_2BzOH	NPM	<1[d]	74
9	L_4 **39**	DCE	*p*-NO_2BzOH	-----	35	-----

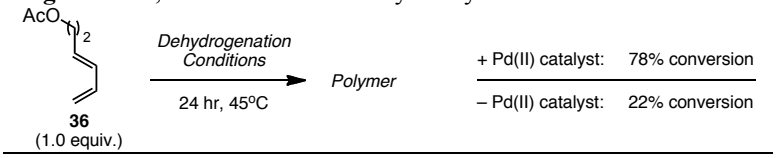


[a] Conditions: **34** (1.0 equiv.), catalyst (10 mol%), 2,6Me_2BQ (1.0 equiv.), solvent (1.0 M), 45°C, 48h. Ligands pre-complexed with $Pd(OAc)_2$ [b] **36** isolated after 24 hr as a 4:1 mixture of E/Z isomers along with rSM [c] isolated yield of **40** [d] Determined by GC analysis [e] NPM = N-phenylmaleimide (1.0 equiv.) [f] 10 mol%. Adapted from reference 95.

to significantly diminished yields, indicating that the 1,3-butadiene product was not stable to the reaction conditions. As further evidence of this, when authentic (E)-diene (**36**) was subjected to the electrophilic Pd(II) conditions, significant conversion occurred after 24h (75% conversion), likely due to polymerization (Figure 33). In the hopes of generating the desired Diels-Alder adduct, one equivalent of the reactive N-phenylmaleimide (NPM) dienophile was included in the dehydrogenation reaction to trap the unstable diene intermediate. Gratifyingly, the dehydrogenative Diels-Alder adduct was furnished in encouraging yield (33% of **40**) and as a single diastereomer (Table 2, entry 6). Switching to chlorinated solvents, such as 1,2-dichloroethane (DCE), dramatically improved the tandem yield to 52% (entry 7). The yield was increased further to 74% upon the addition of 10 mol% *p*-NO_2BzOH (entry 8), which likely aids

with Pd(0) → Pd(II) catalyst reoxidation.[97] For all tandem dehydrogenation/Diels-Alder reactions, very little diene (<1%) could be detected by GC analysis (entries 6-8). Maintaining low concentrations of diene is thought to be critical for retarding polymerization pathways and enabling the use of limiting olefin starting material. Consistent with this, when NPM was excluded from the optimized reaction conditions the diene was isolated in only 35% yield (24 hr), suggesting that diene decomposition pathways were still operative (entry 9).

Figure 33. 1,3-Butadiene Reactivity Study

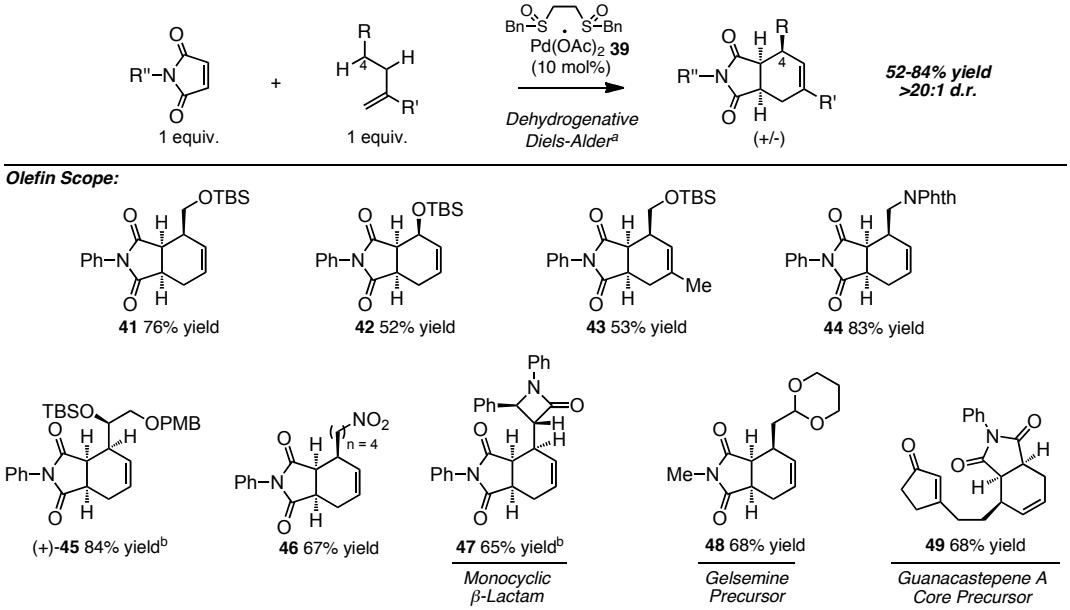


Conditions: Diene **36** (1.0 equiv.), ± catalyst **39** (10 mol%), 2,6Me$_2$BQ (1.0 equiv.), dioxane (1.0 M), 45°C, 24h. Conversion measured by GC analysis.

3.2.2 Developing a Dehydrogenative Diels-Alder Reaction: Olefin and Maleimide Scope

Experiments to probe the scope of both the terminal olefin and maleimide dienophile are summarized in Figure 34 and 35.[95] A wide range of polar groups that can serve as synthetic handles for further elaboration are well-tolerated in terminal olefin dehydrogenations: silyl (**41**,**42**,**43**,**45**) and benzyl ethers (**45**), phthalimide (Phth)-protected amines (**44**), nitro functionality (**46**), amides (**47**), acid sensitive acetals (**48**), and a,β-unsaturated enones (**49**). Although terminal olefins that form 1-oxy-1,3-butadienes and 1,1-disubstituted olefins are less reactive dehydrogenation substrates, they furnish the Diels-Alder adducts in synthetically useful yields (**42** and **43**, respectively). Terminal olefins containing stereogenic branching elements undergo facile tandem dehydrogenation/Diels-Alder cycloaddition without epimerization of the preexisting stereogenic center(s) (adducts **45** and **47**). While the Diels-Alder reaction still

Figure 34. Dehydrogenative Diels-Alder Reaction: Olefin Scope



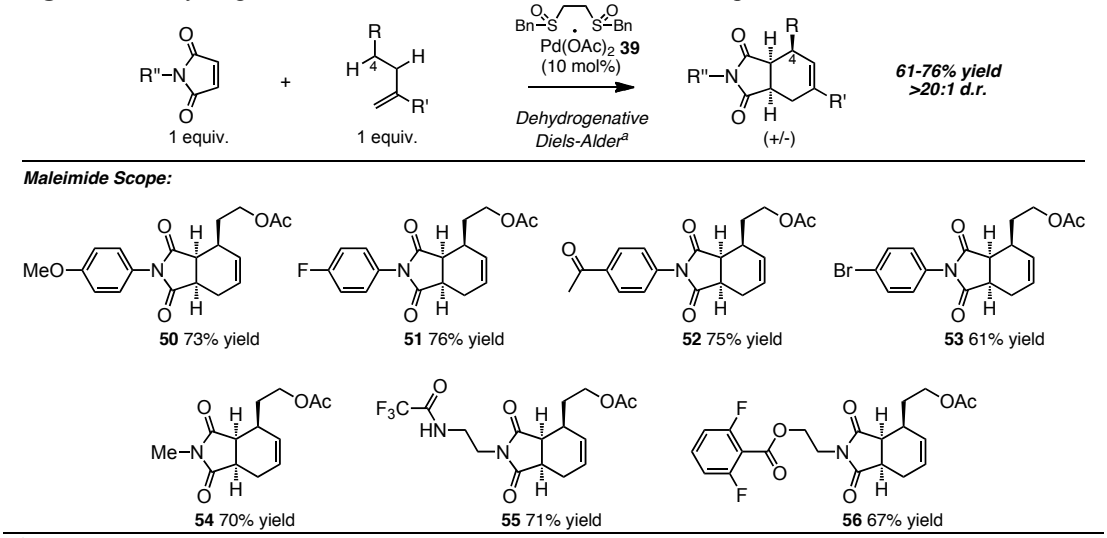
[a] Terminal olefin (1.0 equiv.), catalyst **39** (10 mol%), maleimide (1.0 equiv.), 2,6Me_2BQ (1.0 equiv.), *p*-NO_2BzOH (10 mol%), DCE (1.0 M), 45°C, 48h. All isolated yields. [b] ~1.3:1 Diastereomeric ratio of facial selectivity. Diastereomers separated using standard chromatography. Major diastereomer shown. Adapted from reference 95.

proceeds with exclusive endo selectivity, the chiral substituent displays little control over diastereofacial selectivity (~1:1 d.r.), as expected for maleimide dienophiles.[98] Access to the functionalized dienes traditionally requires differentiation of bifuncitonal starting materials using lengthy protecting group manipulation sequences.[99] Alternatively, this dehydrogenation manifold provides direct access to 1,3-diene intermediates from mono-functional terminal olefins, the majority of which are commercial, or are generated in one step from commercial materials.

The high functional group tolerance of the dehydrogenative Diels-Alder reaction enables rapid access to functionally dense motifs found in biologically active molecules (Figure 34). For example, cycloadducts containing monocyclic β-lactam pharmacophores, known to furnish antibiotics with activity against gram-negative organisms, can be rapidly generated in 3-steps using this methodology (**47**).[100] Furthermore, adduct **48** (generated in just 2 steps from commercial materials) contains the core structure needed for the synthesis of gelsemine,[101] an

alkaloid that possesses anxiolytic and analgesic properties.[102] Because of the high reactivity of maleimides in the Diels-Alder reaction, other potentially reactive dienophiles are tolerated on the diene precursors (e.g. α,β-unsaturated enones, **49**, *vide infra*). Cycloadduct **49** provides an expedient route to synthetic intermediates used to construct the [5-7-6] tricyclic core of Guanacastepene A, an active antibiotic against methicillin- and vancomycin-resistant bacterial strains.[103]

Figure 35. Dehydrogenative Diels-Alder Reaction: Maleimide Scope



[a] Terminal olefin **34** (1.0 equiv.), catalyst **39** (10 mol%), maleimide (1.0 equiv.), 2,6Me_2BQ (1.0 equiv.), *p*-NO_2BzOH (10 mol%), DCE (1.0 M), 45°C, 48h. All isolated yields. Adapted from reference 95.

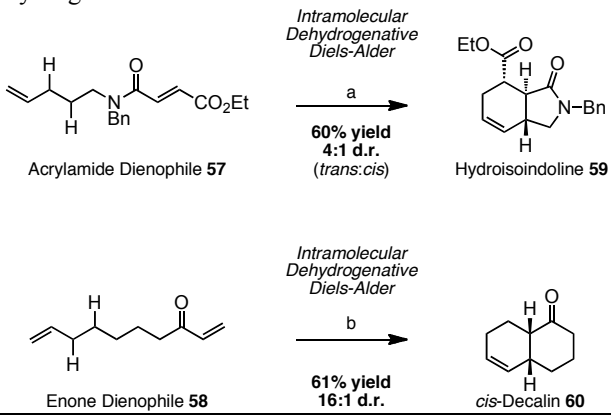
The dehydrogenative Diels-Alder reaction was also examined with a series of maleimide dienophile substrates (Figure 35).[95] Both electron-donating (**50**) and withdrawing (**51** and **52**) N-aryl substituents are well tolerated, including functionalities that can be further elaborated using Pd(0)-catalysis (i.e. aryl bromide **53**). In addition to N-methyl (adducts **48** and **54**), a variety of densely functionalized N-alkylmaleimides also undergo dehydrogenative Diels-Alder reactions with good yields and selectivities. These substituents provide additional opportunities for

synthetic elaboration (e.g. N-ethylamine derivatives can undergo cyclization to furnish imidazolines,[104] **55**) and amide diversification (i.e. potent pharmacophoric esters,[105] **56**).

3.2.3 Developing a Dehydrogenative Diels-Alder Reaction: Dienophile Scope

Maleimides proved to be superior dienophiles for trapping the reactive 1,3-diene intermediates under these dehydrogenation conditions. Less reactive dienophiles, such as α,β-unsaturated esters and quinones, exhibit low reactivity under the current intermolecular conditions (<25% yields), although the dehydrogenation step is still operative. This is a common limitation of non-Lewis acid catalyzed Diels-Alder cycloadditions of unactivated dienes under mild conditions. However, tethering terminal olefin functionality to the dienophile reaction partner, led to significant rate enhancements of the Diels-Alder cycloaddition. Under such intramolecular cyclization conditions, the scope of the dienophile class could be expanded to include acrylamide (**57**) and enone dienophiles (**58**), providing expedient access[106] to synthetically/medicinally important hydroisoindolines (**59**) and *cis*-decalin (**60**) frameworks, respectively (Figure 36).[95]

Figure 36. Dehydrogenative Intramolecular Diels-Alder Reaction: Dienophile Scope

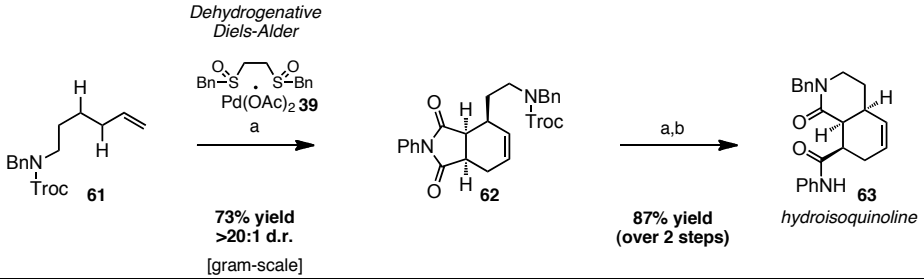


Conditions: (a) acrylamide **57** (1.0 equiv.), catalyst **39** (10 mol%), 2,6Me$_2$BQ (1.0 equiv.), *p*-NO$_2$BzOH (10 mol%), DCE (1.25 M), 45°C, 48h, 4:1 d.r., 60% (b) enone **58** (1.0 equiv.), catalyst **39** (10 mol%), 2,6Me$_2$BQ (1.0 equiv.), *p*-NO$_2$BzOH (10 mol%), DCE (1.5 M), 45°C, 48h, 16:1 *cis:trans*, 61%. Adapted from reference 95.

3.2.4 Synthetic Applications: Hydroisoquinolines and Isoindoloquinolines

Maleimide-based cycloadducts containing synthetic handles at the C4 and nitrogen positions are powerful synthetic intermediates that can be readily elaborated to a wide range of alkaloid frameworks. Towards this end, we incorporated an amine nucleophile onto the α-olefin component for an ultimate intramolecular cyclization onto the succinimide moiety of the cycloadduct. Subjecting Troc-protected hexenamine **61** to the dehydrogenative Diels-Alder reaction gave cycloadduct **62** in 73% yield and >20:1 d.r. (Figure 37). This operationally simple reaction can be conducted on a gram-scale, with no precautions taken to exclude moisture. Removal of the Troc protecting group with zinc dust, followed by a thermally promoted imide acylation, provided the hydroisoquinoline heterocycle **63** in 87% yield over 2 steps. This tandem dehydrogenation/Diels-Alder reaction provides an expedient route to such substituted hydroisoquinolines,[107] which are common structural elements found in a variety of alkaloid natural products.[108]

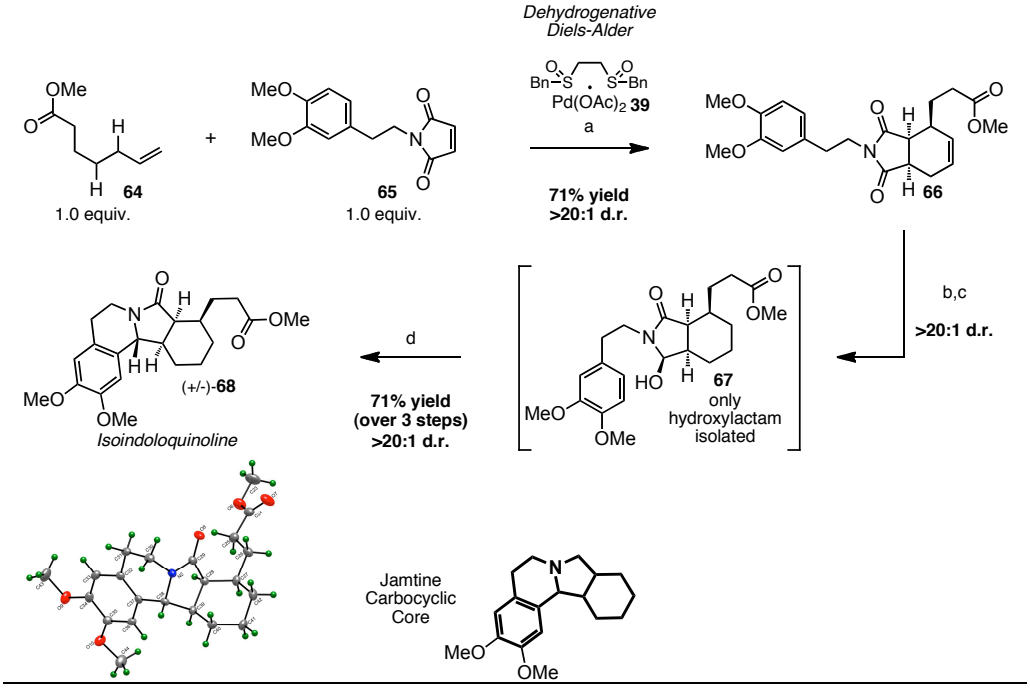
Figure 37. Synthetic Utility: Hydroisoquinoline Synthesis



Conditions: (a) **61** (1.0 equiv.), **39** (10 mol%), NPM (1.0 equiv.), 2,6Me$_2$BQ (1.0 equiv.), *p*-NO$_2$BzOH (10 mol%), DCE (1.0 M), 45°C, 48 hr., >20:1 d.r., 73% (b) Zn (18.4 equiv.), AcOH, THF (c) PhMe, 80°C, 87% over 2-steps. Adapted from ref. 95.

We next incorporated a nucleophilic phenethyl moiety onto the maleimide for an ultimate cyclization onto the succinimide group. One equivalent of 3,4-dimethoxy-phenethyl maleimide (**65**) was coupled to commercially available methyl 6-heptenoate (**64**) using the tandem

Figure 38. Synthetic Utility: Isoindoloquinoline Synthesis



Conditions: (a) **64** (1.0 equiv.), **39** (10 mol%), **65** (1.0 equiv.), 2,6Me$_2$BQ (1.0 equiv.), *p*-NO_2BzOH (10 mol%), DCE (1.0 M), 45°C, 48 hr., >20:1 d.r., 71% (b) Pd/C (cat.), H_2 (1 atm), MeOH (c) $NaBH_4$ (8.0 equiv.), 2 M H_2SO_4 (cat.), EtOH (d) CSA (1.5 equiv.), PhMe, 80°C, >20:1 d.r., 71% over 3-steps. Adapted from reference 95.

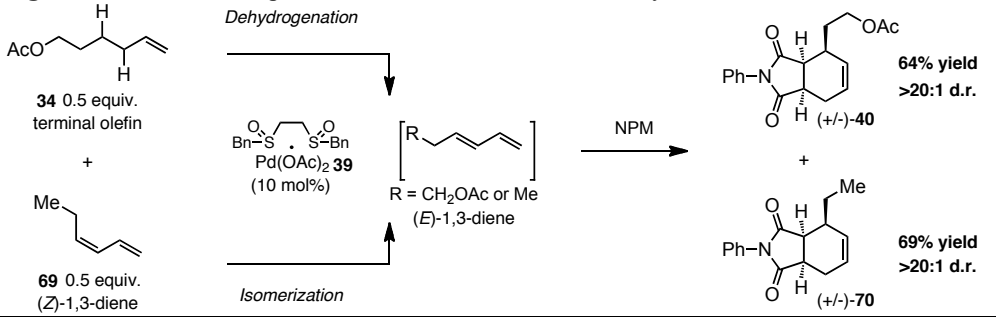
dehydrogenation/Diels-Alder reaction, providing adduct **66** in 71% yield and >20:1 d.r. (Figure 38). With this adduct in hand, we next sought to differentiate the two imide carbonyls as a prelude to regioselective intramolecular cyclization. It had been previously shown on related hexahydrophthalimide compounds that the imide carbonyl distal to the pendant side chain could be mono-reduced with $NaBH_4$ in >95:5 selectivity.[109] In accord with these results, following olefin hydrogenation, a regioselective mono-reduction with $NaBH_4$ afforded a single hydroxylactam compound (**67**), with hydride addition occurring solely at the carbonyl furthest from the methyl ester side chain. With the 3,4-dimethoxyphenyl moiety acting as the nucleophile, hydroxylactam **67** underwent stereoselective (>20:1 d.r.) cyclization under typical N-acyliminium ion conditions,[110] to afford the isoindoloquinoline polycycle **68** as a single diastereomer in 71% yield (over 3 steps). This isoindoloquinoline skeleton is found in several

alkaloids, such as jamtine, which displays significant antihyperglycemic activity.[111] In total, this stereochemically dense azapolycyclic architecture was constructed in just 4 steps from commercially available terminal olefin **64**.[95]

3.2.5 Mechanistic Studies

In all achiral substrates examined, the maleimide-based products were isolated with >20:1 diastereoselectivities, resulting from cycloadditions of (*E*)-1,3-dienes with maleimide dienophiles. It did not escape notice, however, that the dehydrogenation produced a mixture (4:1 *E:Z*) of diene isomers. Based on the low reactivity of (*Z*)-1,3-dienes in the Diels-Alder reaction at these temperatures, this isomer was likely either reacting in non-productive pathways (e.g. polymerization), or isomerizing under the reaction conditions to yield the Diels-Alder capable (*E*)-1,3-diene. To determine the fate of the (*Z*)-1,3-diene, we performed a crossover experiment utilizing 0.5 equiv of terminal olefin **34** and 0.5 equiv of (*Z*)-1,3-diene **69** (Figure 39). Under these reaction conditions, the dehydrogenation cycloadduct **40**, derived from terminal olefin **34**, was formed in 64% yield (>20:1 d.r.). Cycloadduct **70**, derived from isomerization of (*Z*)-diene **69** to the (*E*)-isomer, was formed in good yield (69%) and as a single diastereomer (>20:1 d.r.).

Figure 39. Crossover Experiment: Diene Isomerization Study



Conditions: **34** (0.5 equiv.), **69** (0.5 equiv.), **39** (10 mol%), NPM (1.0 equiv.), 2,6Me$_2$BQ (1.0 equiv.), *p*-NO$_2$BzOH (10 mol%), DCE (1.0 M), 45°C, 48 hr, >20:1 d.r., 64% of **40** and 69% of **70**. Adapted from reference 95.

Interestingly, when pure (*Z*)-diene **69** was reacted with NPM and catalyst **39**, endo cycloadduct **70** was formed in >20:1 d.r., suggesting that diene isomerization is Pd(II)-promoted. In the absence of Pd(II), (*Z*)-diene **69** is fully recovered. These results support a Pd(II)-catalyzed dynamic diene isomerization pathway in which both the (*E*)- and (*Z*)- diene isomers generated during the dehydrogenation step are funneled to the desired cycloadducts *in situ*.[95] Consequently, this dehydrogenation chemistry circumvents the need for geometrically pre-defined diene starting materials.

3.3 CONCLUSIONS

In summary, a novel approach to stereochemically dense cyclohexenyl rings from terminal olefins has been achieved using Pd(II)/sulfoxide C–H activation catalysis. This dehydrogenative Diels-Alder reaction underscores the power of coupling transition metal-catalyzed C–H activation to complexity generating transformations for the rapid synthesis of complex molecular skeletons from topologically simple starting materials. Currently, maleimide dienophiles are unique in terms of the rate of Diels-Alder cycloaddition under intermolecular conditions. However, intramolecular dehydrogenative Diels-Alder reactions show significant promise, broadening the scope of the dienophile to include acrylamides and enones. Further investigations are focused on expanding the scope of this transformation with respect to both the olefin class (internal olefins) and dienophile, specifically through Lewis acid co-catalyst activation. Moreover, based on the general dehydrogenation manifold developed here, future studies will begin to explore this dehydrogenation chemistry in tandem with secondary reactions other than Diels-Alder cycloadditions.

3.4 EXPERIMENTAL SECTION

General Information: All dehydrogenative Diels-Alder reactions were run under air, with no precautions to exclude moisture. All other reactions were conducted in flame-dried glassware with magnetic stirring under an inert atmosphere of dry nitrogen, unless otherwise noted. Solvents tetrahydrofuran (THF), diethyl ether (Et_2O), methanol (MeOH), benzene, toluene, 1,4-dioxane, dimethylformamide (DMF), and methylene chloride (DCM or CH_2Cl_2) were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, California). Deuterochloroform was stored over 3 Å molecular sieves. Diisopropylamine (DIPA) and pyridine were distilled from calcium hydride. The following commercially obtained reagents were used as received: N-phenylmaleimide (NPM, TCI America), N-methylmaleimide (NMM, TCI America), 1,2-dichloroethane (DCE, Sigma-Aldrich), 2,6-dimethylbenzoquinone (2,6-Me_2BQ, Sigma-Aldrich), *p*-nitrobenzoic acid (Sigma-Aldrich), Pd[1,2-bis(phenylsulfinyl)ethane]$(OAc)_2$ catalyst (TCI America), acetic acid 5-hexen-1-yl ester (TCI America), and lithium aluminum hydride (LAH, Sigma-Aldrich, 95%). Oxalyl Chloride (Sigma-Aldrich), benzylbromide, and acrolein were distilled prior to use. Triphenylphosphine was recrystallized from ethanol and stored under argon. $Pd(OAc)_2$ (Johnson-Matthey Chemicals) was recrystallized prior to use (see catalyst preparation). *n*-Butyllithium in hexanes (Sigma-Aldrich, 1.6 M) was titered using No-D NMR spectroscopy with 1,5-cyclooctadiene (Sigma-Aldrich) as the internal standard.[112]

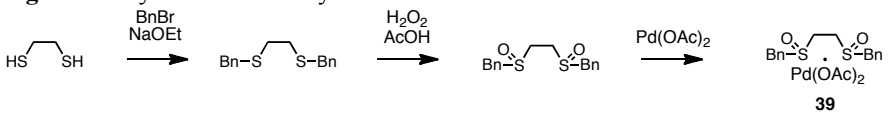
Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Perkin-Elmer 341 polarimeter. Optical rotations were obtained with a sodium lamp and are reported as follows: $[\alpha]_{\lambda}^{T\circ C}$ (c = g/100 mL, solvent). Infrared spectra were recorded as thin films on NaCl plates on a Mattson Galaxy Series FTIR 5000 and are reported in frequency of absorption (cm^{-1}).

High-resolution mass spectra were obtained through the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois. Electrospray ioniztion (ESI) spectra were performed on a Waters Q-Tof Ultima spectrometer and electron ionization (EI) spectra were performed on a Micromass 70-VSE spectrometer. ^{1}H NMR spectra were recorded on a Varian Unity-400 (400 MHz) or Varian Unity-500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, pent = pentet, oct = octet, m = multiplet, br = broad, app = apparent; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C-NMR spectra were recorded on a Varian Unity-400 (100 MHz) or Varian Unity-500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Chiral HPLC analysis was performed on an Agilent 1100 Series instrument (see individual compounds for conditions). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV, potassium permanganate, and ceric ammonium molybdate staining. Flash column chromatography was performed as described by Still et al.[113] using EM reagent silica gel 60 (230-400 mesh).

All dehydrogenative Diels-Alder products were assigned as "endo" products between an (*E*)-1,3-diene and a maleimide dienophile. The relative stereochemistry of the tandem dehydrogenation/Diels-Alder products could not be determined directly through analysis of ^{1}H NMR *J*-values. Therefore, the stereochemistry was determined by direct comparisons to literature compounds (product **47** major, **47** minor, and compound **63**), NOE analysis (products **40** and **41**), and X-ray crystallographic analysis (product **42**, product **44**, and compound **68**). The other dehydrogenative Diels-Alder products were assigned based on analogy to these compounds or similar literature compounds.

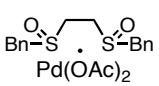
Synthesis of the Palladium Catalyst for Dehydrogenative Diels-Alder Reactions

Figure 40. Synthesis of Catalyst **39**



39

$Pd(OAc)_2$ Recrystallization: $Pd(OAc)_2$ (Johnson-Matthey Chemicals) was dissolved in minimal refluxing benzene (0.5 g $Pd(OAc)_2$/ 8.0 mL benzene). A black precipitate was removed from the refluxing solution by Acrodisc® filtration. The resulting solution was cooled to room temperature, and amber crystals began to form immediately. After 1 hr the solution was filtered to give the recrystallized $Pd(OAc)_2$ as gold plates. The recrystallized $Pd(OAc)_2$ was stored for months under an Ar atmosphere with no deleterious effects. Reported hydrogen values are normalized ratios of the smallest peak in the acetate region. "Old" $Pd(OAc)_2$: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (s, 1H), 2.10 (s, 3.6H), 2.07 (s, 6.1H), 2.06 (s, 6.1H), 2.03 (m, 15.3H), 2.00 (m, 95.7H), 1.97 (s, 5.7H), 1.95 (s, 6.3), 1.89 (s, 9.4H). Recrystalized $Pd(OAc)_2$: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.10 (s, 1H), 2.03 (s, 2.8H), 2.00 (s, 40.1H), 1.97 (s, 1.2H), 1.90 (s, 2.3H).



Pd[1,2-bis(benzylsulfinyl)ethane](OAc)$_2$ [39]: This catalyst was prepared using a modified procedure.[90a] A flame dried 2 L round bottom flask was charged with NaOEt (11.65 g, 171.2 mol 2.0 equiv) and absolute EtOH (800 mL, 0.107 M) and allowed to stir for 5 min, resulting in an orange solution. 1,2-ethanedithiol (Fluka, 7.18 mL, 85.6 mmol, 1.0 equiv) was added to the reaction, followed by a solution of benzylbromide (20.3 mL, 171.2 mmol, 2.0 equiv) in benzene (400 mL, 0.214 M) via cannula. After 4.5 hours, the reaction was concentrated to near dryness *in vacuo*, redissolved in DCM (500 mL), and quenched with satd

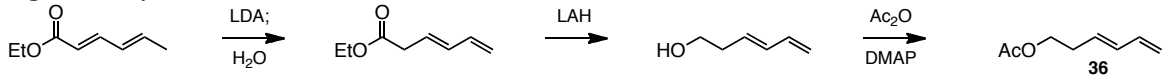
NH_4Cl (200 mL). The layers were then separated and the aqueous layer was extracted with DCM (2 x 200 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a yellow oil. This product was then allowed to sit at 0°C for ~1 hr. The resulting light yellow solid was placed on a fritted funnel, and washed with cold (-20°C) EtOH until the solid was white. This white solid was put under high vacuum to afford bis(benzylthio)ethane (21.14 g, 77.03 mmol, 90% yield).

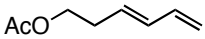
A flame-dried 100 mL round bottom flask was charged with bis(benzylthio)ethane (3.293 g, 12.0 mmol, 1.0 equiv) and dissolved (mostly) in glacial AcOH (30 mL, 0.40 M) and cooled to 0°C. H_2O_2 (50% wt solution, Sigma-Aldrich, 1.25 mL, 20.4 mmol, 1.7 equiv) was then added to reaction dropwise. The reaction was then warmed up to r.t. and allowed to stir for 12 hr. The resulting white suspension was placed under high vacuum to remove the AcOH. The white solids were placed on a fritted funnel and washed with EtOH (6 x 20 mL), and then dried under high vacuum to afford 1,2-bis(benzylsulfinyl)ethane (3.117 g, 10.17 mmol, 85% yield)

A flame-dried 100 mL round bottom flask was charged sequentially with recrystallized $Pd(OAc)_2$ (0.684 g, 3.045 mmol, 1.0 equiv), 1,2-bis(benzylsulfinyl)ethane (0.933 g, 3.045 mmol, 1.0 equiv), and DCM (45 mL, 0.67 M). The reaction was topped with a water condenser and an Ar balloon, and let stir in a 45°C bath for 12 hr. The resulting dark purple solution was concentrated to near dryness *in vacuo*, and placed under a stream of N_2 for 12 hr to dry completely. The dark purple solids were scraped from the sides of the round bottom flask and collected to afford Pd[1,2-bis(benzylsulfinyl)ethane]$(OAc)_2$ (**39**) (1.267 g, 2.386 mmol, 78% yield).

Synthesis of the Diene Authentic Standard for Table 2 and Figure 33

Figure 41. Synthesis of Diene **36** Authentic Standard





(*E*)-hexa-3,5-dien-1-yl acetate [36]: A flame-dried 500 mL round bottom flask was charged with THF (68.5 mL) and DIPA (14.4 mL, 102.7 mmol, 1.80 equiv), and cooled to -78°C. n-BuLi (64.2 mL, 102.7 mmol, 1.80 equiv) was then syringed into the reaction dropwise, and the reaction was warmed to -10°C and stirred for 30 min. The reaction was then re-cooled to -78°C and HMPA (Sigma-Aldrich, 22.8 ml, 2.5 M) was added to the reaction, resulting in a dark green reaction mixture. After stirring at -78°C for 20 min, a solution of ethyl sorbate (Sigma-Aldrich, 8.0 g, 57.07 mmol, 1.0 equiv) in THF (22.8 mL) was cannulated into the LDA/HMPA solution, resulting in a dark red solution. The reaction was allowed to stir for 20 min, at which time it was carefully quenched by pouring into a 1L round bottom flask containing H_2O (115 mL) and glacial AcOH (20.5 mL). After diluting with hexanes, the layers were separated, and the aqueous layer was extracted with hexanes (3 x 125 mL). The combined organic layers were washed with satd $NaHCO_3$ (1 x 75 mL), satd NaCl (1 x 75 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude (E)-3,5-diene-ethyl ester product (>20:1 E:Z, 6.5079 g, 46.4 mmol, 81% crude yield) was taken on to the next step without purification.

A flam-dried 250 mL round bottom flask was charged with LAH (2.39 g, 63.1 mmol, 1.36 equiv), suspended in Et_2O (36 mL), and cooled to 0°C. A solution of (*E*)-3,5-diene-ethyl ester (6.5079 g, 46.4 mmol, 1.0 equiv) in Et_2O (12 mL) was slowly cannulated into the LAH suspension, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 4.5 hr, the reaction was re-cooled to 0°C, diluted with Et_2O, and slowly

quenched with a solution of sat'd rochelle's $salt_{(aq)}$ (100 mL). This biphasic mixture was stirred vigorously for 12 hr. The layers were then separated, and the aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic layers were washed with sat'd NaCl (1 x 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude (*E*)-hexa-3,5-dien-1-ol (4.3667 g, 44.5 mmol, 96% crude yield) was taken on to the next step without purification.

A 50 mL round bottom flask was charged with (E)-hexa-3,5-dien-1-ol (2.488 g, 25.35 mmol, 1.0 equiv), DCM (5.1 mL, 5.0 M), pyridine (6.12 mL, 76.05 mmol, 3.0 equiv), and acetic anhydride (7.18 mL, 76.05 mmol, 3.0 equiv). The reaction flask was then cooled to 0°C, and DMAP (154 mg, 1.26 mmol, 0.05 equiv) was added. The reaction was warmed up to room temperature and stirred for 12 hr. The reaction was quenched by the addition of 1M HCl (20 mL) and the layers were separated. The organic layer was washed with 1M HCl (2 x 20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified through flash chromatography (10% Et_2O/pentane) to afford (*E*)-hexa-3,5-dien-1-yl acetate (**36**) as a clear oil (2.9889 g, 21.334 mmol, 84% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (ddd, *J* = 17.0, 10.5, 10.0 Hz, 1H), 6.12 (dd, *J* = 15.0, 10.5 Hz, 1H), 5.65 (dt, *J* = 15.0, 7.5 Hz, 1H), 5.13 (d, *J* = 17.0 Hz, 1H), 5.02 (d, *J* = 10.0 Hz, 1H), 4.11 (t, *J* = 7.0 Hz, 2H), 2.41 (q, *J* = 7.0 Hz, 2H), 2.04 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 136.7, 133.3, 129.7, 116.0, 63.5, 31.8, 20.9. IR (film, cm^{-1}): 3087, 3039, 3012, 2960, 2902, 1741, 1655, 1604, 1385, 1365, 1238, 1036, 1007, 955. LRMS (EI) *m/z* calc'd for $C_8H_{13}O_2$ $[M + H]^+$: 141.1, found 141.1.

Dehydrogenative Diels-Alder Optimization Studies for Table 2

General Optimization Procedure: A ½ dram borosilicate vial was charged sequentially with Pd(II) catalyst (0.03 mmol, 0.10 equiv), N-phenylmaleimide (51.9 mg, 0.30 mmol, 1.0 equiv, entries 4-6), 2,6-Me_2BQ (40.8 mg, 0.30 mmol, 1.0 equiv), and *p*-nitrobenzoic acid (5.01 mg, 0.03 mmol, 0.10 equiv, entries 6 and 7). Acetic acid 5-hexen-1-yl ester (**34**) substrate (42.6 mg, 0.30 mmol, 1.0 equiv) was then added to the ½ dram vial, and the reaction was immediately dissolved in solvent (0.3 mL, 1.0 M). The resulting dark red reaction mixture was charged with a stir bar, capped with a teflon-lined cap, and suspended in an oil bath at 45°C for 48 hr (or 24 hr for entries 1, 2, and 7). Upon completion, the dark red reaction mixture was filtered through a short silica plug, eluting with ~5 mL EtOAc, and concentrated *in vacuo* at 25°C for entries 3-6 or 0°C for entries 1, 2, and 7 (~25 torr), to afford a dark red crude oil. A small aliquot of this mixture was added to a NMR tube and diluted with $CDCl_3$. After analysis, the sample was returned to the crude mixture and the solvent was removed. Purification by flash chromatography (SiO_2, 20 x 160 mm) furnished either the Diels-Alder adduct **40** or hexa-3,5-dien-1-yl acetate (**36**) as a 4:1 mixture of *E*:*Z* isomers.

Entry 1: $Pd(OAc)_2$ (6.7 mg, 0.030 mmol, 0.10 equiv) and 2,6-Me_2BQ (40.8 mg, 0.30 mmol, 1.0 equiv) were used. 1,4-dioxane (0.30 mL) was used as solvent. Run 1: <1% yield. Run 2: <1% yield. **Average: 0% yield**.

Entry 2: Pd[1,2-bis(phenylsulfinyl)ethane]$(OAc)_2$ **35** (15.1 mg, 0.030 mmol, 0.10 equiv) and 2,6-Me_2BQ (40.8 mg, 0.30 mmol, 1.0 equiv) were used. 1,4-dioxane (0.30 mL) was used as

solvent. Reaction run for 24 hrs. Purification by flash chromatography (10% Et_2O/petroleum ether) produced diene **36**. Run 1: 6% yield. Run 2: 5% yield. **Average: 6% yield**.

Entry 3: Pd(II)-catalyst **37** (11.6 mg, 0.030 mmol, 0.10 equiv) and 2,6-Me_2BQ (40.8 mg, 0.30 mmol, 1.0 equiv) were used. 1,4-dioxane (0.30 mL) was used as solvent. Run 1: <1% yield. Run 2: <1% yield. **Average: 0% yield**.

Entry 4: Pd(II)-catalyst **38** (10.9 mg, 0.030 mmol, 0.10 equiv) and 2,6-Me_2BQ (40.8 mg, 0.30 mmol, 1.0 equiv) were used. 1,4-dioxane (0.30 mL) was used as solvent. Run 1: <1% yield. Run 2: <1% yield. **Average: 0% yield**.

Entry 5: Pd[1,2-bis(benzylsulfinyl)ethane]$(OAc)_2$ **39** (15.9 mg, 0.030 mmol, 0.10 equiv) and 2,6-Me_2BQ (40.8 mg, 0.30 mmol, 1.0 equiv) were used. 1,4-dioxane (0.30 mL) was used as solvent. Reaction run for 24 hrs. Purification by flash chromatography (10% Et_2O/petroleum ether) produced diene **36**. Run 1: 30% yield. Run 2: 26% yield. **Average: 28% yield**.

Entry 6: Pd[1,2-bis(benzylsulfinyl)ethane]$(OAc)_2$ **39** (15.9 mg, 0.030 mmol, 0.10 equiv), N-phenylmaleimide (51.9 mg, 0.30 mmol, 1.0 equiv), and 2,6-Me_2BQ (40.8 mg, 0.30 mmol, 1.0 equiv) were used. 1,4-dioxane (0.30 mL) was used as solvent. Purification by flash chromatography (35% EtOAc/hexanes) produced adduct **40**. Run 1: 32% yield. Run 2: 33% yield. **Average: 33% yield**.

Entry 7: Pd[1,2-bis(benzylsulfinyl)ethane](OAc)$_2$ **39** (15.9 mg, 0.030 mmol, 0.10 equiv), N-phenylmaleimide (51.9 mg, 0.30 mmol, 1.0 equiv), and 2,6-Me_2BQ (40.8 mg, 0.30 mmol, 1.0 equiv) were used. DCE (0.30 mL) was used as solvent. Purification by flash chromatography (35% EtOAc/hexanes) produced adduct **40**. Run 1: 53% yield. Run 2: 51% yield. **Average: 52% yield**.

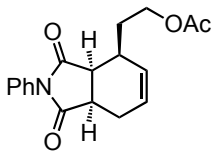
Entry 8: Pd[1,2-bis(benzylsulfinyl)ethane](OAc)$_2$ **39** (15.9 mg, 0.030 mmol, 0.10 equiv), N-phenylmaleimide (51.9 mg, 0.30 mmol, 1.0 equiv), 2,6-Me_2BQ (40.8 mg, 0.30 mmol, 1.0 equiv), and *p*-nitrobenzoic acid (5.0 mg, 0.030mmol, 0.1 equiv) were used. DCE (0.30 mL) was used as solvent. Purification by flash chromatography (35% EtOAc/hexanes) produced adduct **40**. Run 1: 71% yield. Run 2: 76% yield. **Average: 74% yield**.

Entry 9: Pd[1,2-bis(benzylsulfinyl)ethane](OAc)$_2$ **39** (15.9 mg, 0.030 mmol, 0.10 equiv), 2,6-Me_2BQ (40.8 mg, 0.30 mmol, 1.0 equiv), and *p*-nitrobenzoic acid (5.0 mg, 0.030mmol, 0.1 equiv) were used. DCE (0.30 mL) was used as solvent. Reaction run for 24 hrs. Purification by flash chromatography (10% Et_2O/petroleum ether) produced diene **36**. Run 1: 37% yield. Run 2: 33% yield. **Average: 35% yield**.

Dehydrogenative Diels-Alder Olefin Scope for Figure 34

General Procedure: A ½ dram borosilicate vial was charged sequentially with Pd[1,2-bis(benzylsulfinyl)ethane](OAc)$_2$ catalyst **39** (15.9 mg, 0.03 mmol, 0.10 equiv), maleimide (0.30 mmol, 1.0 equiv), 2,6-Me_2BQ (40.8 mg, 0.30 mmol, 1.0 equiv), and *p*-nitrobenzoic acid (5.01

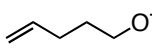
mg, 0.03 mmol, 0.10 equiv). Olefin substrate (0.30 mmol, 1.0 equiv) was then added to the ½ dram vial, and the reaction was immediately dissolved in DCE (0.3 mL, 1.0 M). The resulting dark red reaction mixture was charged with a stir bar, capped with a teflon-lined cap, and suspended in an oil bath at 45°C for 48 hr. Upon completion, the dark red reaction mixture was filtered through a short silica plug, eluting with ~5 mL EtOAc (or 2% MeOH/CH_2Cl_2 when specified), and concentrated *in vacuo* at 25°C (~25 torr) to afford a dark red crude oil. A small aliquot of this mixture was added to a NMR tube and diluted with $CDCl_3$. ^{1}H NMR analysis of the crude product showed a >20:1 endo:exo selectivity. After analysis, the sample was returned to the crude mixture and the solvent was removed. Purification by flash chromatography (SiO_2, 20 x 160 mm) furnished the Diels-Alder products in 52-84% yields with >20:1 d.r. (unless otherwise noted).



(±)-2-((3a*S*,4*S*,7a*R*)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)ethyl acetate [40]: Acetic Acid 5-hexen-1-yl ester **34** (42.6 mg, 0.30 mmol, 1.0 equiv) and N-phenylmaleimide (51.9 mg, 0.30 mmol, 1.0 equiv) were reacted using the general procedure. Purification by flash chromatography (35% EtOAc/hexanes) produced adduct **40** as a pale yellow oil. Run 1 (67.1 mg, 0.214 mmol, 71% yield); Run 2 (71.7 mg, 0.229 mmol, 76% yield). The product was isolated in >20:1 d.r. by ^{1}H NMR for both experiments. **Average: 74% yield**.

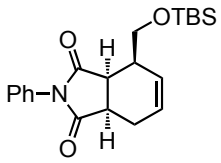
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.20 (dd, *J* = 8.5, 1.0 Hz, 2H), 6.02 (ddd, *J* = 9.5, 6.5, 3.5 Hz, 1H), 5.86 (dt, *J* = 9.0, 3.5 Hz, 1H), 4.36 (ddd, *J* = 11.0, 7.0, 5.5 Hz, 1H), 4.24 (ddd, *J* = 11.5, 6.0, 5.0 Hz, 1H), 3.30-3.34 (m, 2H), 2.84 (ddd, *J* = 14.5, 7.0, 1.5 Hz, 1H), 2.48-2.51 (m, 1H), 2.30-2.36 (m, 1H), 2.23-2.29 (m, 1H), 2.12-

2.20 (m, 1H), 2.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.8, 176.8, 171.1, 133.1, 131.8, 129.0, 128.6, 128.1, 126.5, 62.6, 42.6, 40.2, 32.8, 30.2, 24.5, 21.0; IR (film, cm^{-1}): 3039, 2954, 2931, 2852, 1730, 1709, 1597, 1498, 1385, 1244, 1192, 1171, 1041; HRMS (ESI) *m/z* calc'd for $C_{18}H_{19}NO_4Na$ $[M + Na]^+$: 336.1212, found 336.1214.



***tert*-butyldimethyl(pent-4-en-1-yloxy)silane**: A 50 mL round bottom flask was charged with penten-1-ol (Sigma-Aldrich, 0.861 g, 10.0 mmol, 1.0 equiv) and dissolved in DCM (10 mL, 1.0 M). The reaction was then charged sequentially with tert-Butyldimethylsilyl chloride (1.80 g, 12.0 mmol, 1.0 equiv), imidazole (1.02 g, 15.0 mmol, 1.50 equiv), and DMAP (61.0 mg, 0.50 mmol, 0.05 equiv), and allowed to stir for 1 hr. The reaction slurry was then filtered through a silica plug, eluting with 1% EtOAc/hexanes, and concentrated *in vacuo*, to afford the title compound as a clear oil (1.991 g, 9.94 mmol, 99% yield).

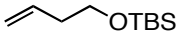
This compound has been reported previously.[114] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddt, J = 17.0, 10.0, 6.5 Hz, 1H), 4.94-5.04 (m, 2H), 3.62 (t, J = 6.5 Hz, 2H), 2.10 (q, J = 7.0 Hz, 2H), 1.58-1.64 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 114.5, 62.5, 32.0, 30.1, 25.9, 18.3, -5.3.



(±)-(3a*S*,4*S*,7a*R*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione [41]: *t*-butyldimethyl(pent-4-en-1-yloxy)silane (60.1 mg, 0.30 mmol, 1.0 equiv) and N-phenylmaleimide (51.9 mg, 0.30 mmol, 1.0 equiv) were reacted using the general procedure. Purification by flash chromatography (15% EtOAc/hexanes) produced adduct **41** as a tan solid.

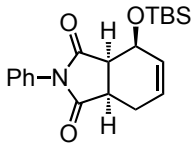
Run 1 (83.2 mg, 0.224 mmol, 75% yield); Run 2 (84.9 mg, 0.229 mmol, 76% yield). The product was isolated in >20:1 d.r. by ^{1}H NMR for both experiments. **Average: 76% yield**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.20-7.22 (m, 2H), 6.01 (ddd, *J* = 9.0, 6.5, 3.0 Hz, 1H), 5.89 (dt, *J* = 9.5, 3.5 Hz, 1H), 4.17 (dd, *J* = 10.0, 7.0 Hz, 1H), 3.98 (dd, *J* = 10.0, 7.5 Hz, 1H), 3.41 (dd, *J* = 9.3, 6.5 Hz, 1H), 3.31 (dt, *J* = 2.0, 9.0 Hz, 1H), 2.80 (ddd, *J* = 16.0, 6.5, 2.5 Hz, 1H), 2.58-2.62 (m, 1H), 2.27-2.33 (m, 1H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 177.0, 132.0, 130.8, 129.0, 128.5, 127.7, 126.5, 63.1, 40.8, 39.9, 39.0, 25.9, 24.7, 18.3, -5.3, -5.4; IR (film, cm^{-1}): 3041, 2954, 2929, 2885, 2856, 1711, 1498, 1471, 1383, 1254, 1188, 1167, 1090, 837; HRMS (ESI) *m/z* calc'd for $C_{21}H_{30}NO_3Si$ $[M + H]^+$: 372.1995, found 372.1999.



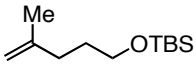
(but-3-en-1-yloxy)(*tert*-butyl)dimethylsilane: A 50 mL round bottom flask was charged with buten-1-ol (Sigma-Aldrich, 0.7211 g, 10.0 mmol, 1.0 equiv) and dissolved in DCM (10 mL, 1.0 M). The reaction was then charged sequentially with tert-Butyldimethylsilyl chloride (1.80 g, 12.0 mmol, 1.0 equiv), imidazole (1.02 g, 15.0 mmol, 1.50 equiv), and DMAP (61.0 mg, 0.50 mmol, 0.05 equiv), and allowed to stir for 1 hr. The reaction slurry was then filtered through a silica plug, eluting with 1% EtOAc/hexanes, and concentrated *in vacuo*, to afford the title compound as a clear oil (1.572 g, 8.43 mmol, 84% yield).

This compound has been reported previously.[115] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 17.5, 10.5, 7.0 Hz, 1H), 5.00-5.09 (m, 2H), 3.66 (t, *J* = 7.0 Hz, 2H), 2.28 (app qt, *J* = 7.0, 1.0 Hz, 2H), 0.90 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 116.3, 62.8, 37.5, 25.9, 18.3, -5.3.



(±)-(3a*R*,4*S*,7a*R*)-4-((*tert*-butyldimethylsilyl)oxy)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione [42]: (but-3-en-1-yloxy)(*tert*-butyl)dimethylsilane (55.9 mg, 0.30 mmol, 1.0 equiv) and N-phenylmaleimide (51.9 mg, 0.30 mmol, 1.0 equiv) were reacted using the general procedure. Purification by flash chromatography (20% EtOAc/hexanes) produced adduct **42** as a white solid. Run 1 (54.7 mg, 0.153 mmol, 51% yield); Run 2 (55.6 mg, 0.156 mmol, 52% yield). The product was isolated in >20:1 d.r. by ^{1}H NMR for both experiments. **Average: 52% yield**. X-ray quality crystals could be obtained by recrystallizing the product in hot hexanes/minimal DCM, followed by sitting at 4°C for 24 hr.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (t, *J* = 7.5 Hz, 2H), 7.33-7.37 (m, 3H), 6.11-6.19 (m, 2H), 4.78 (t, *J* = 4.5 Hz, 1H), 3.20 (ddd, *J* = 19.5, 10.0, 8.0 Hz, 1H), 3.06 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.62-2.74 (m, 2H), 0.79 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 176.0, 132.1, 131.3, 130.6, 128.9, 128.2, 126.2, 64.1, 47.0, 36.8, 25.6, 22.0, 17.9, -4.5, -4.9; IR (film, cm^{-1}): 2947, 2926, 2895, 2854,1778, 1711, 1498, 1389, 1254, 1198, 1180, 1163, 1049, 999; HRMS (ESI) *m/z* calc'd for $C_{20}H_{27}NO_3SiNa$ $[M + Na]^+$: 380.1658, found 380.1657.

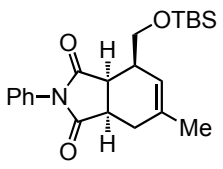


***tert*-butyldimethyl((4-methylpent-4-en-1-yl)oxy)silane**: A flame-dried 100 mL round bottom flask was charged with LAH (1.013 g, 26.7 mmol, 1.90 equiv), suspended in Et_2O (14 mL, 1 M), and cooled to 0°C. Ethyl 4-methyl-4-pentenoate (Sigma-Aldrich, 2.00 g, 14.06 mmol, 1.0 equiv) was syringed into rxn slowly. The reaction was allowed to stir at 0°C for 1.5 hr, at which time it was diluted with Et_2O and quenched SLOWLY with H_2O (10 mL), followed by 1M HCl (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and

concentrated cold *in vacuo*. The resulting primary alcohol was sufficiently pure, and was taken on crude to the next reaction.

A 100 mL round bottom flask was charged with the crude primary alcohol (1.408 g, 14.06 mmol, 1.0 equiv) and dissolved in DCM (14 mL, 1.0 M). The reaction was then charged sequentially with tert-Butyldimethylsilyl chloride (2.532 g, 16.80 mmol, 1.2 equiv), imidazole (1.436 g, 21.1 mmol, 1.50 equiv), and DMAP (86.0 mg, 0.703 mmol, 0.05 equiv), and allowed to stir for 3 hr. The reaction slurry was then filtered through a silica plug, eluting with 1% EtOAc/hexanes, and concentrated *in vacuo*, to afford the title compound as a light yellow oil (2.8891 g, 13.5 mmol, 96% yield over 2 steps).

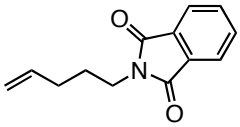
This compound has been reported previously.[116] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (s, 1H), 4.68 (s, 1H), 3.61 (t, *J* = 6.5 Hz, 2H), 2.05 (t, *J* = 7.5 Hz, 2H), 1.72 (s, 3H), 1.64-1.67 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5, 109.8, 62.8, 34.0, 30.8, 25.9, 22.5, 18.3, -5.3.



(±)-(3a*S*,4*S*,7a*R*)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-methyl-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione [43]: *t*-butyldimethyl((4-methylpent-4-en-1-yl)oxy)silane (64.3 mg, 0.30 mmol, 1.0 equiv) and N-phenylmaleimide (51.9 mg, 0.30 mmol, 1.0 equiv) were reacted using the general procedure. Purification by flash chromatography (15% EtOAc/hexanes) produced adduct **43** as a clear oil. Run 1 (57.8 mg, 0.150 mmol, 50% yield); Run 2 (63.8 mg, 0.166 mmol, 55% yield). The product was isolated in >20:1 d.r. by ^{1}H NMR for both experiments. **Average: 53% yield**.

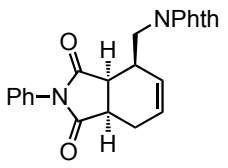
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.18-7.20 (m, 2H), 5.50 (s, 1H), 4.12 (dd, *J* = 10.0, 7.0 Hz, 1H), 3.92 (dd, *J* = 10.0, 7.0 Hz, 1H), 3.36 (dd, *J*

= 9.0, 6.0 Hz, 1H), 3.30 (dt, *J* = 2.5, 9.0 Hz, 1H), 2.65 (dd, *J* = 15.0, 2.3 Hz, 1H), 2.55-2.57 (m, 1H), 2.32 (dd, *J* = 15.5, 7.5 Hz, 1H), 1.80 (s, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 177.1, 136.6, 132.0, 129.0, 128.5, 126.5, 123.1, 63.3, 40.9, 40.2, 39.6, 29.8, 26.0, 23.2, 18.4, -5.3, -5.4; IR (film, cm^{-1}): 3066, 3037, 2954, 2929, 2883, 2856, 1711, 1599, 1500, 1471, 1441, 1383, 1254, 1184, 1109, 1090, 839; HRMS (ESI) *m/z* calc'd for $C_{22}H_{32}NO_3Si$ $[M + H]^+$: 386.2151, found 386.2146.



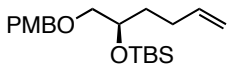
2-(pent-4-en-1-yl)isoindoline-1,3-dione: A flame-dried 50 mL round bottom flask was charged with triphenylphosphine (1.42 g, 5.40 mmol, 1.0 equiv) and THF (10.8 mL, 0.5 M), and cooled to 0°C. DIAD (Sigma-Aldrich, 1.06 mL, 5.40 mmol, 1.0 equiv) was then syringed into the rxn dropwise, resulting in a white slurry which was stirred for 5 min. 4-penten-1-ol (0.55 mL, 5.40 mmol, 1.0 equiv) was then syringed into the reaction mixture and allowed to stir for 5 min, at which time phthalimide (0.794 g, 5.40 mmol, 1.0 equiv) was added to the reaction and let stir for 12 hr at room temperature. The resulting yellow solution was concentrated *in vacuo* and purified directly using flash chromatography (15% EtOAc/hexanes), affording 2-(pent-4-en-1-yl)isoindoline-1,3-dione as a clear oil (0.957 g, 4.445 mmol, 82% yield).

This compound has been reported previously.[117] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.81 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H), 5.05 (dq, *J* = 17.5, 1.5 Hz, 1H), 4.97 (dd, *J* = 10.5, 1.5 Hz, 1H), 3.69 (t, *J* = 7.5 Hz, 2H), 2.11 (dq, *J* = 1.5, 7.5 Hz, 2H), 1.78 (pent., *J* = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 137.2, 133.8, 132.1, 123.1, 115.2, 37.5, 30.9, 27.6.



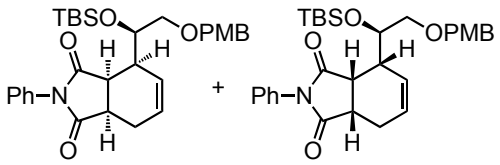
(±)-2-(((3a*S*,4*S*,7a*R*)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)methyl)isoindoline-1,3-dione [44]: 2-(pent-4-en-1-yl)isoindoline-1,3-dione (64.6 mg, 0.30 mmol, 1.0 equiv) and N-phenylmaleimide (51.9 mg, 0.30 mmol, 1.0 equiv) were reacted using the general procedure, except 5 mL of 2% MeOH/CH_2Cl_2 was used to elute the product from a short silica plug. Purification by flash chromatography (1% MeOH/CH_2Cl_2) produced adduct **44** as a white solid. This material could be further purified by recrystallizing from hot EtOAc. Run 1 (91.1 mg, 0.236 mmol, 79% yield); Run 2 (100.2 mg, 0.259 mmol, 86% yield). The product was isolated in >20:1 d.r. by ^{1}H NMR for both experiments. **Average: 83% yield**. X-ray quality crystals could be obtained by recrystallizing the product in refluxing acetone, followed by sitting at r.t. for 24 hr.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 5.5, 3.5 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.23-7.25 (m, 2H), 6.06 (dt, *J* = 9.0, 3.0 Hz, 1H), 6.00 (ddd, *J* = 10.0, 6.5, 3.0 Hz, 1H), 4.46 (dd, *J* = 14.0, 10.5 Hz, 1H), 4.15 (dd, *J* = 14.0, 3.5 Hz, 1H), 3.48 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.36 (dt, *J* = 1.5, 9.0 Hz, 1H), 2.80-2.86 (m, 2H), 2.15-2.21 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 176.6, 168.5, 134.0, 131.9, 131.7, 131.2, 129.1, 128.8, 128.6, 126.5, 123.3, 42.7, 40.3, 39.7, 36.0, 24.6; IR (film, cm^{-1}): 3066, 3047, 2951, 2854, 1770, 1709, 1496, 1389, 1365, 1190, 1174, 1066, 1045, 968; HRMS (ESI) *m/z* calc'd for $C_{23}H_{18}N_2O_4Na$ $[M + Na]^+$: 409.1164, found 409.1162.



(+)-(*R*)-*tert*-butyl((1-((4-methoxybenzyl)oxy)hex-5-en-2-yl)oxy)dimethylsilane: This product was prepared as described previously.[118]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.82 (ddt, *J* = 16.5, 10.0, 6.5 Hz, 1H), 5.00 (dq, *J* = 17.0, 1.5 Hz, 1H), 4.94 (dq, *J* = 10.5, 2.0 Hz, 1H), 4.45 (d, *J* = 2.0 Hz, 2H), 3.80-3.84 (m, 1H), 3.81 (s, 3H), 3.38 (dd, *J* = 9.5, 5.5 Hz, 1H), 3.33 (dd, *J* = 9.5, 5.5 Hz, 1H), 2.11-2.18 (m, 1H), 2.02-2.09 (m, 1H), 1.61-1.68 (m, 1H), 1.49-1.57 (m, 1H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); $[\alpha]_D^{23}$ = +15.7^o (c = 1.17, $CHCl_3$). Literature value for the enantiomer of the title compound: $[\alpha]_D^{23}$ = -14.1^o (c = 1.17, $CHCl_3$).



(3a,4,7a)-4-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)-2-((4-methoxybenzyl)oxy)ethyl)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione [45]: (+)-(*R*)-*tert*-butyl((1-((4-methoxybenzyl)oxy)hex-5-en-2-yl)oxy)dimethylsilane (105.2 mg, 0.30 mmol, 1.0 equiv) and N-phenylmaleimide (51.9 mg, 0.30 mmol, 1.0 equiv) were reacted using the general procedure. ^{1}H NMR analysis of the crude reaction showed a diastereofacial selectivity of 1.4:1 d.r., (both diastereomers being endo products). Purification by flash chromatography (16% EtOAc/hexanes) produced the major diastereomer [(+)-**45**] as a clear oil (rf = 0.30) and the minor diastereomer [(-)-**45**] as a white solid (rf = 0.19). Run 1 (*major diastereomer:* 77.1 mg, 0.148 mmol; *minor diastereomer:* 53.9 mg, 0.103 mmol, 84% combined yield); Run 2 (*major diastereomer:* 77.7 mg, 0.149 mmol; *minor diastereomer:* 55.5 mg, 0.106 mmol, 85% combined yield). Both diastereomers were isolated in >20:1 endo:exo by ^{1}H NMR. **Average: 84% yield, >99% *ee*** for both diastereomers.

Major Diastereomer [(+)-**45**]*:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.16-7.18 (m, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.96 (ddd, *J* = 9.5, 7.0, 3.0 Hz, 1H), 5.87 (dt, *J* = 9.0, 3.5 Hz, 1H), 4.65 (dt, *J* = 11.0, 3.5 Hz, 1H),

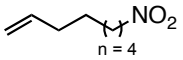
4.45 (q, *J* = 12.0 Hz, 2H), 3.81 (s, 3H), 3.65 (dd, *J* = 9.0, 5.5 Hz, 1H), 3.57 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.50 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.30 (dt, *J* = 1.5, 9.0 Hz, 1H), 2.78 (dd, *J* = 14.5, 6.5 Hz, 1H), 2.53-2.55 (m, 1H), 2.24-2.29 (m, 1H), 0.90 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.2, 177.3, 159.1, 131.9, 130.7, 130.2, 129.2, 129.1, 128.5, 127.5, 126.6, 113.6, 73.3, 72.9, 70.5, 55.2, 40.7, 40.6, 40.3, 26.1, 25.6, 18.3, -4.4, -4.7; IR (film, cm^{-1}): 3045, 2954, 2929, 2900, 2854, 1711, 1612, 1514, 1462, 1383, 1248, 1171, 1095, 833; HRMS (ESI) *m/z* calc'd for $C_{30}H_{39}NO_5SiNa$ $[M + Na]^+$: 544.2495, found 544.2497; $[\alpha]_D^{23}$ = +83.1° (c = 1.17, $CHCl_3$).

Minor Diastereomer [(-)-**45**]*:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.17-7.19 (m, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.05 (dt, *J* = 9.0, 3.5 Hz, 1H), 5.96 (ddd, *J* = 10.0, 7.0, 3.5 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 11.5 Hz, 1H), 4.47 (dt, *J* = 10.0, 2.5 Hz, 1H), 3.96 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.81 (s, 3H), 3.67 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.32 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.26 (dt, *J* = 1.5, 9.0 Hz, 1H), 2.76 (dd, *J* = 15.0, 7.5 Hz, 1H), 2.67-2.70 (m, 1H), 2.22-2.28 (m, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 177.7, 159.2, 132.8, 131.9, 130.4, 129.4, 129.0, 128.6, 126.6, 126.5, 113.7, 73.2, 71.8, 71.6, 55.3, 41.3, 40.9, 39.6, 25.9, 24.8, 18.1, -4.0, -4.7; IR (film, cm^{-1}): 3047, 2954, 2929, 2900, 2856, 1774, 1711, 1612, 1514, 1500, 1464, 1250, 1182, 1119, 1088, 1034, 991, 833, 777; HRMS (ESI) *m/z* calc'd for $C_{30}H_{39}NO_5SiNa$ $[M + Na]^+$: 544.2495, found 544.2489; $[\alpha]_D^{23}$ = -32.9° (c = 1.17, $CHCl_3$).

Determination of enantiomeric purity. Racemic material [(±)-(*R*)-*tert*-butyl((1-((4-methoxybenzyl)oxy)hex-5-en-2-yl)oxy)dimethylsilane → (±)-**45** major and (±)-**45** minor] was independently synthesized using an analogous route from *rac*-glycidol.

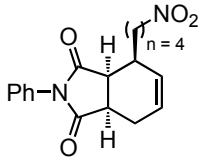
Major Diastereomer: both enantiomers were separated by chiral HPLC (Chiralcel OD-H, 5/95 *i*-PrOH/hexanes, 1.0 mL/min @ 30°C), t_R = 6.8, 7.6 min. Major enantiomer for (+)-**45**, t_R = 6.8 min.

Minor Diastereomer: both enantiomers were separated by chiral HPLC (Chiralcel OD-H, 3/97 *i*-PrOH/hexanes, 1.0 mL/min @ 30°C), t_R = 13.7, 14.7 min. Major enantiomer for (-)-**45**, t_R = 13.7 min.



8-nitrooct-1-ene: A flame-dried 50 mL round bottom flask was charged with $NaNO_2$ (0.453 g, 6.57 mmol, 1.1 equiv) and DMF (13.0 mL, 0.46 M). 8-bromo-1-octene (Sigma-Aldrich, 1.0 mL, 5.98 mmol, 1.0 equiv) was then syringed into the reaction suspension and allowed to stir at r.t. for 4 hrs, at which time the reaction was quenched with H_2O (20 mL) and diluted with Et_2O (15 mL). The layers were separated and the organic layer was washed with H_2O (2 x 20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified through flash chromatography (5% Et_2O/hexanes), affording 8-nitrooct-1-ene as a yellow oil (0.546 g, 3.474 mmol, 58% yield).

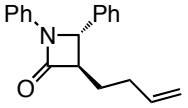
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H), 4.93-5.02 (m, 2H), 4.38 (t, *J* = 7.0, Hz, 2H), 1.98-2.07 (m, 4H), 1.24-1.54 (m, 6H).



(±)-(3a*S*,4*S*,7a*R*)-4-(4-nitrobutyl)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione [46]: 8-nitrooct-1-ene (47.2 mg, 0.30 mmol, 1.0 equiv) and N-phenylmaleimide (51.9 mg, 0.30 mmol, 1.0 equiv) were reacted

using the general procedure. Purification by flash chromatography (35% EtOAc/hexanes) produced adduct **46** as a pale orange oil (65.8 mg, 0.200 mmol, **67% yield**). The product was isolated in >20:1 d.r. by ^{1}H NMR.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 2H), 6.00 (ddd, *J* = 9.5, 6.5, 3.0 Hz, 1H), 5.82 (dt, *J* = 9.0, 3.5 Hz, 1H), 4.43 (t, *J* = 7.0 Hz, 2H), 3.26-3.32 (m, 2H), 2.83 (ddd, *J* = 15.0, 7.0, 1.5 Hz, 1H), 2.32-2.39 (m, 1H), 2.21-2.26 (m, 1H), 2.09 (pent., *J* = 7.0 Hz, 2H), 1.97-2.04 (m, 1H), 1.80-1.88 (m, 1H), 1.51-1.69 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.8, 176.8, 133.4, 131.8, 129.0, 128.5, 127.9, 126.4, 75.4, 42.6, 40.3, 36.0, 30.3, 27.3, 24.7, 24.5; IR (film, cm^{-1}): 3037, 2947, 2931, 2860, 1774, 1707, 1596, 1549, 1498, 1438, 1385, 1192; HRMS (ESI) *m/z* calc'd for $C_{18}H_{20}N_2O_4Na$ $[M + Na]^+$: 351.1321, found 351.1320.

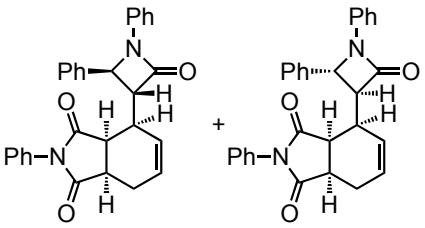


(±)-(3R,4S)-3-(but-3-en-1-yl)-1,4-diphenylazetidin-2-one: The title compound was prepared following a modified procedure.[119] A flame-dried 15 mL round bottom flask was charged with 5-hexenoic acid (Sigma-Aldrich, 0.45 mL, 3.78 mmol, 1.0 equiv), DCM (1.89 mL, 2.0 M), and oxalyl chloride (0.36 mL, 4.17 mmol, 1.1 equiv), and allowed to stir at room temperature for 4 hr. The reaction was then concentrated *in vacuo*, redissolving in DCM (2 mL) several times to afford sufficiently pure 5-hexenoic acid chloride (0.399 g, 3.01 mmol).

A flame-dried 25 mL round bottom flask was charged with N-benzilideneaniline (Sigma-Aldrich, 0.545 g, 3.01 mmol, 1.0 equiv), heptane (Sigma-Aldrich, 1.34 mL, 2.25 M), and tributylamine (Sigma-Aldrich, 1.43 mL, 6.02 mmol, 2.0 equiv), then topped with a condenser and heated to 45°C to dissolve the N-benzilideneaniline. A solution of 5-hexenoic acid chloride

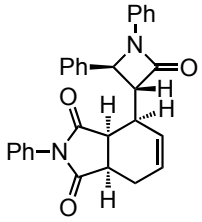
(0.399 g, 3.01 mmol, 1.0 equiv) in toluene (0.67 mL, 4.5 M) was then cannulated into the reaction flask, and the reaction was let stir at 45°C for 4 hr, and 80°C for 12 hr. The reaction was then diluted with EtOAc (5 mL) and quenched with 1M HCl (3 mL). The layers were separated, and the organic layer was washed with 1M HCl (3 x 10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified through three recrystallizations from hot hexanes to afford (±)-(3R,4S)-3-(but-3-en-1-yl)-1,4-diphenylazetidin-2-one in >20:1 d.r. (anti) as a white solid (0.145 g, 0.523 mmol, 17% yield over 2-steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.39 (m, 5H), 7.22-7.29 (m, 4H), 7.03 (t, *J* = 7.0, 1H), 5.79 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H), 4.98 (dd, *J* = 17.0, 10.0 Hz, 2H), 4.68 (d, *J* = 2.5 Hz, 1H), 3.13 (ddd, *J* = 8.5, 6.0, 2.5 Hz, 1H), 2.28 (q, *J* = 7.0 Hz, 2H), 2.03-2.10 (m, 1H), 1.91-1.99 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 137.9, 137.7, 137.1, 129.1, 129.0, 128.4, 125.8, 123.7, 116.9, 115.8, 61.2, 59.9, 31.2, 28.2; IR (film, cm^{-1}): 3070, 3032, 3003, 2978, 2924, 2856, 1745, 1641, 1599, 1500, 1456, 1383, 1354, 1146, 1115, 916; HRMS (ESI) *m/z* calc'd for $C_{19}H_{20}NO$ $[M + H]^+$: 278.1545, found 278.1540.

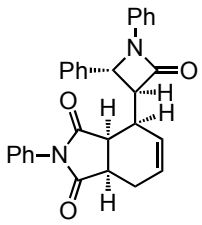


(±)-(3aS,4S,7aR)-4-((3,4)-2-oxo-1,4-diphenylazetidin-3-yl)-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione [47]: (±)-(3R,4S)-3-(but-3-en-1-yl)-1,4-diphenylazetidin-2-one (83.2 mg, 0.30 mmol, 1.0 equiv) and N-phenylmaleimide (51.9 mg, 0.30 mmol, 1.0 equiv) were reacted using the general procedure, except 5 mL of 2% $MeOH/CH_2Cl_2$ was used to elute the product from a short silica plug. ^{1}H NMR analysis of the crude reaction showed a diastereofacial selectivity of 1.28:1 d.r., (both diastereomers being endo products). Purification by flash chromatography (2% $MeOH/CH_2Cl_2$) produced the major

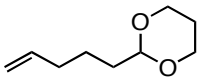
diastereomer **47** as a white solid (rf = 0.53) and the minor diastereomer **47** as a beige solid (rf = 0.38). Run 1 (*major diastereomer:* 46.5 mg, 0.104 mmol; *minor diastereomer:* 36.6 mg, 0.082 mmol, 62% combined yield); Run 2 (*major diastereomer:* 50.5 mg, 0.113 mmol; *minor diastereomer:* 39.5 mg, 0.088 mmol, 67% combined yield). Both diastereomers were isolated in >20:1 endo:exo by ^{1}H NMR. **Average: 65% yield**.



Major Diastereomer: This compound has been reported previously.[120] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.42 (m, 10H), 7.23-7.26 (m, 2H), 7.16-7.18 (m, 2H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.11 (ddd, *J* = 10.0, 7.0, 3.5 Hz, 1H), 5.86 (dt, *J* = 9.0, 3.0 Hz, 1H), 4.74 (d, *J* = 2.5 Hz, 1H), 4.19 (dd, *J* = 12.0, 2.5 Hz, 1H), 3.93 (dd, *J* = 9.0, 5.5 Hz, 1H), 3.35 (dt, *J* = 1.0, 9.0 Hz, 1H), 2.90-2.96 (m, 1H), 2.88 (dd, *J* = 15.5, 7.0 Hz, 1H), 2.28-2.33 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 176.6, 166.5, 137.5, 137.4, 131.7, 130.5, 129.5, 129.3, 129.0 (2 peaks), 128.7, 128.6, 126.4, 126.1, 123.9, 117.0, 61.4, 59.6, 41.9, 39.9, 37.4, 25.1.

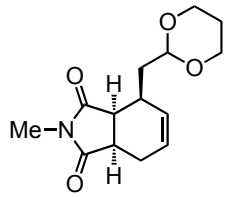


Minor Diastereomer: This compound has been reported previously as a mixture with the major diastereomer.[100] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.41 (m, 10H), 7.24 (t, *J* = 7.5 Hz, 2H), 7.15-7.17 (m, 2H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.32 (dt, *J* = 9.0, 3.0 Hz, 1H), 6.10 (ddd, *J* = 9.5, 6.0, 3.0 Hz, 1H), 4.86 (d, *J* = 2.5 Hz, 1H), 4.08 (dd, *J* = 10.5, 2.0 Hz, 1H), 3.40 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.36 (dt, *J* = 2.0, 9.0 Hz, 1H), 2.95-2.97 (m, 1H), 2.87 (ddd, *J* = 15.5, 6.0, 1.5 Hz, 1H), 2.28-2.33 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 175.9, 166.6, 137.5, 137.0, 131.7, 130.0, 129.1, 129.0 (2 peaks), 128.6 (3 peaks), 126.5, 126.2, 123.9, 117.0, 60.6, 59.5, 41.9, 39.8, 36.6, 24.5.



2-(pent-4-en-1-yl)-1,3-dioxane: A flame-dried 100 mL round bottom flask was charged with THF (34.0 mL, 0.15 M) and bromoethyl-1,3-dioxane (TCI-America, 1.0 g, 5.123 mmol, 1.0 equiv). A solution of allylmagnesium chloride (2 M in THF, 10.25 mL, 20.04 mmol, 4.0 equiv) was then added dropwise via syringe. The reaction was heated to reflux briefly (~10 min.) and then allowed to cool to room temperature and stir overnight. The reaction was then slowly quenched with sat'd NH_4Cl solution (50 ml) and diluted with Et_2O (150 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organics were then washed with H_2O (2 x 15 mL), dried over $MgSO_4$, filtered, and concetrated *in vacuo*. The crude product was purified through flash chromatography (10% EtOAc/hexanes) to afford 2-(pent-4-en-1-yl)-1,3-dioxane as a clear oil (0.793 g, 5.08 mmol, 99% yield).

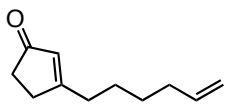
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H), 5.00 (dd, *J* = 17.2, 1.6 Hz, 1H), 4.94 (dd, *J* = 10.0, 1.2 Hz, 1H), 4.52 (t, *J* = 5.2 Hz, 1H), 4.10 (dd, *J* = 10.8, 4.8 Hz, 2H), 3.76 (dt, *J* = 2.4, 12.4 Hz, 2H), 2.03-2.12 (m, 3H), 1.57-1.63 (m, 2H) 1.45-1.52 (m, 2H), 1.34 (d pent, *J* = 13.2, 1.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 114.6, 102.1, 66.8, 34.6, 33.4, 25.8, 23.1; IR (film, cm^{-1}): 3076, 2954, 2927, 2850, 2731, 2657, 1641, 1460, 1431, 1404, 1379, 1286, 1244, 1146, 1084, 995, 910; HRMS (EI) *m/z* calc'd for $C_9H_{15}O_2$ $[M - H]^+$: 155.10721, found 155.10588.



(±)-(3a*S*,4*S*,7a*R*)-4-((1,3-dioxan-2-yl)methyl)-2-methyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione [48]: 2-(pent-4-en-1-yl)-1,3-dioxane (46.8 mg, 0.30 mmol, 1.0 equiv) and N-methylmaleimide (33.3 mg, 0.30 mmol, 1.0 equiv) were reacted using the general procedure. Purification by flash

chromatography (50% EtOAc/hexanes) produced adduct **48** as a white solid. Run 1 (52.8 mg, 0.199 mmol, 66% yield); Run 2 (55.9 mg, 0.211 mmol, 70% yield). The product was isolated in >20:1 d.r. by ^{1}H NMR for both experiments. **Average: 68% yield**.

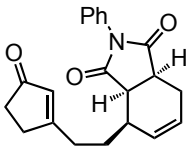
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (ddd, *J* = 9.5, 6.5, 3.5 Hz, 1H), 5.76 (dt, *J* = 9.0, 3.0 Hz, 1H), 4.79 (t, *J* = 5.5 Hz, 1H), 4.10-4.13 (m, 2H), 3.78 (dddd, *J* = 12.5, 12.5, 5.5, 2.5 Hz, 2H), 3.11-3.13 (m, 2H), 2.90 (s, 3H), 2.68 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.53-2.56 (m, 1H), 2.30 (ddd, *J* = 14.0, 7.5, 5.0 Hz, 1H), 2.03-2.19 (m, 3H), 1.35 (dt, *J* = 13.5, 1.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 178.1, 133.8, 127.2, 100.7, 66.9 (2 peaks), 42.9, 40.2, 36.3, 31.0, 25.8, 24.6, 24.2; IR (film, cm^{-1}): 3037, 2962, 2929, 2852, 2735, 1772, 1693, 1435, 1383, 1286, 1142, 1095, 1018, 1001; HRMS (ESI) *m/z* calc'd for $C_{14}H_{19}NO_4Na$ $[M + Na]^+$: 288.1212, found 288.1216.



3-(hex-5-en-1-yl)cyclopent-2-enone: A flame-dried 50 mL round bottom flask was charged with Mg^0 turnings (199.3 mg, 8.20 mmol, 2.3 equiv) and THF (4.24 mL). A solution of 6-bromo-1-hexene (Sigma-Aldrich, 0.756 g, 4.63 mmol, 1.30 equiv) in THF (4.24 mL) was cannulated into the Mg suspension, and the reaction was topped with a condenser and heated to 60°C for 15 min, then cooled to 0°C. Once 0°C was achieved, a solution of 3-methoxy-2-cyclopenten-1-one (Sigma-Aldrich, 0.400 g, 3.56 mmol, 1.0 equiv) in THF (2.12 mL) was cannulated into Grignard reaction dropwise. The reaction flask was then topped with a condenser and heated to 60°C for 2 hr, resulting in a color change from dark brown to bright red to black. Upon completion, the reaction was cooled to 0°C and excess Grignard was quenched slowly with sat'd NH_4Cl (~3 mL). A 10% $HCl_{(aq)}$ solution (20 mL) was then added, and the reaction was allowed to react for an additional 30 min. This solution was then extracted with Et_2O (2 x 20 mL), and the combined organic layers were washed with H_2O (1

x 20 mL), sat'd NaCl (1 x 20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified through flash chromatography (25% EtOAc/hexanes) to afford 3-(hex-5-en-1-yl)cyclopent-2-enone as a clear oil (0.447 g, 2.72 mmol, 76% yield).

This compound has been reported previously.[121] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93-5.94 (m, 1H), 5.78 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H), 5.00 (dd, *J* = 17.0, 1.5 Hz, 1H), 4.95 (dd, *J* = 10.0, 1.0 Hz, 1H), 2.57-2.57 (m, 2H), 2.38-2.42 (m, 4H), 2.08 (q, *J* = 7.0 Hz, 2H), 1.59 (app pent, *J* = 7.5 Hz, 2H), 1.44 (app pent, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1, 182.9, 138.2, 129.4, 114.7, 35.2, 33.3, 33.2, 31.4, 28.4, 26.4.

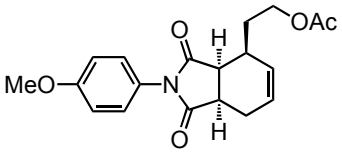


(±)-(3a*R*,4*R*,7a*S*)-4-(2-(3-oxocyclopent-1-en-1-yl)ethyl)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione [49]: 3-(hex-5-en-1-yl)cyclopent-2-enone (49.3 mg, 0.30 mmol, 1.0 equiv) and N-phenylmaleimide (51.9 mg, 0.30 mmol, 1.0 equiv) were reacted using the general procedure. Purification by flash chromatography (75% EtOAc/hexanes) produced adduct **49** as a beige solid. This solid could be recrystallized in refluxing 80% EtOAc/hexanes followed by sitting at -20°C. Run 1 (68.9 mg, 0.206 mmol, 69% yield); Run 2 (68.2 mg, 0.203 mmol, 68% yield). The product was isolated in >20:1 d.r. by ^{1}H NMR for both experiments. **Average: 68% yield**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.19-7.20 (m, 2H), 6.04 (ddd, *J* = 9.5, 6.5, 3.0 Hz, 1H), 6.01 (d, *J* = 1.5 Hz, 1H), 5.85 (dt, *J* = 9.0, 3.0 Hz, 1H), 3.28-3.34 (m, 2H), 2.85 (dd, *J* = 15.5, 7.0 Hz, 1H), 2.57-2.71 (m, 4H), 2.39-2.43 (m, 3H), 2.22-2.31 (m, 2H), 2.05-2.13 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.8, 181.8, 178.7, 176.7, 133.0, 131.7, 129.8, 129.0, 128.6, 128.3, 126.4, 42.5, 40.2, 35.7, 35.2, 31.7, 31.4, 28.6, 24.5; IR

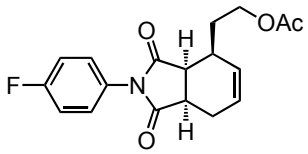
(film, cm^{-1}): 3035, 2953, 2916, 2848, 1774, 1705, 1676, 1614, 1498, 1439, 1385, 1186; HRMS (ESI) *m/z* calc'd for $C_{21}H_{21}NO_3Na$ $[M + Na]^+$: 358.1419, found 358.1414.

Dehydrogenative Diels-Alder Maleimide Scope for Figure 35



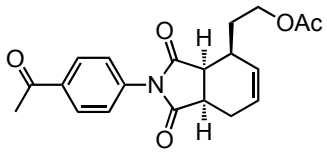
(±)-2-((3a*S*,4*S*,7a*R*)-2-(4-methoxyphenyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)ethyl acetate [50]: Acetic Acid 5-hexen-1-yl ester **34** (42.6 mg, 0.30 mmol, 1.0 equiv) and N-(4-methoxyphenyl)maleimide (Princeton BioMolecular Research, Inc., 60.9 mg, 0.30 mmol, 1.0 equiv) were reacted using the general procedure. Purification by flash chromatography (40% EtOAc/hexanes) produced adduct **50** as a yellow solid (74.8 mg, 0.218 mmol, **73% yield**). The product was isolated in >20:1 d.r. by ^1H NMR.

^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 9.5 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 6.01 (ddd, *J* = 9.5, 6.5, 3.0 Hz, 1H), 5.85 (dt, *J* = 9.5, 3.5 Hz, 1H), 4.35 (ddd, *J* = 11.5, 7.0, 6.5 Hz, 1H), 4.23 (ddd, *J* = 11.5, 6.5, 5.0 Hz, 1H), 3.81 (s, 3H), 3.28-3.30 (m, 2H), 2.83 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.47-2.51 (m, 1H), 2.28-2.35 (m, 1H), 2.23-2.27 (m, 1H), 2.12-2.20 (m, 1H), 2.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 177.0, 171.1, 159.4, 133.0, 128.1, 127.6, 124.4, 114.3, 62.6, 55.4, 42.5, 40.2, 32.8, 30.2, 24.5, 21.0; IR (film, cm^{-1}): 2952, 2849, 1736, 1706, 1609, 1514, 1389, 1249, 1192, 1167, 1033, 829; HRMS (ESI) *m/z* calc'd for $C_{19}H_{21}NO_5Na$ $[M + Na]^+$: 366.1317, found 366.1316.



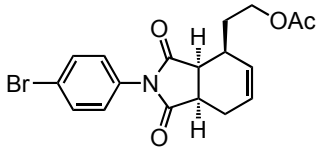
(±)-2-((3a*S*,4*S*,7a*R*)-2-(4-fluorophenyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)ethyl acetate [51]: Acetic Acid 5-hexen-1-yl ester **34** (42.6 mg, 0.30 mmol, 1.0 equiv) and N-(4-fluorophenyl)maleimide (Oakwood Products, Inc., 57.3 mg, 0.30 mmol, 1.0 equiv) were reacted using the general procedure. Purification by flash chromatography (35% EtOAc/hexanes) produced adduct **51** as a pale yellow oil (75.2 mg, 0.227 mmol, **76% yield**). The product was isolated in >20:1 d.r. by ^{1}H NMR.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17-7.20 (m, 2H), 7.11-7.14 (m, 2H), 6.02 (ddd, *J* = 10.0, 6.5, 3.0 Hz, 1H), 5.85 (dt, *J* = 9.0, 3.5 Hz, 1H), 4.36 (ddd, *J* = 11.0, 7.0, 6.0 Hz, 1H), 4.23 (ddd, *J* = 11.5, 6.5, 5.0 Hz, 1H), 3.30-3.34 (m, 2H), 2.83 (dd, *J* = 15.0, 7.5 Hz, 1H), 2.48-2.51 (m, 1H), 2.23-2.35 (m, 2H), 2.11-2.20 (m, 1H), 2.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 176.7, 171.1, 163.1, 161.1, 133.1, 128.3, 128.2, 128.1, 127.7, 127.6, 116.1, 115.9, 62.5, 42.6, 40.2, 32.8, 30.1, 24.5, 21.0; IR (film, cm^{-1}): 3041, 2960, 2921, 2856, 1736, 1709, 1604, 1511, 1389, 1235, 1191, 1170, 1039, 834; HRMS (ESI) *m/z* calc'd for $C_{18}H_{18}NO_4FNa$ $[M + Na]^+$: 354.1118, found 354.1120.



(±)-2-((3a*S*,4*S*,7a*R*)-2-(4-acetylphenyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)ethyl acetate [52]: Acetic Acid 5-hexen-1-yl ester **34** (42.6 mg, 0.30 mmol, 1.0 equiv) and N-(4-acetylphenyl)maleimide (Alfa Aesar, 64.5 mg, 0.30 mmol, 1.0 equiv) were reacted using the general procedure. Purification by flash chromatography (45% EtOAc/hexanes) produced adduct **52** as a pale yellow oil (80.3 mg, 0.226 mmol, **75% yield**). The product was isolated in >20:1 d.r. by ^{1}H NMR.

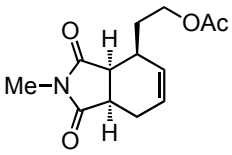
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 6.03 (ddd, *J* = 10.0, 7.0, 3.5 Hz, 1H), 5.87 (dt, *J* = 9.0, 3.5 Hz, 1H), 4.36 (ddd, *J* = 11.5, 7.0, 6.5 Hz, 1H), 4.23 (ddd, *J* = 12.0, 6.5, 6.0 Hz, 1H), 3.33-3.37 (m, 2H), 2.84 (dd, *J* = 15.5, 7.0 Hz, 1H), 2.61 (s, 3H), 2.48-2.52 (m, 1H), 2.22-2.36 (m, 2H), 2.12-2.20 (m, 1H), 2.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.9, 178.3, 176.4, 171.0, 136.6, 135.8, 133.1, 129.0, 128.1, 126.4, 62.5, 42.7, 40.3, 32.8, 30.1, 26.6, 24.5, 21.0; IR (film, cm^{-1}): 2964, 2921, 2857, 1736, 1710, 1686, 1604, 1510, 1381, 1265, 1244, 1185, 1166, 1041, 959; HRMS (ESI) *m/z* calc'd for $C_{20}H_{21}NO_5Na$ $[M + Na]^+$: 378.1317, found 378.1317.



(±)-2-((3a*S*,4*S*,7a*R*)-2-(4-bromophenyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)ethyl acetate [53]: Acetic Acid 5-hexen-1-yl ester **34** (42.6 mg, 0.30 mmol, 1.0 equiv) and N-(4-bromophenyl)maleimide (Alfa Aesar, 75.6 mg, 0.30 mmol, 1.0 equiv) were reacted using the general procedure. Purification by flash chromatography (35% EtOAc/hexanes) produced adduct **53** as an orange solid (71.9 mg, 0.183 mmol, **61% yield**). The product was isolated in >20:1 d.r. by ^{1}H NMR.

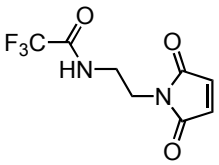
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.01 (ddd, *J* = 10.0, 7.0, 3.5 Hz, 1H), 5.85 (dt, *J* = 9.0, 3.5 Hz, 1H), 4.36 (ddd, *J* = 11.5, 7.0, 5.5 Hz, 1H), 4.23 (ddd, *J* = 11.0, 6.5, 5.0 Hz, 1H), 3.29-3.33 (m, 2H), 2.83 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.46-2.52 (m, 1H), 2.23-2.35 (m, 2H), 2.11-2.18 (m, 1H), 2.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 176.4, 171.0, 133.1, 132.1, 130.7, 128.1, 127.9, 122.3, 62.5, 42.6, 40.3, 32.8, 30.1, 24.5, 21.0; IR (film, cm^{-1}): 3039, 2960, 2848, 1896, 1777, 1740, 1705, 1492, 1442, 1386,

1247, 1188, 1169, 1070, 1039, 1013, 915, 821, 723; HRMS (ESI) *m/z* calc'd for $C_{18}H_{18}NO_4BrNa$ $[M + Na]^+$: 414.0317, found 414.0315.



(±)-2-((3a*S*,4*S*,7a*R*)-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)ethyl acetate [54]: Acetic Acid 5-hexen-1-yl ester **34** (42.6 mg, 0.30 mmol, 1.0 equiv) and N-methylmaleimide (33.3 mg, 0.30 mmol, 1.0 equiv) were reacted using the general procedure. Purification by flash chromatography (40% EtOAc/hexanes) produced adduct **54** as a pale yellow oil. Run 1 (53.2 mg, 0.212 mmol, 71% yield); Run 2 (52.4 mg, 0.209 mmol, 70% yield). The product was isolated in >20:1 d.r. by ^{1}H NMR for both experiments. **Average: 70% yield**.

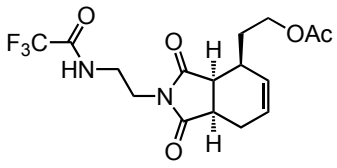
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (ddd, *J* = 9.5, 6.5, 3.0 Hz, 1H), 5.74 (dt, *J* = 9.0, 3.0 Hz, 1H), 4.32 (ddd, *J* = 11.0, 6.0, 6.0 Hz, 1H), 4.21 (ddd, *J* = 11.5, 6.0, 6.0 Hz, 1H), 3.12-3.16 (m, 2H), 2.91 (s, 3H), 2.73 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.38-2.40 (m, 1H), 2.26-2.31 (m, 1H), 2.06-2.17 (m, 2H), 2.06 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.8, 177.8, 171.0, 132.9, 128.0, 62.6, 42.6, 40.2, 32.5, 30.2, 24.7, 24.2, 20.9; IR (film, cm^{-1}): 3035, 2954, 2852, 1770, 1736, 1695, 1437, 1385, 1286, 1242, 1134, 1105, 1043; HRMS (ESI) *m/z* calc'd for $C_{13}H_{17}NO_4Na$ $[M + Na]^+$: 274.1055, found 274.1060.



***N*-(2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl)-2,2,2-trifluoroacetamide**: A flame-dried 25 mL round bottom flask was charged with N-(2-aminoethyl)maleimide trifluoroacetate salt (Sigma-Aldrich, 0.150 g, 0.590 mmol, 1.0 equiv), CH_2Cl_2 (1.18 mL, 0.5 M), and NEt_3 (0.246 mL, 1.77 mmol, 3.0 equiv). Trifluoroacetic anhydride (0.10 mL, 0.708 mmol, 1.2 equiv) was then syringed into the

reaction and allowed to stir at r.t. for 40 min, at which time the reaction was quenched with H_2O (5 mL) and satd. $NaHCO_3$ (5 mL) and diluted with CH_2Cl_2 (10 mL). The layers were separated and the organic layer was washed with H_2O (2 x 20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified through flash chromatography (2% MeOH/ CH_2Cl_2), affording the title compound as a white solid (83.1 mg, 0.352 mmol, 60% yield).

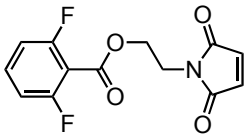
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (br s, 1H), 6.77 (s, 2H), 3.79 (t, J = 5.5 Hz, 2H), 3.58 (q, J = 5.5, Hz, 2H).



(±)-2-((3a*S*,4*S*,7a*R*)-1,3-dioxo-2-(2-(2,2,2-trifluoroacetamido)ethyl)-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)ethyl acetate [55]: Acetic Acid 5-hexen-1-yl ester **34** (42.6 mg, 0.30 mmol, 1.0 equiv) and *N*-(2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl)-2,2,2-trifluoroacetamide (70.8 mg, 0.30 mmol, 1.0 equiv) were reacted using the general procedure. Purification by flash chromatography (50% EtOAc/hexanes) produced adduct **55** as a pale yellow oil (80.3 mg, 0.213 mmol, **71% yield**). The product was isolated in >20:1 d.r. by ^{1}H NMR.

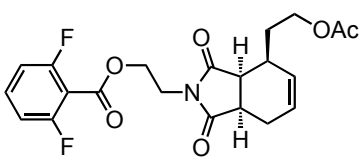
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (br s, 1H), 5.91 (ddd, J = 10.0, 7.0, 3.5 Hz, 1H), 5.75 (dt, J = 9.0, 3.5 Hz, 1H), 4.32 (ddd, J = 11.5, 7.0, 5.5 Hz, 1H), 4.21 (ddd, J = 11.0, 6.5, 5.5 Hz, 1H), 3.72 (dd, J = 7.5, 5.5 Hz, 2H), 3.51 (q, J = 5.5 Hz, 2H), 3.17-3.21 (m, 2H), 2.73 (dd, J = 15.0, 7.0 Hz, 1H), 2.38-2.42 (m, 1H), 2.23-2.30 (m, 1H), 2.08-2.20 (m, 2H), 2.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.2, 178.2, 171.1, 157.6, 157.3, 133.0, 128.0, 116.7, 114.4, 62.5, 42.6, 40.2, 39.1, 37.3, 32.6, 30.1, 24.3, 20.9; IR (film, cm^{-1}): 3333, 3100, 2955, 2857, 1726,

1702, 1561, 1439, 1403, 1366, 1245, 1212, 1185, 1045; HRMS (ESI) *m/z* calc'd for $C_{16}H_{19}N_2O_5F_3Na$ $[M + Na]^+$: 399.1144, found 399.1141.



2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl 2,6-difluorobenzoate: A 25 mL round bottom flask was charged with N-(2-hydroxyethyl)maleimide (Strem, 0.100 g, 0.708 mmol, 1.0 equiv), CH_2Cl_2 (0.94 mL, 0.75 M), and NEt_3 (0.246 mL, 1.77 mmol, 2.5 equiv). 2,6-difluorobenzoyl choride (Sigma-Aldrich, 0.177 mL, 1.42 mmol, 2.0 equiv) was then syringed into the reaction dropwise and allowed to stir at r.t. for 10 min, at which time the reaction was quenched with H_2O (5 mL) and diluted with CH_2Cl_2 (10 mL). The layers were separated and the organic layer was washed with satd. NH_4Cl (2 x 20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified through flash chromatography (35% EtOAc/hexanes), affording the title compound as a white solid (173 mg, 0.615 mmol, 87% yield).

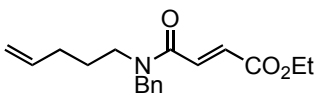
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.44 (m, 1H), 6.93 (t, J = 8.5 Hz, 2H), 6.73 (s, 2H), 4.52 (t, J = 5.5 Hz, 2H), 3.93 (t, J = 5.5, Hz, 2H).



(±)-2-((3a*S*,4*S*,7a*R*)-4-(2-acetoxyethyl)-1,3-dioxo-3a,4,7,7a-tetrahydro-1*H*-isoindol-2(3*H*)-yl)ethyl 2,6-difluorobenzoate [56]: Acetic Acid 5-hexen-1-yl ester **34** (42.6 mg, 0.30 mmol, 1.0 equiv) and 2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)ethyl 2,6-difluorobenzoate (84.4 mg, 0.30 mmol, 1.0 equiv) were reacted using the general procedure. Purification by flash chromatography (40% EtOAc/hexanes) produced adduct **56** as a pale yellow oil (85.0 mg, 0.202 mmol, **67% yield**). The product was isolated in >20:1 d.r. by ^{1}H NMR.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.45 (m, 1H), 6.94 (t, *J* = 8.0 Hz, 2H), 5.86 (ddd, *J* = 10.0, 6.5, 3.0 Hz, 1H), 5.68 (dt, *J* = 9.0, 3.5 Hz, 1H), 4.42-4.51 (m, 2H), 4.29 (ddd, *J* = 11.0, 6.5, 6.0 Hz, 1H), 4.18 (ddd, *J* = 11.5, 6.0, 5.5 Hz, 1H), 3.80-3.88 (m, 2H), 3.14-3.19 (m, 2H), 2.71 (dd, *J* = 15.5, 7.0 Hz, 1H), 2.37-2.40 (m, 1H), 2.21-2.28 (m, 1H), 2.12-2.18 (m, 1H), 2.01-2.09 (m, 1H), 2.05 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 177.4, 171.0, 161.8 (2 peaks), 161.1, 159.8, 159.7, 133.1 (2 peaks), 133.0, 132.8, 127.9, 112.1 (2 peaks), 112.0, 111.9, 62.6, 61.7, 42.4, 40.0, 37.3, 32.4, 30.0, 24.1, 20.9; IR (film, cm^{-1}): 3047, 2956, 2875, 2848, 1736, 1703, 1636, 1595, 1471, 1431, 1402, 1365, 1335, 1290, 1261, 1115, 1016; HRMS (ESI) *m/z* calc'd for $C_{21}H_{21}NO_6F_2Na$ $[M + Na]^+$: 444.1235, found 444.1235.

Intramolecular Dehydrogenative Diels-Alder Reactions for Figure 36

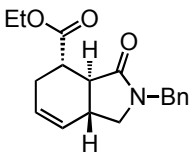


(*E*)-ethyl 4-(benzyl(pent-4-en-1-yl)amino)-4-oxobut-2-enoate [57]: A 25 mL round bottom flask was charged sequentially with 5-bromo-1-pentene (Sigma-Aldrich, 0.275 mL, 2.32 mmol, 1.0 equiv), benzylamine (Sigma-Aldrich, 2.5 mL, 23.2 mmol, 10.0 equiv), and K_2CO_3 (0.32 g, 2.32 mmol, 1.0 equiv), and the reaction was heated at 45°C for 3.5 hr. The reaction was then diluted with Et_2O (5 mL) and H_2O (10 mL), and the layers were separated. The organic layer was then washed with dilute NH_4Cl (3 x 20 mL) in order to remove excess benzylamine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude benzyl pentenamine product was sufficiently pure and taken onto the next step without purification.

The benzyl pentenamine product (2.32 mmol, 1.0 equiv) was dissolved in DCM (3.6 mL) and pyridine (0.24 mL, 3.02 mmol, 1.3 equiv) and cooled to 0°C. A solution of ethyl fumaroyl

chloride (Sigma-Aldrich, 0.49 mL, 3.02 mmol, 1.3 equiv) in DCM (1.0 mL) was then syringed dropwise into the reaction, resulting in a dark red solution that was stirred at room temperature for 3 hr. The reaction was then diluted with DCM (10 mL), and quenched slowly with H_2O (15 mL) and satd $NaHCO_3$ (15 mL). The layers were separated and the organic layer was washed with satd $NaHCO_3$ (1 x 20 mL), H_2O (1 x 20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified through flash chromatography (25% EtOAc/hexanes) to afford the title compound (**57**) as a clear oil (0.685 g, 2.27 mmol, 98% yield over 2 steps).

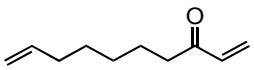
^{1}H NMR (500 MHz, $CDCl_3$, asterisk denotes minor rotomer peaks) δ 7.24-7.43 (m, 5H), 7.17 (d, *J* = 7.0 Hz, 1H), 6.90 (d, *J* = 15.0 Hz, 1H), 6.85* (d, *J* = 15.0 Hz, 1H), 5.70-5.81 (m, 1H), 4.95- 5.04 (m, 2H), 4.68 (s, 2H), 4.62* (s, 2H), 4.27 (d, *J* = 7.0 Hz, 2H), 4.21* (d, *J* = 7.5 Hz, 2H), 3.42* (app t, *J* = 7.5 Hz, 2H), 3.31 (app t, *J* = 7.5 Hz, 2H), 2.04 (pent, *J* = 6.5 Hz, 2H), 1.67 (app sextet, *J* = 7.0 Hz, 2H), 1.33 (t, *J* = 7.0 Hz, 3H), 1.28* (t, *J* = 7.0 Hz, 3H).



(±)-(3a*S*,4*S*,7a*R*)-ethyl 2-benzyl-3-oxo-2,3,3a,4,5,7a-hexahydro-1*H*-isoindole-4-carboxylate [59]: A ½ dram borosilicate vial was charged sequentially with Pd[1,2-bis(benzylsulfinyl)ethane](OAc)$_2$ catalyst **39** (15.9 mg, 0.03 mmol, 0.10 equiv), 2,6-Me_2BQ (40.8 mg, 0.30 mmol, 1.0 equiv), and *p*-nitrobenzoic acid (5.01 mg, 0.03 mmol, 0.10 equiv). Acrylamide **57** (90.4 mg, 0.30 mmol, 1.0 equiv) was then added to the ½ dram vial, and the reaction was immediately dissolved in DCE (0.24 mL, 1.25 M). The resulting dark red reaction mixture was charged with a stir bar, capped with a □eflon-lined cap, and suspended in an oil bath at 45°C for 48 hr. Upon completion, the dark red reaction mixture was filtered through a short silica plug, eluting with ~5 mL EtOAc and concentrated *in vacuo* at 25°C (~25 torr) to afford a dark red crude oil. A small aliquot of this mixture was added

to a NMR tube and diluted with $CDCl_3$. ^1H NMR analysis of the crude product showed a 4:1 *trans*:*cis* selectivity. After analysis, the sample was returned to the crude mixture and the solvent was removed. Purification by flash chromatography (50% Et_2O/hexanes) produced hydroisoindoline **59** as a clear oil (53.6 mg, 0.179 mmol, **60% yield**). The product was isolated with 4:1 d.r. by ^1H NMR.

^1H NMR (500 MHz, $CDCl_3$) *Major diastereomer:* δ 7.30-7.33 (m, 2H), 7.25-7.28 (m, 1H), 7.21 (d, *J* = 7.0 Hz, 2H), 5.75-5.78 (m, 1H), 5.68 (dq, *J* = 10.0, 3.0 Hz, 1H), 4.48 (d, *J* = 14.5 Hz, 1H), 4.39 (d, *J* = 14.5 Hz, 1H), 4.21-4.34 (m, 2H), 3.25 (dd, *J* = 9.0, 6.0 Hz, 1H), 2.97 (t, *J* = 10.0 Hz, 1H), 2.77-2.83 (m, 1H), 2.45-2.61 (m, 3H), 2.33-2.41 (m, 1H), 1.34 (t, *J* = 7.0 Hz, 3H). *Minor diastereomer (diagnostic):* δ 7.16 (d, *J* = 7.0 Hz, 2H), 5.78-5.82 (m, 1H), 5.47-5.51 (m, 1H), 4.55 (d, *J* = 15.0 Hz, 1H), 4.16 (dq, *J* = 2.0, 7.5 Hz, 2H), 3.45 (dd, *J* = 9.5, 7.5 Hz, 1H), 2.89 (dd, *J* = 9.5, 1.5 Hz, 1H), 2.25-2.30 (m, 1H), 1.25 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, asterisk denotes minor diastereomer peaks) δ 174.4, 174.1*, 173.8*, 172.8, 136.6, 136.2*, 128.6, 128.5*, 128.1, 128.0, 127.7*, 127.5, 127.4*, 127.3*, 127.1*, 125.2, 60.8, 60.7*, 51.1*, 49.0, 47.2, 46.4, 42.3*, 40.6, 38.6, 37.1*, 30.4, 30.4*, 23.3*, 14.2; IR (film, cm^{-1}): 3062, 3028, 2980, 2933, 2912, 2966, 1732, 1699, 1496, 1454, 1421, 1306, 1252, 1180, 1119, 1097, 1030; HRMS (ESI) *m/z* calc'd for $C_{18}H_{22}NO_3$ $[M + H]^+$: 300.1600, found 300.1598.

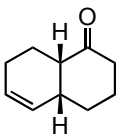


deca-1,9-dien-3-one [58]: A flame-dried 50 mL round bottom flask was charged with Mg^0 turnings (142.0 mg, 5.87 mmol, 1.3 equiv) and Et_2O (3.01 mL). A solution of 7-bromo-1-heptene (Sigma-Aldrich, 0.688 mL, 4.52 mmol, 1.0 equiv) in Et_2O (3.01 mL) was syringed into the Mg suspension over 30 min. The reaction was then cooled to -10°C and freshly distilled acrolein (Sigma-Aldrich, 0.422 mL, 6.32 mmol, 1.4 equiv) was syringed into the

Grignard reaction dropwise over 30 min. Upon completion, the reaction was quenched slowly at -10°C with sat'd NH_4Cl (~3 mL), and diluted with Et_2O (10 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic layers were then washed with H_2O (1 x 20 mL), sat'd NaCl (1 x 20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified through flash chromatography (20% EtOAc/hexanes) to afford deca-1,9-dien-3-ol as a clear oil (0.402 g, 2.60 mmol, 58% yield).

A 50 mL round bottom flask was charged with deca-1,9-dien-3-ol (0.285 g, 1.85 mmol, 1.0 equiv) and acetone (5.6 mL, 0.33 M), and the solution was cooled to 0°C. This alcohol solution was then titrated with Jones' reagent (4 M) until the red color persisted, and allowed to stir for 10 min. The red reaction solution was then quenched with iPrOH until a green color persisted, and let warm to rt. The reaction was diluted with DCM (10 mL) and H_2O (10 mL) was added to dissolve the green solids. The layers were separated and the aqueous layer was extracted with DCM (2 x 40 mL). The combined organic layers were then washed with satd $NaHCO_3$ (1 x 40 mL), sat'd NaCl (1 x 40 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was then filtered through a short silica plug with 100% DCM to afford deca-1,9-dien-3-one (**58**) as a clear oil (0.268 g, 1.76 mmol, 95% yield).

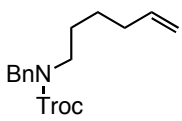
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (dd, J = 17.5, 10.5 Hz, 1H), 6.21 (dd, J = 17.5, 1.0 Hz, 1H), 5.81 (d, J = 10.5 Hz, 1H), 5.80 (ddt, J = 17.0, 10.0, 6.5 Hz, 1H), 4.99 (dd, J = 17.0, 1.5 Hz, 1H), 4.94 (d, J = 10.0 Hz, 1H), 2.58 (t, J = 7.5 Hz, 2H), 2.05 (q, J = 7.5 Hz, 2H), 1.63 (pent, J = 7.5 Hz, 2H), 1.38-1.63 (m, 2H), 1.30-1.36 (m, 2H).



(±)-(4a*R*,8a*S*)-2,3,4,4a,8,8a-hexahydronaphthalen-1(7*H*)-one [60]: A ½ dram borosilicate vial was charged sequentially with Pd[1,2-bis(benzylsulfinyl)ethane](OAc)$_2$ catalyst **39** (15.9 mg, 0.03 mmol, 0.10 equiv), 2,6-Me$_2$BQ (57.2 mg, 0.42 mmol, 1.4 equiv), and *p*-nitrobenzoic acid (5.01 mg, 0.03 mmol, 0.10 equiv). Deca-1,9-dien-3-one **58** (45.6 mg, 0.30 mmol, 1.0 equiv) was then added to the ½ dram vial, and the reaction was immediately dissolved in DCE (0.20 mL, 1.50 M). The resulting dark red reaction mixture was charged with a stir bar, capped with a Teflon-lined cap, and suspended in an oil bath at 45°C for 48 hr. Upon completion, the dark red reaction mixture was filtered through a short silica plug, eluting with ~5 mL EtOAc and concentrated *in vacuo* at 0°C (~25 torr) to afford a dark red crude oil. A small aliquot of this mixture was added to a NMR tube and diluted with $CDCl_3$. ^{1}H NMR analysis of the crude product showed a 16:1 *cis*:*trans* selectivity. After analysis, the sample was returned to the crude mixture and the solvent was removed. Purification by flash chromatography (4% EtOAc/hexanes) produced *cis*-decalin **60** as a clear oil (27.4 mg, 0.182 mmol, **61% yield**). The product was isolated with 16:1 d.r. by ^{1}H NMR.

This compound has been reported previously.[106] ^{1}H NMR (500 MHz, $CDCl_3$)*:* δ 5.71 (dq, *J* = 10.5, 2.5 Hz, 1H), 5.51 (dq, *J* = 10.0, 2.5 Hz, 1H), 2.66-2.72 (m, 1H), 2.49-2.52 (m, 1H), 2.34-2.39 (m, 1H), 2.22-2.27 (m, 1H), 2.13-2.21 (m, 1H), 2.05-2.11 (m, 1H), 1.94-2.01 (m, 1H), 1.67-1.88 (m, 4H), 1.48-1.54 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.2, 129.7, 128.4, 48.0, 40.6, 37.2, 29.5, 23.3, 22.9, 22.2; IR (film, cm^{-1}): 3016, 2927, 2864, 1705, 1444, 1431, 1317, 1227, 1124, 1005; LRMS (EI) *m/z* calc'd for $C_{10}H_{14}O$ $[M]^+$: 150.1, found 150.1.

Dehydrogenative Diels-Alder Route to Hydroisoquinolines for Figure 37

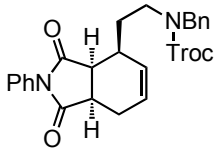


2,2,2-trichloroethyl benzyl(hex-5-en-1-yl)carbamate [61]: A 50 mL round bottom flask was charged sequentially with 6-bromo-1-hexene (Sigma-Aldrich, 0.54 mL, 4.0 mmol, 1.0 equiv), benzylamine (Sigma-Aldrich, 4.4 mL, 40.0 mmol, 10.0 equiv), and K_2CO_3 (0.552 g, 4.0 mmol, 1.0 equiv), and the reaction was heated at 45°C for 4 hr. The reaction was then diluted with Et_2O (20 mL) and H_2O (20 mL), and the layers were separated. The organic layer was then washed with dilute NH_4Cl (3 x 40 mL) in order to remove excess benzylamine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude benzyl hexenamine product was sufficiently pure and taken onto the next step without purification.

The crude benzyl hexenamine product (4.0 mmol, 1.0 equiv) was dissolved in DCM (8.0 mL, 0.5 M) and pyridine (0.42 mL, 5.21 mmol, 1.3 equiv) and cooled to 0°C. 2,2,2-trichloroethylchloroformate (Sigma-Aldrich, 0.72 mL, 5.21 mmol, 1.3 equiv) was then syringed dropwise into the reaction, resulting in a yellow slurry which was stirred at room temperature for 12 hr. The resulting dark green reaction was then quenched slowly with H_2O (15 mL) and satd $NaHCO_3$ (15 mL). The layers were separated and the organic layer was washed with satd $NaHCO_3$ (1 x 40 mL), H_2O (1 x 40 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified through flash chromatography (5% Et_2O/pentane) to afford the title compound (**61**) as a clear oil (1.254 g, 3.44 mmol, 86% yield over 2 steps).

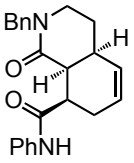
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.35 (m, 5H), 5.76 (ddt, J = 15.5, 10.0, 5.0 Hz, 1H), 4.98 (d, J = 17.0 Hz, 1H), 4.94 (d, J = 10.0 Hz, 1H), 4.81 (d, J = 10.5 Hz, 2H), 4.54 (d, J = 12.0 Hz, 2H), 3.25-3.31 (m, 2H), 2.04 (pent, J = 7.5 Hz, 2H), 1.56-1.62 (m, 2H), 1.33-1.41 (m, 2H); ^{13}C NMR (mixture of rotomers, 125 MHz, $CDCl_3$) δ 154.9, 154.2, 138.3 (2 peaks), 137.2, 128.6,

127.7, 127.5, 127.5 (3 peaks), 114.7, 95.7, 95.6, 75.1 (2 peaks), 50.8, 50.1, 47.0, 46.4, 33.3 (2 peaks), 27.4, 26.7, 25.9, 25.8; IR (film, cm^{-1}): 3068, 3032, 2974, 2933, 2862, 1720, 1641, 1471, 1454, 1425, 1360, 1252, 1225, 1132, 1063; HRMS (EI) *m/z* calc'd for $C_{16}H_{20}Cl_3NO_2Na$ [M + Na]$^+$: 386.0457, found 386.0459.



(±)-2,2,2-trichloroethyl benzyl(2-((3a*S*,4*S*,7a*R*)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)ethyl)carbamate [62]: Olefin **61** (109.4 mg, 0.30 mmol, 1.0 equiv) and N-phenylmaleimide (51.9 mg, 0.30 mmol, 1.0 equiv) were reacted using the general procedure. Purification by flash chromatography (55% Et_2O/pentane) produced adduct **62** as a light yellow oil. Run 1 (111.8 mg, 0.209 mmol, 70% yield); Run 2 (120.9 mg, 0.226 mmol, 75% yield). The product was isolated in >20:1 d.r. by ^{1}H NMR for both experiments. **Average: 73% yield**.

^{1}H NMR (1:1 mixture of rotomers, 500 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.5 Hz, 4H), 7.27-7.39 (m, 12H), 7.19 (d, *J* = 8.0 Hz, 4H), 5.97-6.00 (m, 2H), 5.79-5.82 (m, 2H), 4.72-4.87 (m, 6H), 4.48 (d, *J* = 15.5 Hz, 1H), 4.42 (d, *J* = 15.5 Hz, 1H), 3.65 (pent, *J* = 7.0 Hz, 1H), 3.54-3.60 (m, 1H), 3.33-3.42 (m, 3H), 3.25 (t, *J* = 9.0 Hz, 2H), 3.16 (dd, *J* = 9.0, 6.0 Hz, 1H), 2.81 (dd, *J* = 15.0, 7.0 Hz, 2H), 2.26-2.33 (m, 4H), 2.05-2.19 (m, 4H). ^{13}C NMR (1:1 mixture of rotomers, 125 MHz, $CDCl_3$) δ 178.8, 178.7, 176.9, 176.6, 154.9, 154.5, 137.1, 137.0, 133.3, 133.0, 131.8 (2 peaks), 129.0, 128.6 (2 peaks), 128.5, 128.2, 128.0, 127.9, 127.6 (3 peaks), 126.4 (2 peaks), 95.7, 95.6, 75.1 (2 peaks), 50.7, 49.9, 45.3, 45.0, 42.8, 42.3, 40.2 (2 peaks), 33.5, 33.4, 29.4, 28.7, 24.5, 24.4; IR (film, cm^{-1}): 3064, 3035, 2953, 2850, 1774, 1709, 1599, 1496, 1471, 1454, 1425, 1385, 1267, 1207, 1128, 1061; HRMS (ESI) *m/z* calc'd for $C_{26}H_{25}Cl_3N_2O_4Na$ [M + Na]$^+$: 557.0778, found 557.0787.



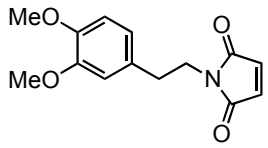
(±)-(4a*S*,8*R*,8a*S*)-2-benzyl-1-oxo-*N*-phenyl-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-8-carboxamide [63]: A 10 mL round bottom flask was charged with adduct **62** (47.5 mg, 0.0886 mmol, 1.0 equiv), THF (1.82 mL, 0.049 M), glacial AcOH (0.20 mL, 0.44 M), and zinc dust (Sigma-Aldrich <10 micron, 106.8 mg, 1.63 mmol, 18.4 equiv), and allowed to stir at room temperature for 1 hr. The reaction was then filtered through a celite plug to remove excess Zn, washing with DCM, and concentrated *in vacuo*. The concentrate was then re-dissolved in DCM and washed with 5% K_2CO_3 (1 x 10 mL). The aqueous layer was extracted with DCM (3 x 15 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude benzylamine adduct was sufficiently pure, and taken onto the next step without purification.

The crude benzylamine adduct (0.0886 mmol) was dissolved in toluene (1.82 mL, 0.049M) in a 25 mL round bottom flask, and the reaction was heated to 80°C for 2.5 hr. The toluene was then removed *in vacuo*, and the crude product was purified through flash chromatography (1.5% MeOH/CH_2Cl_2) to afford octahydroisoquinoline-8-carboxamide (**63**) as a white solid (27.8 mg, 0.077 mmol, 87% yield over 2 steps). This material could be further purified through recrystallization from 50% EtOAc/hexanes.

This compound has been reported previously.[107] ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.89 (br s, 1H), 7.63 (d, *J* = 7.5 Hz, 2H), 7.25-7.32 (m, 5H), 7.17 (d, *J* = 6.5 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 5.91 (ddd, *J* = 9.5, 6.0, 3.0 Hz, 1H), 5.57 (dd, *J* = 10.0, 1.5 Hz, 1H), 4.78 (d, *J* = 15.0 Hz, 1H), 4.48 (d, *J* = 15.0 Hz, 1H), 3.23 (dd, *J* = 5.0, 2.0 Hz, 1H), 3.13 (dd, *J* = 9.0, 4.0 Hz, 2H), 2.95 (t, *J* = 6.5 Hz, 1H), 2.85 (br s, 1H), 2.48-2.51 (m, 2H), 1.94-2.00 (m, 1H), 1.80-1.85 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 171.3, 138.9, 136.5, 129.2, 128.7, 128.6, 128.0, 127.6, 127.4, 123.6, 119.9, 50.6, 44.3, 42.4, 36.1, 27.2, 26.5; IR (film, cm^{-1}): 3319, 3197, 3132, 3062, 3026,

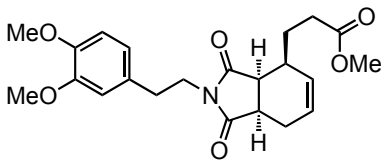
2927, 2868, 1668, 1631, 1599, 1543, 1496, 1441,1356, 1325, 1252, 1194, 1080, 910; HRMS (ESI) *m/z* calc'd for $C_{23}H_{25}N_2O_2$ $[M + H]^+$: 361.1916, found 361.1909.

Dehydrogenative Diels-Alder Route to Isoindoloquinolines for Figure 38



N-(3,4-dimethoxy)phenethyl maleimide [65]: This product was prepared as described previously.[122]

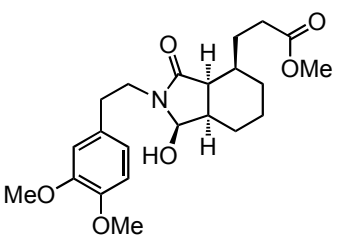
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71-6.79 (m, 3H), 6.66 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.75 (t, *J* = 7.5 Hz, 2H), 2.85 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 148.8, 147.7, 134.0, 130.2, 120.8, 111.8, 111.2, 55.8 (2 peaks), 39.1, 34.0.



(±)-Methyl 3-((3a*S*,4*S*,7a*R*)-2-(3,4-dimethoxyphenethyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)propanoate [66]: Methyl 6-heptenoate **64** (Sigma-Aldrich, 42.7 mg, 0.30 mmol, 1.0 equiv) and 3,4-dimethoxyphenethyl maleimide **65** (78.4 mg, 0.30 mmol, 1.0 equiv) were reacted using the general procedure. Purification by flash chromatography (50% EtOAc/hexanes) produced adduct **66** as a pale yellow oil. Run 1 (81.7 mg, 0.204 mmol, 68% yield); Run 2 (89.1 mg, 0.222 mmol, 74% yield). The product was isolated in >20:1 d.r. by ^{1}H NMR for both experiments. **Average: 71% yield**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (d, *J* = 9.0 Hz, 1H), 6.71 (d, *J* = 6.5 Hz, 2H), 5.79 (ddd, *J* = 10.0, 7.0 Hz, 3.5 Hz, 1H), 5.60 (dt, *J* = 9.5, 3.0 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.69 (s, 3H), 3.66 (t, *J* = 7.5 Hz, 2H), 3.03-3.08 (m, 2H), 2.76 (t, *J* = 7.5 Hz, 2H), 2.66 (dd, *J* = 15.0,

7.0 Hz, 1H), 2.46-2.57 (m, 2H), 2.26-2.28 (m, 1H), 2.15-2.22 (m, 1H), 2.01-2.11 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.5, 177.4, 173.6, 148.7, 147.6, 132.7, 130.1, 127.7, 120.8, 111.9, 111.0, 55.8 (2 peaks), 51.6, 42.2, 40.1, 39.7, 35.0, 33.0, 32.1, 26.3, 24.1; IR (film, cm^{-1}): 3033, 2993, 2951, 2837, 1770, 1736, 1695, 1591, 1516, 1441, 1402, 1360, 1263, 1238, 1153, 1028; HRMS (ESI) *m/z* calc'd for $C_{22}H_{27}NO_6Na$ $[M + Na]^+$: 424.1736, found 424.1734.

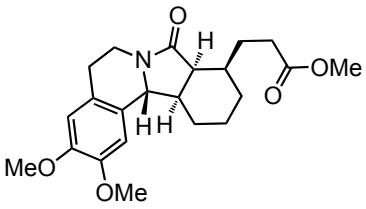


(±)-methyl 3-((1*R*,3a*S*,4*R*,7a*R*)-2-(3,4-dimethoxyphenethyl)-1-hydroxy-3-oxooctahydro-1*H*-isoindol-4-yl)propanoate [67]: A 10 mL round bottom flask was charged with adduct **66** (61.9 mg, 0.154 mmol, 1.0 equiv), H_2 purged MeOH (1.93 mL, 0.08 M), and 30% Pd/C (Sigma-Aldrich, 12.5 mg). The reaction was topped with a H_2 balloon and allowed to stir for 2 hr. The reaction was then filtered through a celite plug, washing with EtOAc, and concentrated *in vacuo* to afford the hexahydrophthalimide product. This crude material was taken onto the next step.

The site-selective mono-reduction of the imide to form hydroxylactam **67** was achieved using a modified procedure.[109] The crude hexahydrophthalimide product (0.154 mmol) was dissolved in absolute EtOH (1.54 mL, 0.10 M), and the reaction was cooled to 0°C. $NaBH_4$ (46.6 mg, 1.23 mmol, 8.0 equiv) was added to the reaction in one portion, and allowed to dissolve (~ 5 min). The mixture was stirred at 0°C while 1 drop of a 2 M solution of H_2SO_4 in EtOH was added every 10 min and monitored by TLC. After 40 min (4 drops of 2 M H_2SO_4 in EtOH) the reaction was quenched slowly at 0°C with sat'd. NH_4Cl (5 mL) and diluted with DCM (5 mL). The mixture was allowed to warm to room temperature, and H_2O was added until the solution clarified. The layers were separated and the aqueous layer was extracted with DCM (3 x 15 mL).

The combined organic layers were washed with sat'd. $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude hydroxylactam **67** as a single isomer. This material was taken onto the next step without purification.

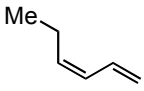
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74-6.80 (m, 3H), 4.86 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.66 (s, 3H), 3.55 (dt, *J* = 13.5, 7.5 Hz, 1H), 3.39-3.45 (m, 1H), 2.80-2.88 (m, 2H), 2.37-2.45 (m, 3H), 2.26-2.33 (m, 2H), 1.93-2.06 (m, 1H), 1.97 (br d, *J* = 10.5 Hz, 1H), 1.74-1.80 (m, 1H), 1.45-1.65 (m, 3H), 1.15-1.23 (m, 1H), 1.07 (dq, *J* = 2.5, 12.5 Hz, 1H), 0.93 (dq, *J* = 4.0, 13.0 Hz, 1H).



(±)-Methyl 3-((8a*S*,9*R*,12a*R*,12b*R*)-2,3-dimethoxy-8-oxo-5,6,8,8a,9,10,11,12,12a,12b-decahydroisoindolo[1,2-*a*]isoquinolin-9-yl)propanoate [68]: The N-acyliminium ion cyclization of hydroxylactam **67** was achieved using a modified procedure.[123] A flame-dried 25 mL round bottom flask was charged with the crude hydroxylactam **67** (0.154) and toluene (1.71 mL, 0.09 M). 10-camphorsulfonic acid (53.6 mg, 0.231 mmol, 1.5 equiv) was added to the reaction in one portion, and the mixture was heated to 80°C for 1.5 hr. The reaction was then cooled, diluted with DCM (5 mL), and quenched with satd $NaHCO_3$. The layers were separated and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified through flash chromatography (65% EtOAc/hexanes) to afford isoindoloquinoline **68** as a white solid (42.1 mg, 0.109 mmol, 71% yield over 3 steps). X-ray quality crystals could be obtained by recrystallizing the product in hot hexanes/minimal EtOAc, followed by sitting at 4°C for 12 hr.

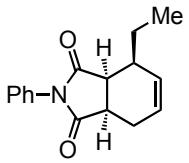
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67 (s, 1H), 6.58 (s, 1H), 4.26 (ddd, *J* = 12.0, 6.0, 2.0 Hz, 1H), 4.20 (s, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.62 (s, 3H), 3.05 (dt, *J* = 4.5, 12.0 Hz, 1H), 2.95-3.02 (m, 1H), 2.22-2.55 (m, 6H), 1.92-2.01 (m, 2H), 1.80 (dt, *J* = 13.0, 3.5 Hz, 1H), 1.50-1.68 (m, 3H), 1.36 (app tq, *J* = 3.0, 12.5 Hz, 1H), 1.13-1.21 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 174.3, 148.0, 147.6, 127.5, 127.1, 112.0, 107.8, 62.0, 56.0, 55.8, 51.4, 43.4, 39.1, 38.5, 36.2, 32.0, 29.2, 28.9, 27.7, 27.2, 24.0; IR (film, cm^{-1}): 2929, 2854, 1734, 1685, 1610, 1516, 1450, 1416, 1360, 1329, 1259, 1227, 1165, 1107, 1012, 874; HRMS (ESI) *m/z* calc'd for $C_{22}H_{29}NO_5Na$ $[M + Na]^+$: 410.1943, found 410.1938.

Diene Isomerization Studies for Figure 39



(Z)-1,3-hexadiene [69]: A 1 dram borosilicate vial was charged with 1,3-hexadiene (Sigma-Aldrich, 3.3:1 Z:E isomeric mixture as determined by ^{1}H NMR analysis, 0.9469 g, 11.527 mmol, 1.0 equiv), DCE (0.53 mL, 21.7 M), and N-phenylmaleimide (0.485 g, 2.80 mmol, 0.243 equiv). The reaction suspension was charged with a stir bar, capped with a teflon-lined cap, and suspended in an oil bath at 45°C bath for 3 hr, resulting in a clear yellow solution. A small aliquot of this solution was added to a NMR tube and diluted with $CDCl_3$. ^{1}H NMR analysis showed only (Z)-1,3-hexadiene (**69**) and Diels-Alder product (**70**). The (Z)-1,3-hexadiene product was isolated from the reaction mixture using a Kugelrohr distillation apparatus (80°C, 760 torr.) to afford the title compound **69** (0.370 g, 4.508 mmol, 51% yield, >50:1 Z:E by ^{1}H NMR) as a 21.3 M solution in DCE. This solution of (Z)-1,3-hexadiene was then used for the following crossover isomerization study.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (dt, *J* = 16.8, 10.0 Hz, 1H), 5.97 (t, *J* = 10.8 Hz, 1H), 5.46 (dt, *J* = 10.8, 7.6 Hz, 1H), 5.18 (d, *J* = 16.8 Hz, 1H), 5.08 (d, *J* = 10.0 Hz, 1H), 2.20 (app dpent, *J* = 1.6, 7.6 Hz, 2H), 1.00 (t, *J* = 7.6 Hz, 3H).

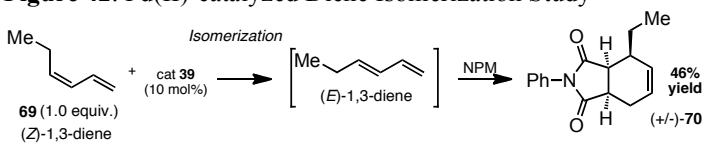


(±)-(3a*S*,4*S*,7a*R*)-4-ethyl-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione [70]: A ½ dram borosilicate vial was charged sequentially with Pd[1,2-bis(benzylsulfinyl)ethane](OAc)$_2$ catalyst **39** (15.9 mg, 0.03 mmol, 0.10 equiv), N-phenylmaleimide (51.9 mg, 0.30 mmol, 1.0 equiv), 2,6-Me_2BQ (40.8 mg, 0.30 mmol, 1.0 equiv), and *p*-nitrobenzoic acid (5.01 mg, 0.03 mmol, 0.10 equiv). Acetic Acid 5-hexen-1-yl ester (**34**) substrate (21.3 mg, 0.15 mmol, 0.5 equiv) and (Z)-1,3-hexadiene **69** (12.3 mg, 0.15 mmol, 0.5 equiv) were then added to the ½ dram vial, and the reaction was immediately dissolved in DCE (0.3 mL, 1.0 M). The resulting dark red reaction mixture was charged with a stir bar, capped with a teflon-lined cap, and suspended in an oil bath at 45°C bath for 48 hr. Upon completion, the dark red reaction mixture was filtered through a short silica plug, eluting with ~5 mL EtOAc, and concentrated *in vacuo* at 25°C (~25 torr) to afford a dark red crude oil. A small aliquot of this mixture was added to a NMR tube and diluted with $CDCl_3$. ^{1}H NMR analysis of the crude product showed a ~1:1 **40**:**70** ratio, both with >20:1 d.r. After analysis, the sample was returned to the crude mixture and the solvent was removed. The crude product was purified through flash chromatography (25% EtOAc/hexanes to 40% EtOAc/hexanes, SiO_2, 20 x 160 mm) to furnish the isomerization/Diels-Alder product **70** (26.6 mg, 0.104 mmol, 69% yield) and the dehydrogenation/Diels-Alder product **40** (29.9 mg, 0.954 mmol, 64% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.20 (dd, *J* = 9.0, 1.5 Hz, 2H), 5.98 (ddd, *J* = 9.5, 6.0, 3.5 Hz, 1H), 5.88 (dt, *J* = 9.5, 3.5 Hz, 1H), 3.27-3.31

(m, 2H), 2.80 (ddd, J = 15.5, 6.5 Hz, 1H), 2.22-2.29 (m, 2H), 1.92-2.01 (m, 1H), 1.76-1.85 (m, 1H), 1.08 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 176.9, 133.9, 131.9, 129.0, 128.4, 127.3, 126.5, 42.8, 40.4, 38.1, 24.4, 24.1, 12.6; IR (film, cm^{-1}): 3037, 2962, 2933, 2906, 2873, 1774, 1709, 1597, 1498, 1456, 1444, 1383, 1190, 1169, 862, 754, 692; HRMS (ESI) *m/z* calc'd for $C_{16}H_{17}NO_2Na$ $[M + Na]^+$: 278.1157, found 278.1154. Note: The structure and relative stereochemistry of isomerization/Diels-Alder product **70** was confirmed through independent synthesis, involving the Diels-Alder reaction between (E)-1,3-hexadiene and N-phenylmaleimide.

Figure 42. Pd(II)-catalyzed Diene Isomerization Study

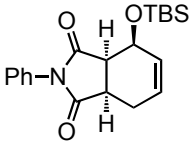


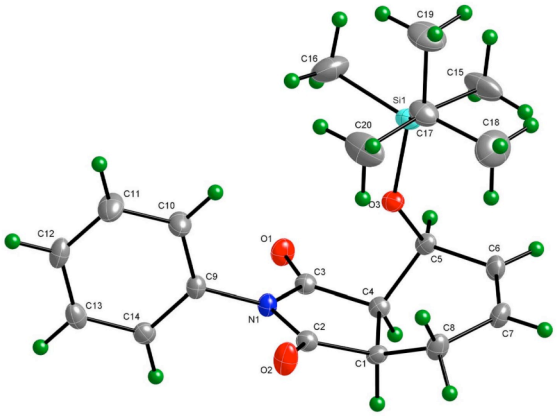
a) Conditions: **39** (10 mol%), NPM (1.0 equiv.), 2,6Me$_2$BQ (1.0 equiv.), *p*-NO_2BzOH (10 mol%), DCE (1M), 45°C, 48 hr. Cycloadduct **70** isolated as a single diastereomer.

Pd(II)-catalyzed Diene isomerization study: A ½ dram borosilicate vial was charged sequentially with Pd[1,2-bis(benzylsulfinyl)ethane](OAc)$_2$ catalyst **39** (15.9 mg, 0.03 mmol, 0.10 equiv), N-phenylmaleimide (51.9 mg, 0.30 mmol, 1.0 equiv), 2,6-Me$_2$BQ (40.8 mg, 0.30 mmol, 1.0 equiv), and *p*-nitrobenzoic acid (5.01 mg, 0.03 mmol, 0.10 equiv). (Z)-1,3-hexadiene **69** (24.6 mg, 0.30 mmol, 1.0 equiv) was then added to the ½ dram vial, and the reaction was immediately dissolved in DCE (0.3 mL, 1.0 M). The resulting dark red reaction mixture was charged with a stir bar, capped with a teflon-lined cap, and suspended in an oil bath at 45°C bath for 48 hr. Upon completion, the dark red reaction mixture was filtered through a short silica plug, eluting with ~5 mL EtOAc, and concentrated *in vacuo* at 25°C (~25 torr) to afford a dark red crude oil. A small

aliquot of this mixture was added to a NMR tube and diluted with $CDCl_3$. ^1H NMR analysis of the crude product showed a >20:1 d.r. of endo adduct **70**. After analysis, the sample was returned to the crude mixture and the solvent was removed. The crude product was purified through flash chromatography (20% EtOAc/hexanes, SiO_2, 20 x 160 mm) to furnish the isomerization/Diels-Alder product **70** (35.2 mg, 0.138 mmol, 46% yield). Note: Following the same procedure, except without Pd(II) catalyst **39**, the (Z)-diene **69** was fully recovered.

X-ray Crystal Structural Data for Figures 34 and 38





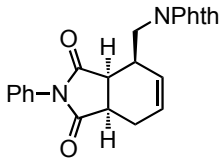
Compound **42** – Deposition number: CCDC 816037

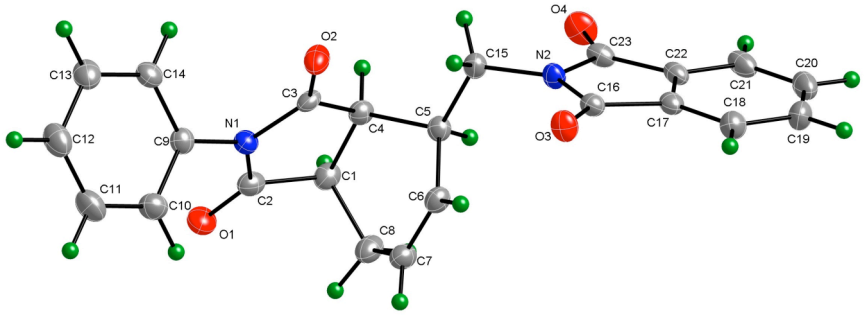
(Note: This crystal sample solved in a centrosymmetric space group and therefore both enantiomers exist in the crystal.)

Table. Crystal data and structure refinement for ba60las.

Identification code	ba60las
Empirical formula	C20 H27 N O3 Si
Formula weight	357.52
Temperature	193(2) K
Wavelength	0.71073 Å

Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 16.0358(8) Å	a= 90°.
	b = 8.2776(5) Å	b= 107.358(3)°.
	c = 15.5407(9) Å	g = 90°.
Volume	1968.90(19) $Å^3$	
Z	4	
Density (calculated)	1.206 Mg/m^3	
Absorption coefficient	0.137 mm^{-1}	
F(000)	768	
Crystal size	0.333 x 0.288 x 0.233 mm^3	
Theta range for data collection	2.66 to 25.40°.	
Index ranges	-19<=h<=19, -9<=k<=9, -18<=l<=18	
Reflections collected	33510	
Independent reflections	3620 [R(int) = 0.0647]	
Completeness to theta = 25.40°	100.0 %	
Absorption correction	Integration	
Max. and min. transmission	0.9842 and 0.9695	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3620 / 0 / 232	
Goodness-of-fit on F^2	1.032	
Final R indices [I>2sigma(I)]	R1 = 0.0387, wR2 = 0.0951	
R indices (all data)	R1 = 0.0527, wR2 = 0.1031	
Largest diff. peak and hole	0.257 and -0.308 $e.Å^{-3}$	





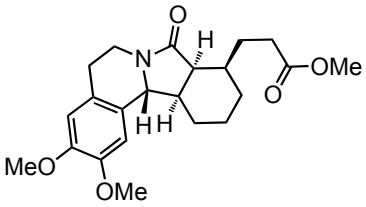
Compound **44** – Deposition number: CCDC 816038

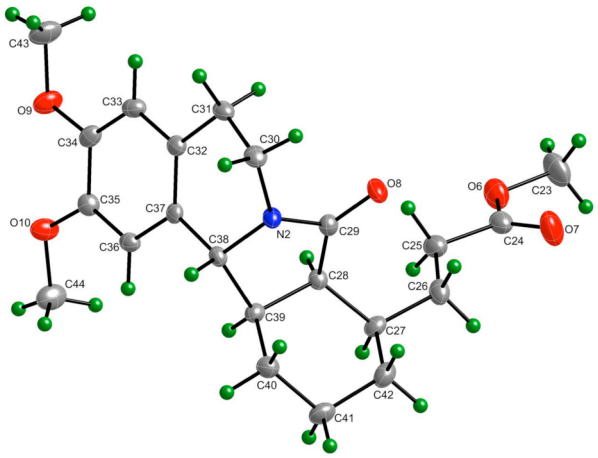
(Note: Four molecules are present in the unit cell. Two molecules of the same enantiomer exist within an asymmetric unit. This crystal sample solved in a centrosymmetric space group and therefore both enantiomers exist in the crystal.)

Table. Crystal data and structure refinement for ba61las.

Identification code	ba61las	
Empirical formula	C23 H18 N2 O4	
Formula weight	386.39	
Temperature	193(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.7991(6) Å	a= 76.317(4)°.
	b = 12.1515(10) Å	b= 89.530(5)°.
	c = 21.4998(16) Å	g = 72.349(4)°.
Volume	1882.1(3) $Å^3$	
Z	4	
Density (calculated)	1.364 Mg/m^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	808	
Crystal size	0.518 x 0.293 x 0.163 mm^3	
Theta range for data collection	1.81 to 25.51°.	
Index ranges	-9<=h<=9, -14<=k<=14, -25<=l<=25	
Reflections collected	33098	
Independent reflections	6957 [R(int) = 0.0714]	

Completeness to theta = 25.51°	99.1 %
Absorption correction	Integration
Max. and min. transmission	0.9913 and 0.9684
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6957 / 0 / 523
Goodness-of-fit on F^2	1.013
Final R indices [I>2sigma(I)]	R1 = 0.0440, wR2 = 0.0915
R indices (all data)	R1 = 0.0814, wR2 = 0.1059
Largest diff. peak and hole	0.148 and -0.219 e.Å^{-3}





Compound **68** – Deposition number: CCDC 816035

(Note: This crystal sample solved in a centrosymmetric space group and therefore both enantiomers exist in the crystal. The enantiomer shown was arbitrarily selected as the 2nd structure in the crystal, and thus the atom numbering starts at C23, O6, N2.)

Table. Crystal data and structure refinement for ba87kas.

Identification code	ba87kas
Empirical formula	C22 H29 N O5
Formula weight	387.46
Temperature	193(2) K
Wavelength	0.71073 Å

Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 10.4545(8) Å	a= 88.953(5)°.
	b = 13.0186(10) Å	b= 75.935(5)°.
	c = 15.2390(13) Å	g = 86.647(5)°.
Volume	2008.4(3) $Å^3$	
Z	4	
Density (calculated)	1.281 Mg/m^3	
Absorption coefficient	0.090 mm^{-1}	
F(000)	832	
Crystal size	0.342 x 0.194 x 0.091 mm^3	
Theta range for data collection	1.57 to 25.44°.	
Index ranges	-12<=h<=12, -15<=k<=15, -18<=l<=18	
Reflections collected	32558	
Independent reflections	7343 [R(int) = 0.0795]	
Completeness to theta = 25.44°	98.7 %	
Absorption correction	Integration	
Max. and min. transmission	0.9932 and 0.9712	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7343 / 0 / 511	
Goodness-of-fit on F^2	1.010	
Final R indices [I>2sigma(I)]	R1 = 0.0505, wR2 = 0.0968	
R indices (all data)	R1 = 0.1097, wR2 = 0.1165	
Largest diff. peak and hole	0.234 and -0.198 $e.Å^{-3}$	

3.5 REFERENCES

[72] For examples of late-stage C–H oxidations in total synthesis, see; (a) Stang, E. M.; White, M. C. *Nat. Chem.* **2009**, *1*, 547. (b) Davies, H. M. L.; Dai, X.; Long, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2485-2490. (c) Kim, J.; Ashenhurst, J. A.; Movassaghi, M. *Science* **2009**, *324*, 238. (d) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Reynaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorenson, E. J. *Nature* **1994**, *367*, 630. (e) Wender, P. A.; Jesudason, C. D.; Nakhira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976.

[73] For selected examples of C–H oxidations to diversify natural products and their analogues, see: (a) Yang, J.; Gabriele, B.; Belvedere, S.; Huang, Y.; Breslow, R. *J. Org. Chem.* **2002**, *67*, 5057 and references therein. (b) Das, S.; Incarvito, C. D.; Crabtree, R. H.; Brudvig, G. W. *Science* **2006**, *312*, 1941. (c) Wang, D.- H.; Wasa, M; Giri, R.; Yu, J.- Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (d) Bigi, M. A.; Reed, S. R.; White, M. C. *Nat. Chem.* **2011**, *3*, 218.

[74] Chau, M.; Jennewein, S.; Walker, K.; Croteau, R. *Chem. & Biol.* **2004**, *11*, 663.

[75] Hinman, A; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510-11511.

[76] Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824.

[77] Wender, P. A.; Hilinski, M. K.; Mayweg, A. V. W. *Org. Lett.* **2005**, *7*, 79.

[78] Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783.

[79] Chen, M. S.; White, M. C. *Science*, **2010**, *327*, 566.

[80] Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681.

[81] (a) Goldman, A. S.; Roy, A. H.; Huang, Z.; Ahuja, R.; Schinski, W.; Brookhart, M. *Science* **2006**, *312*, 257. (b) Burk, M. J.; Crabtree, R. H. *J. Am. Chem. Soc.* **1987**, *109*, 8025. (c) Liu, F.; Pak, E. B.; Singh, B.; Jensen, C. M.; Goldman, A. S. *J. Am. Chem. Soc.* **1999**, *121*, 4086.

[82] For selected examples of dehydrogenative oxidative cyclizations, see: (a) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141. (b) Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, *16*, 11212. (c) Nakao, Y.; Morita, E.; Idei, H.; Hiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 3264.

[83] For alternative ways to construct terminal 1,3-butadienes, see: (a) Qi, X.; Montgomery, J. *J. Org. Chem.* **1999**, *64*, 9310. (b) Keinan, E.; Kumar, S.; Dangur, V.; Vaya, J. *J. Am. Chem. Soc.* **1994**, *116*, 11151. (c) Sen, S.; Singh, S.; Sieburth, S. M. *J. Am. Chem. Soc.* **2009**, *74*, 2884. (d) Wang, Y.; West, F. G. *Synthesis* **2002**, *1,* 99. (e) Mundal, D. A.; Lutz, K. E.; Thompson, R. J. *Org. Lett.* **2009**, *11*, 465. (f) Shi, M.; Wang, B. –Y.; Huang, J. –W. *J. Org. Chem.* **2005**, *70*, 5606. (g) Yamada, S.; Ohsawa, H.; Suzuki, T.; Takayama, H. *J. Org. Chem.* **1986**, *51*, 4934. (h) Muraki, M.; Ubukata, M.; Ito, Y. *Tetrahedron Lett.* **1998**, *39*, 7361.

[84] (a) The Chemistry of Dienes and Polyenes; Rappoport, Z., Ed. Wiley: Chicester, U.K., 1997. (b) The Chemistry of Dienes and Polyenes, 2nd ed.; Rappoport, Z., Ed. Wiley: Chicester, U.K., 2000.

[85] (a) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98. (b) Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*; Wiley: New York, 1990. (c) Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650. (d)

Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668. (e) Lautens, M; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

[86] (a) Backvall, J.-E. Palladium-Catalyzed 1,4-additions to Conjugated Dienes. In *Metal Catalyzed Cross-Coupling Reactions*, 2nd ed.; De Meijere, A., Diederich, F.; Eds.; Wiley-VCH: Weinheim, 2004; pp 479-529. (b) For a recent example, see: Shapiro, N. D.; Rauniyar, V.; Hamilton, G. L.; Wu, J.; Toste, F. D. *Nature* **2011**, *470*, 245.

[87] Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1.

[88] For a recent example of generating molecular complexity from topologically simple olefin starting materials, see: Jui, N. T.; Lee, E. C. Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 10015.

[89] Du, H.; Yuan, W.; Zhao, B.; Shi, Y.; *J. Am. Chem. Soc.* **2007**, *129*, 7496.

[90] (a) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (b) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970. (c) Fraunhoffer, K. F.; Prabagaran, N.; Sirois, L. E.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 9032. (d) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076. (e) Covell, D. J.; White, M. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 6448. (f) Vermeulen, N. A.; Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2010**, *132*, 11323.

[91] (a) Fraunhoffer, K. J.; White, M.C. *J. Am. Chem. Soc.* **2007**, *129*, 7274. (b) Reed, S. A.; White, M.C. *J. Am. Chem. Soc.* **2008**, *130*, 3316. (c) Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11707. (d) Reed, S. A.; Mazzotti, A. R.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11701. (e) Qi, X.; Rice, G. T.; Lall, M. S.; Plummer, M. S.; White, M. C. *Tetrahedron* **2010**, *66*, 4816.

[92] (a) Young, A. J.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 14090. (b) Young, A. J.; White, M. C. *Angew. Chem. Int. Ed.* **2011**, *50*, DOI: 10.1002/anie.201101654 (c) Lin, S.; Song, C.-X.; Cai, G.-X.; Wang, W.-H.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 12901.

[93] (a) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (b) Shimizu, I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons: New York, 2002; pp 1981.

[94] Takacs, J. M. Palladium-Catalyzed Oligomerization and Polymerization of Dienes and Related Compounds, In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons: New York, 2003; pp 1579-1633.

[95] Stang, E. M.; White, M. C. *J. Am. Chem. Soc.* **2011**, "*ASAP"* DOI: 10.1021/ja2059704.

[96] Chung, W.-S.; Wang, J.-Y. *J. Chem. Soc., Chem. Commun.* **1995**, 971.

[97] Greenburg, H.; Gogoll, A.; Bäckvall, J.-E. *Organometallics* **1993**, *12*, 1790.

[98] Tripathy, R.; Franck, R. W.; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257.

[99] (a) The corresponding diene for adduct **43** requires 4 steps while the olefin starting material requires 2, see: Pospísil, J.; Markó, I. E. *Org. Lett.* **2006**, *8*, 5983. (b) The corresponding diene for adduct **46** requires 7 steps, while the olefin starting material requires 1 step, see: Kozikowski, A. P.; Hiraga, K.; Springer, J. P.; Wang, B. C.; Xu, Z.-B. *J. Am. Chem. Soc.* **1984**, *106*, 1845.

[100] Sharma, A. K.; Mazumdar, S. N.; Mahajan, M. P. *J. Org. Chem.* **1996**, *61*, 5506.

[101] (a) Speckamp, W. N.; Newcombe, N. J.; Hiemstra, H.; Ya, F.; Vijn, R. J.; Koot, W.-J. *Pure & Appl. Chem.* **1994**, *66*, 2163. (b) For other expedient routes to gelsemine, see: Earley, W. G.; Jacobsen, J. E.; Madin, A.; Meier, G.

P.; O'Donnel, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 18046 and references therein.

[102] Venard, C.; Boujedaini, N.; Belon, P.; Mensah-Nyagan, A. G.; Patte-Mensah C. *Neuroscience* **2008**, *153*, 154.

[103] Du, X.; Chu, H. V.; Kwon, O. *Org. Lett.* **2003**, *5*, 1923.

[104] Basha, F. Z.; DeBernardis, J. F. *J. Heterocyclic Chem.* **1987**, *24*, 789.

[105] Cesarini, S.; Spallarossa, A.; Ranise, A.; Schenone, S.; La Colla, P.; Collu, G.; Sanna, G.; Loddo, R. *Med. Chem. Res.* **2010**, *19*, 311.

[106] Traditional routes to the corresponding diene of **58** requires 6 steps, compared to 2 steps for olefin **58**, see: Oppolzer, W.; Snowden, R. L.; Simmons, D. P. *Helv. Chim. Acta* **1981**, *64*, 2002.

[107] Frankowski, K. J.; Hirt, E. E.; Zeng, Y.; Neuenswander, B.; Fowler, D.; Schoenen, F.; Aubé, J. *J. Comb. Chem.* **2007**, *9*, 1188.

[108] For selected examples see: (a) Martin, S. F. *J. Heterocyclic Chem.* **1994**, *31*, 679. (b) Baldwin, J. E.; Spring, D. R.; Whitehead, R. C. *Tetrahedron Lett.* **1998**, *39*, 5417.

[109] Vijn, R. J.; Hiemstra, H.; Kok, J. J.; Knotter, M.; Speckamp, W. N. *Tetrahedron*, **1987**, *43*, 5019.

[110] Simpkins, N. S.; Gill, C. D. *Org. Lett.* **2003**, *5*, 535.

[111] Zubkov, F. I.; Ershova, J. D.; Orlova, A. A.; Zaytsev, V. P.; Nikitina, E. V.; Peregudov, A. S.; Gurbanov, A. V.; Borisov, R. S.; Khrustalev, V. N.; Maharramov, A. M.; Varlamov, A. V. *Tetrahedron* **2009**, *65*, 3789.

[112] Hoye, T. R.; Eklov, B. M.; Voloshin, M. *Org. Lett.* **2004**, *6*, 2567-2570.

[113] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[114] Nishimura, T.; Kakiuchi, N.; Onoue, T.; Ohe, K.; Uemura, S. *J. Chem. Soc. Perkin Trans. 1*, **2000**, 1915.

[115] Ferrié, L.; Reymond, S.; Capdevielle, P.; Cossy, J. *Org. Lett.*, **2007**, *9*, 2461.

[116] Cleary, P. A.; Woerpel, K. A. *Org. Lett.* **2005**, *7*, 5531.

[117] Sohn, J.-H.; Kim, K.H.; Lee, H.-Y.; No, Z.S.; Ihee, H. *J. Am. Chem. Soc.* **2008**, *130*, 16506.

[118] Smith, A. B. III; Frohn, M. *Org. Lett.* **2001**, *3*(24) 3979.

[119] Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis Jr., H. R. *Tetrahedron*, **2000**, *56*, 5735.

[120] Bhargava, G.; Mahajan, M. P.; Saito, T.; Otani, T.; Kurashima, M.; Sakai, K. *Eur. J. Org. Chem.* **2005**, 2397.

[121] Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797.

[122] Manteca, I.; Etxarri, B.; Ardeo, A.; Arrasate, S.; Osante, I.; Sotomayor, N.; Lete, E. *Tetrahedron*, **1998**, *54*, 12361.

[123] Gill, C. D.; Greenhalgh, D. A.; Simpkins, N. S. *Tetrahedron*, **2003**, *59*, 9213.