UC Berkeley
UC Berkeley Electronic Theses and Dissertations

Title

Total Synthesis of (+)-Resiniferatoxin and Studies Toward the Total Synthesis of 1-Alkyl Daphnanes

Permalink

https://escholarship.org/uc/item/9497w38m

Author

Spessert, Lukas

Publication Date

2024

Peer reviewed|Thesis/dissertation

eScholarship.org Powered by the California Digital Library
University of California

Total Synthesis of (+)-Resiniferatoxin

and Studies Toward the Total Synthesis of 1-Alkyl Daphnanes

By

Lukas Spessert

A dissertation submitted in partial satisfaction of the
requirements for the degree of
Doctor of Philosophy
In
Chemistry
In
the Graduate Division
of the
University of California, Berkeley

Committee in Charge:

Professor Thomas Maimone, Chair
Professor Felix Fischer
Professor Wenjun Zhang

Spring 2024

Table of Contents

Acknowledgements ii
List of Abbreviations v

Chapter 1. Daphnane Diterpene Orthoesters 1
Chapter 1.1. Resiniferatoxin & Gnidimacrin, Biosynthesis and Related Natural Products 2
Chapter 1.2. Bioactivity of Resiniferatoxin, Gnidimacrin and selected DDOs 5
Chapter 1.3. Previous Syntheses and Studies Toward DDOs and Related Diterpenes 7
Chapter 1.4. Retrosynthetic Analysis of Resiniferatoxin and Potential Entry to Related Daphanes 16

Chapter 2. Total Synthesis of Resiniferatoxin, Asymmetric Synthesis & Studies Toward Gnidimacrin. 22
Chapter 2.1. Synthesis of 5/7-fused bicycle 2.1.10 23
Chapter 2.2. Elaboration of the 5/7-fused System to Arrive at a Suitable Aldol Partner. 24
Chapter 2.3. Synthesis of Aldehyde Fragment for Aldol Reaction 26
Chapter 2.4. Completion of Tricycle Synthesis 26
Chapter 2.5. Installation of the Orthoester and Completion of the Total Synthesis of Resiniferatoxin 28
Chapter 2.6. Asymmetric Entry into the Daphnanes
Chapter 2.7. Synthetic Efforts toward Gnidimacrin and Other Highly Oxygenated DDO's 29
Chapter 2.8. Conclusion 33
Chapter 2.9. Distribution of Credit 33
Chapter 2.10. References 34
Chapter 2.11. Experimental Procedures 35

Apendix – NMR Spectra 66

Acknowledgements:

Prof. Tom Maimone: Dear Tom, first of all thanks a lot for having me join your group for my PhD after my stint in your lab as a visiting scholar! I truly appreciate the creative and hardworking spirit you installed in your research lab, and it helped me a lot becoming a better chemist as well as helping me grow as a person. I know we didn't always saw eye to eye but I'm more than happy to end my time here on a good note! I wish you all the best on your journey back to benching three plates and I will let you know!

Prof. Felix Fischer & **Prof. Wenjun Zhang**: I want to thank both of you for serving on my qualifying exam committee and my PhD thesis committee. The qual helped me level up my game!

909 Dwellers – past and present:
Kuan: Dear Kuan, thanks for always being such a kind and helpful person! It was a great time working together with you in 909 and you really showed me what hard work and dedication means! Without you we wouldn't have been able to finish RTX! I wish you all the best for your future career and I hope to read some of your works in the future!
Kincade: Even though you joined the 909 gang late it was always a pleasure having you in the room! You always have a very rational and refreshing view on things, which I appreciate a lot. I got my fingers crossed for your synthetic journey as well as for the gym endeavors!
Danny Thach: I owe you a lot of gratitude! You were always looking out for me, making sure I am becoming better by the day. I truly appreciate your tough love and I deeply believe you will make it very far in life! You are a natural born leader that leads by example and I'm grateful for the time we shared together! I wish you and Rachel all the best for the future!
Bill: I know we only shared a short time together in 909 but I had a good time working next to you! I wish you all the best for the future and always keep your goal in mind, especially if times get rough.
Vasil: Our journey had its up and downs and didn't end the way we both intended to, but I appreciate the lessons learned on the way and I want to thank you for that. I hope you're doing well, and good things will come your way.

Maimone Lab Members – past and present:
Rachel: I always enjoyed our talks during our time together! You always being able to be kind and good spirited no matter the circumstances left a lasting impression with me! I wish you and Danny all the possible best for the future!
Claire: Despite not having interacted a lot with each other, I was always impressed by your work ethic and dedication to chemistry!
Linus: I appreciate your honest ways and that you were always up to have conversations about almost any topic! Fingers crossed for you and your company!
Bingqi: I truly admired to drive when it came to synthesis while still being able to always keep a smile on your face! All the best for your future!
Andre: I want to thank you for all the conversations we had and for letting everyone around you be themselves. You're a very unorthodox thinker, which I enjoyed witnessing firsthand. I got my fingers crossed for your future career in academia!

Martin: Albeit sharing only a short stint together, it was nice having another fellow German in the group when starting out here. All best best in Vienna and have fun bouldering!
Mikiko: Thanks for bringing a fresh wind into the group when you joined! I enjoyed our conversations and funny interactions we had in lab! All the best for your professionally and personally!
Jordan: You were such a kind and warmhearted when I first joined the lab, and I was really glad seeing that you kept your kindness when you visited! All the best for your synthesis!
Tanner: Thanks for always being yourself and letting me be myself around you. I will miss the fun times we had talking about everything from serious to absurd topics! You're one of the few people that figured out life early on! I wish you all the best for the future and I know you'll be fine off!
Beth: Thanks for always being such a fun and easygoing person in the lab! I know you'll have a great time at Gilead! I already know that you're gonna be a regular at the gym there!
Yi: I think we basically always put up your route up for bootcamp. I'm glad you also joined the Maimone Gym Gang in the end! All the best for your chemistry and gains!
Danny: I was happy seeing you sharing one of my past passions! Glad we got you on the Gym Team and may the Howl go further up in value!
Shang: I was always impressed by your work ethic but got even more impressed seeing your dedication when it comes to the gym and dieting! I have my fingers crossed for your first wheightlifting competition!
Kelvin: Thanks for always being yourself! I enjoyed your passion for antibiotics and for you always making sure we get to learn more about those fascinating molecules.
Vanessa: Your baking skills made the experience here a lot more delicious! Keep your nice and welcoming way! All the best for your future!
Katerina: I was glad that you joined our group and are offering different perspectives! Fingers crossed for your molecule!
Collin: I still remember the day we met at recruitment, and I knew right away you would be an awesome addition to the lab! Enjoy the ride and don't forget to relax.
Adam: You moved from Indiana to California, and I will be moving from California to Indiana, seems like a nice swap. Good luck with your project!

Parents, Friends and Mentors:
Bilal: Ich bin unglaublich dankbar dich direct im ersten Semester an der LMU kennengelernt zu haben. Wir haben beide zusammen ne Menge erlebt und sind sowohl wissenschaftlich, aber noch wichtiger, persönlich enorm gewachsen. Wir kennen uns jetzt einfach schon seit mehr als 10 Jahren und ich freue mich schon enorm Ende des Jahres zu feiern, dass du deine Zeit bei Erick überlebt hast! Ich bin stolz dich einen treuen Freund nennen zu können, ohne den dieser Weg wahrscheinlich niemals solche Wendungen genommen hätte. Danke für alles!
Christina: Dear Christina, I am more than happy that we two had overlapping office hours in your first year and that this developed into a real friendship! You've seen me fall of the roof, you've seen my highs and lows and always supported me throughout my journey with everything! You helped me to become a better version of myself, helped me get an IRA, a credit score and even more that I can't list here. I deeply appreciate your honesty and ability to also point out uncomfortable truths! I wish you all the best and I know you will do great in life!

Suh: Ich danke dir für deine offene und herzliche Art! Ich erinnere mich noch daran als wir uns das erste mal in Chem300 unterhalten haben und ich direkt von deiner Einstellung in Sachen Work Ethic mehr als beindruckt war! Dein Geschmack ist auch erste Sahne wenn es um die Wahl deiner Lieblingsfahrer und Teams in der Formel 1 geht! Ich drücke dir weiterhin die Daumen für deine Zukunft! Mögen deine Reaktionen klappen, sowie Liverpool and Carlos bald die Meisterschaft gewinnen!
Alex: Wir hatten echt ne gute Zeit in München und ich habe mich sehr gefreut zu sehen wie du dich über die Zeit sowohl als Chemiker aber auch als Mensch entwickelt hast! Ich drücke dir die Daumen für dein Abenteuer hier in den Staaten! Bist immer gerne willkommen!
Rakan: Ich erinnere mich noch genau wie ich damals mit 15 Jahren mit deinem Vater zusammengearbeitet habe und dann Jahre später wir zusammen am gleichen Campus studiert haben! Du hast dich gut entwickelt und ich freu mich schon dich nächsten Mal wieder zu sehen wenn ich nach Europa komme!
Julius: Oh boy, it's been a while since we first met! I knew we would get along when I saw Fernando Alonso's F1 car on your desk! Thank you for treating me like a brother and teaching me a ton of things during our time in Munich! You put me on the right track and without you I wouldn't have made it so far! I'm really excited for your wedding, and I know we'll be enjoying a Formula One race in person after having watched like two seasons in lab together!
Héloïse: Thanks for the great time we had together in the Bay exploring all the culinary variations this place has to offer! I wish you all the best for your remaining time in the PhD with Erick, I know it can be a lot, but you have what it takes!
Stefan: Ohne dich wäre 805 einfach nicht der selbe Ort gewesen. Ich bin sehr froh dich während des Großteils des PhDs hier gehabt zu haben und ich freu mich schon dich demnächst in Deutschland zu besuchen! Die Runde Bacardi Cola geht dann auf mich, wenn du die Mische machst. Ich wünsche dir und Elena das
Jonas: Ich hab mich sehr gefreut hier deine Bekanntschaft gemacht zu haben. Deine ehrliche authentische Art fand ich immer sehr ansprechend und ich bin mir sicher, dass dir diese Attribute in deiner independent career enorm zu gute kommen werden! Ich freu mich schon darauf dich dann an der NYU zu besuchen!
Mama, Papa und Leon: Ohne euch wäre das alles nie möglich gewesen! Ich bin euch unendlich dankbar für alles was ihr für mich getan habt! Es war nicht immer einfach mit mir, aber ich bin froh am Ende des Tages immer zuwissen dass ihr mich unterstützt! Ich freu mich schon euch bald hier zu sehen, euch ein wenig die Gegend zu zeigen und mal zu mir nach Indy einzuladen!

List of Abbreviations

Ac	acetate
AIBN	azobisisobutyronitrile
AZADO	2-azaadamantane, N-Oxyl
AZADOL	N-hydroxy 2-azaadamantane
Bn	benzyl
BTC	(bis(trichloromethyl) carbonate
Bz	benzoyl
CSA	Camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DIBAL	diisobutyl aluminum hydride
DIPEA	N,N-Diisopropylethylamine
DBAD	di-*tert*-butyl azodicarboxylate
DIPT	Diisopropyl tartrate
DMAP	dimethylamino pyridine
DMDO	Dimethyldioxirane
DMF	N,N-Dimethylformamide
DMP	Dess-Martin Periodinane
DMS	dimethyl sulfide
DET	Diethyl tartrate
DMSO	dimethyl sulfoxide
EDC	N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide
ee	enantiomeric excess
fod	6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato
HG-2	Hoveyda-Grubbs 2nd generation catalyst
HIV	Human immunodeficiency virus
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
IBX	2-iodoxybenzoic acid
Imid	imidazole
LAH	lithium aluminum hydride
LDA	lithium diisopropylamine
m-CPBA	*meta*-chloroperoxybenzoic acid
MeCN	Acetonitrile
Ms	Methansulfonyl
MSTFA	N-methyl-N-(trimethylsilyl)trifluoroacetamide
NBS	*N*-bromosuccinimide
NMO	N-methylmorpholine N-oxide
ODCB	1,2-dichlorobenzene
Ph	phenyl
PIDA	(diacetoxyiodo)benzene
TES	triethylsilyl

PMHS	polymethylhydrosiloxane
PMP	1,2,2,6,6-pentamethylpiperidine
Ppm	parts per million
PPTS	pyridinium p-toluenesulfonate
Pyr	pyridine
SEM	2-(trimethylsilyl)ethoxymethyl
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TCBC	2,4,6-trichlorobenzoyl chloride
TCDI	thiocarbonyldiimidazole
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
TPP	tetraphenyl porphyrin
TsOH	*p*-Toluenesulfonic acid
V-40	1,1'-azobis(cyclohexanecarbonitrile)

Chapter 1.
Daphnane Diterpene Orthoesters
Background, Significance, Biological Profile and Retrosynthetic Analysis

1.1 *Resiniferatoxin & Gnidimacrin: Biosynthesis and Related Natural Products*

Resiniferatoxin (RTX, **1.1.1**, Figure 1.1.1) belongs to the family of daphnane diterpene orthoesters (DDO's), a structurally and biologically very diverse subfamily of the daphnane diterpene natural products of with over 200 members have been isolated to date[1,2]. RTX was isolated and characterized in 1975 by Hecker *et al.* from the fresh latex of *Euphorbia resinifera*[3]. This spurge plant is native to the Morrocan Atlas Mountains and was discovered by King Juba of Mauretania, naming it "Euphorbia" after his personal physician Euphorbus, according to the roman author Pliny the Elder. The resin obtained from drying said fresh latex was referred to as "Euphorbium" and has been used to treat pain for over 2000 years.[4] Structurally, RTX exhibits a 5/7/6-fused tricyclic core, in which all the rings are joined in a *trans* fashion. Three of the seven contiguous stereocenters make up the characteristic orthoester moiety, tying together the hydroxygroups on C-9, C-13 and C-14.[5] A unique feature of resiniferatoxin is its homovanillic ester attached to the oxygen on C-20. Despite being the flagship molecule of the daphnanes, RTX is one of the least oxidized daphnanes known. Other family members usually share additional oxidation on C5, C6 and C7. DDO's containing an epoxide on C6 and C7 form the subfamily of the so called 6-epoxydaphnanes members of which include kirkinine (**1.1.3**),[6] maprouneacin (**1.1.4**),[7] yuanhuapin (**1.1.5**)[8] and trigocherrin A (**1.1.7**)[9] as shown below. It is also possible for daphnanes to exhibit differing oxidation pattern at C6 and C7, for example the *trans* diol present in yuanhuaoate B (**1.1.2**)[10] or the ether bridge between C4 and C6, forming an oxetane found in trigonostempene B (**1.1.6**).[5] Other common sites of additional oxidation are C15 and C18, found for example in maprouneacin (**1.1.4**), together with C12 oxidation with varying stereochemistry. Said oxygen atoms found at C12 can also be part the orthoester as in trigonostempene B (**1.1.6**) thus having an orthoester tying together the C12, C13 and C14 oxygens thereby further increasing the overall structural diversity of the family of DDO's by "shifting" the hallmark orthoester moiety most commonly formed between the C9, C13 and C14 oxygens. Additionally, trigocherrin A (**1.1.7**) stands out not only by its orthoester, but by also being the first chlorinated terrestrial

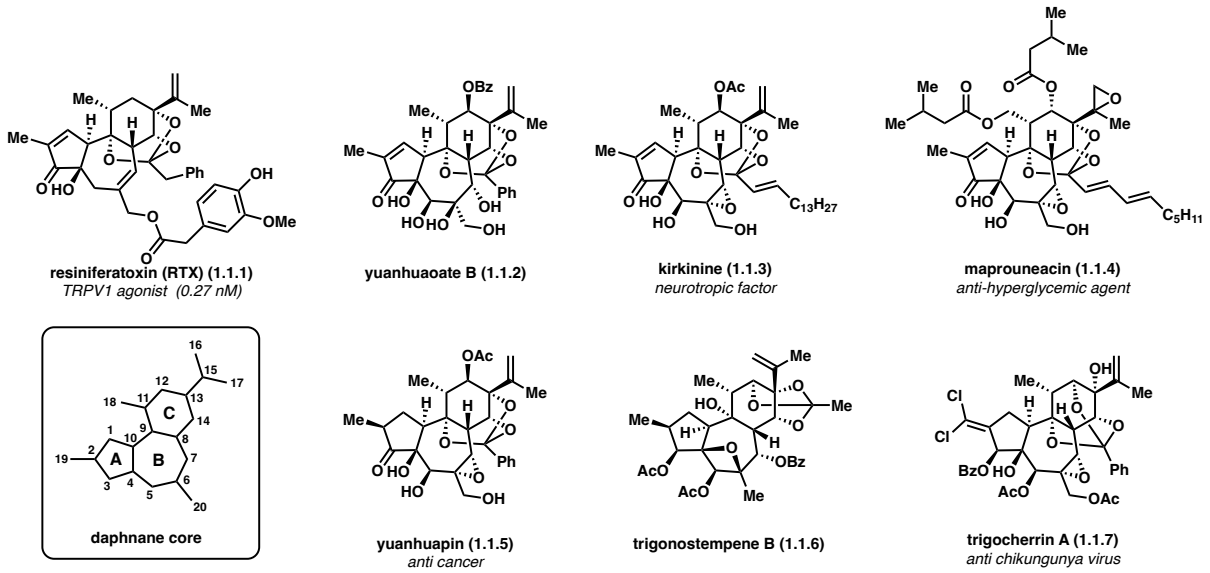


Figure 1.1.1. Structures of resiniferatoxin, selected DDO's and the general daphnane diterpene core together with selected biological activities.

diterpene. Its dichloromethylene motif has been proposed to arise from a series of sequential radical chlorinations carried out by a non-heme iron enzyme, followed by an elimination to afford this unique functional group on the A-ring of the molecule.

Nature further increases the structural complexity of the DDO family by attaching a carbon chain from the orthoester onto the 5-membered ring of the tricyclic core ultimately forming a large macrocyclic belt. If this carbon chain is attached to the α-face of the C1 position of the daphnane core, molecules are deemed 1-alkyldaphnanes, with gnidimacrin (**1.1.8**) being the flagship member.[11,12] Usually, this chain consists of 10 carbon atoms of which only 9 make up the additional ring, resulting in a stereocenter adjacent to the to A-ring. This center can either have (*R*)- or (*S*)- configuration, like in gnidimacrin (**1.1.8**) and wikstroelide K (**1.1.10**)[5], respectively. Pimelotide A (**1.1.12**)[13] not only features the same (*S*)-configurated methyl stereocenter on its carbon tether but also an unprecedented bicyclic ketal-lactone in place of the usual 5-membered A-ring of the daphnane core, serving as another example of the fascinating structural diversity showcased by diterpenes from the plant families *Thymelaeaceae* and *Euphorbiaeace.* Other than the 1-alkyldaphnanes, the macrocyclic belt spanning the terpene sector in the rediocides is a macrolactone appended to the C16/C17 position of the daphnane core as well as the *β*-face of the oxygen found on C3.[14] Rediocide A (**1.1.9**), the hallmark structure for this subfamily of DDO's, exhibits a highly decorated macrocyclic belt of high structural complexity and unknown biosynthetic origins as compared to the related 1-alkyldaphnanes. Structural motifs found in the rediocide macrolactones range from higher degrees of unsaturation, accompanied by the incorporation of 3-, 5-, or 6-membered ring to a fully saturated ring with only two stereocenters, like in trigonolactone B (**1.1.11**).[15] Another shared structural feature among this subclass of natural products is the different orthoester connectivity (i.e. C9, C12, C14) compared to its less complex relatives in which the orthoester is connected to the C9, C13 and C14 hydroxyl groups. The incredibly diversity of DDO structures also leads to broad and variable biological activities, from anticancer and anti-HIV properties to insecticidal activity; these features will be discussed in more detail later.

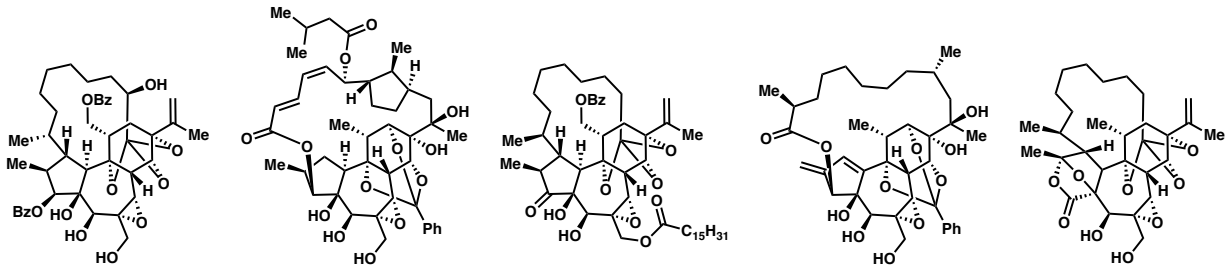


Figure 1.1.2 Selected examples of 1-alkyldaphnanes and rediocide-type macrocyclic DDO's

During the process of isolating natural products from *Thymelaeaceae* and *Euphorbiaeace*, researchers usually isolate compounds from a family of secondary metabolites related to the daphnanes. Those diterpenes also featuring a 5/7/6-tricyclic core, with similar oxidation patterns and the characteristic *trans* ring junctions. What sets them apart from the daphnanes, and more specific from the DDOs, is an additional bond between C14 and C15, making up the extra carbocycle of the molecule, while also being devoid of the DDOs characteristic ortho ester moiety. The molecules are known as tiglianes and have been heavily studies from a synthetic and medicinal perspective. This cyclopropane usually features an attached tertiary alcohol at C13 that is acylated

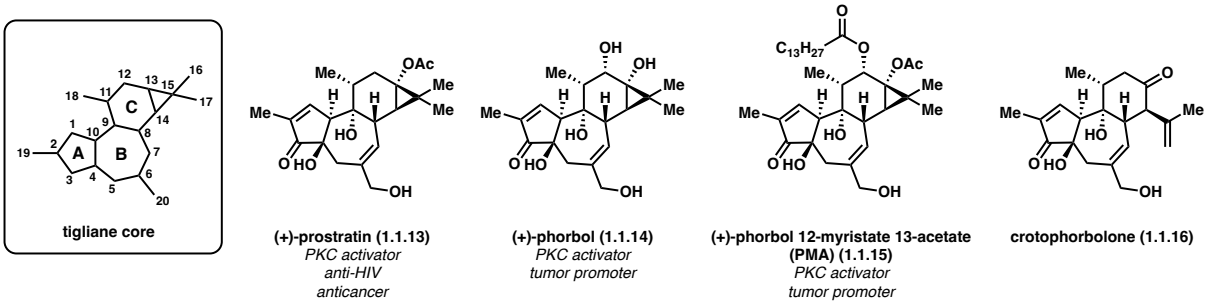
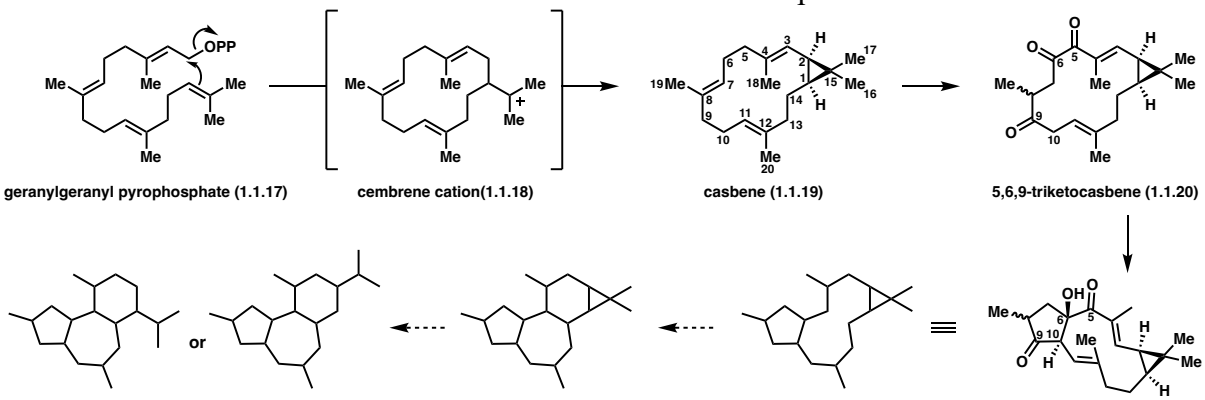


Figure 1.1.3. Selected tiglianes, crotophorbolone and general tigliane core

in the case of (+)-prostratin (**1.1.13**).[16] (+)-Phorbol (**1.1.14**)[17,18] being the most investigated tigliane possesses a free alcohol at C13 as well as another free alcohol at C12, while its most common diester, (+)-phorbol 12-myristate 13-acetate (**1.1.15**)[19] have both alcohols acylated, yet both exhibit similar biological activity acting as tumor promoters. Crotophorbolone (**1.1.16**)[17] neither falls into the category of being a daphnane or tigliane but being the most prominent member of the rhamnofolanes. This class of natural products also shares the *trans*/*trans* 5/7/6 fused tricyclic core but instead of a cyclopropane found in the tiglianes, crotophorbolone features an isopropenyl group at C14 as well as a ketone on C13.

These close structural similarities between the families of daphnanes, tiglianes and rhamnofolanes are most likely attributed to a proposed common biosynthetic pathway leading to the formation of those three different classes of natural products.[20] It is proposed that the biosynthesis of those diterpenes isolated from *Thymelaeaceae* and *Euphorbiaeace,* starts with the enzyme catalyzed cyclization of geranylgeranyl pyrophosphate (**1.1.17**, Scheme 1.1.1), forming the intermediate cembrene cation (**1.1.18**) which is ultimately converted by a series of hydride shifts into the macrocyclic diterpene casbene (**1.1.19**) with the *gem*-dimethylcyclopropane found in the tiglianes already formed.[21] A series of oxidations, most likely performed by cytochrome enzymes, leads to the formation 5,6,9-triketocasbene (**1.1.20**) thereby installing functional handles necessary for the formation of new C-C bonds. This was achieved by transannular aldol reaction connecting C10 and C6 thus forming jolkinol C (**1.1.21**)[22] together with its C8 epimer, both exhibiting the lathyrane skeleton. This serves as an extra point of evidence for the common biosynthetic pathway going through casbene, since lathyrane diterpenes are usually isolated from *Thymelaeaceae* and *Euphorbiaeace* together with daphnanes and tiglianes. From the lathyrane skeleton only one more transannular bond formation is needed to form the tigliane core. Breaking the C14-C15 bond or the C13-C15 bond delivers the daphnane- and rhamnofolane core,



Scheme 1.1.1 Biosynthesis of jolkinol C & proposed biosynthesis of daphnane, tigliane and rhamnofolane diterpenes.

respectively. All the steps after the formation of jolkinol C are hypothesized, enzymes and other intermediates on that pathway have yet to be identified.

1.2 *Bioactivity of Resiniferatoxin, Gnidimacrin and selected DDO's*

The distinguishing homovanillic moiety of resiniferatoxin sets it apart from other DDO's and contributes to its unique bioactivity. This structural characteristic is also shared by capsaicin (Figure 1.2.1, **1.2.1**), the active compound found in chili peppers. Like capsaicin, Resiniferatoxin (RTX) exhibits strong binding affinity to the transient receptor potential cation channel subfamily V member 1 (TRPV1), a receptor involved in the perception of heat and pain in humans.[23,24,25] RTX exhibits a binding affinity found to be orders of magnitude stronger than capsaicin, rendering it the spiciest molecule known to mankind. The analgesic effects of RTX stem from its activation of TRPV1, which leads to calcium influx into cells, ultimately resulting in calcium-induced cell death. This mechanism disrupts pain signal transduction pathways, thereby offering relief from pain. This necrosis only affects TRPV1-expressing neurons, creating a long-lasting analgesic effect until after a couple of weeks the neurons regrow while preserving other nerve driven functions such as motor control and pressure sensing.[26] Importantly, this mode of action differs from that of morphine derivatives, which target opioid receptors. As a result, resiniferatoxin is not expected to produce habit-forming effects or respiratory depression, making it a potentially safer alternative to opioids amidst the ongoing opioid epidemic.[27] Furthermore, research suggests that TRPV1 may interact with the μ-opioid receptor (MOR1) and inhibit opioid-dependent phosphorylation.[28] This inhibition disrupts the β-arrestin pathway, which is implicated in various opioid-related side effects such as tolerance development and respiratory depression. The combination of TRPV1 activation and its orthogonal mechanism of action for the analgesia suggests that RTX could serve as a safer alternative to opioids and a valuable tool in addressing the challenges of opioid misuse and addiction.[29] In summary, RTX's unique structural features and mechanism of action position it as a promising candidate in combating pain with reduced risk of addiction and adverse effects compared to traditional opioids. Further research into its therapeutic potential and safety profile could offer new avenues for pain management and contribute to addressing the opioid epidemic.

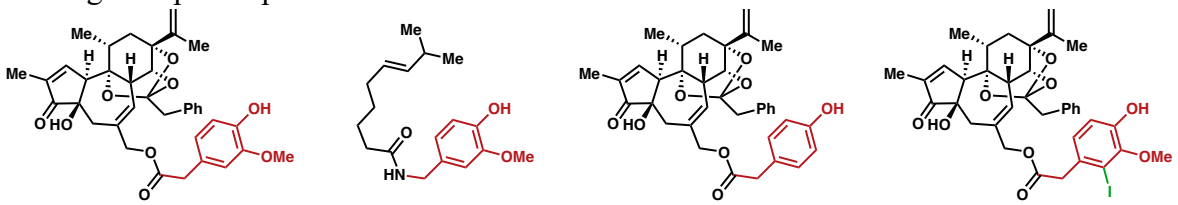


Figure 1.2.1 Stuctures of resiniferatoxin and related bioactive compounds.

Structure-activity relationship (SAR) investigations have yielded crucial insights into the molecular determinants underlying the extraordinary potency of RTX. These studies have underscored the indispensability of the daphnane diterpene core and its pendant orthoester for resiniferatoxin's pronounced pharmacological activity.[30-34] Notably, SAR analysis have revealed that while variations in the orthoester sidechain have minimal effects on its activity toward binding to TRPV1, the presence of the orthoester motif itself is imperative for the ensuring the potent binding affinity. This assertion is supported by the diminished potency observed in the structurally closely related tiglianes in which a homovanillic acid ester at C20 was attached. Furthermore, the

oxidation at C3 plays a crucial role in resiniferatoxin's bioactivity by potentially serving as an additional hydrogen bond acceptor. Another noteworthy example from SAR investigations includes tinyatoxin (**1.2.2**),[35] a DDO only varying in lacking the methoxygroup found in RTX, resulting in three times lower potency than resiniferatoxin. In contrast, iodo-RTX (**1.2.3**)[36] exhibits an additional iodine atom on the aryl ring of the homovanillic part of the molecule, resulting in acting as an TRPV1 antagonist. Although treatment with RTX leads to a loss of heat sensation due to TRPV1 involvement, its enduring analgesic effects and neuronal selectivity have positioned it as a promising alternative to opioid-based therapies for chronic pain management. Resiniferatoxin's clinical potential is currently under exploration in Phase II trials for pain management in advanced cancer and knee arthritis patients, with the FDA granting Orphan Drug Status for its use in intractable cancer pain, highlighting the compelling pharmacological attributes of this DDO.

In contrast to resiniferatoxin, most DDO's lack the homovanillic ester sidechain attached to C20 and therefore exhibit generally low binding affinities for TRPV1. Having a free hydroxyl group at C20 allows the DDO's to engage with different protein classes, thereby showcasing the incredibly diverse biological activities of their family of natural products. Of particular interest are their interactions with a variety of protein kinase C (PKC) isoforms, resulting in anti-viral, neuroprotective, and especially anticancer activities.[37,38] Despite the majority of PKC activators featuring a free hydroxyl group at C20, resiniferatoxin interacts with PKC, most likely due to hydrolysis of the homovanillic ester under physiological conditions.[39] The structural resemblance of DDO's and tigliane esters to diacylglycerols (DAGs), PKC cofactors, suggests a mechanism where the hydroxyl group at C20 mimics DAGs' free hydroxyl moiety, while ester side chains emulate the DAG lipid tails. These interactions likely involve hydrogen bonding with PKC C1 subunits and hydrophobic anchoring to cell membranes, exposing the catalytic domain of PKC for overall activation.[40,41] Gnidimacrin exemplifies this phenomenon by inhibiting leukemia K562 cell growth via PKC activation, particularly involving the βII isoform crucial for its sub-nanomolar antitumor activity.[42] Additionally, through its activation of PKC, gnidimacrin triggers downstream signaling cascades that modulate the transcription factors such as nuclear factor kappa B (NFκB) and activator protein 1 (AP-1), which are involved in the regulation of HIV gene expression. PKC activation by gnidimacrin can trigger the phosphorylation and subsequent activation of transcription factors crucial for HIV gene expression and replication. Moreover, this process may influence various cellular components involved in HIV infection dynamics. For instance, PKC activation has been linked to the reactivation of latent HIV reservoirs within infected cells, potentially rendering them more susceptible to antiretroviral therapy. Additionally, PKC-mediated signaling pathways could modulate the expression of cell surface receptors and co-receptors pivotal for HIV entry into target cells, as well as the intracellular trafficking of viral components throughout the viral life cycle. Rediocide A (**1.1.9**)[14] exhibits a variety of fascinating biological activities like anticancer, antitoxin against cobra venom as well as being an outstandingly potent insecticide. This can be attributed to its PKC activation and accompanying desensitization of *Methuselah* (Mth) G-protein coupled receptors (GPCR) involved in the stress response and biological aging in *Drosophila.* Furthermore, rediocide was found to exhibit specifically outstanding activity against mosquito larvae and fleas (*Ctenocephalides felis*) with LD_{90} values of 1 and 0.25 ppm respectively, potentially rendering rediocide A a powerful tool for combating malaria and other vector-borne diseases.

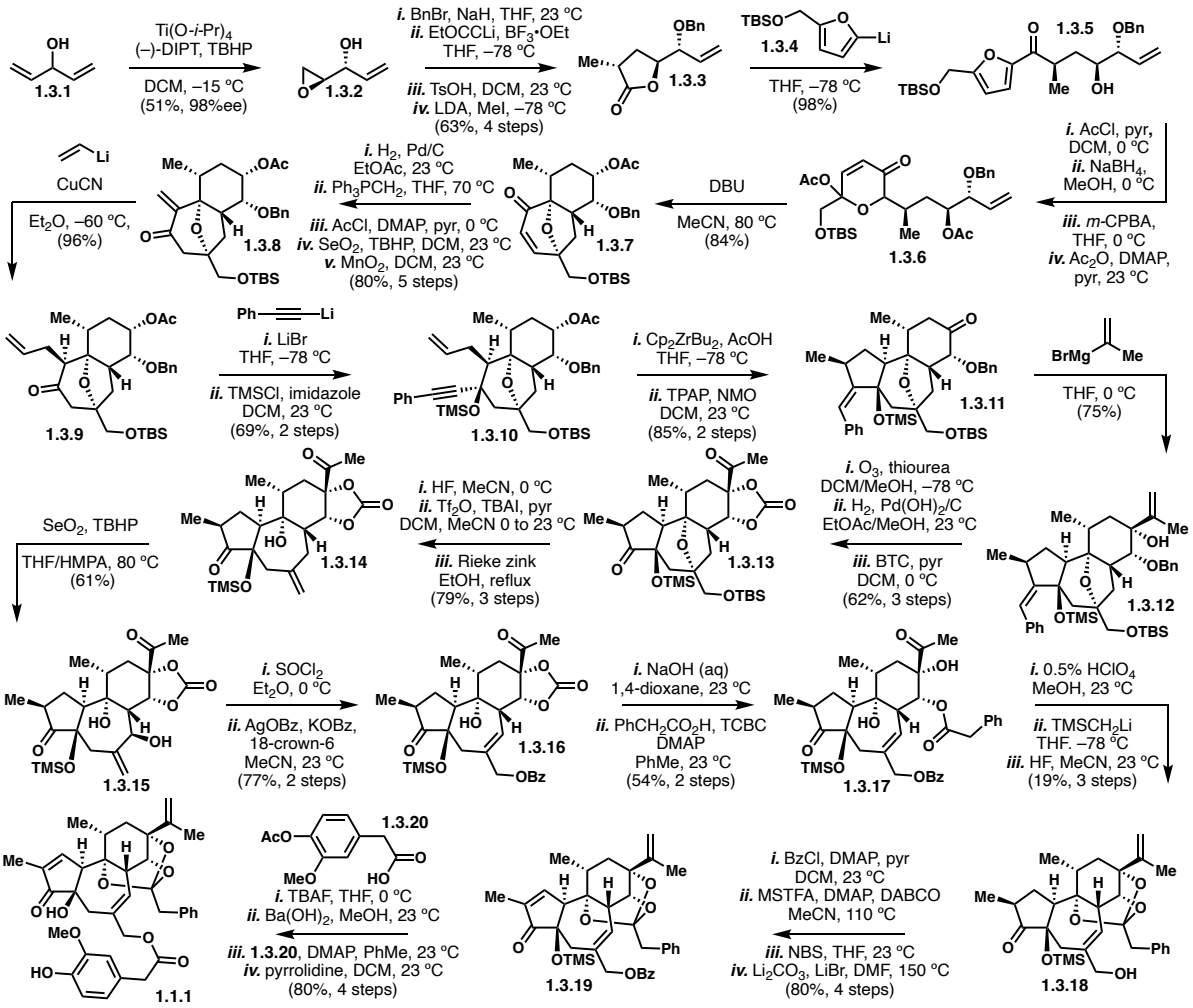
1.3 *Previous Syntheses and Studies Toward DDOs and Related Diterpenes*

The significant level of oxidation present within the stereochemically dense carbocyclic cores of the daphnanes, paired with their intriguing biological activities, has garnered considerable attention from both synthetic chemists and researchers in the field of biology. Despite extensive efforts, only resiniferatoxin and tinyatoxin have thus far been successfully synthesized among the DDOs. This chapter will thoroughly examine the initial synthesis of RTX by the Wender lab[43] and the first route by Inoue and coworkers,[44] along with their subsequent developments in their second-generation route to resiniferatoxin and related natural products.[45] Moreover, the impressive attempt of Wender and coworkers to obtain yuanhuapin through total synthesis,[46] Fu and Liu's progress toward a highly oxygenated core that maps onto the daphnanes,[47] and Inoue's work on the synthesis of multiple of structurally intricate tilgianes[48] will be discussed. These endeavors offer invaluable insights that may hold implications for the synthesis and understanding of closely related daphnanes.

While initially isolated in 1975, the first successful synthesis of RTX was not published until 1997, by the group of Paul Wender and coworkers.[43] Their synthesis commenced with a Sharpless asymmetric epoxidation of divinyl carbinol **1.3.1** yielding epoxy alcohol **1.3.2** followed by benzylation of the secondary allylic alcohol. Addition of the lithiate of ethoxyacetylene to the epoxide followed by treatment with TsOH resulted in the formation of the desired lactone, which was methylated stereoselectively to afford γ-lactone **1.3.3**, and thereby setting the methyl stereocenter of the 6-membered ring of RTX. Ketone **1.3.5** was obtained by the addition of lithiate **1.3.4** to lactone **1.3.3**. Acylation of the remaining free alcohol and reduction of the ketone were followed by an Achmatowicz rearrangement which, after acylation, then provided dihydropyran **1.3.6**. Upon heating with DBU in MeCN, **1.3.6** engaged in a [5+2] oxidopyrilium cycloaddition forging bicyclic enone **1.3.7**, thereby accessing the 7/6 bicyclic ring system of RTX in 11 steps. The next goal in Wender's synthetic endeavor was to complete the tricyclic core of the natural product by construction of the A-ring of the molecule. Hydrogenation, Wittig-Olefination and re-acylation were followed by allylic oxidation and MnO_2 mediated oxidation of the secondary alcohol to afford exocylic enone **1.3.8**. Conjugate addition of vinyl lithiate appended the two carbon atoms required for the the construction of the A ring, as well as correctly setting the stereocenter in tricycle **1.3.9**. Addition of lithium phenyl acetylide to the ketone ensured the desired *trans* stereochemical relationship required to construct the 5-membered ring of the target compound. Silylation of the newly formed tertiary alcohol afforded **1.3.10** thereby setting the stage for the formation of the A-ring. Assembly of the 5-membered ring proceeded through zirconocene mediated enyne cyclization of **1.3.10** followed Ley-oxidation to arrive at tetracycle **1.3.11**, affording the 5/7/6 ring system of the daphnane skeleton. Grignard addition to the ketone proceeded from the desired face, thereby installing the isopropenyl group in **1.3.12** which was inadvertently converted into the corresponding methyl ketone during global oxidative cleavage in an effort to unveil the ketone of the A ring. Hydrogenolysis of the benzyl group and carbonate formation then gave rise to diketone **1.3.13**. Selective desilylation of the primary TBS group was followed by transformation of the resulting primary alcohol to the corresponding iodide. Subsequent treatment with Rieke zink resulted in fragmentation of the ether bridge to furnish the tertiary hydroxyl group on the 7,6-fused ring junction, affording exocyclic olefin **1.3.14**. Allylic alcohol **1.3.15** was obtained by SeO_2 mediated allylic oxidation. This newly generated alcohol was converted into its corresponding allylic chloride which served as a functional handle for the transposition to install the desired oxidation of a C20 affording **1.3.16**. The carbonate was removed

using aqueous NaOH unveiling all three hydroxy required for installing the ortho ester motif. Yamaguchi esterification with phenylacetic acid then gave orthoester precursor **1.3.17**.

Scheme 1.3.1. Total synthesis of resiniferatoxin by Wender and coworkers.

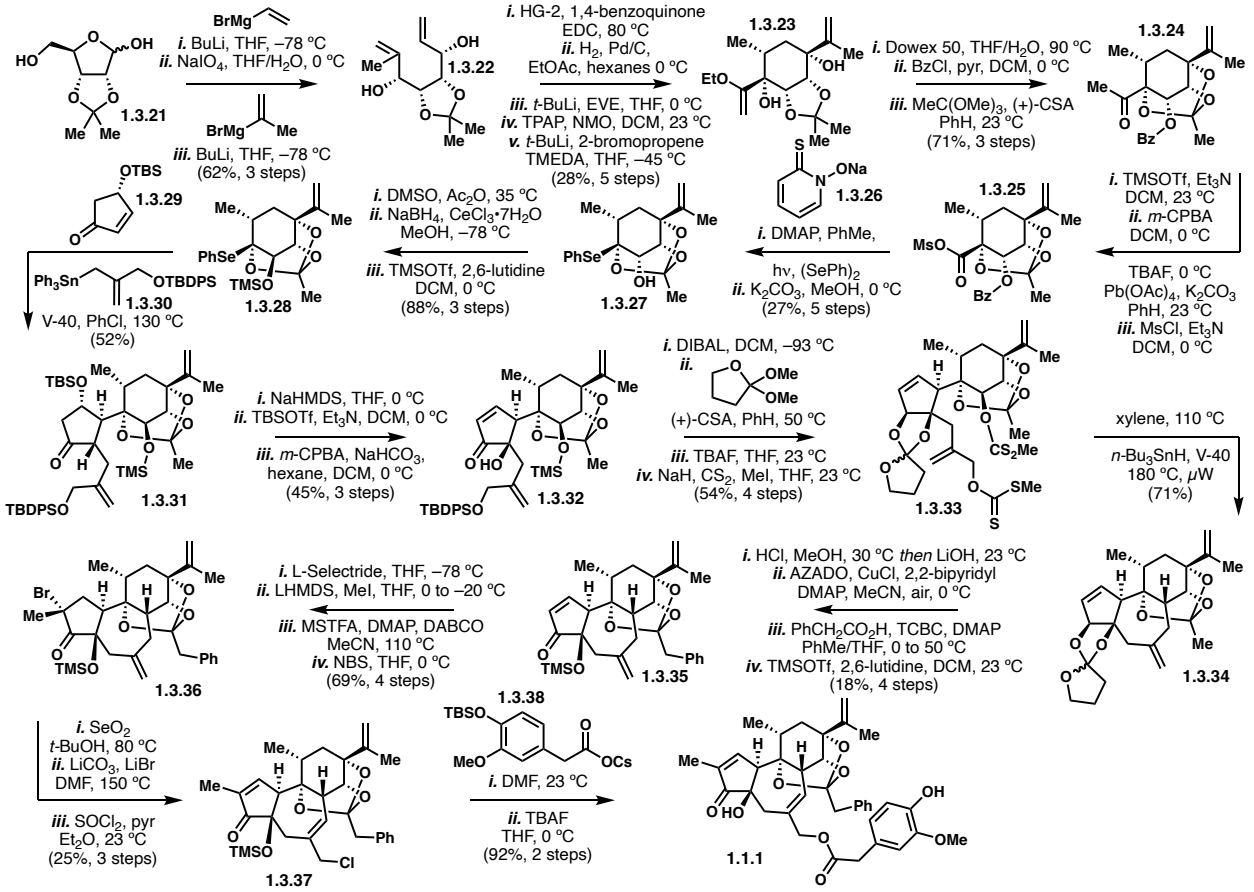


Treatment with dilute perchloric acid in MeOH furnished the desired orthoester moiety, followed a two-step Peterson olefination, restoring the isoprenyl group and affording orthoester **1.3.18** thereby completing daphnane core. The primary alcohol was re-benzoylated before the ketone on the A-ring was converted into the corresponding silyl enol ether, the newly formed silyl enol ether treated with NBS. The resulting bromide was then eliminated to afford cyclopentenone **1.3.19**. Global silyl group deprotection was achieved using TBAF, and following methanolysis of the benzoyl group, a Steglich esterification using acetylated homovanillic acid **1.3.20** and subsequent cleavage of the acetyl group completed the first synthesis of RTX in 44 steps.

It was not until 20 years later that the second total synthesis of resiniferatoxin was disclosed by the Inoue group.[44] In contrast to Wender's effort, Inoue and coworkers leveraged radical chemistry to construct the carbocyclic framework of RTX from chiral pool starting materials. Inoue's sequence begins with vinyl Grignard addition to (*D*)-ribose **1.3.21**. The resulting diol was oxidatively cleaved to the corresponding aldehyde which was in turn subjected to isopropenyl

Grignard addition affording allylic diol **1.3.22**. Ring closing metathesis forged the 6-membered of the natural product, followed by heterogeneous hydrogenation which not only correctly set the key methyl-containing stereocenter, but also led to oxidation of the adjacent alcohol at C9. Lithiated ethyl vinyl ether was then added to the newly generated ketone and the remaining alcohol was transformed into the corresponding ketone by Ley oxidation. Installation of the isoprenyl group by 1,2-addition led Inoue and coworkers to obtain densly functionalized cyclohexanol **1.3.23**.

Scheme 1.3.2. Inoue's first-generation route to resiniferatoxin.

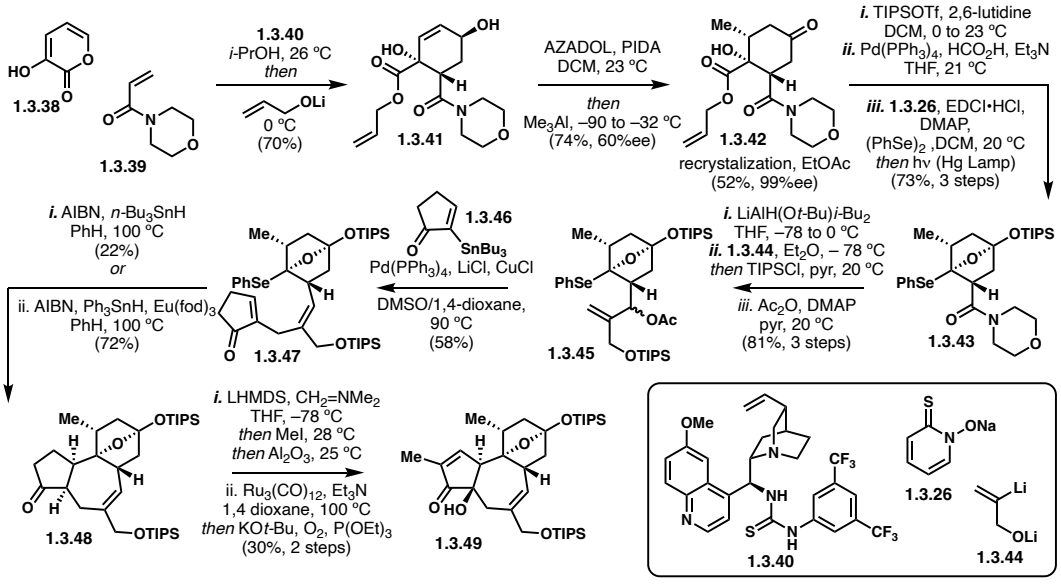


Treatment of **1.3.23** with Dowex 50W resulted in the removal of the acetal group as well as unveiling the methyl ketone. Selective benzoylation of the secondary hydroxygroup at C8 delivered a suitable susbtrate for the installation of a model orthoester motif to tie together the three remaining alcohols to obtain orthoester **1.3.24**. Three steps were spent to arrive at mesyl ester **1.3.25**, which was then transformed into the Barton ester using 2-mercaptopyridine *N*-oxide sodium salt **1.3.26**. The desired bridgehead selenide **1.3.27** was obtained by photoirradiation and subsequent trapping of the generated radical with $(SePh)_2$ and debenzoylation. Inversion of the free alcohol and subsequent silylprotection required three steps to arrive at **1.3.28**. With radical precursor **1.3.28** in hand, Inoue and coworkers executed an exceedingly effective three-component radical coupling with enone **1.3.29** and stannane **1.3.30** to afford the coupling product **1.3.31** in 52%, thus completing the 5- and 6-membered rings of RTX in 22 steps. NaHMDS induced elimination introduced desaturation on the A-ring of RTX followed by a Rubottom oxidation sequence to install the tertiary alcohol and thereby achieving the desired *trans* configuration of the future 5/7-ring junction, yielding **1.3.32**. DIBAL reduction of the enone and subsequent generation

of the oxacyclopentylidene orthoester in combination with the formation of both xanthates set the stage for the ultimate ring closing event of Inoue's synthesis. Subjecting dixanthate **1.3.33** to radical generating conditions forged the remaining 7-membered ring of the the daphnane skeleton, affording tricycle **1.3.34** via a 7-*endo* radical cyclization. Global deprotection and subsequent selective oxidation was followed by Yamaguchi esterification to install the desired orthoester on the C-ring, as well as a silyl protection of the free tertiary alcohol to arrive at advanced intermediate **1.3.35**. Four steps were required for the geminal introduction of a methyl group and a bromide at C2 resulting in ketone **1.3.36**. Allylic oxidation and elimination were followed by introduction of a primary chloride through transposition affording allylic chloride 1.3.37. The two ultimate steps were spent on attaching the homovanillic sidechain and desylilation, culminating in a 45-step synthesis of RTX.

Only four years later Inoue and coworkers published a streamlined second-generation route, maintaining the general retrosynthetic blueprint but being able to reduce the step count significantly while making the route more convergent.[45] This also allowed for the synthesis of additional, related natural products. Their new route began with an asymmetric Diels-Alder cycloaddition between hydroxy pyrone **1.3.38** and acrylamide **1.3.39** catalyzed by quinine-derived thiourea **1.3.40**. Treatment of the Diels-Alder product with the allyl alcohol lithium salt in a single pot generated cyclohexanol **1.3.41**. The secondary allylic alcohol was oxidized to its corresponding enone, followed by the introduction of the methyl stereocenter on the future C-ring by conjugate addition to give ketone **1.3.42**. This compound was able to be recrystallized thereby increasing its optical purity from 60 to 99% ee. Ketalization and deallylation then set the stage for the installation of the bridgehead selenide using the intermediate Barton ester **1.3.26** like in Inoue's previous report affording selenide **1.3.43**. The remaining amide was selectively reduced to the aldehyde which was reacted with dilithiate **1.3.44**. Acylation of the newly generated alcohol then gave access to **1.3.45**, which underwent Stille coupling with stannane **1.3.46** resulting in the formation of the cyclization precursor **1.3.47** as a single olefin isomer. Subjecting **1.3.47** to radical generating conditions forged the remaining 7-membered ring of the natural product via a Giese addition delivering tricycle **1.3.48**. Eschenmoser methenylation installed an exocyclic olefin that was

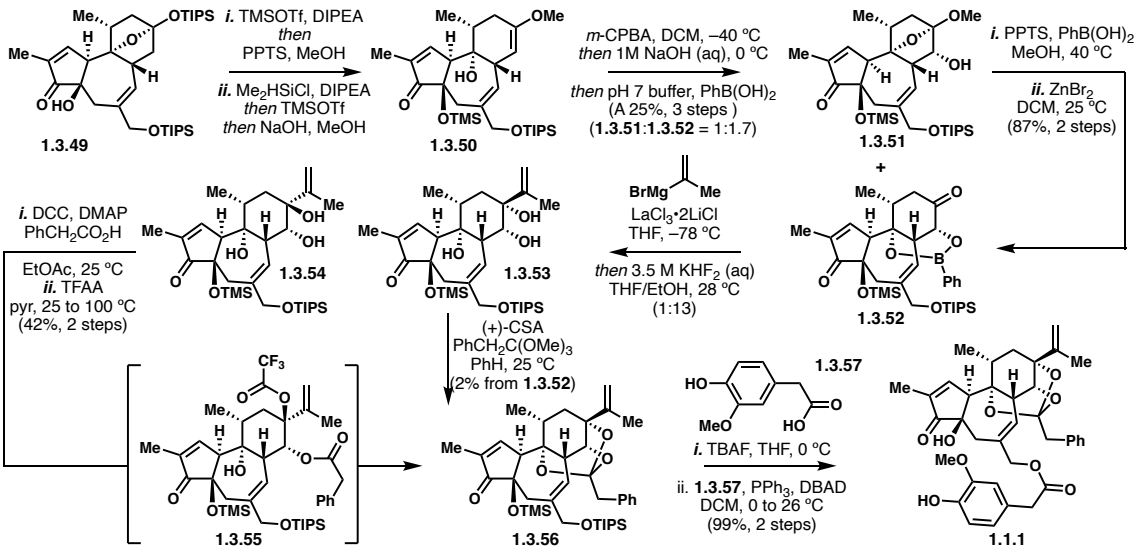
Scheme 1.3.3. Inoue's 2nd generation route to key intermediate **1.3.49**



isomerized into the ring using ruthenium catalysis and ultimately introduction of the tertiary alcohol on the 5,7-fused ring junction giving access to key intermediate **1.3.49**.

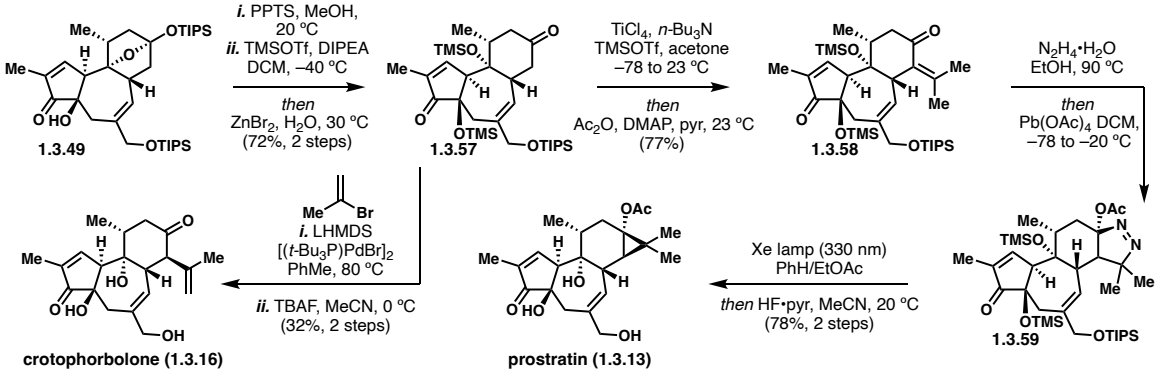
En route to RTX, Inoue and coworkers turned the silyl ketal **1.3.49** into enol ether **1.3.50** via a two-step procedure. Epoxidation of the methyl enol ether and subsequent treatment with phenyl boronic acid set the hydroxy group required for the later installation of the orthoester, giving rise to **1.3.51** and **1.3.52**. To the delight of the Inoue group, they were able to transform **1.3.51** into **1.3.52** in two steps and thereby increasing overall material throughput. With **1.3.52** in hand the stage was set for the installation of the isopropenyl motif, which was achieved using isopropenyl Grignard in combination with lanthanum chloride, work originally developed by the Knochel and coworkers.[49] Unfortunately, the addition proceeded predominantly from the bottom face (**1.3.53**:**1.3.54** = 1:13). Orthoester **1.3.56** was obtained by means of transorthoesterifaction using $PhCH_2(OMe)_3$. Another two-step workaround was able to convert the undesired diastereomer of the isopropenyl Grignard addition into orthoester **1.3.56** by intermediacy of **1.3.55**. Global deprotection followed by a Mitsunobu reaction with homovanillic acid 1.3.57 to complete the total synthesis of RTX **1.1.1** in 20 steps starting from commercially available hydroxy pyrone **1.3.38**.

Scheme 1.3.4. Inoue's 2nd generation route to resiniferatoxin



Due to this new concise and modular approach, Inoue and coworkers were not only able to access the daphnane RTX, but also other related members from the *Euphorbiaceae* family of natural products. Transacetalization to the dimethoxy acetal and subsequent silylation of both tertiary alcohols then was followed by treatment with $ZnBr_2$ to convert the acetal into the corresponding ketone **1.3.57**. At this point an enolate vinylation could be performed to access rhamnofolane crotophorbolone **1.1.16** in 16 steps. On route to accessing the tigliane skeleton, the sequence began with a condensation of acetone on **1.3.57**, resulting in the formation of exocyclic enone **1.3.58**. From here a modified procedure pioneered by Wender in coworkers in the seminal synthesis of phorbol began by condensation with hydrazine gave rise to diazine **1.3.59**. Upon light

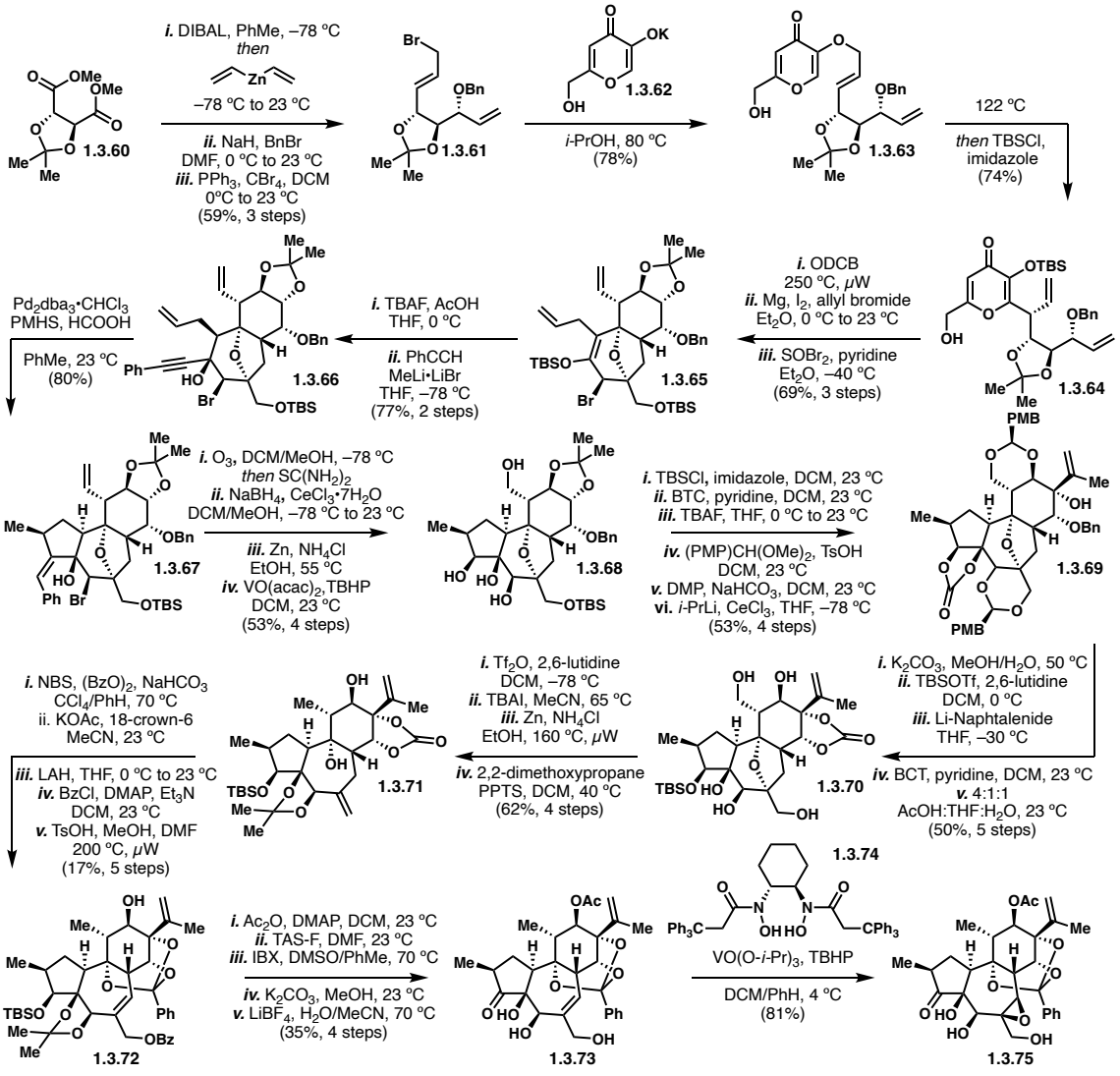
Scheme 1.3.5. Inoue's synthetic route to crotophorbolone and prostratin.



irradiation **1.3.59** would extrude dinitrogen to forge the cyclopropane ring of the tigliane and ultimately deliver prostratin **1.1.13** in 17 steps.

Despite a considerable amount of synthetic effort, none of the natural products from the more complex classes of daphnanes exhibiting higher degrees of oxygenation have been

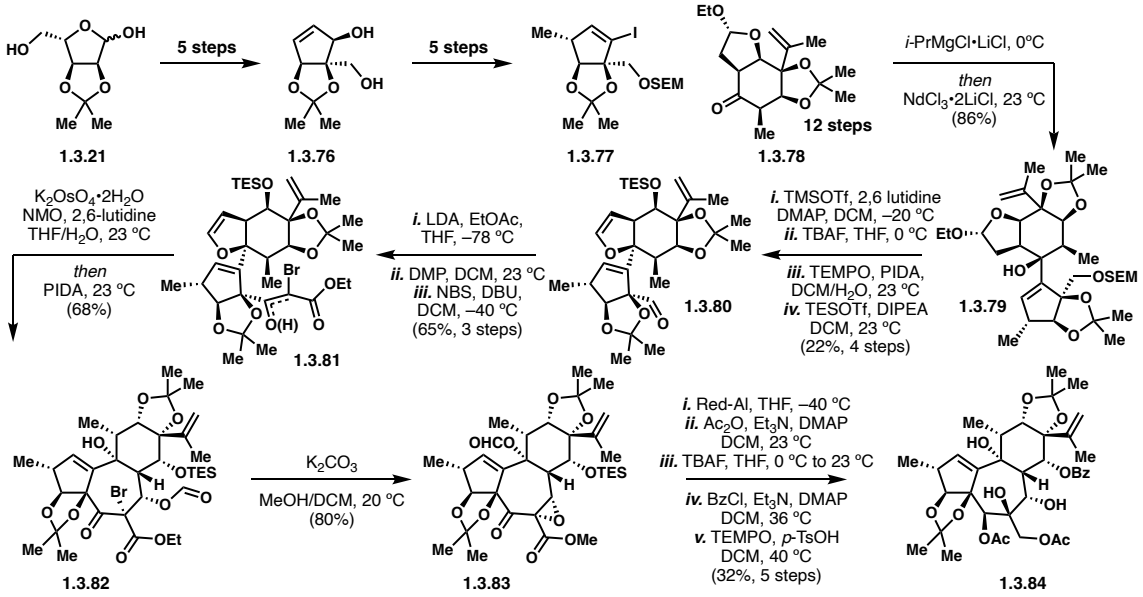
Scheme 1.3.6. Wender's route to C6,C7-epi yuanhuapin.



synthesized so far although Wender's team came close in their pursuit of synthesizing Yuanhuapin, in 2011.[46] Their sequence began by reduction of *D*-dimethyltartrate derivative **1.3.60** to the corresponding aldehyde and subsequent addition of divinyl zinc. Monobenzylation resulted in desymetrization of the compound and the remaining free alcohol was subjected to Appel reaction conditions resulting in the formation of primary allylic bromide **1.3.61**. Potassium kojate **1.3.62** was added and the alkoxide successfully displaced the allylic bromide affording pyrone **1.3.63**, which upon heating underwent a Claisen rearrangement with subsequent silylation to obtain cyclization precursor **1.3.64**. Heating under microwave irradiation resulted in the desired oxidopyrylium [5+2] cycloaddition and thereby forging the 7/6-fused bicycle of the natural product. Allyl Grignard addition and treatment of the newly generated alcohol with thionyl bromide resulting in a *syn* 1,3 transposition giving rise to tricycle **1.3.65**. Selective desilylation unveiled the ketone from the silyl enol ether which was then subjected to phenylacetylide affording enyne **1.3.66**. Palladium catalyzed enyne cyclization closed the remaining A-ring of Kirkinine, thereby accessing the tricyclic core in only 11 steps from tartrate **1.3.60**. With tricycle **1.3.67** in hand, ozonolysis of the remaining olefins was followed by reduction to the corresponding alcohols, zinc mediated fragmentation of the THF-ring was followed by epoxidation of the newly generated olefin, resulting in the reinstallation of the ether ring while installing the required oxidation of the 7-memebered ring affording tetraol **1.3.68**. A multitude of protecting group manipulations and a DMP oxidation were necessary to arrive at the ketone required for the introduction of the isopropenyl group by treatment with isopropenyl lithium to afford advanced intermediate **1.3.69**. At this stage Wender and coworkers removed the carbonate, protected the secondary alcohol on the A-ring, debenzylated the secondary benzylether on the C-ring, protected the resulting diol as the carbonate and ultimately removed the PMB acetals to access polyol **1.3.70**. Selective triflation of the primary alcohols and s subsequent treatment with TBAI afforded the corresponding iodides. Zinc mediated ether fragmentation installed the exocyclic olefin and removed the other primary iodide leaving behind the desired methyl group on the C-ring. Acetalization then afforded 1,1-disubstituted olefin **1.3.71**. Allylic bromination resulted in the transposition of the double bond giving access to the primary allylic bromide that was displaced with an acetate. Lithium aluminum hydride took off the carbonate as well as turning the newly introduced acetate into the primary alcohol. Selective benzoylation and concomitant exposure to tosic acid under microwave irradiation gave access to orthoester **1.3.72**. A series of functional group manipulations and adjustments of the oxidation state led the Wender group to *des*-epoxy Yuanhuapin **1.3.73**. The ultimate step to Yuanhuapin **1.1.5** was the epoxidation of the remaining olefin which was attempted by employing a protocol developed by Yamamoto and coworkers (citation angewandte paper). Wender and coworkers hypothesized that by using chiral hydroxamic acid catalyst **1.3.74** they would be able to overcome the inherit facial bias of the system but unfortunately this proved challenging as they formed C6,C7-*epi*-Yuanhuapin **1.3.75** instead of Yuanhuapin, thereby showcasing another synthetic challenge in the field of daphnane diterpene synthesis – epoxide formation.

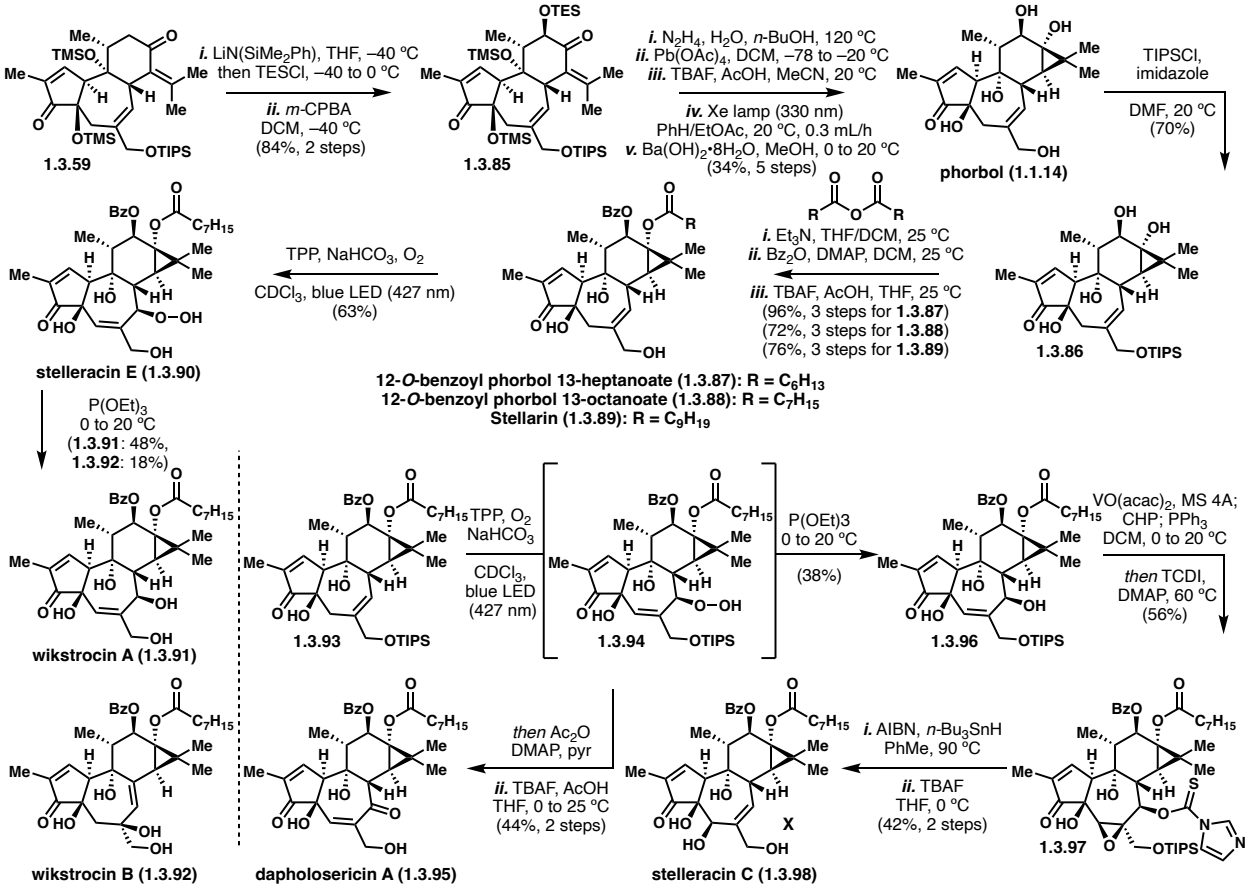
12 years later, Fu and Liu reported their progress toward the more oxygenated daphnanes.[X] Like Inoue's first route, the synthesis made use of the chiral pool by first elaborating *D*-ribose acetonide **1.3.21** to allylic alcohol **1.3.76** via a 5-step literature known procedure (carbohydrate research paper). Another 5 steps were spent on the protection of the primary alcohol, introduction

Scheme 1.3.7. Fu and Liu's approach to a highly functionalized daphnane skeleton.



of the methyl stereocenter on the A-ring albeit with the wrong configuration and to install the vinyl iodide affording bicycle **1.3.77**. Magnesium-Halogen exchange was accomplished with *i*-PrMgCl•LiCl and addition of $NdCl_3$•2LiCl helped increase the yield of the addition to ketone **1.3.78**, which was prepared in 12 steps through a literature known procedure.[50] Grignard addition product **1.3.79** was then turned into dihydrofuran **1.3.80** via a 4-step procedure. Addition of the enolate of ethyl acetate into the pending aldehyde was followed oxidation to the corresponding beta keto ester, which was then brominated, giving rise to cyclization precursor **1.3.81**. Selective dihydroxylation and concomitant diol cleavage resulting in formation of tricycle **1.3.82**. Formation of the desired epoxide was achieved by treatment with K_2CO_3 affording epoxide **1.3.83**, thereby making Fu and Liu the first group to report the installation of the C6-C7-epoxide with the correct stereochemistry. In another 5 steps, functional group manipulation, protecting group changes and hydrolysis of the epoxide then affording **1.3.84** which oxidations pattern maps onto yuanhuaoate B **1.1.2**.

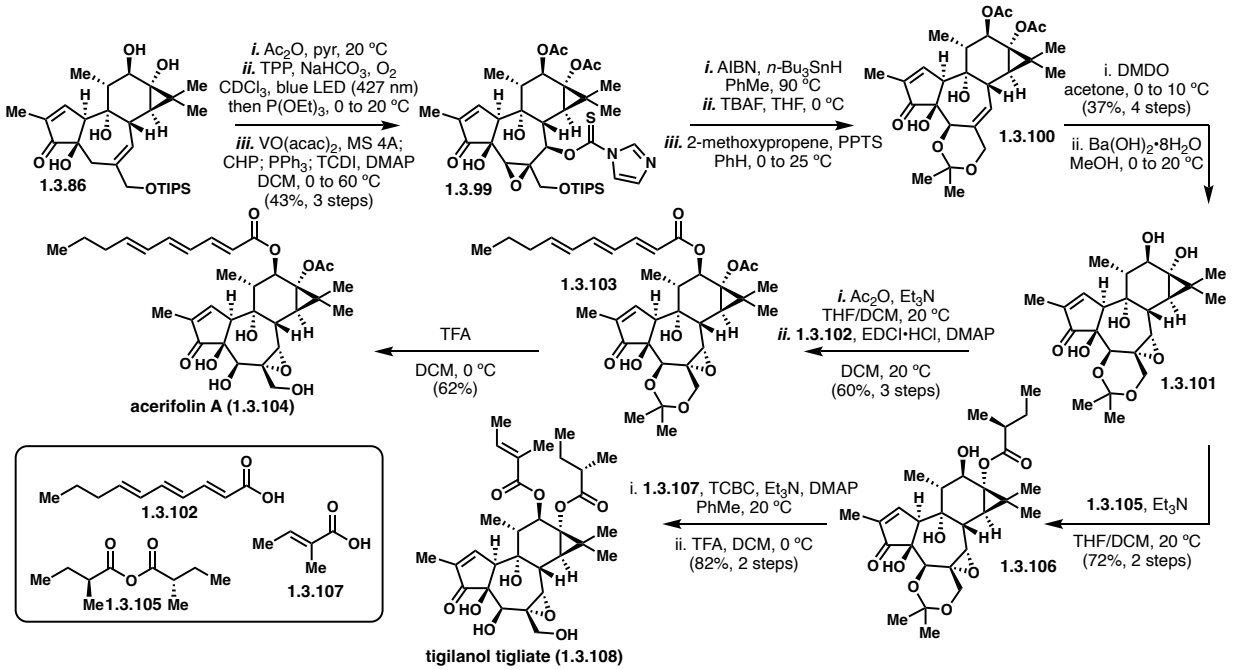
Scheme 1.3.8. Inoue's approach to access more highly oxidized congeners.



In 2024, Inoue and coworkers published yet another paper on the synthesis of diterpenes from *Thymelaeaceae* and *Euphorbiaeace*.[48] In this article, a multitude of tiglianes were synthesized from previously reported intermediate **1.3.59**,[45] thereby gaining insight on the introduction of more oxygenation that could potentially be translated to other diterpene classes such as daphnanes. Introduction of the required extra oxidation on the C-ring was accomplished by selective silyl enol ether formation and subsequent treatment with *m*-CPBA to afford enone **1.3.85**. The procedure that successfully installed the cyclopropane moiety, and thereby enabled the synthesis of prostratin, proved to deliver phorbol **1.1.14** through a similar 5 step sequence. To set the stage for site selective acylations, the primary alcohol was silylated to afford TIPS ether **1.3.86**. The tertiary alcohol at C13 was selective acylated with anhydrides of variable chain lengths in the presence of three free alcohols. Benzoylation of the C12 alcohol followed by removal of the TIPS-group gave access to 12-*O*-benzoyl phorbol 13-heptanoate **1.3.87**, 12-*O*-benzoyl phorbol 13-octanoate **1.3.88** and stellerarin **1.3.89**. When **1.3.88** was subjected to Schenk-ene conditions, Inoue and coworkers were delighted to observe the formation of allylic hydroperoxide stelleracin E **1.3.90**, which upon treatment with $P(OEt)_3$ was transformed into wikstrocin A **1.3.91** and wikstrocin B **1.3.92**. When exposing TIPS protected **1.3.93** to the same singlet oxygen generating conditions the corresponding intermediate hydroperoxide **1.3.94** was formed. Acylation of the hydroperoxide with acetic anhydride triggered the elimation of AcOH and removal of the TIPS group completed the total synthesis of daphlosericin A X **1.3.95**. Alternatively, the hydroperoxide could be reduced resulting in allylic alcohol **1.3.96**. Thiocarbamic ester **1.3.97** was obtained via Sharpless epoxidation (citation 45 in Inoue's paper) and treatment of the remaining free secondary

alcohol with TCDI and DMAP. Subjecting **1.3.97** to radical generating conditions resulted in the deoxygenation and opening the epoxide, subsequent TBAF deprotection then yielded stelleracin C **1.3.98**. In the last part of their communication Inoue and coworkers focused on the synthesis of tiglianes with the intricate C6-C7 epoxide on the α-face of the molecule, namely acerifolin A **1.3.104** and tiglianol tiglate **1.3.108**. Acylation of the C-ring of **1.3.86** and Schenk-ene reaction were followed by Sharpless epoxidation and treatment with TCDI affording thiocarbamic ester **1.3.99**. Under radical-generating conditions deoxygenation was accompanied by opening of the epoxide and treatment with TBAF removed the TIPS group. These newly freed hydroxyl group were then tied together by using 2-methoxypropene resulting in the formation of acetonide **1.3.100** in the hopes to be able to bias the formation of the epoxide required on C6-C7. Upon treatment with DMDO, Inoue and coworker's hypothesis proved to be right by installing the epoxide from the desired α-face. Hydrolysis of the acetyl groups then afforded **1.3.101**. From here selective acylation of the tertiary cyclopropyl alcohol and esterification of the secondary C-ring alcohol with **1.3.102** gave rise to **1.3.103** which was ultimately deprotected to yield acerifolin A **1.3.104**. In contrast treating **1.3.101** with methylbutyric anhydride **1.3.105** afforded **1.3.106**, subsequent esterifaction with tiglic acid **1.3.107** and removal of the acetonide resulted in the total synthesis of tigilanol tiglate **1.3.108**.

Scheme 1.3.9. Inoue's installation of the C6,C7-epoxide and total syntheses of tiglianes.

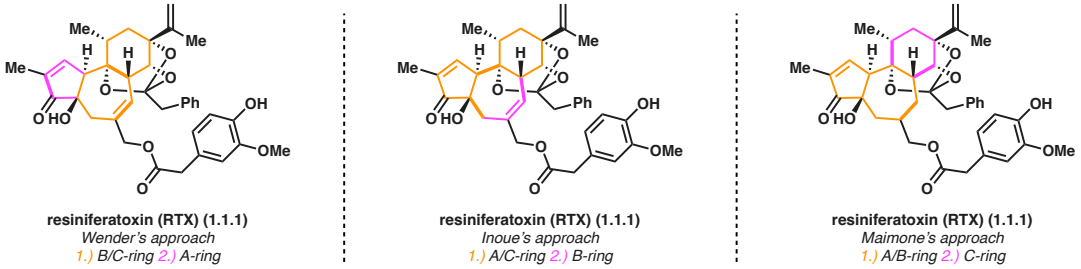


1.4 *Retrosynthetic Analysis of Resiniferatoxin and Potential Entry to Related Daphanes*

Despite enduring recognition spanning nearly five decades and representing a significant target within the synthetic organic community, the total synthesis of daphnanes, namely RTX, has only been achieved by only two other groups. Notably, the synthesis of highly oxygenated and structurally complex subclasses like the 6-epoxydaphnanes, 1-alkyldaphnanes, and rediocides still remains elusive within laboratory setting to this day. Central to synthetic endeavors targeting RTX has been the early construction of the densely functionalized 6-membered ring, recognized as the structurally most challenging part of the molecule. In the first ever reported synthesis of RTX, Wender and coworkers forged the C-ring together with the B-ring through an oxidopyrilium [5+2]

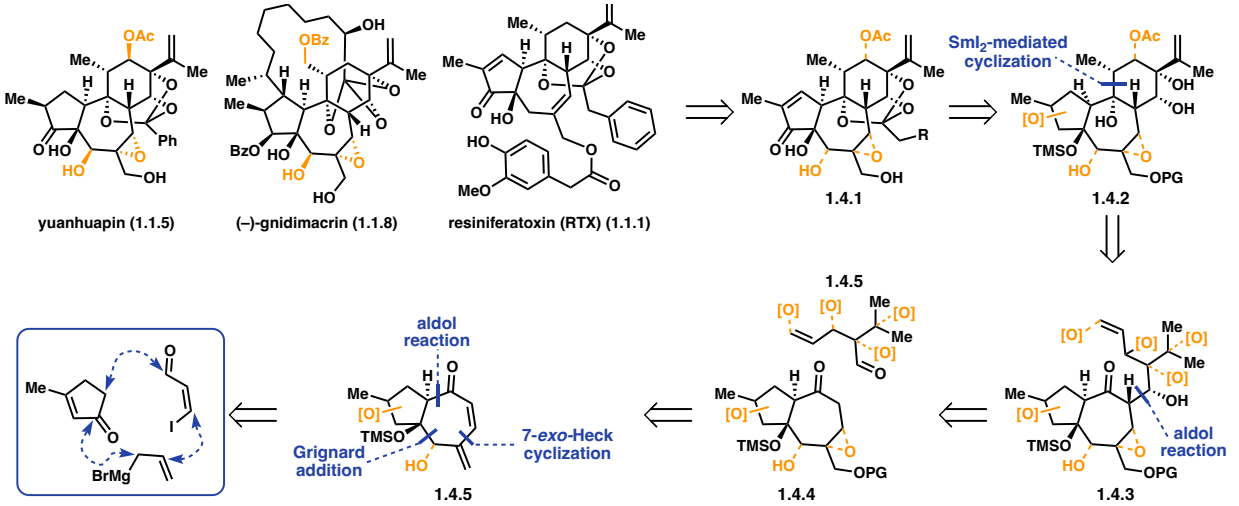
cycloaddition followed by zirconocene-mediated enyne cyclization to arrive at the tricyclic core of RTX.[43] Conversely, the Inoue lab initially constructed and decorated the C-ring, followed by

Scheme 1.4.1 Strategic comparison between Wender's, Inoue's and our approach.



attachment of the A-ring and subsequent radical cyclization to construct the remaining 7-membered ring of the daphnane skeleton.[44,45] Recognizing the imperative to innovate beyond existing strategies, we sought to devise a novel strategy. Our approach centered on the early assembly of the 5/7-fused bicycle (**1.4.4**) succeeded by a two-step process for constructing the C-ring utilizing a linear aldehyde component (**1.4.5**). This strategy not only promises a more streamlined synthetic route but also holds potential for accessing not only RTX and structurally more complex daphnanes but also tiglianes and rhamnofolanes, which differ solely in the C-ring configuration of their tricyclic cores. Given the departure from conventional synthetic paradigms employed in daphnane synthesis, our strategy presents a promising avenue for gain more insight into the underlying chemistry of the 5/7/6-fused ring system. Furthermore, it might facilitate the

Scheme 1.4.2. Retrosynthetic approach focused on late-stage assembly of C-ring of the DDO's.



synthesis of tool compounds essential for elucidating the interaction between PKC and DDOs that have been so far inaccessible, thereby helping to understand PKC's pivotal roles in oncology and immunology.

With the goal of a general route to not only RTX (**1.1.1**) but also the 6-epoxy daphnanes and 1-alkyl daphnanes exemplified by yuanhuapin (**1.1.5**) and gnidimacrin (**1.1.8**) respectively, we traced those different daphnane subfamilies back to highly oxygenated orthoester **1.4.1** with the suitable oxygenation for the 6-epoxy- and 1-alkyldaphnanes highlighted in orange. We planned to introduce the orthoester at this late stage to push the point of diversification as far back as possible to be able to access the biggest variety of daphanes possible, knowing that there differ a lot in the orthoester portion of their skeleton and to be able to potentially access tiglianes and rhamnoloflanes, which lack this orthoester motif. For the case of RTX, appending the homovanillic

acid sidechain was also planned to take place in the ultimate steps of the synthesis to circumvent undesired regio- and chemoselectivity issues potentially arising from the electron rich arene. The common intermediate **1.4.1** was streamlined to a less functionally complex derivative **1.4.2**, the potential product of a SmI_2-mediated 6-*exo*-trig cyclization connecting C9 and C11 to form the C-ring of the molecule. The precursor **1.4.3** for the cyclization resulting in formation of the 6-membered ring was planned to be accessed by an aldol reaction between the 5/7-fused bicycle **1.4.4** and linear aldehyde **1.4.5**. Disconnecting the C-ring at that stage would allow us to introduce differently substituted aldehyde partners for the aldol with the desired oxidations that map onto the specific natural product of interest, thereby gaining access to a plethora of new chemical space in the realm of daphnane total synthesis. Simplified 5/7-fused bicycle **1.4.6** was envisioned to be elaborated to aldol precursor 1.4.4 via 1,6-addition of a boronate to the vinylogous enone of **1.4.6** and subsequent installation of a protecting group to circumvent undesired reactivity. To arrive at **1.4.6,** we envisioned to commercially obtain the A-ring of the molecule and append the 7-membered B-ring a short series of the transformations. This was planned to take place via a 7-exo-trig Heck cyclization forging the B-ring, which preceded installation of the halogen-bearing sidechain via aldol addition of the cyclopentenone followed by addition of allylmagnesium bromide to the carbonyl of the 5-membered enone. This way the 5,7-fused bicycle **1.4.6** could be ultimately traced back to the three orthogonally bifunctional pieces capable of undergoing the desired C-C bond-forming steps necessary arrive at the desired bicyclic system. Introduction of the oxidations highlighted in orange would take place at suitable stages that allow the introduction without the need of excessive functional group manipulations. Our novel approach would allow for a rapid construction of the 5/7/6-fused core of the daphnane skeleton and hopefully would grant access to differently substituted C-ring, thereby resulting in a general and convergent route to a plethora of so far inaccessible daphnane natural products.

1.5. References

(1) Liao, S.-G.; Chen, H.-D.; Yue, J.-M. Plant Orthoesters. *Chem. Rev.* **2009**, *109*, 1092–1140.

(2) Nie, Y.-W.; Li, Y.; Luo, L.; Zhang, C.-Y.; Fan, W.; Gu, W.-Y.; Shi, K.-R.; Zhai, X.-X.; Zhu,J.-Y. Phytochemistry and Pharmacological Activities of the Diterpenoids from the Genus Daphne. *Molecules* **2021**, *26*, 6598.

(3) Hergenhahn, M.; Adolf, W.; Hecker, E. Resiniferatoxin and Other Esters of Novel Polyfunctícnal Diterpenes from Euphorbia Resinifera and Unispina. *Tetrahedron Lett.* **1975**, 16, 1595-1598.

(4) Totelin, L. Botanizing Rulers and their Herbal Subjects: Plants and Political Power in Greek and Roman Literature. *Phoenix* **2012**, *66*, 122.

(5) Jin, Y.-X.; Shi, L.-L.; Zhang, D.-P.; Wei, H.-Y.; Si, Y.; Ma, G.-X.; Zhang, J. A Review on Daphnane-Type Diterpenoids and Their Bioactive Studies. *Molecules* **2019**, *24*, 1842.

(6) He, W.; Cik, M.; Lesage, A.; Van der Linden, I.; De Kimpe, N.; Appendino, G.; Bracke, J.; Mathenge, S.G.; Mudida, F.P.; Leysen, J.E.; Van Puyvelde, L. Kirkinine, a New Daphnane Orthoester with Potent Neurotrophic Activity from *Synaptolepis kirkii. J. Nat. Prod.* **2000**, *63*, 1185-1187

(7) Carney, J.R.; Krenisky, J.M.; Williamson, R.T.; Luo, J.; Carlson, T.J.; Hsu, V.L.; Moswa, J.L. Mapruneacin, a New Daphnane Diterpenoid with Potent Antihyperglycemic Activity from *Maprouneaafricana*. *J. Nat. Prod.* **1999**, *62*, 345-347

(8) Chen, Y.; Guo, J.; Tang, Y.; Wu, L.; Tao, W.; Qian, Y.; Duan, J. Pharmacokinetic Profile and

Metabolite Identification of Yuanhuapin, a Bioactive Component in Daphne Genkwa by Ultra-High Performance Liquid Chromatography Coupled with Tandem Mass Spectrometry. *J. Pharm. Biomed. Anal.* **2015**, *112*, 60-69

(9) Allard, P-M.; Martin, M-T.; Tran Huu Dau, M-E.; Leyssen, P.; Guéritte, F.; Litaudon, M. Trigocherrin A, the First Natural Chlorinated Daphnane Diterpene Orthoester from *Trigonostemon cherrieri. Org. Lett.* **2012**, *14*, 342-345

(10) Zeng, Y.-M.; Zuo, W.-J.; Sun, M.-G.; Meng, H.; Wang, Q.-H.; Wang, J.-H.; Li, X. Three New Daphne Diterpenes from the Buds of Daphne genkwa Sieb. et Zucc. Processed by Rice Vinegar. *Helv. Chim. Acta* **2009**, *92*, 1273–1281.

(11) Adolf, W.; Seip, E. H.; Hecker, E.; Dossaji, S. F. Irritant Principles of the Mezereon Family (Thymelaeaceae), V. New Skin Irritants and Tumor Promoters of the Daphnane and 1α-Alkyldaphnanes Type from Synaptolepsis Kirkii and Synaptolepsis Retusa. *J. Nat. Prod.* **1988**, *51*, 662-674

(12) Yoshida, M.; Feng, W.; Saijo, N.; Ikekawa, T. Antitumor Activity of Daphnane-Type Diterpene Gnidimacrin Isolated from Stellera Chamaejasme L. *Int. J. Cancer* **1996**, *66*, 268-273.

(13) Hayes, P.Y.; Chow, S.; Somerville, M.J.; De Voss, J.J.; Fletcher, M.T. Pimelotides A and B, Diterpenoid Ketal-Lactone Orthoesters with an Unprecedented Skeleton from *Pimela* elongata. *J. Nat. Prod.* **2009**, *72*, 2081-2083.

(14) Jayasuriya, H.; Zink, D. L.; Singh, S. B.; Borris, R. P.; Nanakorn, W.; Beck, H. T.; Balick, M.J.; Goetz, M. A.; Slayton, L.; Gregory, L.; Zakson-Aiken, M.; Shoop, W.; Singh, S. B. Structure and Stereochemistry of Rediocide A, A Highly Modified Daphnane from Trigonostemon Reidiodes Exhibting Potent Insecticidal Activity. *J. Am. Chem. Soc.* **2000**, *122*, 4998- 4999.

(15) Tan, C.-J.; Li, S.-F.; Huang, N.; Zhang, Yu,; Di, Y.-T.; Zheng, Y.-T.; Hao, X.-J. Daphnane Diterpenoids from Trigonostemon lii and Inhibition Activities against HIV *Nat. Prod. Bioprospect.* **2020**, *10,* 37-44.

(16) Cashmore, A. R.; Seelye, R. N.; Cain, B. F.; Mack, H.; Schmidt, R.; Hecker, E. The Structure of Prostratin: A Toxic Tetracyclic Diterpene Ester from Pimelea Prostrata. *Tetrahedron Lett.* **1976**, *17*, 1737-1738.

(17) Flaschenträger, B.; von Falkenhausen, F. Frhr. Über Den Giftstoff Im Krotonöl. II Zur Konstitution von Krotophorbolon. *Justus Liebigs Ann. Chem.* **1934**, *514*, 252-260.

(18) Hecker, E.; Kubinyi, H.; Szczepanski, Ch. v.; Härle, E.; Bresch, H. Phorbol - ein neues tetracyclisches diterpen aus crotonöl. *Tetrahedron Lett.* **1965**, *6*, 1837–1842.

(19) Damascena, H. L.; Silveira, W. A. A.; Castro, M. S.; Fontes, W. Neutrophil Activated by the Famous and Potent PMA (Phorbol Myristate Acetate). *Cells* **2022**, *11*, 2889.

(20) Kirby, J.; Nishimoto, M.; Park, J. G.; Withers, S. T.; Nowroozi, F.; Behrendt, D.; Rutledge, E. J. G.; Fortman, J. L.; Johnson, H. E.; Anderson, J. V.; Keasling, J. D. Cloning of Casbene and Neocembrene Synthases from Euphorbiaceae Plants and Expression in Saccharomyces Cerevisiae. *Phytochemistry* **2010**, *71*, 1466–1473.

(21) King, A. J.; Brown, G. D.; Gilday, A. D.; Forestier, E.; Larson, T. R.; Graham, I. A. A Cytochrome P450-Mediated Intramolecular Carbon–Carbon Ring Closure in the Biosynthesis of Multidrug-Resistance-Reversing Lathyrane Diterpenoids. *ChemBioChem,* **2016**, *17*, 1593–1597.

(22) Luo, D.; Callari, R.; Hamberger, B.; Wubshet, S. G.; Nielsen, M. T.; Andersen-Ranberg,

J.; Hallström, B. M.; Cozzi, F.; Heider, H.; Møller, B. L.; Staerk, D.; Hamberger, B. Oxidation and Cyclization of Casbene in Biosynthesis of Euphorbia Factors from Mature Seeds of Euphorbia Lathyris L. *Proc. Natl. Acad. Sci.* **2016**, *113*, E5082-E5089.

(23) Szallasi, A.; Blumberg, P. M. Resiniferatoxin, a Phorbol-Related Diterpene, Acts as an Ultrapotent Analog of Capsaicin, the Irritant Constituent in Red Pepper. *Neuroscience* **1989**, *30*, 515-520.

(24) Szallasi, A.; Blumberg, P. M. Specific Binding of Resiniferatoxin, an Ultrapotent Capsaicin Analog, by Dorsal Root Ganglion Membranes. *Brain Res.* **1990**, *524*, 106–111.

(25) Cao, E.; Liao, M.; Cheng, Y.; Julius, D. TRPV1 Structures in Distinct Conformations Reveal Activation Mechanisms. *Nature* **2013**, *504*, 113-118.

(26) Mishra, S.K.; Hoon, M.A. Ablation of TrpV1 neurons reveals their selective role in thermal pain sensation. *Mol. Cell. Neurosci.* **2010**, *43*, 157-163.

(27) Salas, M.M.; Clifford, J.L.; Hayden, J.R.; Iadarola, M.J.; Averitt, D.L. Local Resiniferatoxin Induces Long-Lasting Analgesia in a Rat Model of Full Thickness Thermal Injury. *Pain Med.* **2017**, *18*, 2453-2465.

(28) Scherer, P.C.; Zaccor, N.W.; Neumann, N.M.; Vasvda, C.; Barrow, R.; Ewald, A.J.; Rao, F.; Sumner, C.J.; Snyder, S.H. TRPV1 is a physiological regulator of μ-opioid receptors. *Proc. Natl. Acad. Sci.* **2017**, *114*, 13561-13566.

(29) Bateman, J.T.; Levitt, E.S. Evaluation of G Protein bias and β-arrestin 2 signaling in opioid-induced respiratory depression. *Am. J. Physiol. Cell. Physiol.* **2021**, *321*, C681-C683.

(30) Appendino, G.; Bertolino, A.; Minassi, A.; Annunziata, R.; Szallasi, A.; de Petrocellis, L.; Di Marzo, V. Synthesis and Biological Evaluation of Phorbol-Resiniferatoxin (RTX) Hybrids. *Eur. J. Org. Chem.* **2004**, *2004*, 3413–3421.

(31) Appendino, G.; Ech-Chahad, A.; Minassi, A.; Bacchiega, S.; Petrocellis, L. D.; Marzo, V. D.Structure–Activity Relationships of the Ultrapotent Vanilloid Resiniferatoxin (RTX): The Homovanillyl Moiety. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 132–135.

(32) Appendino, G.; Ech-Chahad, A.; Minassi, A.; De Petrocellis, L.; Marzo, V. D. Structure– Activity Relationships of the Ultrapotent Vanilloid Resiniferatoxin (RTX): The Side Chain Benzylic Methylene. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 97–99.

(33) Appendino, G.; Cravotto, G.; Palmisano, G.; Annunziata, R.; Szallasi, A. Synthesis and Evaluation of Phorboid 20-Homovanillates: Discovery of a Class of Ligands Binding to the Vanilloid (Capsaicin) Receptor with Different Degrees of Cooperativity. *J. Med.Chem.* **1996**, *39*, 3123–3131.

(34) Appendino, G.; Ech-Chahad, A.; Minassi, A.; De Petrocellis, L.; Marzo, V. D. Structure– Activity Relationships of the Ultrapotent Vanilloid Resiniferatoxin (RTX): The Side Chain Benzylic Methylene. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 97–99.

(35) Williamson, E. M.; Westwick, J.; Evans, F. J. The Effect of Daphnane Esters on Platelet Aggregation and Erythema of the Mouse Ear. *J. Pharm. Pharmacol.* **1980**, *32*, 373–374.

(36) Wahl, P.; Foged, C.; Tullin, S.; Thomsen, C. Iodo-Resiniferatoxin, a New Potent Vanilloid Receptor Antagonist. *Mol. Pharmacol.* **2001**, *59*, 9–15.

(37) He, S.; Li, Q.; Huang, Q.; Cheng, J. Targeting Protein Kinase C for Cancer Therapy. *Cancers* **2022**, *14*, 1104.

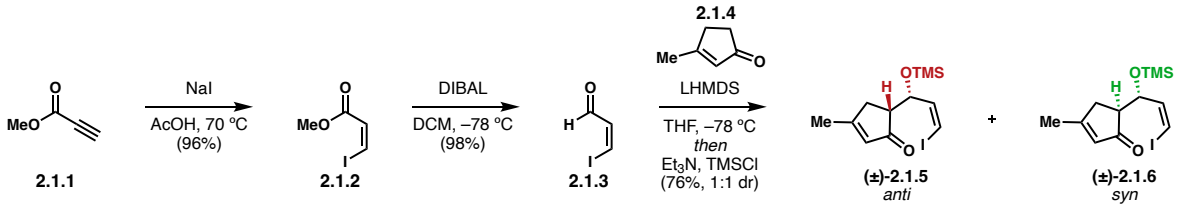
(38) Remy, S.; Litaudon, M. Macrocyclic Diterpenoids from Euphorbiaceae as A Source of Potent and Selective Inhibitors of Chikungunya Virus Replication. *Molecules* **2019**, *24*, 2336.
(39) Ryves, W. j; Garland, L. g.; Evans, A. t.; Evans, F. j. A Phorbol Ester and a Daphnane Ester Stimulate a Calcium-Independent Kinase Activity from Human Mononuclear Cells. *FEBS Lett.* **1989**, *245*, 159–163.
(40) Irie, K.; Oie, K.; Nakahara, A.; Yanai, Y.; Ohigashi, H.; Wender, P. A.; Fukuda, H.; Konishi, H.; Kikkawa, U. Molecular Basis for Protein Kinase C Isozyme-Selective Binding: The Synthesis, Folding, and Phorbol Ester Binding of the Cysteine-Rich Domains of All Protein Kinase C Isozymes. *J. Am. Chem. Soc.* **1998**, *120*, 9159–9167.
(41) Newton, A. C. Protein Kinase C: Structure, Function, and Regulation. *J. Biol. Chem.* **1995**, *270*, 28495–28498.
(42) Yoshida, M.; Feng, W.; Saijo, N.; Ikekawa, T. Antitumor activity of daphnane-type diterpene gnidimacrin isolated from Stellera chamaejasme L. *Int. J. Cancer* **1996**, *66*, 268-273.
(43) Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. The First Synthesis of a Daphnane Diterpene: The Enantiocontrolled Total Synthesis of (+)- Resiniferatoxin. *J. Am. Chem. Soc.* **1997**, *119*, 12976–12977.
(44) Hashimoto, S.; Katoh, S.; Kato, T.; Urabe, D.; Inoue, M. Total Synthesis of Resiniferatoxin Enabled by Radical-Mediated Three-Component Coupling and 7-Endo Cyclization. *J. Am. Chem. Soc.* **2017**, *139*, 16420–16429.
(45) Hirose, A.; Watanabe, A.; Ogino, K.; Nagatomo, M.; Inoue, M. Unified Total Syntheses of Rhamnofolane, Tigliane, and Daphnane Diterpenoids. *J. Am. Chem. Soc.* **2021**, *143*, 12387–12396.
(46) Wender, P.A.; Buschmann, N.; Cardin, N.B.; Jones, L.R.; Kan, C.; Kee, J.-M.; Kowalski, J.A.; Longcore, K.E. Gateway synthesis of daphnane congeners and their protein kinase C affinities and cell-growth activities. *Nature Chem.* **2011**, *3*, 615-619
(47) Sun, Y.; Feng, J.; Qin, S.; Fu, S.; Liu, B.; Asymmetric Construction of the Core of C_6, C_7-Epoxy Daphnane Diterpenoid Orthoesters. *Org. Lett.* **2023**, *25*, 8072-8076
(48) Watanabe, A.; Nagatomo, M.; Hirose, A.; Hikone, Y.; Kishimoto, N.; Miura, S.; Yasutake, T.; Abe, T.; Misumi, S.; Inoue, M. Total Syntheses of Phorbol and 11 Tigliane Diterpenoids and Their Evaluation as HIV Latency-Reversing Agents. *J. Am. Chem. Soc.* **2024**, *146*, 8746-8756.
(49) Krasovskiy, A.; Kopp, F.; Knochel, P. Soluble Lanthanide Salts ($LnCl_3$•2 LiCl) for the Improved Addition of Organomagnesium Reagents to Carbonyl Compounds. *Angew. Chem. Int. Ed.* **2006**, *45*, 497-500.
(50) Feng, J.; Yu, T.; Zhang, Z.; Li, J.; Fu, S.; Chen, J.; Liu, B. Asymmetric Synthesis of the fully functionalized six-membered ring of trigoxyphin A. Chem. Commun. **2018**, *54*, 7665-7668.

Chapter 2.
Total Synthesis of Resiniferatoxin, Asymmetric Synthesis & Studies Toward Gnidimacrin

2.1 *Synthesis of 5/7-fused bicycle 2.1.10*

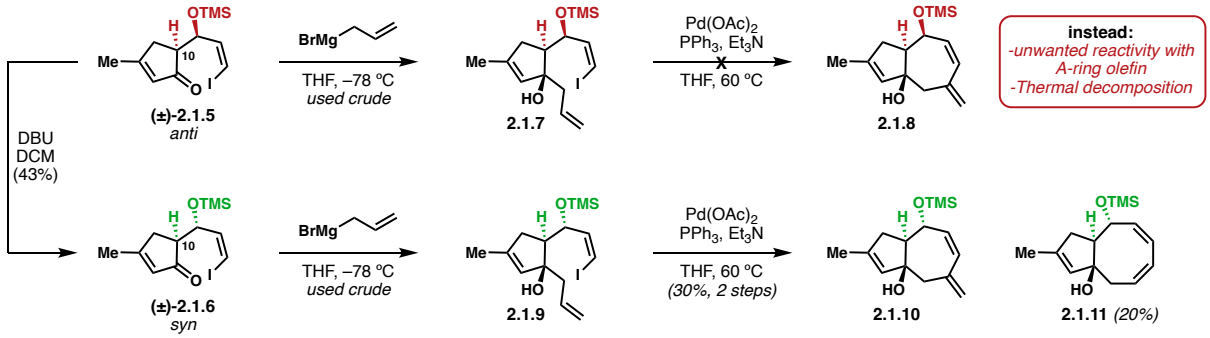
Our retrosynthetic strategy's first objective, as outlined in Chapter 1.4, was the rapid construction of the A- and B-ring of the daphnane core, we therefore sought out to arrive at a suitably substituted hydroazulene. Despite its commercial availability, we decided to obtain (*Z*)-methyl 3-iodoacrylate **2.1.2** by treating methyl propiolate **2.1.1** with sodium iodide in acetic acid due to the cost of acquiring large amounts of the compound this early in the sequence.[1] DIBAL reduction yielded the corresponding aldehyde **2.1.3**, possessing two functional handles for C-C bond formations, as outlined in our retrosynthetic considerations.[2] Aldehyde **2.1.3** proved to violently decompose upon prolonged (20-30 mins) exposure to light and/or temperature in its neat form. Fortunately, aldehyde **2.1.3** could be handled without issues when kept in solution and at low temperatures and was subjected to the lithium enolate of 3-methyl cyclopentenone **2.1.4**, resulting in a 1:1 diastereomeric mixture of *anti*- and *syn*-aldol products **2.1.5** and **2.1.6** respectively in a combined yield if 76%. Despite theory predicting a preference in generating the anti-aldol product **2.1.5** since only generation of the (E)-enolate can occur which should lead to a closed Zimmerman-Traxler transition state, observation of a 1:1 diastereomeric ratio suggest the reaction proceeds through an open transition state or a combination of both.[3,4]

Scheme 2.1.1 First C-C bond formation via aldol on the route to RTX.



Both aldol products **2.1.5** and **2.1.6** were successfully treated with allylmagnesium bromide, affording the corresponding tertiary alcohols **2.1.7** and **2.1.9** respectively, providing the desired *trans* relationship between the vinyl iodide portion and the newly appended allyl chain, as essentially a single diastereomer. This stereochemical outcome was ensured by capping the lithium alkoxide generated during the aldol with a TMS-group increase steric bulk and thereby promoting addition from the desired, less hindered α-face of the molecule. After having installed the two functional handles necessary for forging the last bond we sought out to complete the synthesis of the 5/7-fused bicycle by means of 7-*exo*-Heck cyclization.[5-7] When subjecting crude **2.1.7** to palladium catalysis no formation of the desired bicycle **2.1.8** was observed; instead, the crude reaction mixture contained a complex mixture of products, with part of the products being the result of thermal decomposition and reactions involving the olefin of the A-ring.

Scheme 2.1.2. Reactivity difference between aldol diastereomers in bicycle synthesis.

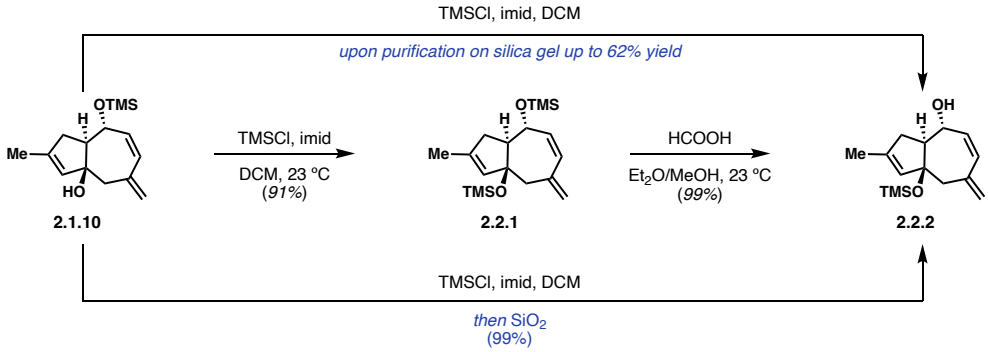


Fortunately, *syn*-cyclization precursor **2.1.9** successfully engaged in Heck cyclization, delivering the 5,7-fused bicycle **2.1.10** in 30% yield over 2 steps, the result from the intended 7-*exo*-trig Heck cyclization. Additionally, we observed the formation of **2.1.11** in 20% yield, the product of the competing 8-*endo*-trig Heck cyclization and since we were still missing roughly 50% of our mass balance, which most likely can be attributed to a similar thermally induced decomposition of vinyl iodide **2.1.9**. Despite having successfully accessed the desired bicyclic system, the yield of the Heck cyclization would require labor intensive scale-up to afford enough material to further investigate subsequent transformations. To our delight, we were able to epimerize *anti* aldol product **2.1.5** at the C10 position, resulting in an equimolar mixture of the diastereomeric pair **2.1.5** and **2.1.6** in 88% yield based on recovered **2.1.5** or 43% yield based on **2.1.6**, thereby being able to obtain **2.1.10** in 51% yield per batch of aldol addition and subsequent epimerization.

2.2 *Elaboration of the 5/7-fused System to Arrive at a Suitable Aldol Partner*

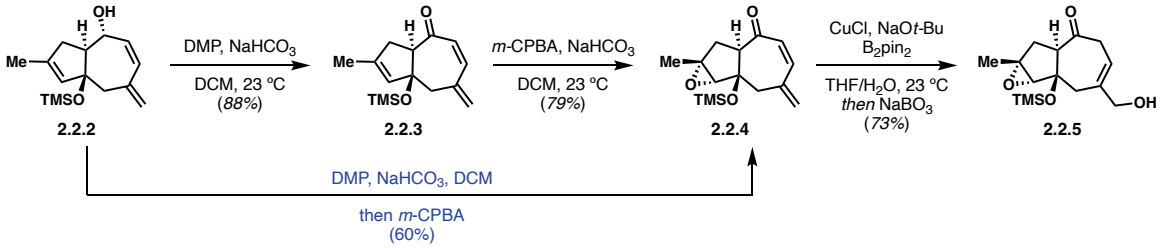
With synthetic access to **2.1.10** already established, we set out to further functionalize the core to arrive at a bicyclic ketone resembling **1.4.4**. Treatment of **2.1.10** with TMSCl and imidazole cleanly delivered bis-silylated bicycle **2.2.1** in 91% yield. Selective desilylation was achieved by treatment of **2.2.1** with formic acid in Et_2O/MeOH,[8] resulting in formation of free secondary alcohol **2.2.2**. During scale up of the silylation, we observed the persistence of a spot on the TLC that was co-polar with the starting material, despite the crude NMR only containing one single compound with two silyl groups on it. Surprisingly this spot reappeared on TLC upon purification on silica gel. Investigation by ^{1}H-NMR revealed that the secondary silyl group fell off upon expose to silica gel, resulting in amounts of up to 62% yield. This observation led us to try to shorten the step count as well as well as increasing the practicality of the sequence. This formal silyl shift was achieved by addition of SiO_2 after all the starting material was consumed judging by TLC, stirring the reaction mixture for three hours until the newly formed spot disappeared again, affording the desired free secondary alcohol in essentially quantitative yield.

Scheme 2.2.1. Formal silyl migration on 5,7-fused bicycle 2.1.10.



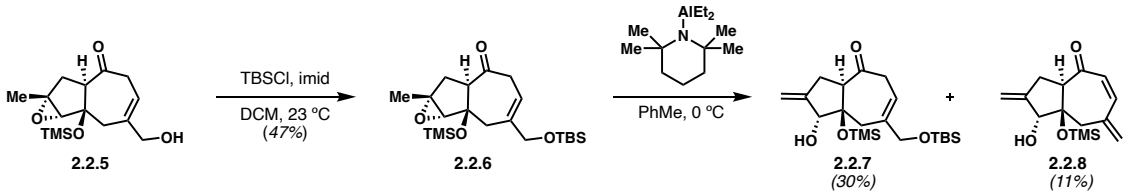
With this formal silyl shift granting us access to the desired free alcohol we set out to install the oxidation pattern found on the 5/7-fused bicycle of the tricyclic core of the daphnanes. Therefore, we subjected the secondary alcohol **2.2.2** to DMP resulting in the formation of the vinylogous enone **2.2.3**. Oxidation to the enone was essential for the next step, rendering the A-ring olefin the most electron rich double bond and thereby limiting any unwanted reactivity that could stem from the remaining olefins in the molecule, thus delivering epoxide **2.2.4** without considerable amounts of regioselectivity issues. We found that both of those oxidations could be

Scheme 2.2.2. Oxidative manipulations of the bicyclic system.



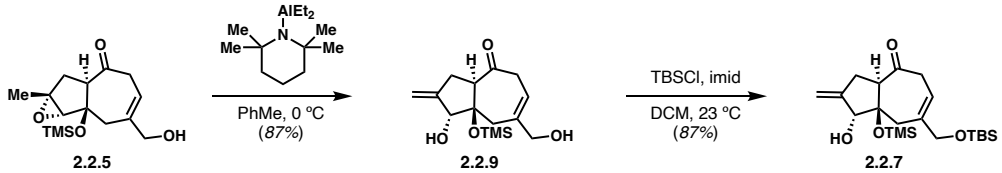
carried out in a single operation, thereby increasing practicality while decreasing the step-count to the detriment of the yield. The next goal was the introduction of the oxidation on C20 for the latter installation of the homovanillic ester moiety. This was achieved by selective 1,6-addition of Bpin to the vinylogous enone, delivering the boron ester.[9] Due to the reaction being run in THF/H_2O we were able to oxidize the boronate *in-situ* to its corresponding primary alcohol **2.2.5** by employing $NaBO_3$ as a suitable oxidant for this transformation.

Scheme 2.2.3. First attempt at olefin isomerization sequence.



Since we were successful at installing the desired C20 oxidation, our next goal was to obtain a suitable ketone for the planned aldol reaction, joining the 5/7-fused bicycle with a suitable aldehyde partner capable of forging the remaining C-ring of the molecule. We first silylated the recently introduced primary alcohol on **2.2.5** giving rise to silanol **2.2.6**. Next, we attempted to open the epoxide on the A-ring of the molecule. When subjecting 2.1.17 to freshly prepared diethyl aluminum 2,2,6,6-tetramethylpiperidine (DATMP),[10] we observed formation of the desired bicycle **2.2.7** featuring the 1,1 disubstituted olefin albeit in moderate yield of 30%. Additionally, we observed the formation of vinylogous enone **2.2.8**, most likely the product of a E1cB elimination reaction after opening of the epoxide. Unsatisfied with the yield of the desired produced we planned to suppress this side reactivity by switching the order of reactions.

Scheme 2.2.4. Optimized sequence to aldol precursor **2.2.7**.



We were delighted to find our hypothesis to increase the overall efficiency by switching the order of transformations was correct. The epoxide isomerization cleanly delivered diol **2.2.9** in 87% yield with no observed amount of product of an E1cB elimination. The primary alcohol was selectively silylated in presence of the newly formed secondary allylic alcohol, resulting in formation of silanol **2.2.7**.

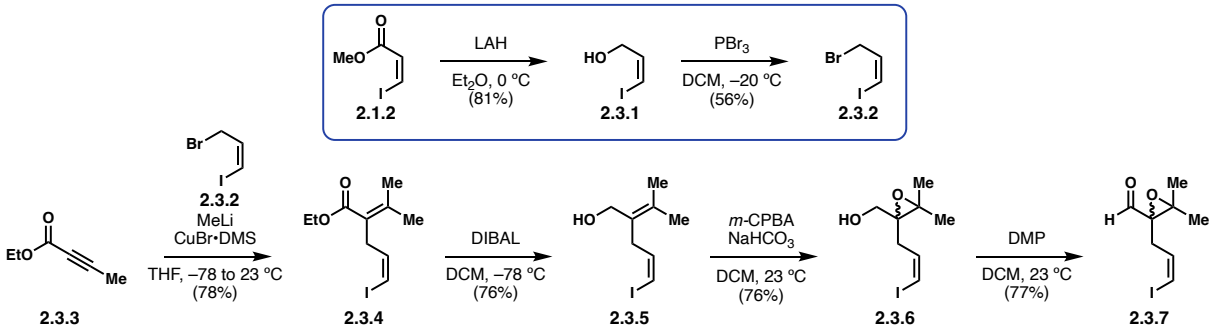
In summary, we were able to rapidly construct the targeted 5/7-fused bicycle **2.1.10** in only 5 steps from methyl propiolate **2.1.1** as well as other commercially available building blocks. Despite the inability to favor one products of the aldol reaction between the lithiate of 3-methyl cyclopentenone **2.1.4** and the vinyl iodide containing aldehyde **2.1.3**, we were able to increase

material throughput by epimerization of the non-productive *anti* product **2.1.5**. Allyl Grignard addition was followed by 7-exo-trig Heck cyclization, forging the 7-membered ring of the daphnane core. Additionally, 5 more steps were necessary to introduce the desired oxidation pattern along the newly constructed core, accessing aldol precursor **2.2.7** in a total of 10 steps.

2.3 *Synthesis of Aldehyde Fragment for Aldol Reaction*

With **2.2.7** in hand as one of the two aldol partners, we set out to synthesize its partner to investigate ways to form the remaining ring of the daphnane skeleton. We decided to target an aldehyde that could potentially be used as a C-ring fragment for a multitude of different DDOs, including specifically RTX (**1.1.1**) and gnidimacrin (**1.1.8**) Fortuitously, we were able to utilize the same starting material used for the construction of the 5/7-fused bicycle for the aldehyde partner. Instead of reducing the ester to the aldehyde by using DIBAL in DCM, this time the ester was reduced to the primary alcohol **2.3.1** using LAH. Subsequent treatment with PBr_3 transformed the alcohol into its corresponding bromide, affording allylic bromide **2.3.2**, which would serve as an electrophile in the next reaction. Firstly, the DMS complex of copper bromide and methyl lithium were stirred together to generate a methyl cuprate, which was then used in a conjugate addition to ethyl 2-butynoate **2.3.3**. The copper species persisting after the addition was then quenched with allyl bromide **2.3.2** to generate α,β-unsaturated ester **2.3.4** in good yield.[11] This very modular approach to generate an all-carbon-precursor for the formation of the C-ring could also be expanded to more complex targets like rediocide (**1.1.9**) by employing a differently substituted cuprate and well as quench with a multitude of different electrophiles. The ester **2.3.4** was then reduced to the corresponding primary alcohol using DIBAL resulting in the formation of **2.3.5**. Next, treatment with *m*-CPBA installed the desired oxidation, affording epoxide 2.3.6, which after Dess-Martin oxidation finally let us to obtain aldehyde **2.3.7**.

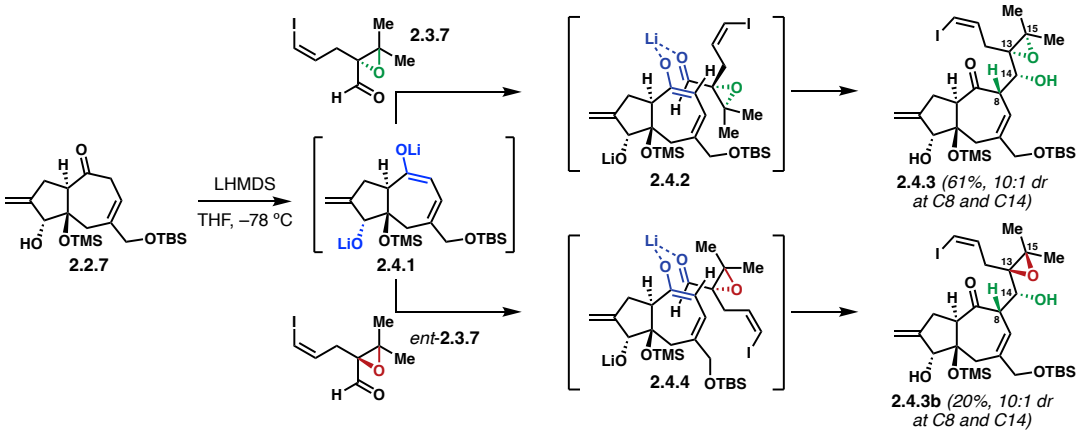
Scheme 2.3.1. Synthesis of the aldehyde fragment for the aldol reaction.



2.4. *Completion of Tricycle Synthesis*

After having successfully synthesized both coupling partners for the planned aldol reaction, we set out to append the aldehyde fragment to ultimately forge the remaining C-ring of the molecule. First, we treated ketone **2.2.7** with 2.5 equivalent of LHMDS to generate lithium enolate 2.4.1. Since we obtained aldehyde **2.3.7** as a racemate, both enantiomers in that mixture would

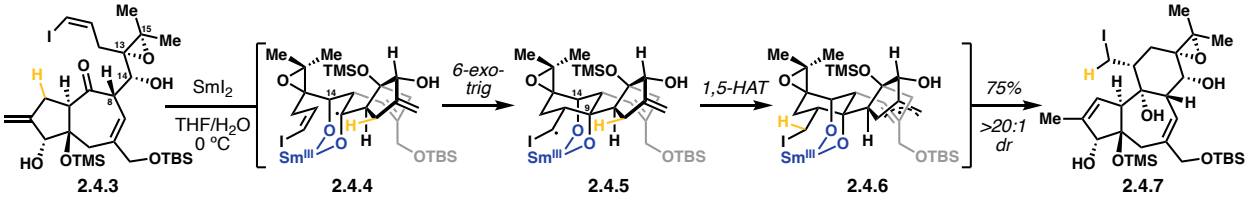
Scheme 2.4.1. Aldol reaction of 2.2.7 via closed transition state with aldehyde partner 2.3.7



lead to different diastereomeric products. The desired enantiomer of **2.3.7** would engange in a Zimmerman-Traxler transition state **2.4.2**,[3] eventually forming the desired aldol product **2.4.3** in 61% yield with both new stereocenters at C8 and C14 being set in a 10:1 diastereomeric ratio. In contrast, the other aldehyde enantiomer ***ent*-2.3.7** also engages in a similar transition state albeit with a different orientation of the aldehyde partner. This orientation results in the formation of **2.4.3b**, in which the C8 and C14 stereocenters are set correctly but the epoxide at C13 and C15 exhibits the undesired stereochemistry. To our delight, the undesired diastereomer was only formed in 20% yield, rendering the aldol reaction overall stereoselective with a 3:1 d.r. at C13 and C15. It is important to note, that quenching the aldol reaction at –78 ºC using AcOH was crucial for suppressing the retro-aldol pathway, since capping of the newly formed alkoxide from the aldol addition with TMSCl was not feasible since we envisioned the free secondary alcohol at C14 would play a crucial role in chelating to ensure the correct stereochemical outcome when forming the C9-C11 bond in the next step.

With only one bond left to complete the construction of the C-ring, we subjected aldol product **2.4.3** to samarium diiodide resulting in the generation of the corresponding ketyl-radical **2.4.4** which should chelate samarium together with the hydroxyl group at C14, thereby correctly setting the stereocenter on C9. The steric bulk from the vinyl iodide should force the radical acceptor to evade steric clash with the top face of the molecule, thus positioning the iodo methylene group on the same face as the newly formed tertiary alcohol in **2.4.5**. Unexpectedly, the carbon centered α-iodo radical abstracted an allylic proton from the A-ring in a 1,5-HAT fashion, giving rise to **2.4.6**. Finally, proton quench of the allylic radical on the A-ring led to transposition of the 1,1 disubstituted double bond into the ring to form a more substituted tri-substituted olefin, delivering **2.4.7** as essentially a single diastereomer at C9-C11. Overall, our hypothesis of constructing the C-ring last proved to be fruitful and may allow for a more modular approach to access more highly oxygenated daphnanes in the future. Additionally, the primary iodide on C18 could potentially serve as a functional handle for the introduction of extra oxidation for other family members like installing the benzoate found in gnidimacrin.

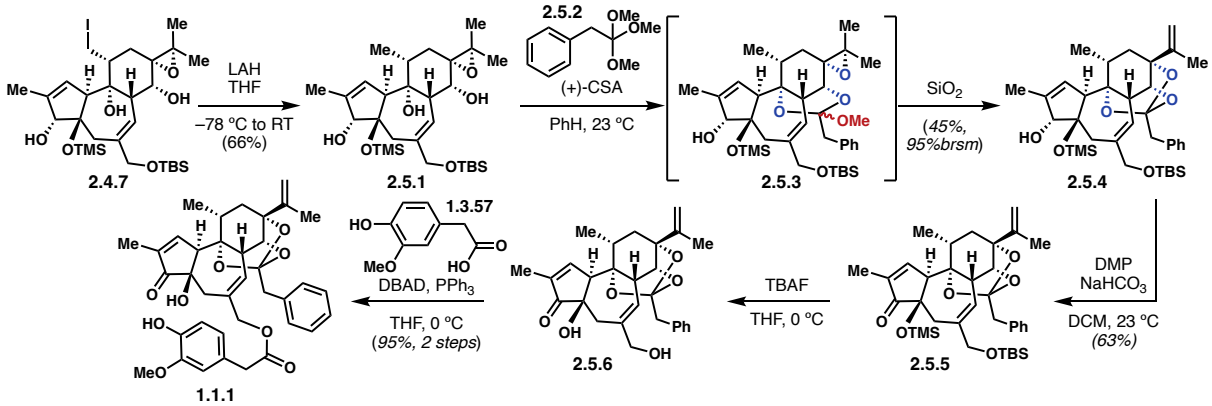
Scheme 2.4.2. SmI_2-mediated 6-*exo*-trig cyclization of ketone **2.4.3**.



2.5 *Installation of the Orthoester and Completion of the Total Synthesis of Resiniferatoxin*

We were delighted to find our hypothesis on the straightforward construction of the C-ring turning out the way we intended and even observing the 1,5-HAT that worked in our favor, saving a step later down the route that would be required to isomerize the exocyclic olefin into the A-ring. With those encouraging results, we set out to finish the synthesis of RTX for which the iodide on C18 would need to be removed. This was accomplished by treatment of **2.4.7** with LAH at cryogenic temperature and letting the reaction mixture slowly come to ambient temperature overnight, resulting in the formation of tricycle **2.5.1**. To our dismay, we found the reaction to be suffering from scalability issues, limiting the scale to 5 mg at a time or a significant drop in yield was observed. Despite this issue, we were able to still increase the overall material throughput by running multiple reactions in parallel but pooling them for workup and purification. With the tricycle in hand, our next objective was the introduction of the key name's sake structural feature of the DDOs, its ortho ester. Transorthoesterification was attempted by treatment of **2.5.1** with the trimethyl orthoester of phenylacetic acid (**2.5.2**) and camphorsulfonic acid. After consumption of the starting material, the crude reaction mixture was analyzed by NMR spectroscopy, indicating the formation of a mixed orthoester with the epoxide still intact, most likely forming **2.5.3**. Upon exposure to silica gel trying to obtain a pure sample for characterization we fortuitously observed the formation of the orthoester while also installing the isopropenyl group, giving rise to orthoester **2.5.4**. Oxidation of the remaining allylic alcohol by DMP furnished the A-ring enone **2.5.5**, leaving us with only the homovanillic acid side chain to install. To set the stage for the final transformation, TBAF removed the two remaining silyl groups affording diol **2.5.6**. A modified Mitsunobu reaction with homovanillic acid **1.3.57** then eventually completed the total synthesis of resiniferatoxin in a total of 15 steps from commercially available **2.1.2**, marking the shortest synthesis of RTX to date.

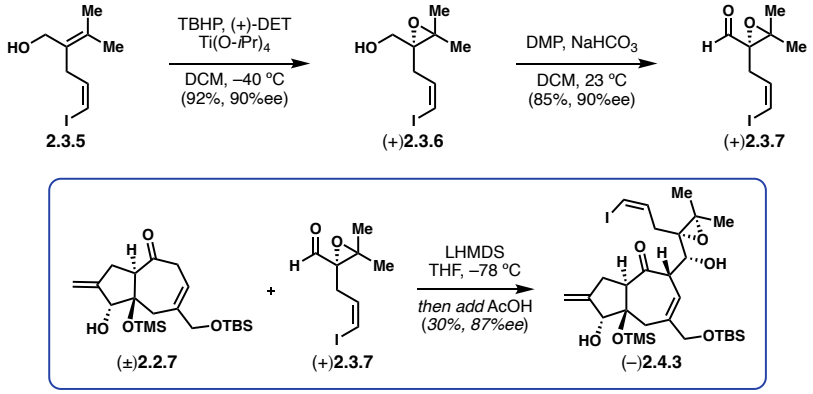
Scheme 2.5.1. Completion of the total synthesis of resiniferatoxin.



***2.6** Asymmetric Entry into the Daphnanes*

Despite accomplishing the shortest total synthesis of resiniferatoxin so far, our synthesis remained racemic. To achieve an asymmetric synthesis, we first set out to render the aldehyde fragment enantioenriched, potentially swapping the racemic *m*-CPBA epoxidation for a Sharpless asymmetric epoxidation. During our literature survey we noted that there is very limited precedent for the enantioselective epoxidations of tetrasubstituted olefins, especially ones featuring two geminal methyl groups like in our case, but thankfully a report by Frejd and coworkers reported a very similar instant in their synthetic endeavor toward Taxol.[12] Applying their condition on our substrate not only gave satisfactory levels of optical enrichment but also increased the yield of the transformation by 16%, resulting in enantioenriched **(+)-2.3.6**. Subsequent DMP oxidation delivered the desired aldehyde **(+)-2.3.7** without any considerable amount of stereo erosion. Having successfully rendered the synthesis of the aldehyde fragment enantioenriched, we employed the freshly prepared C-ring fragment **(+)-2.3.7** in the aldol reaction for constructing the 6-membered ring of the natural product. As expected, the yield dropped significantly due to only half of the racemic mixture of **(±)2.2.7** being able to form the correct diastereomer, while surprisingly observing a slight decrease in optical purity of the product compared to the starting material.

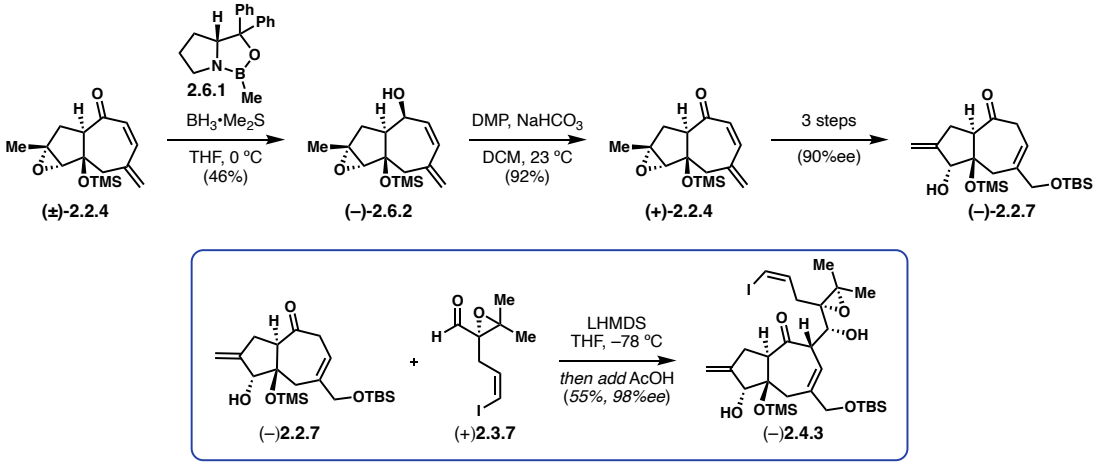
Scheme 2.6.1. Asymmetric synthesis of aldehyde partner and subsequent aldol reaction



After having synthesized the aldehyde fragment in an asymmetric fashion and successfully employed it in the aldol reaction affording **(–)-2.4.3**, we were hoping to further improve the yield as well as the enantiomeric excess by having the 5/7-fused bicycle be optically enriched as well. Since attempts of rendering the first aldol in the sequence enantioselective by employing chiral Lewis's acids, organocatalysis and the use of a chiral base for generating the enolate fell short, we would not be able to achieve optical enrichment without sacrificing roughly half of the material in a chiral resolution. Attempts at asymmetric hydrogenation of the bicyclic ketone resulted exclusively in the recovery of starting material with no formation of any reduced product observed. To our delight, we were able to reduce racemic **(±)-2.2.4** by using a Corey-Bakshi-Shibata reduction protocol employing the (*R*)-enantiomer of the oxazaborolidine catalyst **2.6.1**.[13] affording the desired diastereomeric product **(–)-2.6.2**. Subsequent reoxidation with DMP had us obtain enantiomerically enriched vinylogous enone **(+)-2.2.4**, which was subjected to the previously discussed conditions to arrive at aldol precursor **(–)-2.2.7** in 90% ee. With both aldehyde fragment as well as the 5/7-fused bicycle being enantioenriched, we were excited for the outcome of the aldol reaction. To our delight, the reaction proceeded in almost identical yield to its racemic counterpart while affording an enantiomeric excess of 98%. Since this material could be carried

forward to the natural product, this results in 17 steps asymmetric total synthesis of (+)-resiniferatoxin **1.1.1**.

Scheme 2.6.2. Asymmetric synthesis of ketone **2.2.7.** and subsequent aldol reaction.



2.7 *Synthetic Efforts toward Gnidimacrin and Other Highly Oxygenated DDO's*

Having successfully established a synthetic route to resiniferatoxin, we planned on utilizing our modular route to gain access to the 6-epoxydaphnanes and 1-alkyldaphnanes with yuanhuapin (**1.1.5**) and gnidimacrin (**1.1.8**) being flagship targets. The first challenge along the way would be the introduction of extra oxidation on C5 of the B-ring of the tricyclic core, together with the installation of the epoxide on C6 and C7. We believe that by choosing an adequate C-ring fragment we would be able to access the additional oxidation usually found on C12 like in yuanhuapin, while the primary iodide found on C18 after the SmI_2-mediated cyclization could be replaced by using silver benzoate to achieve the oxidation required in the case of gnidimacrin. Obviously, the increased structural complexity of the intermediates along the way would also change the reactivity

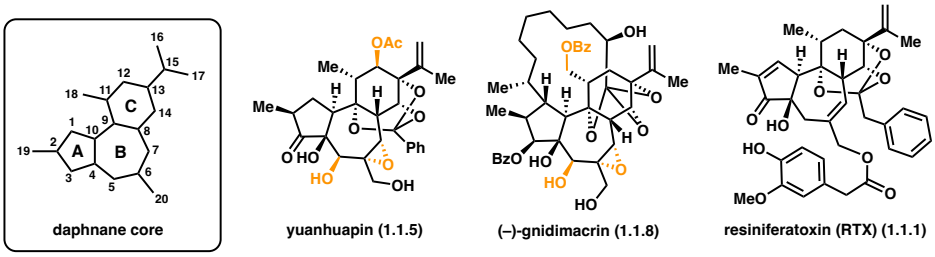
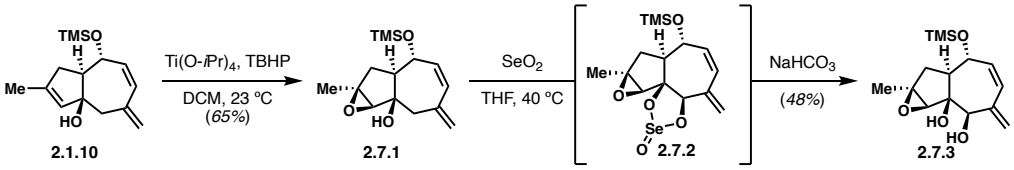


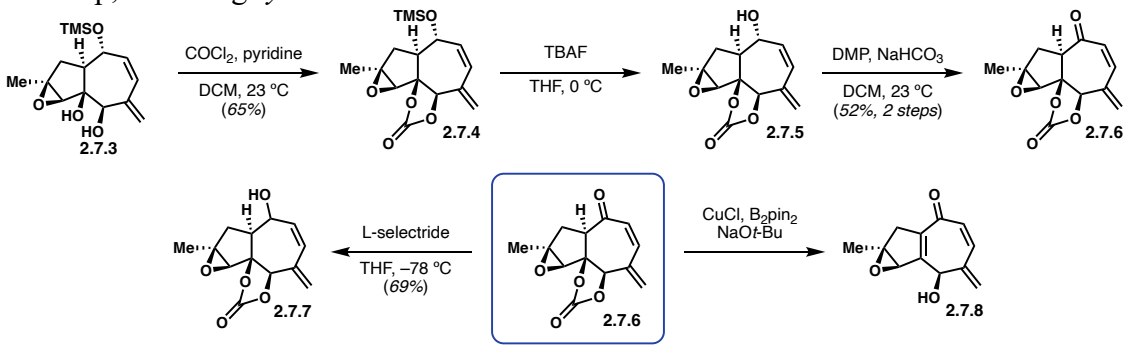
Figure 2.7.1. Yuanhuapin, gnidimacrin, RTX and the general daphnane diterpene core.

profile of the substrates to a considerable amount, together with the fact no synthetic entry has been found into those subfamilies of daphnanes, makes the total syntheses of those intriguing structures an attempt worth pursuing.



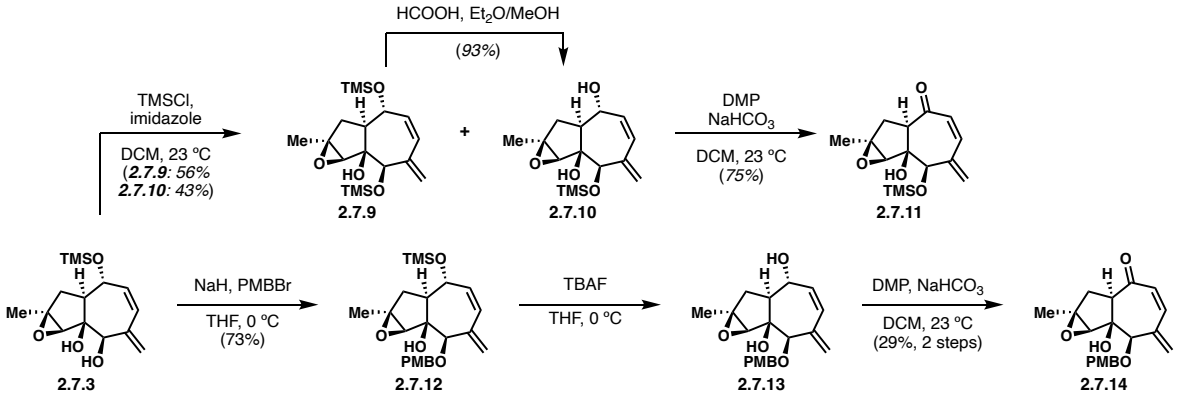
Scheme 2.7.1. Oxidation of Heck-cyclization product 2.1.10.

We planned on using the tertiary alcohol on C4 to direct the oxidations in the sequence, therefor we took Heck cyclization product **2.1.10** and subjected it to a ligandless Sharpless epoxidation. As expected, the alcohol guided the epoxidation resulting in formation of epoxide **2.7.1** with the opposite stereochemistry at C2-C3 as the one in the RTX sequence. Our next goal was the introduction of the secondary hydroxygroup on the 7-membered ring. To our delight, we were able to isolate *syn*-diol **2.7.3** after exposing **2.7.2** to SeO_2 in THF. We hypothesize that the tertiary alcohol directs the SeO_2 and after oxidation form cyclic selenite 2.7.2, which would be saponified upon workup, unveiling *syn*-diol **2.7.3**.[14]



Scheme 2.7.2. Attempts to functionalize C20 position in the carbonate series.

For the protection of the newly formed diol, we opted for a carbonate, since attempts of tying the vicinal hydroxy groups together as an acetal or silanol fell short. Said carbonate was installed by treatment of **2.7.3** with phosgene and pyridine in DCM affording carbonate **2.7.4**. TBAF desilylation afforded allylic acohol **2.7.5**, which was taken forward without purification and oxidized to the vinylogous enone **2.7.6** by DMP-oxidation, thereby setting the stage to perform a selective 1,6 functionalization. Our oxidative functionalization attempt did not prove to be fruitful, since we isolated E1cB elimation product **2.7.8**. When switching to L-selectride in hopes to obtain the 1,6-reduction product, we were only able to observe the undesired 1,2 reduction product 2.7.7. Our inability to further advance this substrate let us to investigate other protecting groups in the hopes of identifying a suitable substrate for either a 1,6-conjugate addition of a boronate or hydride.



Scheme 2.7.3. Exploration of protecting groups toward gnidimacrin building blocks.

Next, we attempted to silylate 5/7-fused bicycle **2.7.4** under conventional reaction conditions by employing TMSCl and imidazole in DCM. After purification, we isolated two products, the major product being the bis-silylated bicycle **2.7.10** with the minor product being identified as diol **2.7.11**. The latter most likely arises from a silica gel mediated desilylation, like

the one previously described in our route to resiniferatoxin. We again took inspiration from our previous worked and proved to be successful in selectively deprotecting secondary allylic silylether at C9 over the one on C5, yielding diol **2.7.11** in great yield. Subsequent DMP oxidation then afforded the vinylogous enone 2.7.12, which sadly was not able to productively engage in the conjugate delivery of either a boronate or hydride. We hypothesized that the vicinity of the TMS group to the C20 position of the vinylogous enone might interfere with the reaction by blocking the approach of the reagent, so we decided to employ a less sterically congested PMB group instead. Installation of the PMB group proceeded smoothly by using NaH as the base, delivering PMB-ether **2.7.13**. Treatment with TBAF resulted in the formation of allylic alcohol **2.7.14**, which was used crude in the oxidation, yielding PMB-protected vinylogous enone **2.7.15**.

2.8 *Conclusion*

In summary, the intricate daphnane diterpene orthoester resiniferatoxin was successfully synthesized through a sophisticated, 15-step process characterized by a convergent and stereoselective approach. This synthetic pathway was designed to be complementary to the ones that successfully delivered RTX by introducing an innovative strategy involving the late-stage construction of the 6-membered ring. The use of a (Z)-vinyl halide as a cyclization terminus, modulating the stereochemical outcome through steric and electronic factors, proved to be the key to achieve a rapid construction of the C-ring of the tricyclic core. Furthermore, exploiting the nature of the C18 halide facilitated a beneficial A ring olefin isomerization, while a novel method for installing the orthoester moiety circumvented handling sensitive C-ring triol intermediates and other complexities associated with multifunctional intermediates.

This streamlined approach enabled rapid access to resiniferatoxin, validating the hypothesis that the densely stereochemical 6-membered ring of daphnanes could be forged late in the synthesis with high selectivity. With its low step count and modular design, this synthetic strategy holds promise for the synthesis of other daphnane diterpene orthoesters, potentially paving the way for the production of more highly oxidized daphnane natural products. Some initial attempts at introducing the required oxidations found on the B-ring of related daphnanes proved to be successful, but still requires optimization which should be a priority for future research on this family of intriguing natural products. Additionally, the sequence was rendered asymmetric by enantioselective Sharpless epoxidation of the vinyliodide bearing aldehyde partner for the aldol reaction as well as accessing the ketone partner in an optically enriched fashion by means of Corey-Bakshi-Shibata reduction.

2.9 *Distribution of Credit*

The synthetic strategy to access resiniferatoxin disclosed in Section 1.4 was conceived as a collaborative effort between Prof. Tom Maimone, Dr. Vasil Vasilev, Dr. Kuan Yu, and me. Dr. Vasil Vasilev came up with the general strategy under the guidance of Prof. Tom Maimone, while Dr. Danny Thach suggested to close the B-ring using a 7-*exo-trig* Heck. Dr. Kuan Yu is credited with optimization of the 7-*exo-trig* Heck cyclization, identification of the 1,5-HAT by use of 2D-NMR spectroscopy as well as figuring out the selective 1,6-borylation. My contributions to the route were suggesting the use of the vinyl iodide bearing aldehyde partner to ensure the correct stereocenter of the methyl group on the C-ring as well as the use of the exocylic A-ring olefin to be then transposed into the ring through an observed 1,5-HAT. Most of the front-line chemistry was carried out by Dr. Vasil Vasilev using material I prepared. The asymmetric synthesis of **2.3.7**. was conducted as a collaborative effort between Dr. Kuan Yu and me under the guidance of Prof. Tom Maimone. The asymmetric synthesis of 2.2.7 and 2.4.3 were carried out by me. All compounds shown in section 2.7 were synthesized and characterized by me.

2.10 References

(1) Piers, E.; Wong, T.; Coish, P. D.; Rogers, C. A Convenient Procedure for the Efficient Preparation of Alkyl (Z)-3-Iodo-2-Alkenoates. *Can. J. Chem.* **1994**, *72*, 1816‑1819.

(2) Marek, I.; Meyer, C.; Normant, J.-F. A Simple and Convenient Method for the Preparation of (Z)- β -Iodoacrolein and of (Z)- or (E)- γ -Iodo Allylic Alcohols: (Z)- and (E)-1-Iodohept-1-En-3-Ol: 2-Propenal, 3-Iodo-, (Z)- and 1-Hepten-3-Ol, 1-Iodo-, (Z)- and (E)-. In *Organic Syntheses*; John Wiley & Sons, Inc., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2003; pp 194‑194.

(3) Zimmerman, H. E.; Traxler, M. D. The Stereochemistry of the Ivanov and Reformatsky Reactions. I. *J. Am. Chem. Soc.* **1957**, *79*, 1920‑1923.

(4) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. Acyclic Stereoselection. 7. Stereoselective Synthesis of 2-Alkyl-3-Hydroxy Carbonyl Compounds by Aldol Condensation. *J. Org. Chem.* **1980**, *45*, 1066–1081.

(5) Beletskaya, I. P.; Cheprakov, A. V. The Heck Reaction as a Sharpening Stone of Palladium Catalysis. *Chem. Rev.* **2000**, *100*, 3009–3066.

(6) Gao, P.; Cook, S. P. A Reductive-Heck Approach to the Hydroazulene Ring System: A Formal Synthesis of the Englerins. *Org. Lett.* **2012**, *14*, 3340–3343.

(7) Overman, L. E. Application of Intramolecular Heck Reactions for Forming Congested Quaternary Carbon Centers in Complex Molecule Total Synthesis. *Pure Appl. Chem.* **1994**, *66*, 1423–1430.

(8) Sapkota, K.; Huang, F. Selective Protection of Secondary Alcohols by Using Formic Acid as a Mild and Efficient Deprotecting Reagent for Primary *tert*-Butyldemethylsilyl Ethers. *Synlett* **2019**, *30*, 1895-1898.

(9) Chea, H.; Sim, H.-S.; Yun, J. Ligandless Copper-Catalyzed β-Boration of a α,β-Unsaturated Compounds in Aqueous Solution. *Bull. Korean Chem. Soc*. **2010**, *31*, 551.

(10) Yamamoto, H.; Nozaki, H. Selective Reactions with Organoaluminum Compounds *Angew. Chem. Int. Ed*. **1978**, *17*, 169-175.

(11) Zhu, N.; Hall, D.G. Effect of Additives on the Stereochemical Integrity and Reactivity of a-Alkoxycarbonyl Alkenylcopper Intermediates. Optimal Conditions for the Synthesis of Isomerically Pure Tetrasubstituted Alkenes. *J. Org. Chem*. **2003**, *68*, 6066

(12) Pettersson, L.; Magnusson, G.; Frejd, T. Synthesis of Optically Active A-Ring Fragments of Taxol via Electrophilic Ring Closure of an Epoxy-Allylsilane *Acta Chem. Scand*. **1993**, *47*, 196-207.

(13) Watarai, Y.; Ishizawa, M.; Ikura, T.; Zacconi, F.C.; Uno, S.; Ito, N.; Mouriño, A.; Tokiwa, H.; Makishima, M.; Yamada, S. Synthesis, Biological Activities, and X-Ray Crystal Structure Analysis of 25-Hydroxy-25(or 26)-adamantyl-17-[20(22)23-dinyl]-21-norvitamin D Compounds. *J. Med. Chem.* **2015**, *58*, 9510-9521

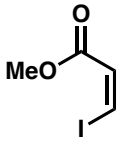
(14) Snider, B.; Shi, B. Syntheses of (E)- and (Z)-Volkendousin. *Tetrahedron* **1999**, *55*, 14823-14828

2.11 *Experimental Procedure and Characterization Data*

2.11.1 General Procedures:

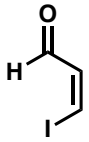
All reactions were performed in flame- or oven-dried glassware under positive pressure of nitrogen or argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe. When indicated, solvents or reagents were degassed by sparging with argon for 10 minutes in an ultrasound bath at 25 °C. Volatile solvents were removed under reduced pressure rotary evaporation. Analytical and preparative thin-layer chromatography (TLC) were performed using glass plates coated with silica gel (0.25-mm, 60-Å pore size, Merck TLC Silicagel 60 F254) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and then were stained by submersion in an ethanolic anisaldehyde solution or potassium permanganate solution followed by brief heating on a hot plate. Flash column chromatography was performed with silica gel purchased from Fisher Scientific (230-40 mesh, Grade 60). All samples were loaded onto flash columns either as solutions in EtOAc/hexanes or dry loaded by resuspension of the crude mixture in Et_2O followed by careful concentration to dryness under reduced pressure. Triethylamine, chlorotrimethylsilane, and 2,2,6,6-tetramethylpiperidine were distilled over calcium hydride prior to use. Anhydrous acetonitrile (MeCN), tetrahydrofuran (THF), toluene (PhMe), dichloromethane (DCM) were obtained by passing these previously degassed solvents through activated alumina columns. Anhydrous benzene (PhH) was purchased from Sigma Aldrich. All other reagents were used as received from commercial sources, unless otherwise noted. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker AVB400, AV500, AV600, and AV700 spectrometers at 23 oC. Proton chemical shifts are expressed as parts per million (ppm, δ scale) and are referenced to residual solvent ($CHCl_3$, δ 7.26 (s), C_6D_5H δ 7.16 (s)). Carbon chemical shifts are expressed as parts per million (ppm, δ scale) and are referenced to the solvent ($CHCl_3$, δ 77.0, C_6D_6, δ 128.06). Data is presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublet, dt = triplet of doublet, t = triplet, q = quartet, m = multiplet, br = broad, coupling constant (*J*) in Hertz (Hz), and integration. Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer as thin films and are reported as frequency of absorption (cm^{-1}). Only selected resonances are reported. High-resolution mass spectra (HRMS) were obtained by the mass spectrometry facility at the University of California, Berkeley using a Finnigan LTQFT mass spectrometer (Thermo Electron Corporation).

2.11.2 Experimental procedures and Tabulated Characterization Data



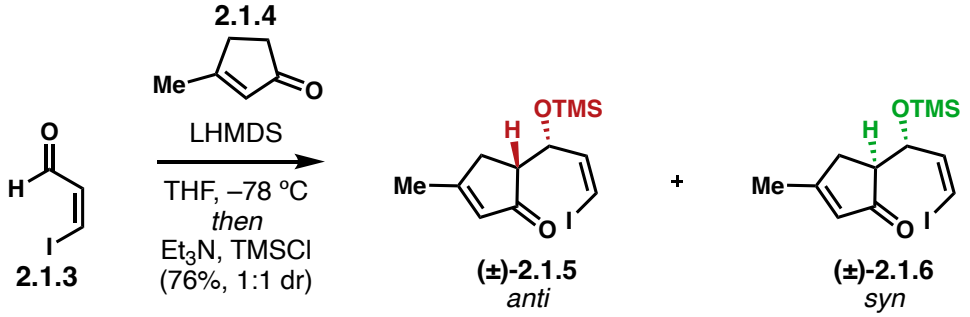
Ester 2.1.2: **2.1.2**

Ester **2.1.2** was prepared from commercially available methyl propiolate according to a literature procedure and was used without purification. The spectral data were found to match those reported in literature.[1]



Aldehyde 2.1.3: **2.1.3**

Aldehyde **2.1.3** was prepared from methyl (*Z*)-3-iodoprop-2-enoate, according to a literature procedure and was used without purification. The spectral data were found to match those reported in the literature. [2]



Aldol product 2.1.5:

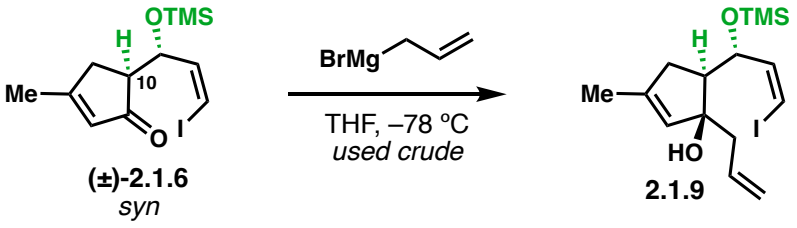
A flame-dried 500 mL round-bottom flask was charged with THF (56 mL) and LHMDS (56 mL, 1M in THF, 56 mmol, 1.2 equiv.) and was subsequently cooled to 0 ºC. 3-methyl cyclopentenone (4.70 mL, 4.54 g, 47.2 mmol, 1.0 equiv.) was added neat and the resulting red-orange colored solution was stirred for 15 minutes before being cooled to – 78 ºC. Aldehyde **2.1.3** (8.59 g, 47.2 mmol, 1.0 equiv.) was dissolved in THF (38.0 mL) and the resulting solution was added dropwise using a syringe pump at a flow rate of 50 mL/h. After stirring for an additional 1 hour, Et_3N (14.3 g, 20.0 mL, 142 mmol, 3.0 equiv.) and TMSCl (7.69 g, 9.00 mL, 70.8 mmol, 1.5 equiv.) were added dropwise. The reaction mixture was allowed to warm to ambient temperature over 2.5 hours before being quenched by the addition of saturated *aq*. NH_4Cl (100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was passed through a short plug of silica gel (0 to 20% EtOAc/hexanes in 10% increments) to afford

aldol product **2.1.5** and its C10-epimer **2.1.6** (12.5 g, 35.1 mmol, 76%, 1:1 dr) as a yellow oil. These diastereomers can be separated by careful flash column chromatography (0 to 15% EtOAc/hexanes in 2.5% increments) to provide pure **2.1.5** and **2.1.6**. *aldol product*

2.1.6:
TLC: R_f = 0.37 (10% EtOAc/hexanes)
^{1}H NMR (600 MHz, C_6D_6): δ 6.01 (t, *J* = 7.7 Hz, 1H), 5.84 (dd, *J* = 7.7, 1.2 Hz, 1H), 5.76 (h, *J* = 1.5 Hz, 1H), 5.25 (ddd, *J* = 7.7, 2.4, 1.2 Hz, 1H), 2.46 (dddt, *J* = 17.7, 3.2, 2.0, 1.1 Hz, 1H), 2.37 – 2.32 (m, 1H), 1.83 – 1.75 (m, 1H), 1.45 (s, 3H), 0.17 (s, 9H).
^{13}C NMR (150 MHz, C_6D_6): δ 206.3, 176.8, 143.1, 130.7, 80.0, 74.4, 52.0, 33.2, 18.9, 0.4.
IR (thin film) n_{max} (cm^{-1}): 2956, 2907, 1698, 1623, 1250, 1102, 1056, 1027, 856.
HRMS (m/z): (ESI) calcd. for $C_{12}H_{19}O_2{}^{127}I^{23}Na^{28}Si$ $[M+Na]^+$: 373.0091, found 373.0093.

C10-epimer **2.1.5**:
TLC: R_f = 0.31 (10% EtOAc/hexanes)
^{1}H NMR (600 MHz, C_6D_6): δ 6.76 (t, *J* = 7.8 Hz, 1H), 5.89 (dd, *J* = 7.5, 0.9 Hz, 1H), 5.69 (s, 2H), 4.70 (dd, *J* = 8.0, 3.6 Hz, 1H), 2.48 (dt, *J* = 6.7, 3.1 Hz, 1H), 2.19 – 2.12 (m, 1H), 2.02 (dd, *J* = 18.1, 7.2 Hz, 1H), 1.43 (s, 3H), 0.12 (s, 9H).
^{13}C NMR (150 MHz, C_6D_6) δ 206.1, 175.3, 142.4, 131.4, 81.3, 76.3, 51.9, 36.6, 18.6, 0.4.

The undesired aldol product **2.1.5** can be epimerized as follows: an oven-dried 500 mL round-bottom flask was charged with undesired C10-epimer **2.1.5** (8.40 g, 24 mmol, 1.0 equiv.), DCM (240 mL), and DBU (7.2 mL, 48.0 mmol, 2.0 equiv.). The resulting solution was stirred at room temperature for 12 hours before being quenched with satd. *aq*. NH_4Cl (200 mL). The organic layer was separated, and the aqueous layer extracted with DCM (3 x 200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to obtain a crude mixture of **2.1.5** and **2.1.6**, which was purified as detailed above to provide the desired diastereomer **2.1.6** (3.60 g, 10.3 mmol, 43% yield).

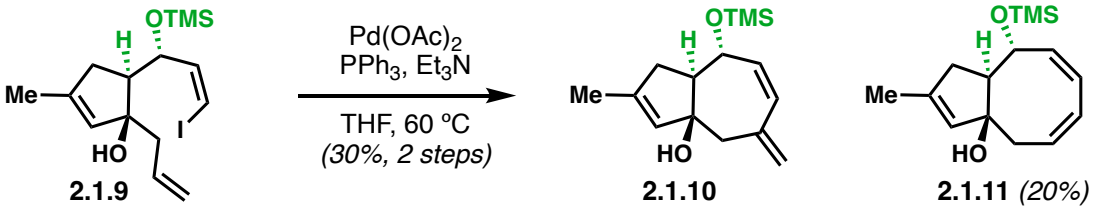


Tertiary alcohol 2.1.9:

An oven-dried 250 mL round-bottom flask was charged with *syn*-aldol product **2.1.5** (4.60 g, 13.1 mmol, 1.0 equiv.) and THF (131 mL). The resulting solution was cooled to –78 ºC and a solution of allylmagnesium bromide (15.7 mL, 1 M in Et_2O, 15.7 mmol, 1.2 equiv.) was added dropwise. After 3 minutes the reaction mixture was quenched with satd. *aq.* NH_4Cl (100 mL) and allowed to warm to room temperature. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to provide crude allylic alcohol **2.1.9**, which was used in the subsequent step without purification.

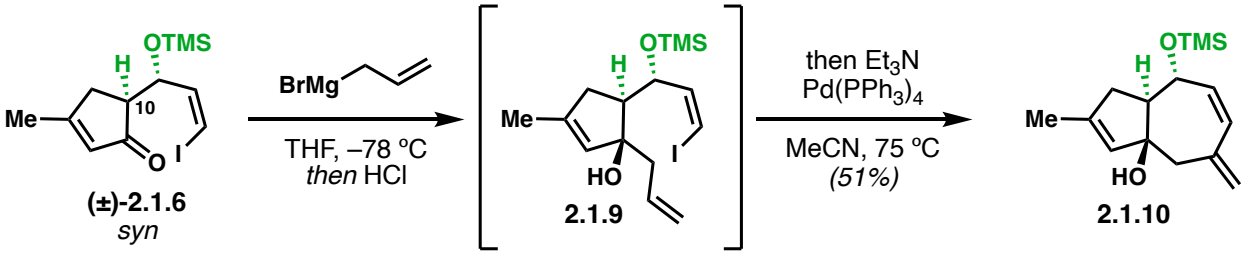
TLC: R_f = 0.50 (10% EtOAc/hexanes)
^{1}H NMR: (600 MHz, C_6D_6) δ 6.12-6.07 (m, 2H), 5.79 (dd, *J* = 7.6, 1.0 Hz, 1H), 5.43 (d, *J* = 1.6 Hz, 1H), 5.20 (ddt, *J* = 17.2, 2.5, 1.4 Hz, 1H), 5.15 (d, *J* = 10.3 Hz, 1H), 4.94 (dd, *J* = 8.2, 2.4 Hz, 1H), 3.14 (br s, 1H, OH), 2.66 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.62 – 2.53 (m, 2H), 2.29 (ddd, *J* = 9.3, 6.4, 3.1 Hz, 1H), 1.98 (dd, *J* = 16.2, 8.7 Hz, 1H), 1.55 (d, *J* = 1.1 Hz, 3H), 0.12 (s, 9H).

***Trans*-fused hydroazulene 2.1.10**:



*Two-step procedure with crude allylation product **2.1.9**:* An oven-dried 500 mL round-bottom flask was charged with $Pd(OAc)_2$ (540 mg, 2.4 mmol, 0.18 equiv.), PPh_3 (1.26 g, 4.8 mmol, 0.37 equiv.), and THF (100 mL). The resulting suspension was stirred at room temperature for 5 minutes, then Et_3N (9 mL, 65 mmol, 4.96 equiv.) was added and the reaction mixture was stirred at 60 ºC for 5 minutes, resulting in a deep red color. At this stage a solution of crude tertiary alcohol **2.1.9** (assumed 13.1 mmol, 1.0 equiv.) in THF (30 mL) was added and stirring was continued at 60 ºC for 12 hours or until consumption of the starting material was complete as judged by TLC. The reaction mixture was cooled to room temperature and quenched with satd. *aq*. $NaHCO_3$ (100 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to provide crude hydroazulene **2.1.10**. The resulting crude mixture was purified using flash column chromatography (0 to 15% EtOAc/hexanes in 2.5% increments) to provide pure *trans*-fused hydroazulene **2.1.10** (1.04 g, 3.93 mmol, 30% from ketone **2.1.5**) as a colorless to pale yellow oil alongside 5,8-fused bicycle **2.1.11** (692 mg, 2.62 mmol, 20% from ketone **2.1.5**).

*One-step procedure from aldol product **2.1.5**:*

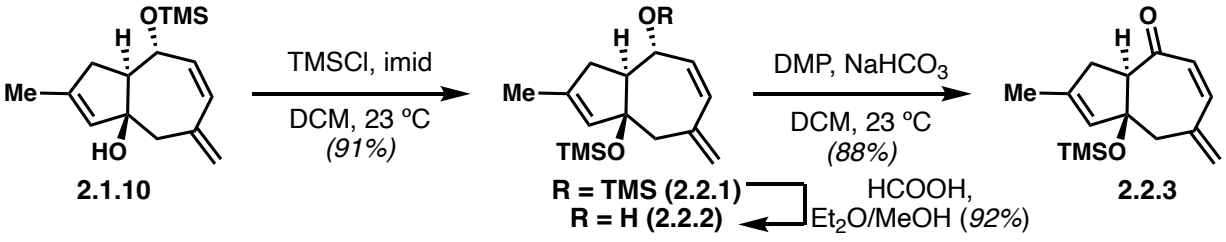


An oven-dried reaction tube was charged with enone **2.1.5** (100 mg, 0.285 mmol, 1.0 equiv.) and

dry THF (2.8 mL). The resulting solution was cooled to –78 ºC and a solution of allylmagnesium bromide (0.34 mL, 1 M in THF, 0.34 mmol, 1.2 equiv.) was added dropwise. After stirring for 3 minutes, hydrogen chloride (0.20 mL, 2 M in Et_2O, 0.40 mmol, 1.4 equiv.) and triethylamine (0.400 mL, 2.88 mmol, 10.0 equiv.) were added sequentially. The reaction mixture was warmed to 0 oC, diluted with acetonitrile (2.8 mL), and stirred for 10 min, at which point $Pd(PPh_3)_4$ (16 mg, 0.014 mmol, 0.05 equiv.) was added and the reaction flask placed into a pre-heated 75 ºC oil bath. Conversion was monitored by TLC and an additional portion of $Pd(PPh_3)_4$ was added after 3 hours if starting material was still present in the reaction mixture. Once conversion was complete as judged by TLC, the reaction flask was cooled to room temperature and quenched with satd. *aq*. $NaHCO_3$ (5 mL). The organic layer was separated, and the aqueous layer extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude mixture was purified using flash column chromatography (0 to 15% EtOAc/hexanes in 2.5% increments) to provide pure *trans*-fused hydroazulene **2.1.10** (38.0 mg, 0.144 mmol, 51%) as a colorless to pale yellow oil.

*Trans-fused hydroazulene **2.1.10**:*
TLC: R_f = 0.29 (10% EtOAc/hexanes)
^{1}H NMR (600 MHz, C_6D_6): δ 6.09 (ddd, *J* = 13.1, 2.3, 1.0 Hz, 1H), 5.74 – 5.68 (m, 1H), 5.14 (hept, *J* = 1.5 Hz, 1H), 4.99 (ddq, *J* = 2.4, 1.6, 0.8 Hz, 1H), 4.94 (td, *J* = 2.3, 1.2 Hz, 1H), 4.59 (dt, *J* = 10.3, 2.3 Hz, 1H), 2.68 (dd, *J* = 15.1, 0.9 Hz, 1H), 2.53 (dt, *J* = 15.1, 2.5 Hz, 1H), 2.49 – 2.41 (m, 1H), 2.40 – 2.35 (m, 2H), 1.54 (s, *J* = 1.2 Hz, 3H), 0.16 (s, 9H).
^{13}C NMR (150 MHz, C_6D_6): δ 144.7, 142.4, 135.8, 132.4, 129.2, 81.5, 73.1, 55.6, 47.7, 41.7, 16.9, 0.6.
IR (thin film) n_{max} (cm^{-1}): 3500, 2956, 2911, 2850, 1441, 1249, 1054, 1043, 883, 836.
HRMS (m/z): (ESI) calcd. for $C_{15}H_{23}O_2{}^{28}Si$ $[M–H]^-$: 263.1473, found 263.1474.
*5,8-fused bicycle **2.1.11**:*
TLC: R_f = 0.32 (10% EtOAc/hexanes)
^{1}H NMR: (600 MHz, C_6D_6) δ 5.97 (dd, *J* = 11.3, 3.8 Hz, 1H), 5.94 (dd, *J* = 11.9, 5.4 Hz, 1H), 5.69 (dd, *J* = 12.0, 3.6 Hz, 1H), 5.64 (dt, *J* = 11.1, 8.0 Hz, 1H), 5.30 (s, 1H), 4.75 – 4.71 (m, 1H), 2.57 (dd, *J* = 12.9, 8.6 Hz, 1H), 2.36 (dddd, *J* = 15.2, 9.6, 2.2, 1.3 Hz, 1H), 2.28 (td, *J* = 9.7, 6.6 Hz, 1H), 2.20 (dd, *J* = 15.3, 6.6 Hz, 1H), 2.14 (dt, *J* = 12.7, 6.4 Hz, 1H), 1.53 (s, 3H), 0.18 (s, 9H).
^{13}C NMR: (151 MHz, C_6D_6) δ 146.5, 140.8, 134.2, 129.2, 128.8, 122.7, 80.5, 69.2, 55.6, 37.6, 37.2, 17.2, 0.3.
HRMS (m/z): (ESI) calcd. for $C_{15}H_{24}O_2{}^{23}Na^{28}Si$ $[M+Na]^+$: 287.1438, found 287.1438.

Silanol 2.2.1:



A flame-dried 250 mL round-bottom flask was charged with *trans*-fused hydroazulene **2.1.10** (2.00

g, 7.55 mmol, 1.0 equiv.) and DCM (75 mL). Imidazole (1.54 g, 22.64. mmol, 3.0 equiv.) was added, followed by dropwise addition of TMSCl (1.44 mL, 11.32 mmol, 1.5 equiv.), resulting in formation of a white precipitate. The reaction mixture was stirred for 1 hour, at which point conversion was complete as judged by TLC. The suspension was quenched with satd. *aq.* $NaHCO_3$ (75 mL) and the layers were separated. The aqueous layer was extracted with DCM (3 x 50 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to provide crude silanol **2.2.1**. This compound was purified by a short silica plug (0 to 15% EtOAc/hexanes), resulting in pure bicycle **2.2.1** (2.31 mg, 6.86 mmol, 91%) as a pale-yellow oil.

TLC: R_f = 0.92 (25% EtOAc/hexanes).
^{1}H NMR: (600 MHz, C_6D_6) δ 6.12 (d, *J* = 13.0 Hz, 1H), 5.74 (d, *J* = 13.0 Hz, 1H), 5.24 (s, 1H), 4.99 (d, *J* = 2.1 Hz, 1H), 4.92 (s, 1H), 4.67 (d, *J* = 9.1 Hz, 1H), 2.76 (d, *J* = 15.2 Hz, 1H), 2.53 (dt, *J* = 15.2, 2.2 Hz, 1H), 2.48 – 2.36 (m, 3H), 1.55 (s, 3H), 0.19 (s, 9H), 0.11 (s, 9H).
^{13}C NMR: (151 MHz, C_6D_6) δ 145.3, 143.3, 135.6, 132.0, 129.1, 119.3, 84.3, 73.1, 57.0, 48.4, 41.5, 16.7, 2.1, 0.5.

Secondary alcohol 2.2.2:

*Via deprotection of **2.2.1**:* A flame-dried 250 mL RBF was charged with silanol **2.2.2** (2.31 g, 6.86 mmol, 1.0 equiv.), Et_2O (1.4 mL) and MeOH (1.4 mL). Neat formic acid (390 µL, 10.29 mmol, 1.5 equiv.) was added and the resulting mixture was stirred at room temperature. Conversion was monitored by TLC and additional HCOOH (130 µL, 3.43 mmol, 0.5 equiv.) was added if there was still starting material present after 1 hour. Once all silanol **2.2.2** was consumed, the reaction mixture was *carefully* quenched by dropwise addition of satd. *aq.* $NaHCO_3$ (50 mL or until all formic acid was neutralized). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to provide crude alcohol **2.2.6**. Purification by column chromatography (0 to 25% EtOAc/hexanes in 5% increments) resulted in pure secondary alcohol **2.2.2** (1.80 mg, 6.81 mmol, 99%) as a colorless oil.

*One-step procedure from Heck product **2.1.10**:* An oven-dried 25 mL round-bottom flask was charged with *trans*-fused hydroazulene **2.1.10** (105 mg, 0.398 mmol, 1.0 equiv.) and DCM (4.0 mL). To this solution were added imidazole (54.1 mg, 0.796 mmol, 2.0 equiv.) and TMSCl (0.060 mL, 0.48 mmol, 1.2 equiv.) and the resulting suspension was stirred for 3 hours at room temperature until full consumption of the starting material was observed by TLC. At this stage, silica gel (5.0 g) was added and stirring was continued for another 3 h to liberate the C9 alcohol. The resulting suspension was concentrated under reduced pressure and the crude residue was loaded onto a flash column and purified (0 to 25% EtOAc/hexanes in 5% increments) to obtain the pure free secondary alcohol **2.2.2** (104 mg, 0.394 mmol, 99% yield) as a colorless oil.

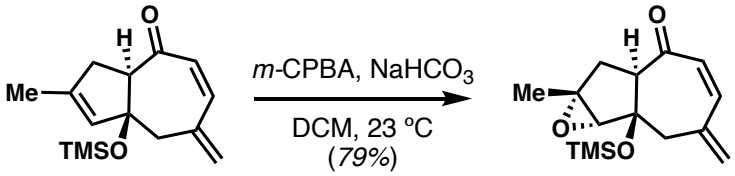
TLC: R_f = 0.26 (10% EtOAc/hexanes)
^{1}H NMR (600 MHz, C_6D_6): δ 6.07 (ddd, *J* = 13.0, 2.4, 1.1 Hz, 1H), 5.66 – 5.60 (m, 1H), 5.22 (hept, *J* = 1.3 Hz, 1H), 4.99 (tt, *J* = 2.4, 0.9 Hz, 1H), 4.91 (td, *J* = 2.4, 1.2 Hz, 1H), 4.37 (ddt, *J* = 10.1, 7.8, 2.4 Hz, 1H), 2.76 (d, *J* = 15.2 Hz, 1H), 2.49 (dt, *J* = 15.2, 2.5 Hz, 1H), 2.38 – 2.30 (m,

1H), 2.23 (dd, J = 16.1, 7.3 Hz, 1H), 2.07 (ddd, J = 10.5, 8.9, 7.2 Hz, 1H), 1.56 – 1.51 (s, 3H), 0.88 (br s, 1H of OH), 0.08 (s, 8H).
^{13}C NMR (150 MHz, C_6D_6): δ 145.4, 143.4, 134.9, 131.9, 129.6, 119.7, 84.5, 72.3, 57.2, 48.5, 41.2, 16.8, 2.2.
IR (thin film) n_{max} (cm^{-1}): 3304, 2959, 2931, 2910, 1594, 1438, 1248, 1140, 1020, 865, 762.
HRMS (m/z): (ESI) calcd. for $C_{15}H_{23}O_2{}^{28}Si$ $[M–H]^-$: 263.1473, found 263.1479.

Enone 2.2.3:

A flame-dried 100 mL round-bottom flask was charged with secondary alcohol **2.2.2** (1.13 g, 4.27 mmol, 1.0 equiv.) and DCM (42 mL). Then, solid $NaHCO_3$ (717 mg, 8.54 mmol, 2.0 equiv.) was added, followed by Dess-Martin periodinane (2.72 mg, 6.41 mmol, 1.5 equiv.). After 5 minutes conversion was complete as judged by TLC. The reaction mixture was quenched with satd. *aq*. $NaHCO_3$ (20 mL) and satd. *aq*. $Na_2S_2O_3$ (20 mL) and the layers were separated. The aqueous layer was extracted with DCM (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to provide crude enone **2.2.7**. This compound can be used in its crude form or, alternatively, can be purified by column chromatography (0 to 20% EtOAc/hexanes) to provide pure enone **2.2.7** (984 mg, 3.75 mmol, 88%) as a pale-yellow oil.

TLC: R_f = 0.75 (25% EtOAc/hexanes)
^{1}H NMR: (600 MHz, C_6D_6) δ 6.32 (d, J = 12.9 Hz, 1H), 5.99 (d, J = 12.9 Hz, 1H), 5.12 (s, 1H), 5.06 (s, 1H), 4.96 (s, 1H), 3.22 (dd, J = 16.8, 8.3 Hz, 1H), 2.95 (t, J = 8.0 Hz, 1H), 2.82 (d, J = 16.1 Hz, 1H), 2.54 (dt, J = 16.1, 2.2 Hz, 1H), 1.49 (s, 3H), 0.02 (s, 9H).
^{13}C NMR: (151 MHz, C_6D_6) δ 196.1, 145.7, 143.1, 141.2, 129.5, 128.9, 125.7, 83.8, 63.2, 47.4, 36.3, 16.5, 1.7.
HRMS (m/z): (ESI) calcd. for $C_{15}H_{22}O_2{}^{23}Na^{28}Si$ $[M+Na]^+$: 285.1281, found 285.1284.



2.2.3 **2.2.4**

Epoxide 2.2.4
*From enone **2.2.3**:*

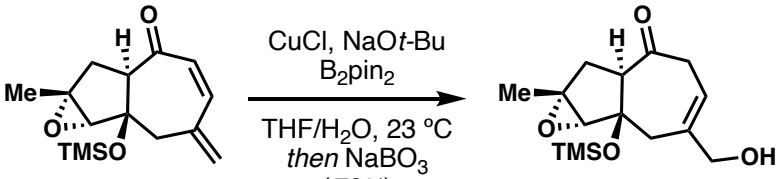
A flame-dried 50 mL round-bottom flask was charged with enone **2.2.4** (460 mg, 1.75 mmol, 1.0 equiv.), $NaHCO_3$ (294 mg, 3.50 mmol, 2.0 equiv.) and DCM (18 mL). Then, *m*-CPBA (363 mg, 2.10 mmol, 1.2 equiv.) was added and stirring was continued at room temperature until conversion was complete as judged by TLC. At this point the reaction mixture was quenched with satd. *aq.* $NaHCO_3$ (10 mL) and satd. *aq*. $Na_2S_2O_3$ (10 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction product was purified by flash column

chromatography (10 to 30% EtOAc/hexanes in 5% increments) to provide pure epoxide **2.2.4** (385 mg, 1.38 mmol, 79% yield) as a colorless oil.

*One-step procedure from secondary alcohol **2.2.2**:* An oven-dried 50 mL round-bottom flask was charged with secondary alcohol **2.2.2** (215 mg, 0.814 mmol, 1.0 equiv.), $NaHCO_3$ (138 mg, 1.62 mmol, 2.0 equiv.) and DCM (8.0 mL). Dess-Martin periodinane (385 mg, 0.908 mmol, 1.1 equiv.) was added and within 3 minutes full conversion to the enone was observed by TLC. At this point *m*-CPBA (224 mg, 1.30 mmol, 1.6 equiv.) was added and stirring was continued at room temperature until conversion to the A ring epoxide was complete as judged by TLC. The reaction mixture was quenched with satd. *aq*. $NaHCO_3$ (5 mL) and satd. *aq*. $Na_2S_2O_3$ (5 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction product was purified by flash column chromatography (10 to 30% EtOAc/hexanes in 5% increments) to provide pure epoxide **2.2.4** (136 mg, 0.489 mmol, 60% yield) as a colorless oil.

TLC: R_f = 0.52 (25% EtOAc/hexanes)
^{1}H NMR (600 MHz, C_6D_6): δ 6.20 (dd, *J* = 13.1, 0.9 Hz, 1H), 5.89 (d, *J* = 12.9 Hz, 1H), 4.97 (d, *J* = 2.3 Hz, 1H), 4.88 (dt, *J* = 2.2, 1.1 Hz, 1H), 2.96 (s, 1H), 2.84 (dt, *J* = 16.4, 2.5 Hz, 1H), 2.76 – 2.68 (m, 2H), 2.49 (dd, *J* = 14.2, 9.9 Hz, 1H), 2.04 (dd, *J* = 14.2, 7.4 Hz, 1H), 1.25 (s, 3H), -0.03 (s, 8H).
^{13}C NMR (150 MHz, C_6D_6): δ 196.4, 142.0, 140.9, 128.9, 126.5, 80.7, 67.6, 63.3, 59.2, 43.1, 32.5, 17.4, 2.0.
IR (thin film) n_{max} (cm^{-1}): 2959, 2935, 1663, 1595, 1446, 1249, 1111, 1050, 838.
HRMS (m/z): (EI) calcd. for $C_{15}H_{22}O_3Si$ $[M]^+$: 278.1338, found 278.1339.

Allylic alcohol 2.8.1:



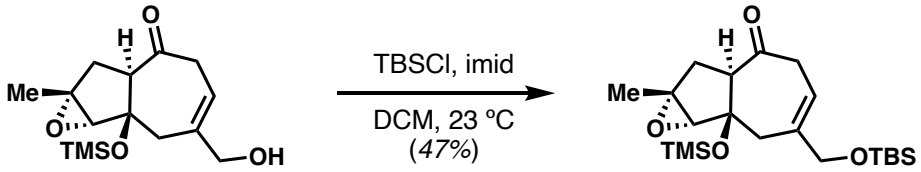
2.2.4 **2.2.5**

A flame-dried 100 mL round-bottom flask was charged with CuCl (12 mg, 0.121 mmol, 0.1 equiv.), NaO*t*-Bu (12 mg, 0.121 mmol, 0.1 equiv.), and THF (5 mL). These reagents were stirred together for 10 min at room temperature, at which point a solution of B_2pin_2 (340 mg, 1.335 mmol, 1.1 equiv.) in THF (5 mL) was added and stirring was continued for another 10 minutes. Then, enone **2.2.4** (338 mg, 1.214 mmol, 1.0 equiv.) in THF (5 mL) was added, followed by H_2O (10 mL). The resulting mixture was stirred at room temperature for 0.5 hours, at which point conversion was complete as judged by TLC. Solid $NaBO_3$•$4H_2O$ (560 mg, 3.642 mmol, 3.0 equiv.) was added and stirring was continued for 1 hour or until all boronate was oxidized. The reaction mixture was quenched with satd. *aq.* $Na_2S_2O_3$ (20 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction product was loaded on a chromatography column, which was eluted with 10 to 50% Et_2O/DCM. The fractions containing the product were combined, concentrated, and re-purified using another chromatography column

(25 to 45% EtOAc/hexanes) to provide pure allylic alcohol **2.2.5** (263 mg, 0.887 mmol, 73% yield) as a colorless oil.

TLC: R_f = 0.48 (50% EtOAc/hexanes)
^{1}H NMR (700 MHz, C_6D_6): δ 5.16 (ddd, *J* = 7.8, 3.2, 1.7 Hz, 1H), 3.61 (s, 2H), 3.26 (dq, *J* = 20.6, 2.5 Hz, 1H), 3.03 (s, 1H), 2.87 (dd, *J* = 20.2, 7.6 Hz, 1H), 2.77 (t, *J* = 8.6 Hz, 1H), 2.68 (d, *J* = 18.4 Hz, 1H), 2.51 – 2.45 (m, 2H), 2.02 (dd, *J* = 14.3, 7.9 Hz, 1H), 1.24 (s, 3H), -0.01 (d, *J* = 0.8 Hz, 9H).
^{13}C NMR (175 MHz, C_6D_6): δ 205.8, 137.0, 117.4, 81.6, 69.3, 67.6, 64.6, 60.0, 42.8, 39.5, 32.5, 17.5, 2.1.
IR (thin film) n_{max} (cm^{-1}): 3420, 2957, 2932, 1707, 1252, 1104, 1063, 986, 840.
HRMS (m/z): (ESI) calcd. for $C_{15}H_{24}O_4{}^{23}Na^{28}Si$ $[M+Na]^+$: 319.1336, found 319.1337.

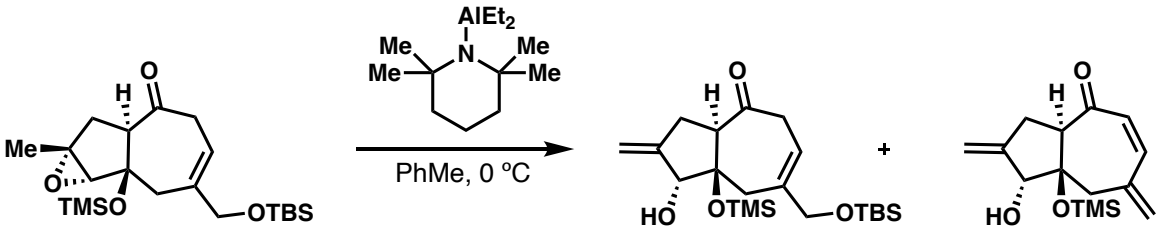
Protected epoxide 2.2.6:



A 20 mL vial containing allylic alcohol 2.2.5 (100 mg, 0.337 mmmol, 1.0 equiv.) was charged with DCM (5 mL) and imidazole (69 mg, 1.012 mmol, 3.0 equiv.). TBSCl (76 mg, 0.506 mmol, 1.5 equiv.) was added and the reaction mixture was stirred for 30 mins before being quenched by addition of satd. aq. $NaHCO_3$ (5 mL). The layers were separated and the aqeous layer was extracted using DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (0 to 30% EtOAc/hexanes in 5% increments) to provide pure protected epoxide 2.2.6 (65 mg, 0.157 mmol, 47%) as colorless oil.

TLC: R_f = 0.67 (25% EtOAc/hexanes)
^{1}H NMR (700 MHz, C_6D_6) δ 5.39 (ddt, *J* = 7.7, 3.2, 1.6 Hz, 1H), 3.88 (d, *J* = 1.9 Hz, 2H), 3.31 (dq, *J* = 20.1, 2.5 Hz, 1H), 3.05 (s, 1H), 2.92 (dd, *J* = 20.3, 7.7 Hz, 1H), 2.85 – 2.80 (m, 1H), 2.80 – 2.74 (m, 1H), 2.63 (d, *J* = 18.4 Hz, 1H), 2.48 (dd, *J* = 14.3, 9.4 Hz, 1H), 2.01 (dd, *J* = 14.3, 7.9 Hz, 1H), 1.24 (s, 3H), 1.00 (s, 9H), 0.07 (d, *J* = 2.5 Hz, 6H), 0.02 (s, 9H).

Allylic alcohol 2.2.7:

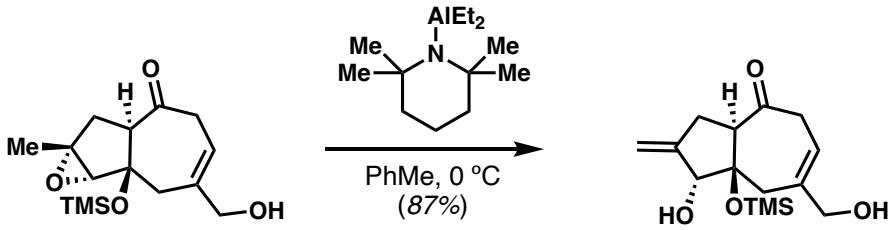


2.2.6
2.2.7 *(30%)*
2.2.8 *(11%)*

An ovendried reaction tube was charged with 2,2,6,6- tetramethylpiperidine (80 µL, 0.471 mmol, 3.0 equiv.) and toluene (0.8 mL). This solution was cooled to 0 ºC and a solution of *n*-BuLi (190 µL, 2.5 M in hexanes, 0.471 mmol, 3.0 equiv.) was added dropwise and stirring was continued for 30 minutes at 0 ºC, during which time the reaction mixture transitions from clear colorless solution to bright yellow suspension. Then, a solution of diethylaluminum chloride (470 µL, 1 M in hexanes, 0.471 mmol, 3.0 equiv.) was added, upon which the yellow color disappeared. The resulting white suspension was stirred for 40 minutes at 0 ºC and a solution of allylic alcohol **2.2.6** (65 mg, 0.157 mmol, 1.0 equiv.) in toluene (0.8 mL) was added dropwise. Conversion after 2 minutes was complete as judged by TLC, so the reaction mixture was quenched with satd. *aq.* Rochelle salt (3 mL) and diluted with EtOAc (3 mL). This biphasic mixture was vigorously stirred for 30 minutes, at which point the organic layer was separated and the aqueous layer was extracted with EtOAc (4 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction product was purified with flash column chromatography (50 to 100% EtOAc/hexanes) to provide pure allylic alcohol **2.2.7** (19.4 mg, 0.047 mmol, 30% yield) as a colorless oil together with E1cB product **2.2.8** (5 mg, 0.017 mmol, 11%) also as a colorless oil.

2.2.7:
TLC: R_f = 0.43 (25% EtOAc/hexanes)
^{1}H NMR (400 MHz, C_6D_6): δ 5.60 – 5.52 (m, 1H), 4.92 (d, *J* = 2.5 Hz, 1H), 4.86 (dq, *J* = 2.1, 1.1 Hz, 1H), 4.05 – 3.98 (m, 2H), 3.96 (d, *J* = 3.3 Hz, 1H), 3.32 (ddt, *J* = 18.1, 4.4, 2.0 Hz, 1H), 3.20 – 3.07 (m, 2H), 3.02 – 2.91 (m, 2H), 2.57 – 2.41 (m, 2H), 1.00 (s, 9H), 0.09 (s, 6H), 0.05 (s, *J* = 0.7 Hz, 9H).
^{13}C NMR (150 MHz, C_6D_6): δ 205.4, 152.5, 138.3, 116.9, 111.0, 85.0, 82.9, 69.1, 58.8, 43.2, 36.8, 30.1, 26.2, 18.6, 2.1, -5.1.
IR (thin film) n_{max} (cm^{-1}): 3420, 2924, 2854, 1740, 1436, 1254, 1158, 1012, 948.
HRMS (m/z): (ESI) calcd. for $C_{21}H_{38}O_4{}^{23}Na^{28}Si_2$ $[M+Na]^+$: 433.2201, found 433.2203.

Diol 2.8.2:



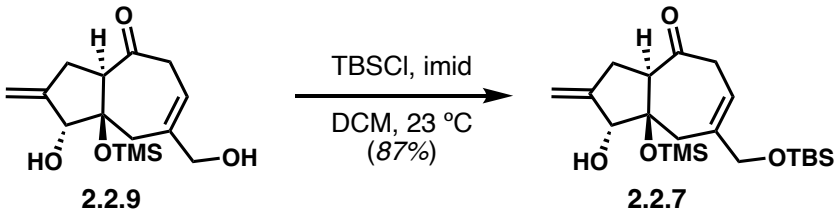
2.2.5 **2.2.9**

A flame-dried 25 mL round-bottom flask was charged with 2,2,6,6- tetramethylpiperidine (1.20 mL, 7.10 mmol, 4.0 equiv.) and toluene (6.0 mL). This solution was cooled to 0 ºC and a solution of *n*-BuLi (2.80 mL, 2.5 M in hexanes, 7.10 mmol, 4.0 equiv.) was added dropwise and stirring was continued for 30 minutes at 0 ºC, during which time the reaction mixture transitions from clear colorless solution to bright yellow suspension. Then, a solution of diethylaluminum chloride (7.1 mL, 1 M in hexanes, 7.10 mmol, 4.0 equiv.) was added, upon which the yellow color disappeared. The resulting white suspension was stirred for 40 minutes at 0 ºC and a solution of allylic alcohol **2.2.5** (526 mg, 1.77 mmol, 1.0 equiv.) in toluene (15.0 mL) was added dropwise. Conversion after 2 minutes was complete as judged by TLC, so the reaction mixture was quenched with satd. *aq.*

Rochelle salt (30 mL) and diluted with EtOAc (20 mL). This biphasic mixture was vigorously stirred for 30 minutes, at which point the organic layer was separated and the aqueous layer was extracted with EtOAc (4 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude reaction product was purified with flash column chromatography (50 to 100% EtOAc/hexanes) to provide pure diol **2.8.2** (78.0 mg, 0.264 mmol, 75% yield) as a colorless oil.

TLC: R_f = 0.23 (50% EtOAc/hexanes)
^{1}H NMR (400 MHz, C_6D_6): δ 5.35 (t, *J* = 5.6 Hz, 1H), 5.02 – 4.96 (m, 1H), 4.91 (d, *J* = 2.4 Hz, 1H), 4.00 (s, 1H), 3.85 (t, *J* = 5.0 Hz, 2H), 3.30 – 3.04 (m, 3H), 2.98 – 2.84 (m, 2H), 2.53 – 2.41 (m, 2H), 0.03 (d, *J* = 1.5 Hz, 9H).
^{13}C NMR (150 MHz, C_6D_6): δ 205.0, 152.2, 139.7, 119.1, 111.4, 85.2, 83.0, 68.9, 58.3, 43.0, 37.1, 29.8, 2.2.
IR (thin film) n_{max} (cm^{-1}): 3350, 2955, 2923, 2854, 1706, 1252, 1116, 1041, 841.
HRMS (m/z): (ESI) calcd. for $C_{15}H_{24}O_4{}^{23}Na^{28}Si$ $[M+Na]^+$: 319.1336, found 319.1336.

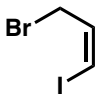
Protected allylic alcohol 2.8.3:



2.2.9 2.2.7

An oven-dried reaction tube was charged with diol **2.8.2** (78.0 mg, 0.264 mmol, 1.0 equiv.) and DCM (2.6 mL). Imidazole (40 mg, 0.59 mmol, 2.2 equiv.) and TBSCl (48 mg, 0.32 mmol, 1.2 equiv.) were added and stirring was continued for 15 minutes, at which point conversion was complete as judged by TLC. The reaction mixture was quenched with satd. *aq.* $NaHCO_3$ (3 mL), the organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction product was purified by column chromatography (10% to 50% EtOAc/hexanes) to provide pure TBS-protected primary allylic alcohol **2.8.3** (94 mg, 0.23 mmol, 87% yield) as a colorless oil.

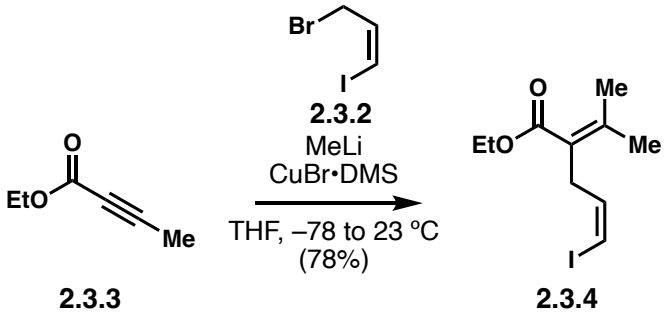
TLC: R_f = 0.43 (25% EtOAc/hexanes)
^{1}H NMR (400 MHz, C_6D_6): δ 5.60 – 5.52 (m, 1H), 4.92 (d, *J* = 2.5 Hz, 1H), 4.86 (dq, *J* = 2.1, 1.1 Hz, 1H), 4.05 – 3.98 (m, 2H), 3.96 (d, *J* = 3.3 Hz, 1H), 3.32 (ddt, *J* = 18.1, 4.4, 2.0 Hz, 1H), 3.20 – 3.07 (m, 2H), 3.02 – 2.91 (m, 2H), 2.57 – 2.41 (m, 2H), 1.00 (s, 9H), 0.09 (s, 6H), 0.05 (s, *J* = 0.7 Hz, 9H).
^{13}C NMR (150 MHz, C_6D_6): δ 205.4, 152.5, 138.3, 116.9, 111.0, 85.0, 82.9, 69.1, 58.8, 43.2, 36.8, 30.1, 26.2, 18.6, 2.1, -5.1.
IR (thin film) n_{max} (cm^{-1}): 3420, 2924, 2854, 1740, 1436, 1254, 1158, 1012, 948.
HRMS (m/z): (ESI) calcd. for $C_{21}H_{38}O_4{}^{23}Na^{28}Si_2$ $[M+Na]^+$: 433.2201, found 433.2203.



Iodide 2.3.2 **2.3.2**

(*Z*)-3-bromo-1-iodoprop-1-ene (**2.3.2**) was prepared in two steps from commercially available methyl (*Z*)-3-iodoprop-2-enoate according to ref. 3 and was used in the next reaction without purification. The spectral data for **2.3.2** were found to match those reported in the literature.[3]

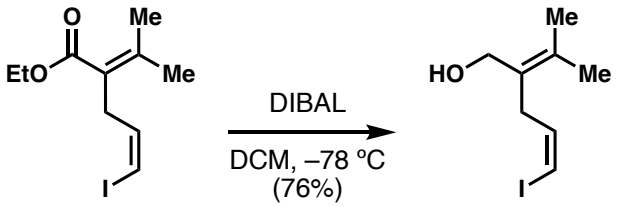
Ester 2.3.4:



A flame-dried 250 mL round-bottom flask was charged with CuBr•DMS (1.15 g, 5.59 mmol, 1.0 equiv.) inside a glovebox. THF (40 mL, degassed) was added, and the resulting suspension was cooled to 0 ºC. Methyllithium (7.0 mL, 1.6 M in Et_2O, 11 mmol, 2.0 equiv.) was added and the resulting clear solution was cooled to –78 ºC. Ethyl 2-butynoate (0.650 mL, 5.59 mmol, 1.0 equiv.) in THF (10 mL, degassed) was added dropwise and the reaction mixture was stirred for 1 hour. Then, **2.3.3** (2.76 g, 11.2 mmol, 2.0 equiv.) in THF (6 mL, degassed) was added dropwise and the reaction mixture was stirred overnight while being allowed to slowly warm to ambient temperature. The reaction mixture was quenched by addition of satd. *aq.* NH_4Cl (50 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (0 to 15% Et_2O in hexanes) to give ester **2.3.4** (1.29 g, 4.38 mmol, 78%) as a pale-yellow oil.

TLC: R_f = 0.62 (25% EtOAc/hexanes)
^{1}H NMR (700 MHz, $CDCl_3$): δ 6.22 (dt, *J* = 7.4, 1.7 Hz, 1H), 6.12 (ddd, *J* = 7.6, 6.8, 6.0 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.17 – 3.10 (m, 2H), 2.03 (s, 3H), 1.86 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (150 MHz, C_6D_6) δ 168.0, 146.1, 139.7, 124.7, 82.0, 60.0, 36.3, 23.2, 22.7, 14.4.
IR (thin film) n_{max} (cm^{-1}): 2980, 2932, 1709, 1472, 1369, 1286, 1203, 1166, 1074, 949.
HRMS (m/z): (EI) calcd. for $C_{10}H_{15}O_2{}^{127}I$: 294.0117, found 294.0119.

Allylic alcohol 2.3.5:

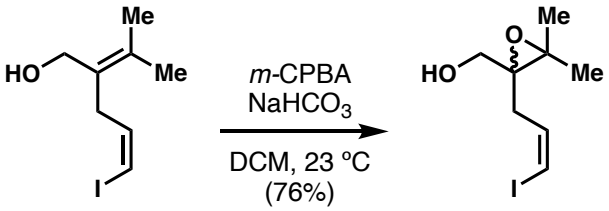


2.3.4 **2.3.5**

A flame-dried 100 mL round-bottom flask was charged with **2.3.4** (1.29 g, 4.38 mmol, 1.0 equiv.) and DCM (30 mL) and was subsequently cooled to –78 ºC. DIBAL (15.3 mL, 1 M in hexanes, 15.3 mmol, 3.5 equiv.) was added and the reaction mixture was stirred for 3 hours before being quenched by addition of EtOAc (1.2 mL) and satd. *aq.* NH_4Cl (4 mL). The resulting mixture was allowed to warm to ambient temperature and stirred for 1 hour. The resulting suspension was filtered over a pad of celite, and the filter cake was washed with Et_2O (200 mL) and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10 to 50% Et_2O in hexanes) to afford **2.3.5** (843 mg, 3.34 mmol, 76%) as a clear oil.

TLC: R_f = 0.32 (25% EtOAc/hexanes)
^{1}H NMR (600 MHz, $CDCl_3$): δ 6.23 (dt, *J* = 7.3, 1.6 Hz, 1H), 6.14 (q, *J* = 6.9 Hz, 1H), 4.15 (d, *J* = 3.1 Hz, 2H), 3.04 – 3.00 (m, 2H), 1.77 (s, 3H), 1.74 (s, 3H), 1.26 (br s, 1H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 139.8, 132.5, 128.9, 82.5, 62.4, 36.8, 21.2, 20.4.
IR (thin film) n_{max} (cm^{-1}): 3500, 2978, 2931, 1374, 1254, 1151, 1039, 758.
HRMS (m/z): (EI) calcd. for $C_8H_{13}O_2{}^{127}I$: 252.0011, found 252.0010.

Epoxide 2.3.6:

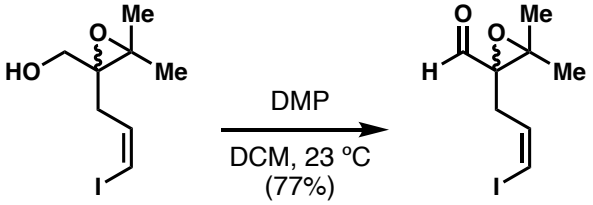


2.3.5 **2.3.6**

A flame dried 50 mL round-bottom flask was charged with **2.3.5** (563 mg, 2.23 mmol, 1.0 equiv.), DCM (23 mL) and $NaHCO_3$ (980 mg, 11.4 mmol, 5.0 equiv.). *m*CPBA (770 mg, 70w%, 3.12 mmol, 1.4 equiv.) was added and the reaction mixture was stirred for 40 minutes before being quenched by addition of satd. *aq.* $NaHCO_3$ (10 mL) and satd. *aq.* $Na_2S_2O_3$ (10 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10 to 50% Et_2O in hexanes) to afford **2.3.6** (455 mg, 1.70 mmol, 76%) as a clear oil.

TLC: R_f = 0.31 (25% EtOAc/hexanes)
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.41 (dq, *J* = 7.6, 1.5 Hz, 1H), 6.29 (td, *J* = 7.3, 6.3 Hz, 1H), 3.74 (dd, *J* = 11.8, 1.4 Hz, 1H), 3.68 (dd, *J* = 11.8, 1.1 Hz, 1H), 2.71 (ddd, *J* = 15.5, 6.3, 1.7 Hz, 1H), 2.48 (ddt, *J* = 15.5, 7.2, 1.6 Hz, 1H), 1.41 (s, 3H), 1.39 (s, 3H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 136.6, 85.2, 65.9, 63.2, 63.2, 36.4, 21.7, 20.7.
IR (thin film) n_{max} (cm^{-1}): 3411, 3002, 2960, 2928, 1412, 1320, 1277, 1121, 1033, 844.
HRMS (m/z): (EI) calcd. for $C_8H_{13}O_2{}^{127}I$: 267.9960, found 267.9958.

Aldehyde 2.3.7

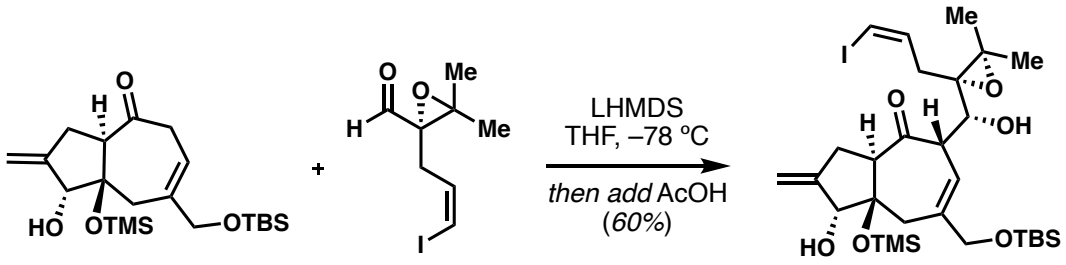


2.3.6 **2.3.7**

A flame dried 50 mL round-bottom flask was charged with **2.3.6** (400 mg, 1.49 mmol, 1.0 equiv.) and DCM (15 mL). DMP (886 mg, 2.08 mmol, 1.4 equiv.) was added and the reaction mixture was stirred for 10 minutes before being quenched by addition of satd. *aq.* $NaHCO_3$ (5 mL) and satd. *aq.* $Na_2S_2O_3$ (5 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (3 x 15 mL portions). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (0 to 20% EtOAc in hexanes) to afford aldehyde **2.3.7** (304 mg, 1.14 mmol, 77%) as a pale-yellow oil.

TLC: R_f = 0.64 (25% EtOAc/hexanes)
^{1}H NMR (700 MHz, $CDCl_3$): δ 9.49 (s, 1H), 6.40 (dt, *J* = 7.5, 1.7 Hz, 1H), 6.27 – 6.22 (m, 1H), 2.87 (ddd, *J* = 15.8, 7.1, 1.5 Hz, 1H), 2.51 (ddd, *J* = 15.8, 6.1, 1.7 Hz, 1H), 1.46 (s, 3H), 1.45 (s, 2H).
^{13}C NMR (150 MHz, C_6D_6): δ 201.6, 135.4, 85.5, 68.3, 64.7, 33.6, 22.2, 20.7.
IR (thin film) n_{max} (cm^{-1}): 3001, 2928, 2831, 1710, 1400, 1278, 1120, 837, 764.
HRMS (m/z): (EI) calcd. for $C_8H_{11}O_2{}^{127}I$: 265.9804, found 265.9803.

Aldol product 2.4.3:

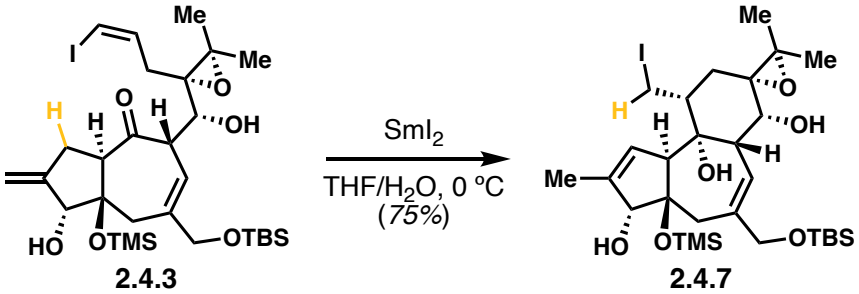


2.2.7 **2.3.7** **2.4.3**

An oven-dried reaction tube was charged with ketone **2.2.7** (26 mg, 63 µmol, 1.0 equiv.) and THF (0.4 mL). The resulting solution was cooled to –78 ºC and a solution of LHMDS (160 µL, 1 M in THF, 0.160 mmol, 2.5 equiv.) was added. The reaction mixture was stirred at –78ºC for 30 minutes, at which point a solution of aldehyde **2.3.7** (33.0 mg, 0.126 mmol, 2.0 equiv.) in THF (0.4 mL) was added dropwise. After 5 minutes, conversion was complete as judged by TLC and the reaction was quenched with neat acetic acid (20 µL) before being quickly warmed up to room temperature. Then, satd. *aq.* $NaHCO_3$ (2 mL) was added carefully, the organic layer was separated, and the aqueous layer was extracted with EtOAc (5 x 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction product was purified by flash column chromatography (0 to 60% EtOAc/hexanes) to provide pure vinyl iodide **2.4.3** (26 mg, 38 µmol, 60% yield) as a white solid.

TLC: R_f = 0.67 (50% EtOAc/hexanes)
^{1}H NMR (600 MHz, C_6D_6): δ 6.47 (td, *J* = 7.1, 5.3 Hz, 1H), 5.98 (dt, *J* = 7.4, 2.1 Hz, 1H), 5.69 (dt, *J* = 7.3, 1.5 Hz, 1H), 5.01 (t, *J* = 2.5 Hz, 1H), 4.94 (qd, *J* = 2.1, 1.1 Hz, 1H), 4.30 (dd, *J* = 10.3, 2.5 Hz, 1H), 4.04 – 4.01 (m, 2H), 3.99 (s, 1H), 3.76 (dd, *J* = 10.4, 7.1 Hz, 1H), 3.53 – 3.45 (m, 2H), 3.11 (ddt, *J* = 16.7, 10.8, 2.8 Hz, 1H), 2.97 (d, *J* = 16.6 Hz, 1H), 2.94 – 2.88 (m, 1H), 2.64 (ddd, *J* = 17.0, 5.3, 2.4 Hz, 1H), 2.47 (ddd, *J* = 16.6, 11.8, 3.6 Hz, 2H), 1.53 (s, 1H), 1.34 (s, 3H), 1.25 (s, 3H), 0.97 (s, 9H), 0.11 (s, 9H), 0.08 (d, *J* = 2.0 Hz, 6H).
^{13}C NMR (150 MHz, C_6D_6): δ 206.8, 152.3, 140.7, 138.6, 116.8, 112.2, 85.7, 83.2, 82.4, 73.6, 67.9, 67.1, 63.7, 56.6, 56.2, 36.9, 34.9, 30.0, 26.2, 26.2, 22.2, 21.9, 18.6, 2.4, -5.2.
IR (thin film) n_{max} (cm^{-1}): 3450, 2954, 2928, 2856, 1707, 1405, 1251, 1103, 1008, 837.
HRMS (m/z): (ESI) calcd. for $C_{29}H_{49}O_6{}^{127}I^{23}Na^{28}Si_2$ $[M+Na]^+$: 699.2005, found 699.2008.

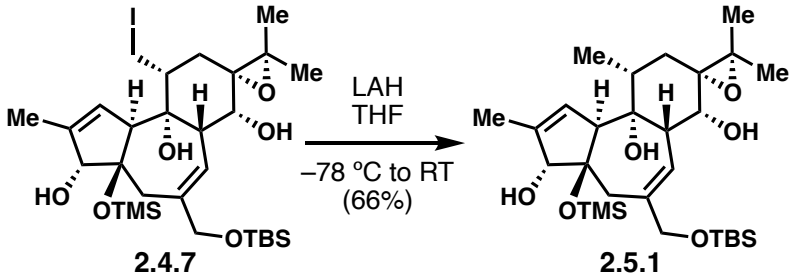
Tricycle 2.4.7:



An oven-dried 10 mL round-bottom flask was charged with vinyl iodide **2.4.3** (43 mg, 63 µmol, 1.0 equiv.), degassed THF (900 µL), and H_2O (90 µL). The resulting solution was degassed for 5 minutes with sonication and argon sparging and was then cooled to 0 ºC. A solution of SmI_2 (3.2 mL, 0.1 M in THF, 0.32 mmol, 5.0 equiv.) was added dropwise until the blue color persisted, at which point conversion was complete as judged by TLC. The reaction mixture was quenched with satd. *aq.* Rochelle salt (10 mL) and diluted with EtOAc (10 mL). The resulting biphasic mixture was vigorously stirred for 30 minutes at room temperature and then the organic layer was separated. The aqueous layer was extracted with EtOAc (5 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction product was purified by flash column chromatography (10 to 60% EtOAc/hexanes) to provide pure 5,7,6-fused tricycle **2.4.7** (32 mg, 47 µmol, 75% yield, > 20:1 dr) as a white solid.

TLC: R_f = 0.82 (50% EtOAc/hexanes)
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.92 (d, *J* = 7.0 Hz, 1H), 5.71 (s, 1H), 4.52 (br s, 1H), 4.15 (d, *J* = 12.8 Hz, 1H), 4.11 (d, *J* = 12.7 Hz, 1H), 3.94 (s, 1H), 3.90 – 3.86 (m, 2H), 3.20 (s, 1H), 3.11 – 3.04 (m, 2H), 2.72 (br s, 1H), 2.54 – 2.43 (m, 2H), 2.37 – 2.28 (m, 2H), 1.97 (d, *J* = 13.7 Hz, 1H), 1.81 (s, 3H), 1.65 (br s, 1H), 1.48 (s, 3H), 1.36 (s, 3H), 0.90 (s, 9H), 0.17 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 144.2, 136.4, 129.7, 122.8, 85.5, 84.3, 76.5, 73.9, 68.1, 67.3, 64.6, 59.6, 48.5, 46.9, 38.5, 29.0, 26.1, 21.2, 18.7, 14.8, 12.4, 2.4, -5.1.
IR (thin film) n_{max} (cm^{-1}): 3400, 2926, 2855, 1580, 1252, 1126, 1034, 936, 906, 839.
HRMS (m/z): (ESI) calcd. for $C_{29}H_{51}O_6{}^{127}I^{23}Na^{28}Si_2$ $[M+Na]^+$: 701.2161, found 701.2164.

Reduction product 2.5.1:

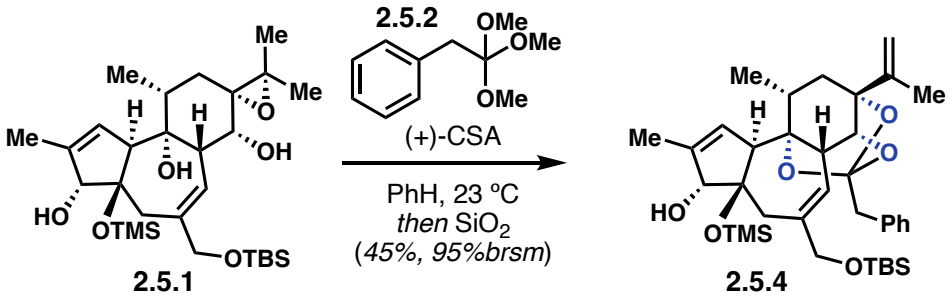


2.4.7 **2.5.1**

An oven-dried reaction tube was charged with iodide **2.4.7** (5.0 mg, 7.3 μmol, 1.0 equiv.) and THF (0.5 mL). The mixture was cooled to –78 ºC and a solution of lithium aluminum hydride in THF (100 μL, 0.5 M in THF, 50.0 μmol, 6.8 equiv.) was added dropwise. The resulting solution was left to slowly warm up to room temperature over the course of 12 hours. At this point, the reaction mixture was quenched with EtOAc (1 mL) and stirred vigorously with satd. *aq.* Rochelle salt (2 mL) for 30 minutes. The organic layer was separated, and the aqueous layer was extracted with EtOAc (5 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude mixture was purified by flash column chromatography (10 to 50% EtOAc/hexanes) to provide reduction product **2.5.1** (2.7 mg, 4.8 μmol, 66% yield) as a white solid.

TLC: R_f = 0.89 (50% EtOAc/hexanes)
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.92 (d, *J* = 7.7 Hz, 1H), 5.78 (s, 1H), 4.12 (d, *J* = 6.2 Hz, 2H), 3.92 (s, 1H), 3.86 (s, 1H), 3.11 (m, 1H), 3.05 (d, *J* = 16.6 Hz, 1H), 2.65 (d, *J* = 6.1 Hz, 1H), 2.40 – 2.31 (m, 2H), 2.28 (ddd, *J* = 13.4, 6.6, 3.1 Hz, 1H), 1.79 (dd, *J* = 2.8, 1.5 Hz, 3H), 1.39 (s, 3H), 1.35 (s, 3H), 1.19 (d, *J* = 12.7 Hz, 1H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 9H), 0.12 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 143.1, 135.2, 130.8, 123.4, 85.7, 84.7, 76.5, 73.7, 67.9, 67.6, 64.2, 60.2, 46.4, 39.2, 38.4, 31.1, 26.2, 21.2, 21.1, 18.7, 17.9, 14.7, 2.4, -5.1.
IR (thin film) n_{max} (cm^{-1}): 3380, 2929, 2856, 1406, 1251, 1120, 1054, 963, 830.
HRMS (m/z): (ESI) calcd. for $C_{29}H_{52}O_6{}^{23}Na^{28}Si_2$ $[M+Na]^+$: 575.3195, found 575.3198.

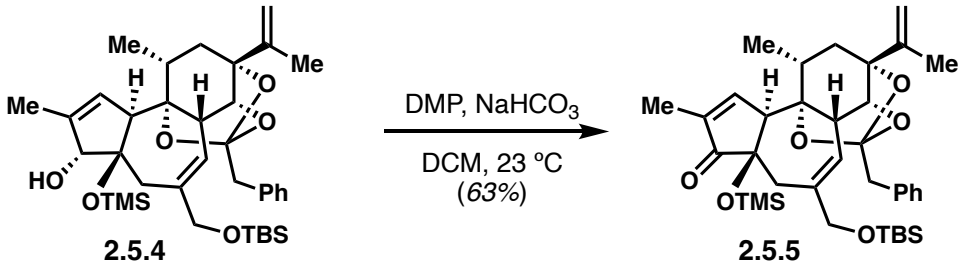
Orthoester 2.5.4:



An oven-dried reaction tube was charged with reduction product **2.5.1** (5.0 mg, 9.0 µmol, 1.0 equiv.), benzene (0.5 mL), (2,2,2-trimethoxyethyl)benzene (5.3 mg, 27 µmol, 3.0 equiv.), and (+)-camphorsulfonic acid (0.5 mg, 2.0 µmol, 0.24 equiv.). The resulting solution was stirred at room temperature until conversion was complete as judged by TLC; additional portions of (2,2,2-trimethoxyethyl)benzene (**2.5.2**) (5.3 mg) and (+)-camphorsulfonic acid (1.0 mg) were added as necessary for full consumption of diol **2.5.1**. At this stage the reaction mixture was quenched with satd. *aq.* $NaHCO_3$ (1.5 mL), the organic layer was separated, and the aqueous layer was extracted with Et_2O (4 x 1 mL). The combined organic layers were dried over Na_2SO_4 and combined with silica gel (2 g) and the resulting suspension was concentrated to dryness under reduced pressure. The silica-gel absorbed material was then chromatographically purified (0 to 15% EtOAc/hexanes in 2.5% increments) to obtain pure orthoester **2.5.4** (2.4 mg, 3.6 µmol, 40% yield) as a colorless oil. [**Note**: As an alternative to the procedure above, the same reaction can be carried out on larger scale (13 mg of **2.5.1**, 24 µmol) but quenched at ~25% conversion to obtain **2.5.4** (2.5 mg, 3.8 µmol, 95% brsm) as well as recovered **2.5.1** (11 mg, 20 µmol), which can be recycled repeatedly to increase the overall material throughput of the orthoester product. In this case, flash column chromatography is carried out as follows: 0 to 15% EtOAc/hexanes in 2.5% increments to isolate desired **2.5.4**; then 20 to 50% EtOAc/hexanes in 10% increments to recover unreacted **2.5.1**.]

TLC: R_f = 0.78 (25% EtOAc/hexanes)
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 6.6, 1.4 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.22 – 7.18 (t, 1H), 5.79 (s, 1H), 5.71 (t, *J* = 1.8 Hz, 1H), 4.72 (s, 1H), 4.71 (t, *J* = 1.6 Hz, 1H), 4.20 (d, *J* = 2.8 Hz, 1H), 4.13 (s, 1H), 4.10 (d, *J* = 3.3 Hz, 2H), 3.16 (s, 2H), 2.95 (s, 1H), 2.77 – 2.72 (m, 2H), 2.65 (p, *J* = 7.2 Hz, 1H), 2.41 (d, *J* = 18.4 Hz, 1H), 2.05 (dd, *J* = 14.1, 8.6 Hz, 1H), 1.81 – 1.78 (m, 3H), 1.54 – 1.51 (m, 4H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.92 (s, 9H), 0.12 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 147.0, 139.8, 137.3, 135.5, 131.0, 130.6, 127.8, 126.5, 123.6, 117.9, 110.6, 87.7, 84.3, 84.2, 82.3, 80.8, 69.4, 59.2, 41.3, 39.1, 39.1, 36.6, 33.3, 26.2, 20.9, 18.9, 18.6, 14.5, 2.2, -5.0, -5.1.
IR (thin film) n_{max} (cm^{-1}): 3500, 2952, 2924, 2854, 1602, 1497, 1465, 1436, 1254, 1158, 1102, 948.
HRMS (m/z): (ESI) calcd. for $C_{37}H_{56}O_6{}^{23}Na^{28}Si_2$ $[M+Na]^+$: 675.3508, found 675.3507.

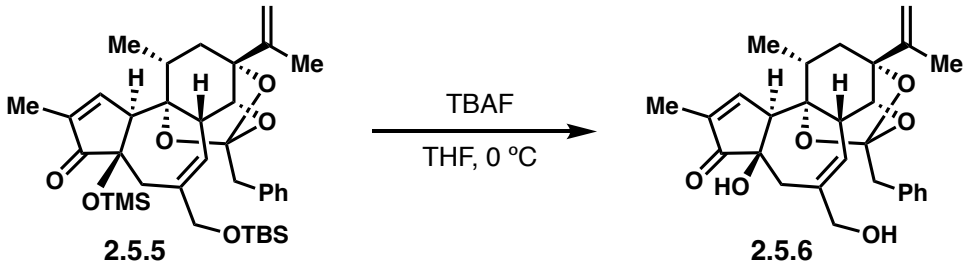
Enone 2.5.5:



An oven-dried reaction tube was charged with orthoester **2.5.4** (10 mg, 15 µmol, 1.0 equiv.) and DCM (0.3 mL). A stock solution of acid-free Dess-Martin periodinane (DMP) was prepared by suspending DMP (70.0 mg, 165 µmol, 11 equiv.) and $NaHCO_3$ (20.0 mg) in DCM (1.0 mL), shaking vigorously, and allowing the inorganic solids to settle. An appropriate aliquot of the supernatant (0.100 mL, containing 16.5 µmol of DMP, 1.1 equiv.) was added to the DCM solution of orthoester **2.5.4** and the resulting mixture was stirred at room temperature for 1 hour. If conversion was incomplete at this point, an additional amount of DMP solution (20 µL, 0.22 equiv. DMP) was added as necessary. Once all **2.5.4** was consumed as judged by TLC, the reaction was quenched with satd. *aq.* $NaHCO_3$ (0.5 mL) and satd. *aq.* $Na_2S_2O_3$ (0.5 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction product was purified by flash column chromatography (0 to 20% Et_2O/hexanes) to provide pure enone **2.5.5** (6.3 mg, 9.6 µmol, 63%) as a colorless amorphous solid.

TLC: R_f = 0.62 (10% EtOAc/hexanes)
^{1}H NMR (600 MHz, C_6D_6): δ 7.49 (s, 1H), 7.48 (s, 1H), 7.21 (t, *J* = 7.6 Hz, 3H), 7.14 – 7.09 (m, 1H), 6.00 (s, 1H), 4.89 (s, 1H), 4.75 (s, 1H), 4.21 (d, *J* = 2.7 Hz, 1H), 3.99 (d, *J* = 12.6 Hz, 1H), 3.97 (d, *J* = 12.6 Hz, 1H), 3.40 (d, *J* = 14.0 Hz, 1H), 3.37 (d, *J* = 14.1 Hz, 1H), 3.15 (s, 1H), 3.05 (s, 1H), 2.89 (d, *J* = 18.7 Hz, 1H), 2.64 (p, *J* = 7.3 Hz, 1H), 2.13 – 2.03 (m, 2H), 1.62 – 1.59 (m, 4H), 1.50 (s, 3H), 1.17 (d, *J* = 7.2 Hz, 3H), 1.00 (s, 9H), 0.19 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H).
^{13}C NMR (150 MHz, C_6D_6): δ 206.3, 156.4, 147.0, 139.1, 137.4, 135.7, 131.4, 126.9, 124.5, 118.4, 110.9, 84.7, 82.0, 81.3, 76.8, 69.7, 56.6, 41.8, 39.9, 39.2, 36.5, 33.7, 26.2, 20.6, 18.9, 18.6, 10.3, 1.7, 1.4, -5.0.
IR (thin film) n_{max} (cm^{-1}): 2952, 2924, 2854, 1716, 1457, 1360, 1252, 1076, 1014, 843.
HRMS (m/z): (ESI) calcd. for $C_{37}H_{54}O_6{}^{23}Na^{28}Si_2$ $[M+Na]^+$: 673.3351, found 673.3345.

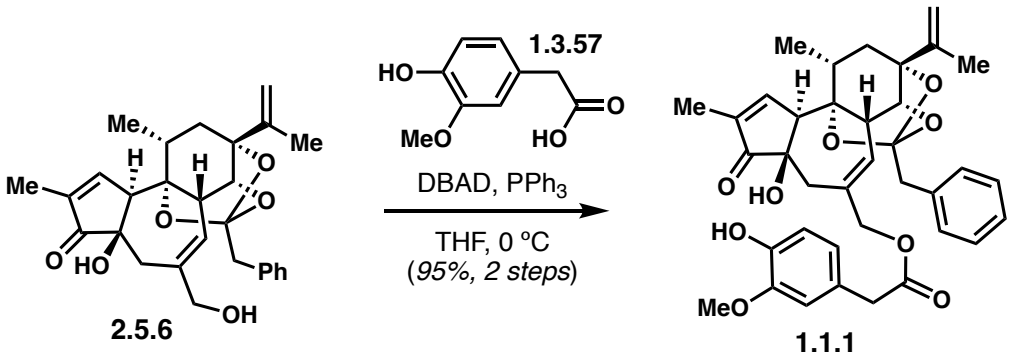
Resiniferonol-9,13,14-orthophenyl aetate 2.5.6:



Resiniferonol-9,13,14-orthophenyl acetate (ROPA, **2.5.6**) was prepared by deprotecting enone **2.5.5** with TBAF according to a modified literature procedure.[3] An oven-dried reaction tube was charged with enone **2.5.5** (6.9 mg, 11 µmol, 1.0 equiv.) and THF (300 µL). The resulting solution was cooled to 0 ºC and a solution of TBAF (50 µL, 1 M in THF, 50 µmol, 4.7 equiv.) was added. The reaction mixture was stirred for 2 hours, at which point conversion was complete as judged by TLC and was quenched with satd. *aq.* NH_4Cl (1 mL) and diluted with EtOAc (1 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (5 x 1 mL). The combined organic layers were washed with satd. *aq.* $NaHCO_3$ (1 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (20 to 100% Et_2O/hexanes then 50 to 80% EtOAc/hexanes) to provide pure ROPA (**2.5.6**) (4.9 mg, 11 µmol) as a colorless amorphous solid.

TLC: R_f = 0.33 (50% EtOAc/hexanes)
^{1}H NMR (600 MHz, $CDCl_3$): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 2.4, 1.4 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.28 (dd, *J* = 8.2, 6.6 Hz, 2H), 7.24 – 7.20 (m, 1H), 5.87 (s, 1H), 4.71 (dd, *J* = 3.0, 1.4 Hz, 2H), 4.26 (d, *J* = 2.8 Hz, 1H), 4.11 (d, *J* = 12.8 Hz, 1H), 4.08 (d, *J* = 12.8 Hz, 1H), 3.22 (d, *J* = 14.2 Hz, 1H), 3.19 (d, *J* = 14.2 Hz, 1H), 3.13 (br s, 1H), 3.10 (s, 1H), 2.60 – 2.51 (m, 2H), 2.28 (br s, 1H), 2.16 (dd, *J* = 14.4, 8.9 Hz, 1H), 1.82 (dd, *J* = 2.8, 1.4 Hz, 3H), 1.54 (m, 1H), 1.52 (s, 3H), 0.96 (d, *J* = 7.2 Hz, 3H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 208.7, 158.3, 146.4, 138.9, 136.5, 135.0, 130.8, 127.7, 126.5, 125.4, 117.8, 110.7, 84.5, 81.2, 80.8, 73.5, 69.3, 55.5, 41.0, 39.8, 38.9, 35.7, 33.1, 19.9, 18.8, 10.2. **IR** (thin film) n_{max} (cm^{-1}): 3347, 3319, 2958, 2925, 2855, 1708, 1447, 1378, 1287, 1238, 1159, 1048, 948.
HRMS (m/z): (ESI) calcd. for $C_{28}H_{33}O_6$ $[M+H]^+$: 465.2272, found 465.2271.

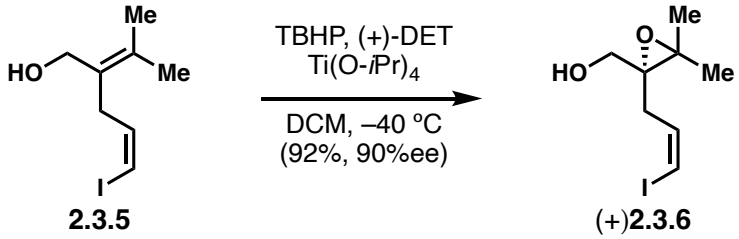
Resiniferatoxin 1.1.1:



Resiniferatoxin (**1.1.1**) was synthesized from ROPA (**2.5.6**) via a modified literature procedure.[3] An oven-dried reaction tube was charged with ROPA (4.9 mg, 11 µmol), DBAD (6.3 mg, 27 µmol, 2.6 equiv.), homovanillic acid (5.0 mg, 27 µmol, 2.6 equiv.), and PPh_3 (7.1 mg, 27 µmol, 2.6 equiv.) and was cooled to 0 ºC. THF (0.3 mL) was added down the side of the tube and the reaction mixture was stirred at 0 ºC for 15 minutes, during which time a change from a bright yellow solution to pale yellow suspension was observed. At this time conversion was complete as judged by TLC, so the reaction mixture was transferred onto a silica (4.0 g) column. The reaction tube was washed twice with 10% Et_2O/hexanes (0.2 mL) to render the transfer quantitative. The column was eluted with 20 to 100% Et_2O/hexanes followed by 50 to 75% EtOAc/hexanes. The fractions containing the desired product were combined and re-purified with another chromatography column (10 to 60% EtOAc/hexanes in 10% increments) to provide pure resiniferatoxin (**1.1.1**) (6.2 mg, 10 µmol, 95% over 2 steps) as a white solid.

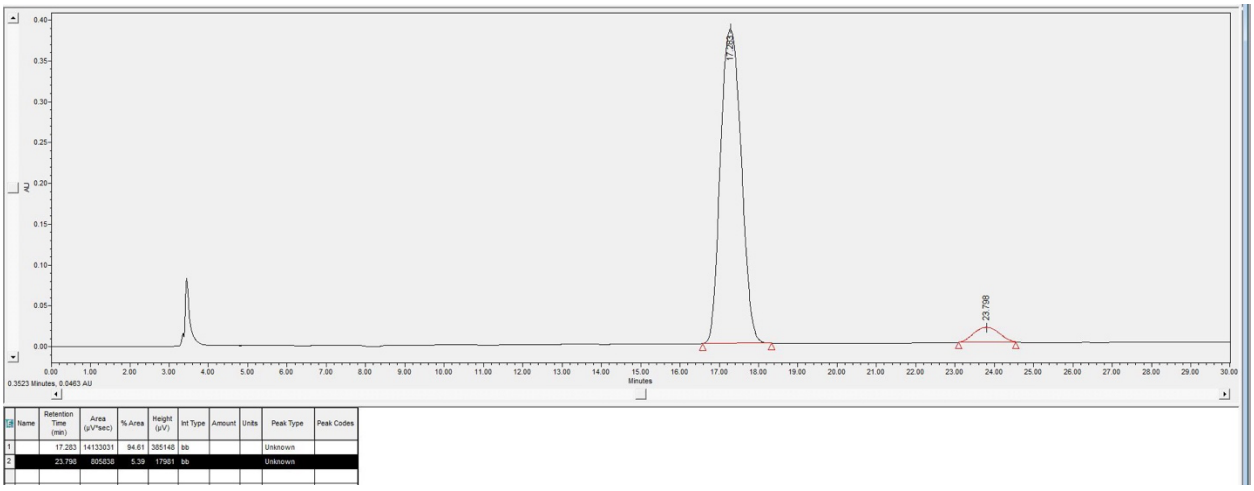
TLC: R_f = 0.58 (50% EtOAc/hexanes)
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 (s, 1H), 7.37 (d, *J* = 7.1 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 1.9 Hz, 1H), 6.76 (dd, *J* = 8.0, 1.9 Hz, 1H), 5.87 (s, 1H), 5.54 (s, 1H), 4.71 (s, 2H), 4.59 (d, *J* = 12.2 Hz, 1H), 4.54 (d, *J* = 12.2 Hz, 1H), 4.20 (d, *J* = 2.7 Hz, 1H), 3.88 (s, 3H), 3.56 (s, 2H), 3.22 (d, *J* = 14.5 Hz, 1H), 3.19 (d, *J* = 14.5 Hz, 1H), 3.08 (s, 1H), 3.04 (s, 1H), 2.55 (p, *J* = 7.3 Hz, 1H), 2.43 (d, *J* = 18.9 Hz, 1H), 2.18 –2.10(dd,*J*=14.3,8.8Hz,1H),2.15(brs,1H),2.04(d,*J*=18.9 Hz,1H),1.82(dd,*J*=2.7,1.3 Hz, 3H), 1.55 (d, *J* = 14.3 Hz, 1H), 1.51 (s, 3H), 0.96 (d, *J* = 7.2 Hz, 3H).
^{13}C NMR (150 MHz, $CDCl_3$): δ 208.4, 171.5, 158.2, 146.5, 146.3, 144.8, 136.5, 134.9, 134.1, 130.8, 128.6, 127.7, 126.5, 125.6, 122.2, 117.8, 114.4, 111.7, 110.7, 84.4, 81.1, 80.6, 73.3, 70.5, 56.0, 55.3, 41.0, 40.9, 39.9, 39.1, 35.7, 33.0, 19.8, 18.8, 10.2.
IR (thin film) n_{max} (cm^{-1}): 3447, 2971, 2926, 1724, 1629, 1604, 1515, 1271, 1149, 1029, 982.
HRMS (m/z): (ESI) calcd. for $C_{37}H_{41}O_9$ $[M+H]^+$: 629.2745, found 629.2754.

Epoxide (+)-2.3.6:

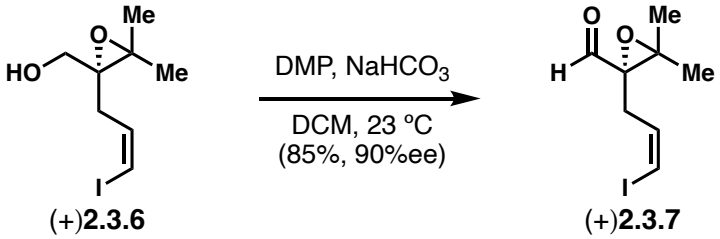


A flame dried 25 mL round-bottom flask was charged with **2.3.5** (300 mg, 1.190 mmol, 1.0 equiv.), DCM (8 mL) and powdered molecular sieves (0.200 g, 4 Å, activated at 170 ºC under vacuum) and was subsequently cooled to –15 ºC. (+)-(*L*)-Diethyl tartrate (70 µL, 0.393 mmol, 0.33 equiv.) and Ti(O-*i*Pr)$_4$ (100 µL, 0.321 mmol, 0.27 equiv.) were added and the reaction mixture was stirred for 15 minutes before being cooled down to –40 ºC. TBHP (320 µL, 5.5 M in undecane, 1.785 mmol, 1.5 equiv.) was added dropwise and the reaction mixture was stirred for 30 minutes at –40 ºC, at which point conversion was complete judged by TLC. The reaction mixture was quenched at –40 ºC by addition of a solution of $FeSO_4$ (670 mg) and (+)-tartaric acid (300 mg) in water (4 mL). The resulting mixture was transferred to a 250 mL Erlenmeyer flask, diluted with H_2O (10 mL) and Et_2O (50 mL) and was vigorously stirred for 20 mins. The layers were separated, and the aqueous layer was extracted using Et_2O (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10 to 50% Et_2O in hexanes) to afford epoxide **(+)-2.3.6** (292 mg, 1.089 mmol, 92%, 90% ee) as a clear oil.

$[\alpha]_D^{25}$ +26º (*c* 0.1, $CHCl_3$)



Aldehyde (+)-2.3.7:

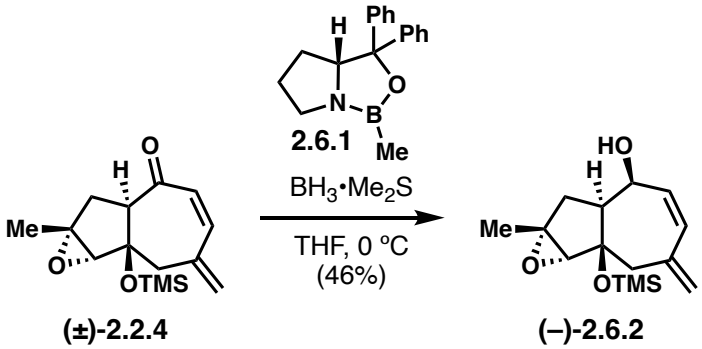


(+)**2.3.6** (+)**2.3.7**

A 20 mL vial containing **(+)-2.3.6** (123 mg, 0.4588 mmol, 1.0 equiv.) was charged with $NaHCO_3$ (77 mg, 0.9176 mmol, 2.0 equiv.) and DCM (6 mL). DMP (253 mg, 0.5964 mmol, 1.3 equiv.) was added and the reaction mixture was stirred for 10 mins before being quenched by addition of satd. aq. $NaHCO_3$ (4 mL) and satd. aq. $Na_2S_2O_3$ (4 mL). The mixture was stirred for 10 minutes, and the layers were separated. The aqueous layer was extracted using DCM (3x4 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (0 to 20% EtOAc in hexanes) to afford aldehyde **(+)-2.3.7** (104 mg, 0.3908 mmol, 85%, 90%ee) as a clear oil.

$[\alpha]_D^{25}$ +146º (*c* 0.1, $CHCl_3$)

Reduction product (–)-2.6.2:



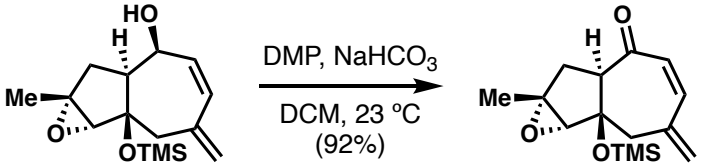
(±)-2.2.4 (–)-2.6.2

A flame-dried 50 mL round-bottom flask was charged with (*R)*-(+)-2-methyl-CBS-oxazaborolidine (370 mg, 1.332 mmol, 1.0 equiv.) inside a N_2 filled glovebox. The round-bottom flask was sealed with a septum and brought out of the glovebox under inert atmosphere. THF (10 mL) was added, and the mixture was subsequently cooled to 0 ºC. BH_3•Me_2S (160 mL, 1.732 mmol, 1.3 equiv.) was added dropwise and the reaction mixture was stirred for 15 minutes. **(±)-2.2.4** (371 mg, 1.332 mmol, 1.0 equiv.) in THF (7 mL) was added dropwise to the reaction mixture. Upon completion of the reaction as indicated by TLC, MeOH (3 mL) was added, and the mixture was stirred for 5 minutes at ambient temperature before being concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (0 to 20% EtOAc in hexanes) to afford **(–)-2.6.2** (173 mg, 0.617 mmol, 46%) as a colorless oil.

TLC: R_f = 0.48 (25% EtOAc in hexanes)
^{1}H NMR (600 MHz, C_6D_6) δ 6.04 (d, *J* = 12.7 Hz, 1H), 5.85 (dd, *J* = 12.7, 6.1 Hz, 1H), 4.97 (s,

1H), 4.81 (s, 1H), 4.04 (ddd, *J* = 11.3, 6.2, 3.7 Hz, 1H), 3.37 (d, *J* = 11.3 Hz, 1H), 2.91 (s, 1H), 2.72 (s, 1H), 2.46 (dd, *J* = 13.5, 10.5 Hz, 1H), 1.98 (ddd, *J* = 10.7, 7.2, 3.7 Hz, 1H), 1.76 (dd, *J* = 13.5, 7.2 Hz, 1H), 1.31 (s, 3H), -0.02 (s, 6H).
^{13}C NMR (151 MHz, C_6D_6) δ 142.2, 131.8, 130.9, 121.1, 85.2, 68.8, 67.8, 63.7, 48.1, 44.0, 34.0, 17.6, 2.1.
HRMS (m/z): (EI) calc for $C_{15}H_{24}O_3Si$: 280.1495, found 280.1486.
$[\alpha]_D^{25}$ +112° (*c* 0.1, $CHCl_3$)

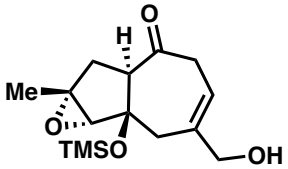
Enone (+)-2.2.4:



(–)-2.6.2 **(+)-2.2.4**

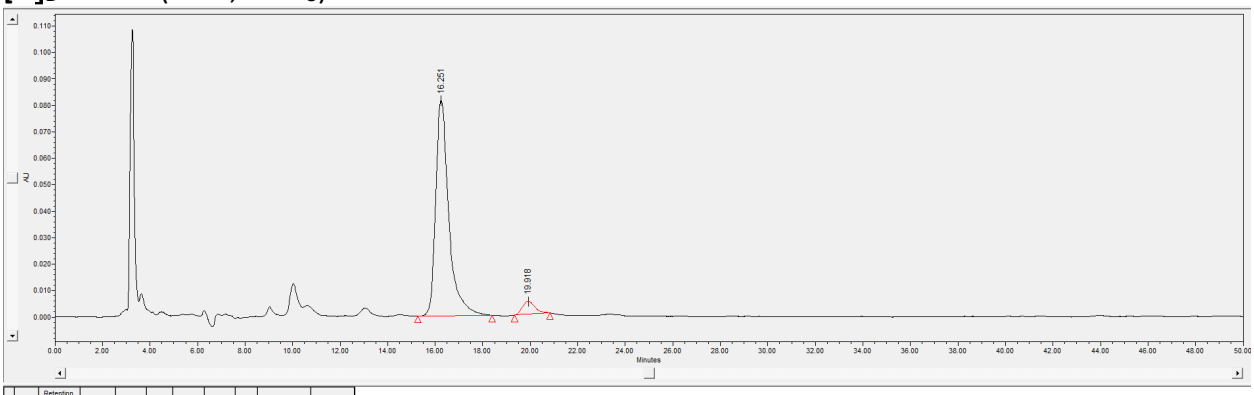
An oven dried reaction tube was charged with **(–)-2.6.2** (60 mg, 0.2139 mmol, 1.0 equiv.), $NaHCO_3$ (36 mg, 0.4278 mmol, 2.0 equiv.) and DCM (2.2 mL). DMP (118 mg, 0.2781 mmol, 1.3 equiv.) was added to the stirring reaction mixture. Upon completion of the reaction as indicated by TLC, satd. aq. $NaHCO_3$ (1.5 mL) and satd. aq. $Na_2S_2O_3$ (1.5 mL) were added. The layers were separated, and the aqueous layer was extracted using DCM (3 x 3 mL). The combined organic layers were dried over Na_2SO_4 under concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (0 to 30% EtOAc in hexanes) to afford enone **(+)-2.2.4** (55 mg, 0.1975 mmol, 92% yield) as colorless oil.
$[\alpha]_D^{25}$ +73º (*c* 0.1, $CHCl_3$)

Allylic alcohol (–)-2.2.5:



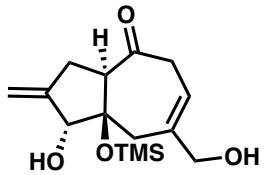
(–)-2.2.5

$[\alpha]_D^{25}$ –51º (*c* 0.1, $CHCl_3$)



	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1		16.251	3132714	94.59	81485	bb			Unknown	
2		19.918	179081	5.41	4899	bb			Unknown	

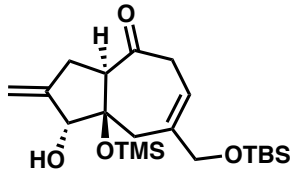
Diol (–)-2.2.6:



(–)-2.2.6

$[\alpha]_D^{25}$ –202º (*c* 0.1, $CHCl_3$)

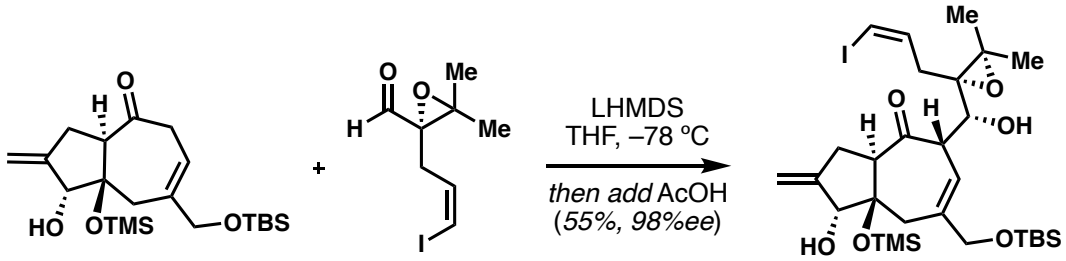
Silanol (–)-2.2.7:



(–)-2.2.7

$[\alpha]_D^{25}$ –9º (*c* 0.1, $CHCl_3$)

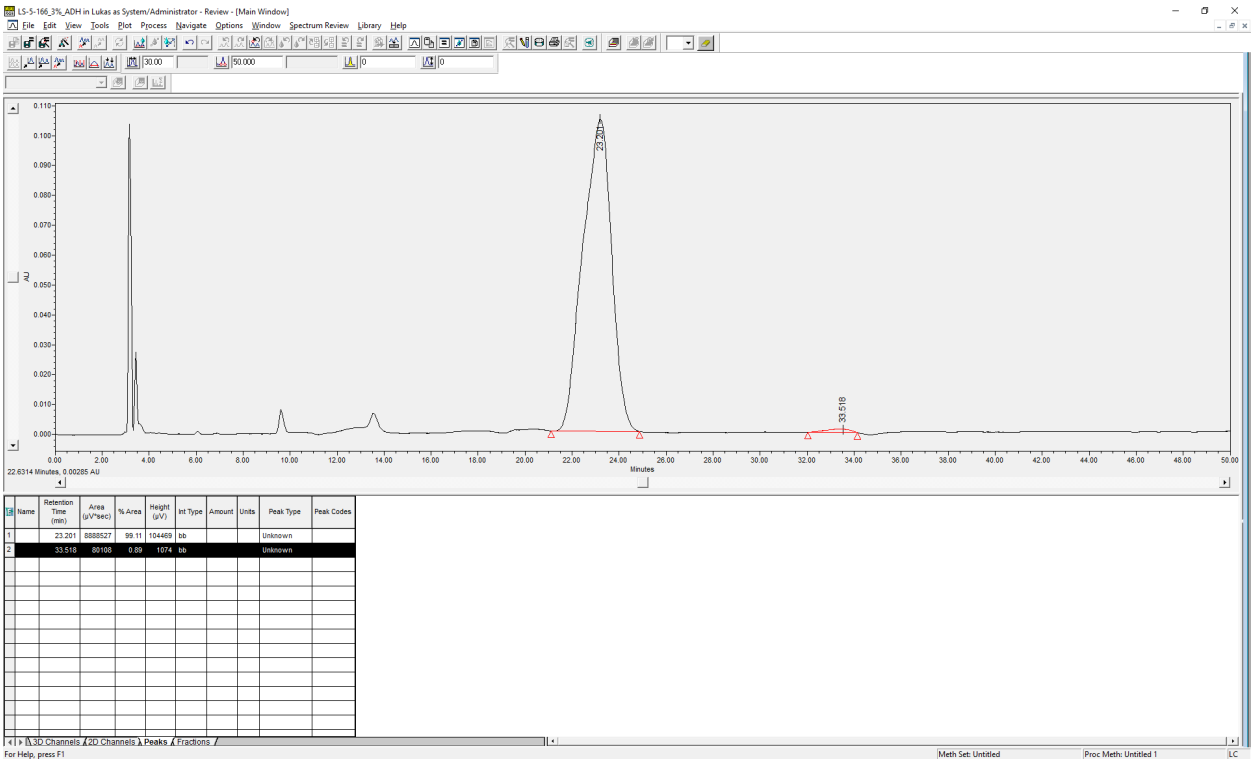
Asymmetric Aldol product (–)-2.4.3:



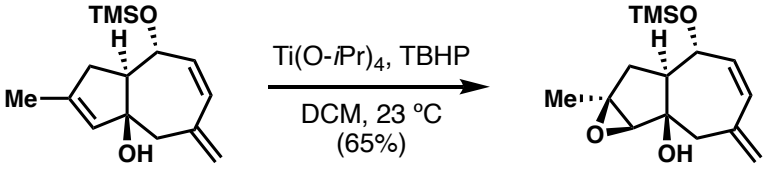
(–)**2.2.7** (+)**2.3.7** (–)**2.4.3**

An oven-dried reaction tube was charged with ketone **(–)-2.2.7** (20 mg, 49 µmol, 1.0 equiv.) and THF (0.4 mL). The resulting solution was cooled to –78 ºC and a solution of LHMDS (120 µL, 1 M in THF, 0.120 mmol, 2.4 equiv.) was added. The reaction mixture was stirred at –78 ºC for 30 minutes, at which point a solution of aldehyde **(+)-2.3.7** (15 mg, 58 µmol, 1.2 equiv.) in THF (0.3 mL) was added dropwise. After 5 minutes, conversion was complete as judged by TLC and the reaction was quenched with neat acetic acid (20 µL) before being quickly warmed up to room temperature. Then satd. aq. $NaHCO_3$ (2 mL) was added carefully, the organic layer was separated, and the aqueous layer was extracted with EtOAc (5 x 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude reaction product was purified by flash column chromatography (0 to 60% EtOAc/hexanes) to provide pure vinyl iodide X (18 mg, 27 µmol, 55%, 98% ee) as a colorless solid.

$[\alpha]_D^{25}$ –90º (*c* 0.1, $CHCl_3$)



Epoxide 2.7.1:

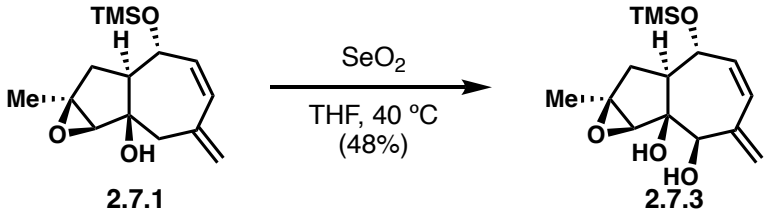


2.1.10 **2.7.1**

A flame-dried 250 mL round-bottom flask was charged with **2.1.10** (500 mg, 1.89 mmol, 1.0 equiv.) and DCM (60 mL). Ti(O-*i*Pr)$_4$ (560 µL, 1.89 mmol, 1.0 equiv.) was added and the resulting mixture was stirred for 15 minutes. TBHP (380 µL, 5.5M in decane, 2.08 mmol, 1.1 equiv.) was added dropwise. Upon completion of the reaction as indicated by TLC, satd. aq. $NaHCO_3$ (30 mL) and satd. aq. Rochelle salt (30 mL) were added, and the mixture was vigorously stirred for 1.5 hours. The layers were separated, and the aqueous layer was extracted using DCM (3 x 30 mL) and the combined organic layers were dried over Na_2SO_4. The crude residue product was purified by flash column chromatography (0 to 30% EtOAc/hexanes) to provide pure epoxide **2.7.1** (347 mg, 1.24 mmol, 65%) as a colorless liquid.

^{1}H NMR (600 MHz, C_6D_6) δ 6.11 (d, *J* = 12.8 Hz, 1H), 5.62 (d, *J* = 13.0 Hz, 1H), 5.04 (s, 1H), 5.00 (s, 1H), 4.32 (d, *J* = 10.4 Hz, 1H), 2.83 (s, 1H), 2.70 (d, *J* = 15.0 Hz, 2H), 2.40 (q, *J* = 10.2 Hz, 1H), 2.30 (d, *J* = 15.1 Hz, 1H), 1.95 (dd, *J* = 14.2, 9.0 Hz, 1H), 1.79 (dd, *J* = 14.3, 11.0 Hz, 1H), 1.07 (s, 3H), 0.10 (s, 9H).
^{13}C NMR (151 MHz, C_6D_6) δ 141.9, 134.7, 129.3, 120.4, 74.9, 74.0, 72.2, 68.1, 59.6, 45.4, 37.8, 18.9, 0.5.

Diol 2.7.3:

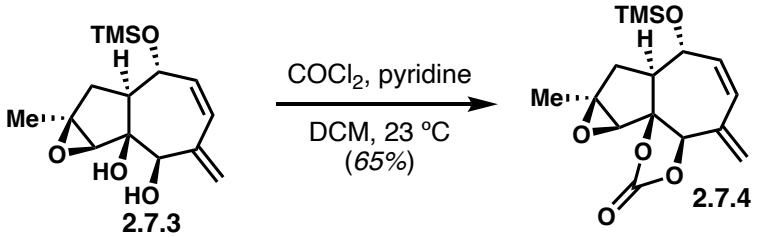


2.7.1 2.7.3

A flame-dried 250 mL round-bottom flask was charged with **2.7.1** (347 mg, 1.24 mmol, 1.0 equiv.) and THF (120 mL). SeO_2 (1372 mg, 12.37 mmol, 10.0 equiv.) was added and the reaction mixture was placed in a preheated oilbath (40 ºC). Upon completion of the reaction as indicated by TLC, satd. aq. $NaHCO_3$ (30 mL) and satd. aq. $Na_2S_2O_3$ (30 mL) were added, and the mixture was stirred for 30 minutes. The layers were separated, and the aqueous layer was extracted using EtOAc (3 x 30 mL) and the combined organic layers were dried over Na_2SO_4. The crude residue product was purified by flash column chromatography (0 to 50% EtOAc/hexanes) to provide pure diol **2.7.3** (176 mg, 0.59 mmol, 48%) as a colorless liquid.

^{1}H NMR (500 MHz, C_6D_6) δ 5.85 (ddt, *J* = 13.1, 2.1, 1.0 Hz, 1H), 5.64 (ddt, *J* = 13.0, 1.8, 0.8 Hz, 1H), 4.97 (d, *J* = 12.4 Hz, 2H), 4.43 (dt, *J* = 10.6, 2.2 Hz, 1H), 4.27 (d, *J* = 1.5 Hz, 1H), 3.41 (s, 1H), 3.35 (td, *J* = 10.7, 9.2 Hz, 1H), 2.88 (s, 1H), 2.05 (dd, *J* = 14.1, 9.2 Hz, 1H), 1.84 (ddd, *J* = 14.2, 11.0, 0.8 Hz, 1H), 1.17 (d, *J* = 3.4 Hz, 1H), 1.14 (s, 3H), 0.10 (s, 9H).
^{13}C NMR (126 MHz, C_6D_6) δ 146.7, 135.9, 125.9, 123.0, 77.8, 76.9, 74.1, 72.3, 68.5, 50.4, 37.5, 18.9, 0.5.

Carbonate 2.7.4:

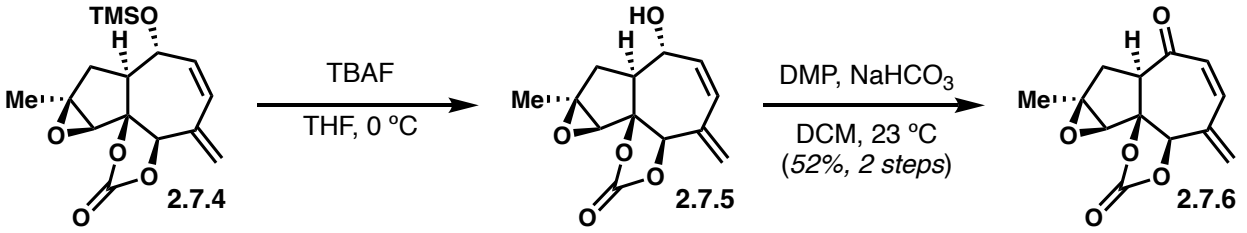


2.7.3 2.7.4

A flame-dried 25 mL round-bottom flask was charged with **2.7.3** (14 mg, 0.048 mmol, 1.0 equiv.) and DCM (5 mL) and pyridine (110 µL, 1.426 mmol, 30.0 equiv.). Phosgene (100 µL, 15% in PhMe, 0.142 mmol, 3.0 equiv.) was added dropwise. Upon completion of the reaction as indicated by TLC, satd. aq. $NaHCO_3$ (30 mL) was added, and the mixture was stirred for 30 minutes. The layers were separated, and the aqueous layer was extracted using DCM (3 x 30 mL) and the combined organic layers were dried over Na_2SO_4. The crude residue product was purified by flash column chromatography (0 to 25% EtOAc/hexanes) to provide pure carbonate **2.7.4** (10 mg, 0.031 mmol, 65%) as a colorless liquid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 5.73 (dt, *J* = 12.7, 1.8 Hz, 1H), 5.39 – 5.34 (m, 2H), 5.24 (s, 1H), 4.01 (dt, *J* = 10.4, 2.2 Hz, 1H), 3.72 (d, *J* = 1.5 Hz, 1H), 3.17 (s, 1H), 2.76 (q, *J* = 9.7 Hz, 1H), 1.98 (d, *J* = 9.5 Hz, 2H), 1.40 (s, 3H), 0.05 (s, 5H).

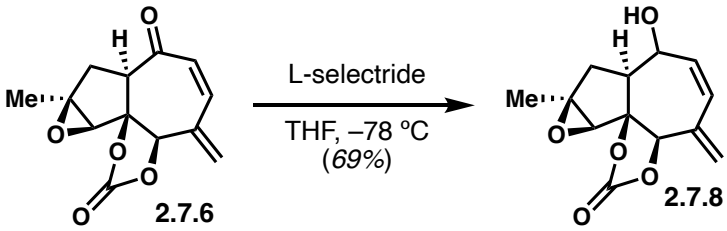
Vinylogous enone 2.7.6:



An oven-dried reaction tube was charged with **2.7.4** (8 mg, 0.025 mmol, 1.0 equiv.) and THF (500 µL) and was subsequently cooled to 0 ºC. TBAF (40 µL, 1M/THF, 0.040 mmol, 1.6 equiv.) was added and the reaction mixture was stirred for 1 hour before being quenched by addition of satd. aq. NH_4Cl (2 mL). The layers were separated, and the aqueous layer was extracted using EtOAc (3 x 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product **2.7.5** was taken forward without purification.
An oven-dried reaction tube was charged with crude 2.7.5, DCM (500 µL) and $NaHCO_3$ (21 mg, 0.250 mmol, 10 equiv.) DMP (17 mg, 0.040 mmol, 1.6 equiv.) was added and the reaction mixture was stirred for 15 minutes before being quenched by addition of satd. aq. $NaHCO_3$ (1 mL) and satd. aq. $Na_2S_2O_3$ (1 mL). The layers were separated, and the aqueous layer was extracted using DCM (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue product was purified by flash column chromatography (0 to 25% EtOAc/hexanes) to provide pure vinylogous enone **2.7.6** (3.2 mg, 0.013 mmol, 52%, 2 steps) as a colorless liquid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 6.46 (d, *J* = 12.6 Hz, 1H), 5.83 (d, *J* = 12.6 Hz, 1H), 5.74 (s, 1H), 5.61 (s, 1H), 3.94 (s, 1H), 3.67 – 3.62 (m, 1H), 3.18 (s, 1H), 2.84 (dd, *J* = 14.7, 7.8 Hz, 1H), 1.78 (dd, *J* = 14.7, 10.3 Hz, 1H), 1.44 (s, 3H).

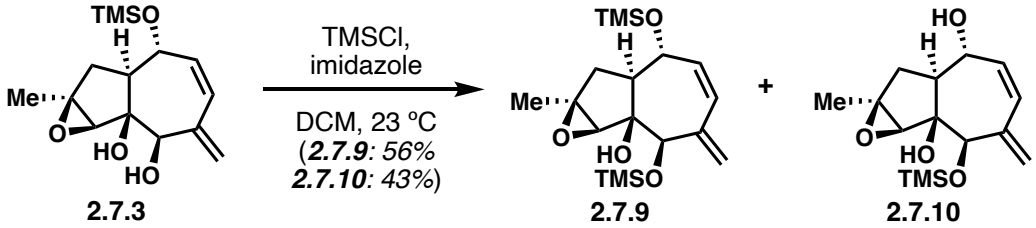
Allylic alcohol 2.7.8:



A An oven-dried reaction tube was charged with **2.7.6** (3 mg, 0.012 mmol, 1.0 equiv.) and THF (500 µL) and was subsequently cooled to –78 ºC. L-selectride (15 µL, 1M/THF, 0.015 mmol, 1.25 equiv.) was added and the reaction mixture was stirred for 10 minutes before being quenched by addition of satd. aq. NH_4Cl (2 mL). The layers were separated, and the aqueous layer was extracted using EtOAc (3 x 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue product was purified by flash column chromatography (0 to 25% EtOAc/hexanes) to provide pure allylic alcohol **2.7.8** (2.1 mg, 0.008 mmol, 69%) as a colorless liquid.

^{1}H NMR (700 MHz, C_6D_6) δ 5.65 (dd, *J* = 12.3, 6.6 Hz, 1H), 5.59 (d, *J* = 12.3 Hz, 1H), 5.08 (s, 1H), 4.95 (s, 1H), 3.72 – 3.60 (m, 2H), 3.42 (s, 1H), 3.03 (d, *J* = 12.1 Hz, 1H), 2.62 (s, 1H), 2.47 – 2.40 (m, 2H), 1.10 (s, 3H).

Silanol 2.7.9:

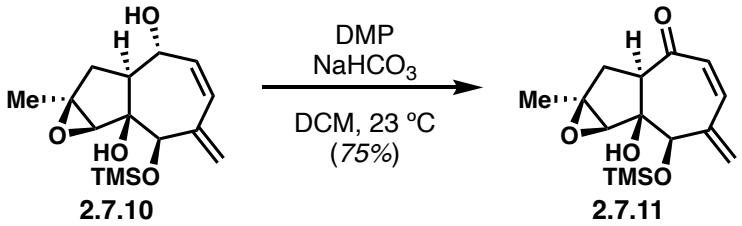


A An oven-dried reaction tube was charged with **2.7.3** (6 mg, 0.020 mmol, 1.0 equiv.) and DCM (1 mL) and imidazole (7 mg, 0.1012 mmol, 5.0 equiv.). TMSCl (6 µL, 0.051 mmol, 2.5 equiv.) was added and the reaction mixture was stirred for 1 hour before being quenched by addition of satd. aq. $NaHCO_3$ (2 mL). The layers were separated, and the aqueous layer was extracted using DCM (3 x 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue product was purified by flash column chromatography (0 to 25% EtOAc/hexanes) to provide pure disilanol **2.7.9** (4.2 mg, 0.011 mmol, 56%) as a colorless liquid together with mono silanol 2.7.10 (2.6 mg, 0.087 mmol, 43%) as colorless oil.
Silanol **2.7.10** can also be optained in an extra step from **2.7.9**
A 20 mL vial containing **2.7.9** (59 mg, 0.160 mmol, 1.0 equiv) was charged with Et_2O/MeOH (6 mL, 1:1). HCOOH (6 drops) was added, and the reaction mixture was stirred until all 2.7.9 was consumed judging by TLC. The reaction mixture was quenched by addition of satd. aq. $NaHCO_3$ (6 mL). The layers were separated, and the aqueous layer was extracted using Et_2O (3x 3 mL) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (0 to 25% EtOAc/hexanes) to provide pure silanol **2.7.10** (44 mg, 0.148 mmol, 93%).

Silanol 2.7.9
^{1}H NMR (500 MHz, C_6D_6) δ 5.94 – 5.88 (m, 1H), 5.67 (dt, *J* = 13.1, 1.2 Hz, 1H), 5.12 (t, *J* = 1.4 Hz, 1H), 5.01 (dd, *J* = 1.8, 0.9 Hz, 1H), 4.49 (d, *J* = 1.1 Hz, 1H), 4.46 (dt, *J* = 10.7, 2.2 Hz, 1H), 3.51 (td, *J* = 11.0, 9.1 Hz, 1H), 3.30 (s, 1H), 2.86 (s, 1H), 2.07 (dd, *J* = 14.1, 9.1 Hz, 1H), 1.84 (ddd, *J* = 14.1, 11.3, 0.7 Hz, 1H), 1.18 (s, 3H), 0.10 (s, 9H), 0.07 (s, 9H).

Silanol 2.7.10
^{1}H NMR (500 MHz, C_6D_6) δ 5.87 (ddt, *J* = 13.1, 2.2, 1.0 Hz, 1H), 5.58 – 5.51 (m, 1H), 5.09 (s, 1H), 5.00 (dd, *J* = 1.8, 0.9 Hz, 1H), 4.46 (d, *J* = 1.0 Hz, 1H), 4.14 – 4.08 (m, 1H), 3.28 – 3.21 (m, 2H), 2.75 (s, 1H), 1.87 (dd, *J* = 14.2, 9.3 Hz, 1H), 1.72 (ddd, *J* = 14.1, 11.0, 0.8 Hz, 1H), 1.18 (s, 3H), 0.07 (s, 9H).

Vinylogous enone 2.7.11:

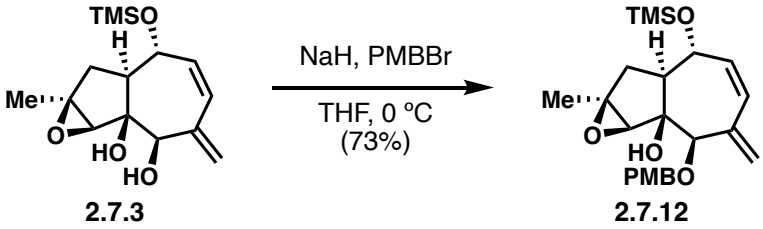


2.7.10 2.7.11

An oven-dried reaction tube was charged with 2.7.10 (27 mg, 0.091 mmol, 1.0 equiv.), DCM (2 mL) and $NaHCO_3$ (15 mg, 0.182 mmol, 2.0 equiv.) DMP (58 mg, 0.136 mmol, 1.5 equiv.) was added and the reaction mixture was stirred for 15 minutes before being quenched by addition of satd. aq. $NaHCO_3$ (2 mL) and satd. aq. $Na_2S_2O_3$ (2 mL). The layers were separated, and the aqueous layer was extracted using DCM (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue product was purified by flash column chromatography (0 to 25% EtOAc/hexanes) to provide pure vinylogous enone **2.7.11** (20 mg, 0.068 mmol, 75%) as a colorless liquid.

^{1}H NMR (500 MHz, C_6D_6) δ 6.14 (d, *J* = 13.0 Hz, 1H), 5.97 (d, *J* = 13.0 Hz, 1H), 5.15 (d, *J* = 1.5 Hz, 1H), 5.06 (d, *J* = 1.5 Hz, 1H), 4.44 (s, 1H), 4.22 (t, *J* = 9.8 Hz, 1H), 3.11 (s, 1H), 2.96 (s, 1H), 2.75 (dd, *J* = 14.7, 10.0 Hz, 1H), 1.67 (dd, *J* = 14.7, 9.5 Hz, 1H), 1.09 (s, 3H), -0.01 (s, 9H).

PMB-ether 2.7.12:

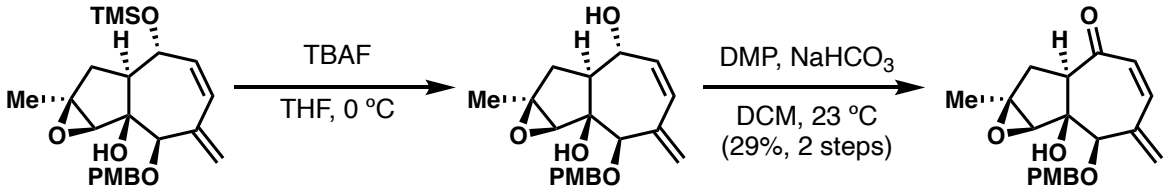


2.7.3 2.7.12

An oven-dried reaction tube was charged with **2.7.3** (5 mg, 0.017 mmol, 1.0 equiv.), THF (700 µL) and was subsequently cooled to 0 °C. NaH (1 pipette tip) was added and the reaction mixture was stirred for 10 minutes. PMBBr (7mg, 0.035 mmol, 2.0 equiv.) in THF (100 µL) was added and the the reaction mixture was stirred for 14 hours. The reaction being quenched by addition of satd. aq. NH_4Cl (2 mL). The layers were separated, and the aqueous layer was extracted using EtOAc (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue product was purified by flash column chromatography (0 to 25% EtOAc/hexanes) to provide pure vinylogous enone **2.7.12** (5.1 mg, 0.012 mmol, 73%) as a colorless liquid.

^{1}H NMR (700 MHz, C_6D_6) δ 7.14 (d, *J* = 8.5 Hz, 1H), 6.75 (d, *J* = 8.6 Hz, 1H), 6.00 – 5.95 (m, 1H), 5.76 – 5.71 (m, 1H), 5.18 (t, *J* = 1.4 Hz, 1H), 5.09 (t, *J* = 1.5 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.49 (dt, *J* = 10.6, 2.2 Hz, 1H), 4.11 (d, *J* = 11.5 Hz, 1H), 4.08 (d, *J* = 1.2 Hz, 1H), 3.53 (td, *J* = 11.0, 9.1 Hz, 1H), 3.32 – 3.30 (m, 1H), 3.29 (s, 3H), 2.04 (dd, *J* = 14.0, 9.1 Hz, 1H), 1.82 (dd, *J* = 14.0, 11.2 Hz, 1H), 1.13 (s, 3H), 0.11 (s, 9H).

Vinylogous enone 2.7.14:



2.7.12 **2.7.13** **2.7.14**

An oven-dried reaction tube was charged with **2.7.4** (5.1 mg, 0.012 mmol, 1.0 equiv.) and THF (1.2 mL) and was subsequently cooled to 0 ºC. TBAF (20 µL, 1M/THF, 0.020 mmol, 1.6 equiv.) was added and the reaction mixture was stirred for 1 hour before being quenched by addition of satd. aq. NH_4Cl (2 mL). The layers were separated, and the aqueous layer was extracted using EtOAc (3 x 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product **2.7.5** was taken forward without purification.
An oven-dried reaction tube was charged with crude **2.7.13**, DCM (1 mL) and $NaHCO_3$ (2 mg, 0.024 mmol, 2.0 equiv.) DMP (6.4 mg, 0.015 mmol, 1.5 equiv.) was added and the reaction mixture was stirred for 15 minutes before being quenched by addition of satd. aq. $NaHCO_3$ (1 mL) and satd. aq. $Na_2S_2O_3$ (1 mL). The layers were separated, and the aqueous layer was extracted using DCM (3 x 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue product was purified by flash column chromatography (0 to 25% EtOAc/hexanes) to provide pure vinylogous enone **2.7.14** (3.2 mg, 0.013 mmol, 29%, 2 steps) as a colorless liquid.

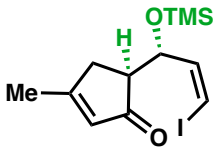
^{1}H NMR (700 MHz, C_6D_6) δ 7.05 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.22 – 6.17 (m, 1H), 6.00 (d, *J* = 13.1 Hz, 1H), 5.19 (d, *J* = 1.7 Hz, 1H), 5.10 (d, *J* = 1.5 Hz, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 4.26 (t, *J* = 9.7 Hz, 1H), 4.07 – 4.02 (m, 2H), 3.29 (s, 3H), 3.08 (s, 1H), 3.03 (s, 1H), 2.69 (dd, *J* = 14.6, 10.1 Hz, 1H), 1.65 (dd, *J* = 14.7, 9.3 Hz, 1H), 1.06 (s, 3H).

2.12.4 *References for Section 2.12*

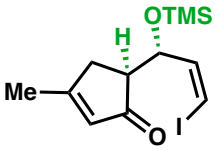
SI-1 Piers, E.; Wong, T.; Coish, P. D.; Rogers, C. A Convenient Procedure for the Efficient Preparation of Alkyl (Z)-3-Iodo-2-Alkenoates. *Can. J. Chem.* **1994**, *72* (8), 1816–1819.

SI-2 Marek, I.; Meyer, C.; Normant, J.-F. A Simple and Convenient Method for the Preparation of (Z)-β-Iodoacrolein and of (Z)- or (E)-γ-Iodo Allylic Alcohols: (Z)- and (E)-1-Iodohept-1-En-3-Ol: 2-Propenal, 3-Iodo-, (Z)- and 1-Hepten-3-Ol, 1-Iodo-, (Z)- and (E)-. In *Organic Syntheses*; John Wiley & Sons, Inc., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2003; pp 194–194.

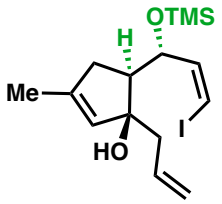
SI-3 Hirose, A.; Watanabe, A.; Ogino, K.; Nagatomo, M.; Inoue, M. Unified Total Synthesis of Rhamnofolane, Tigliane, and Daphnane Diterpenoids. *J. Am. Chem. Soc.* **2021**, *143*, 12387.



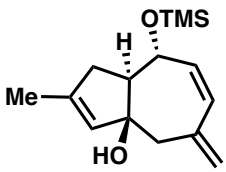
(±)-2.1.6
(600 MHz, C_6D_6)



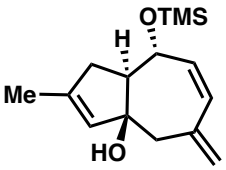
(±)-2.1.6
(150 MHz, C_6D_6)



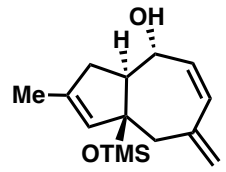
2.1.9
(600 MHz, C_6D_6)



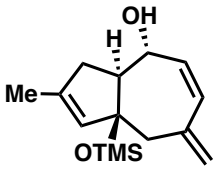
2.1.10
(600 MHz, C_6D_6)



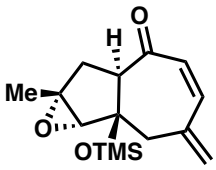
2.1.10
(150 MHz, C_6D_6)



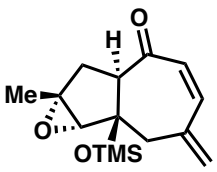
2.2.2
(600 MHz, C_6D_6)



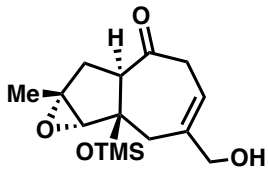
2.2.2
(150 MHz, C_6D_6)



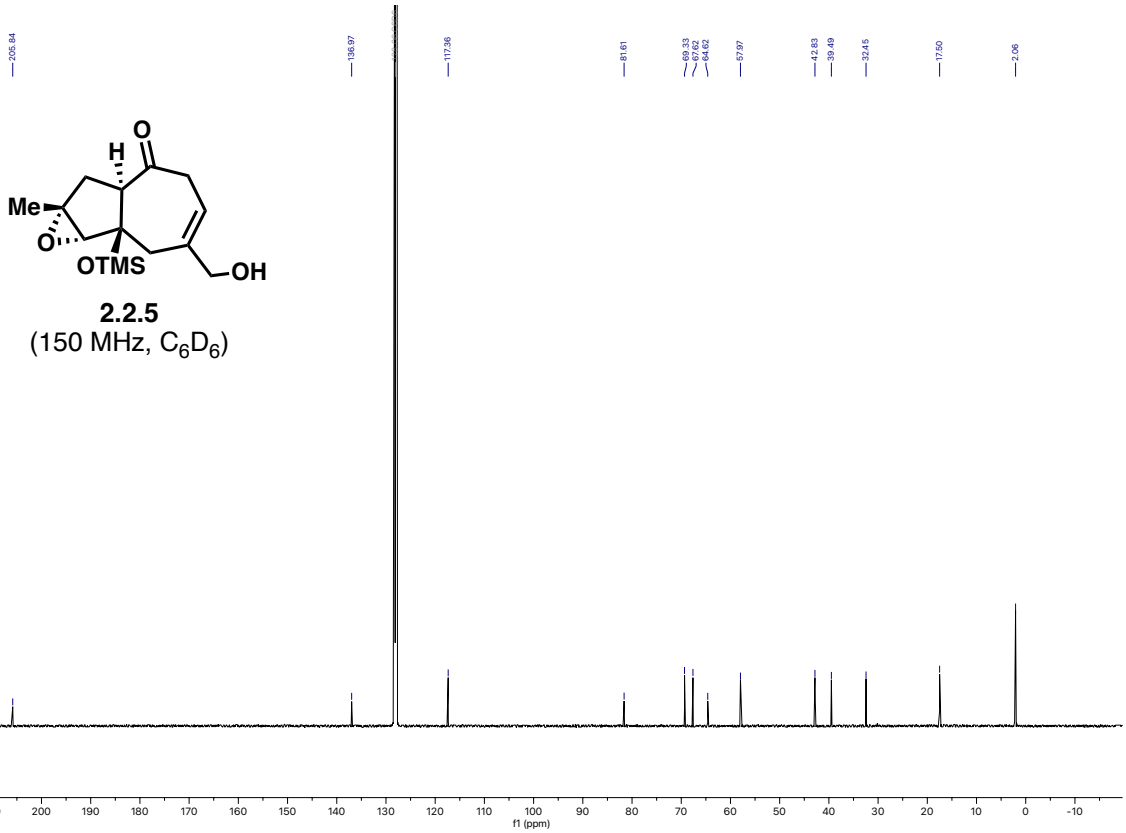
2.2.4
(600 MHz, C_6D_6)



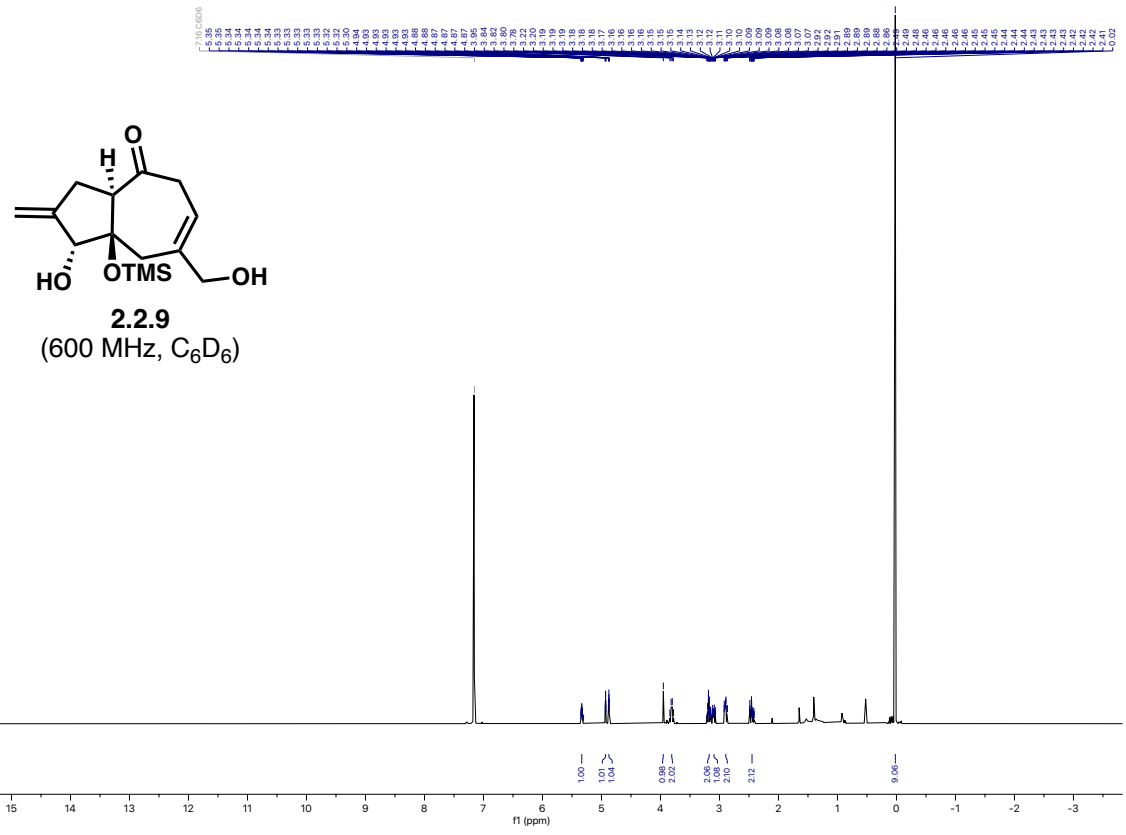
2.2.4
(150 MHz, C_6D_6)



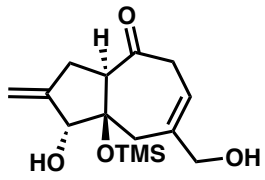
2.2.5
(600 MHz, C_6D_6)



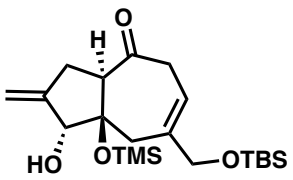
2.2.5
(150 MHz, C_6D_6)



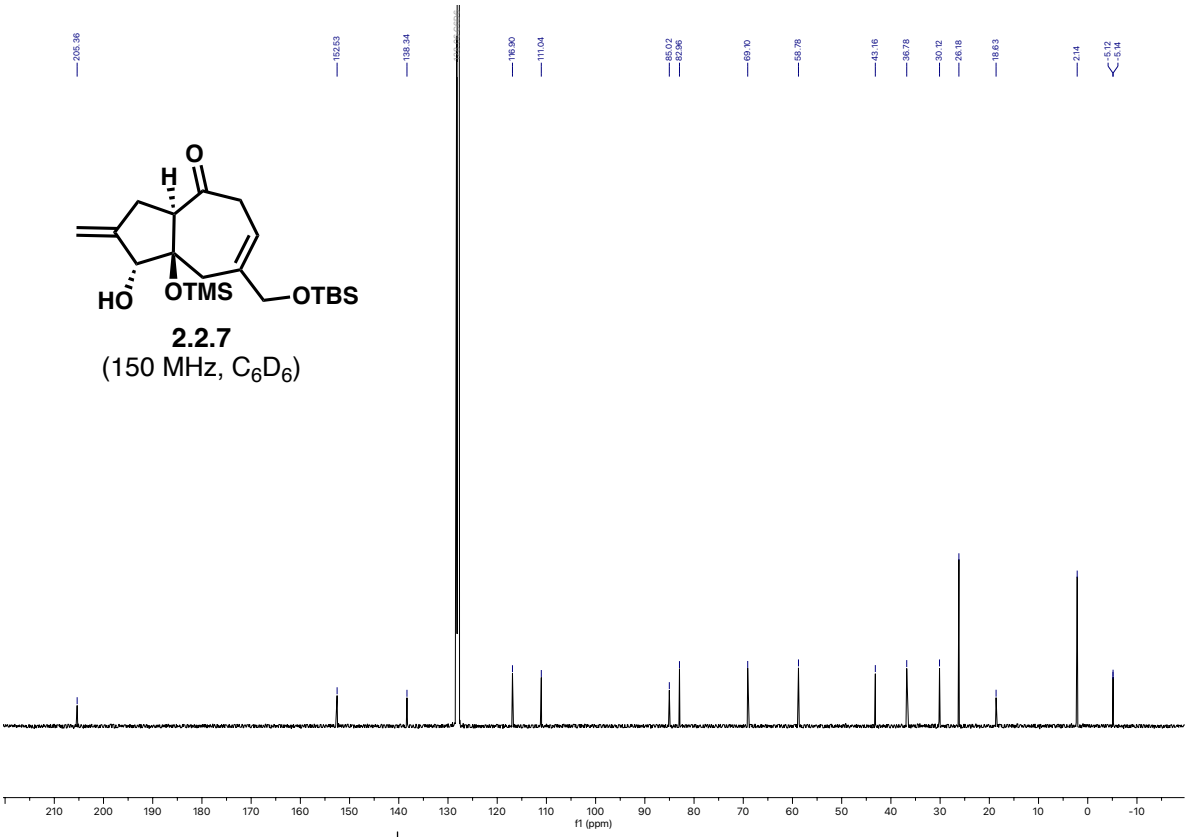
2.2.9
(600 MHz, C_6D_6)



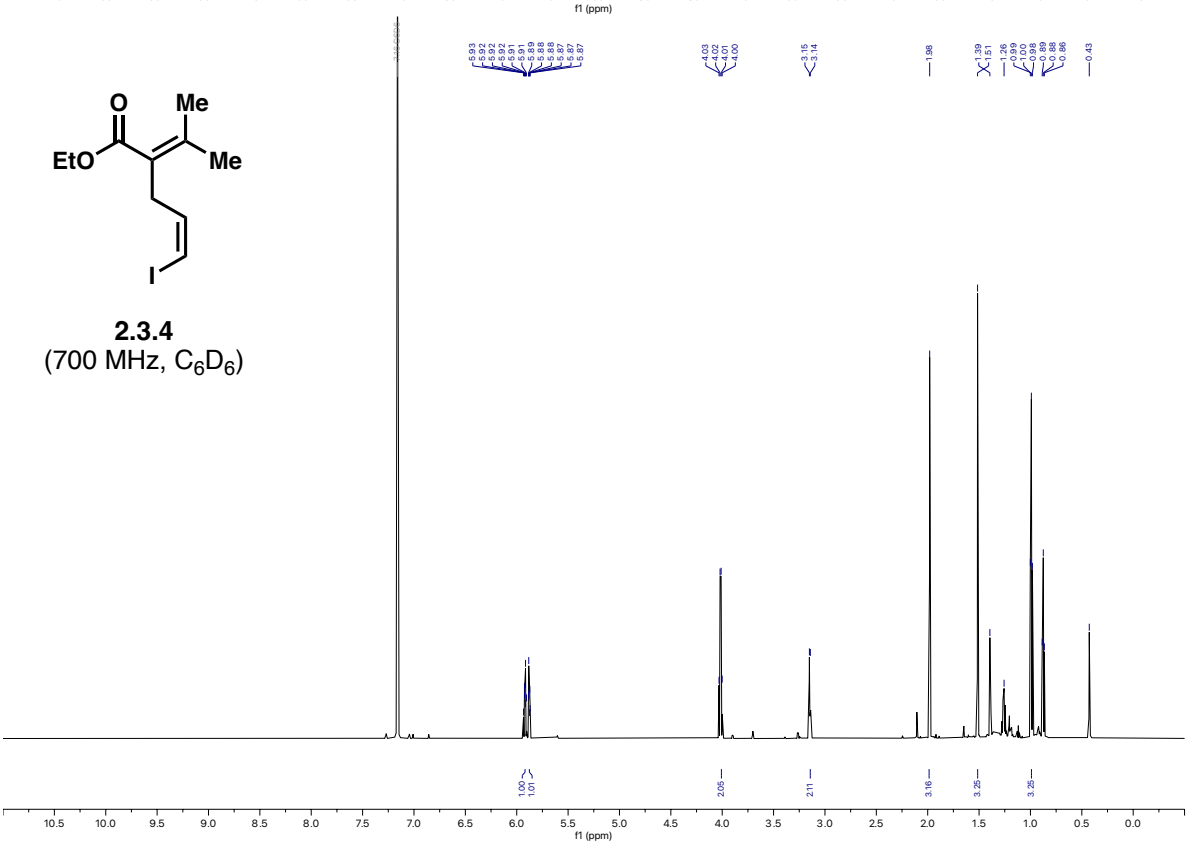
2.2.9
(150 MHz, C_6D_6)



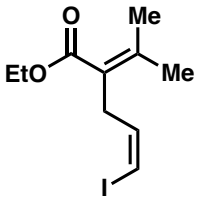
2.2.7
(600 MHz, C_6D_6)



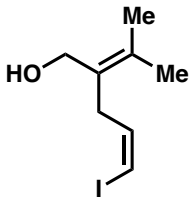
2.2.7
(150 MHz, C_6D_6)



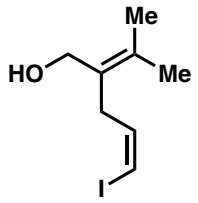
2.3.4
(700 MHz, C_6D_6)



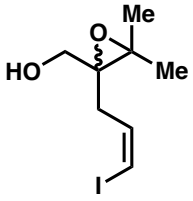
2.3.4
(150 MHz, C_6D_6)



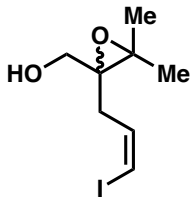
2.3.5
(600 MHz, $CDCl_3$)



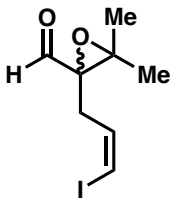
2.3.5
(150 MHz, $CDCl_3$)



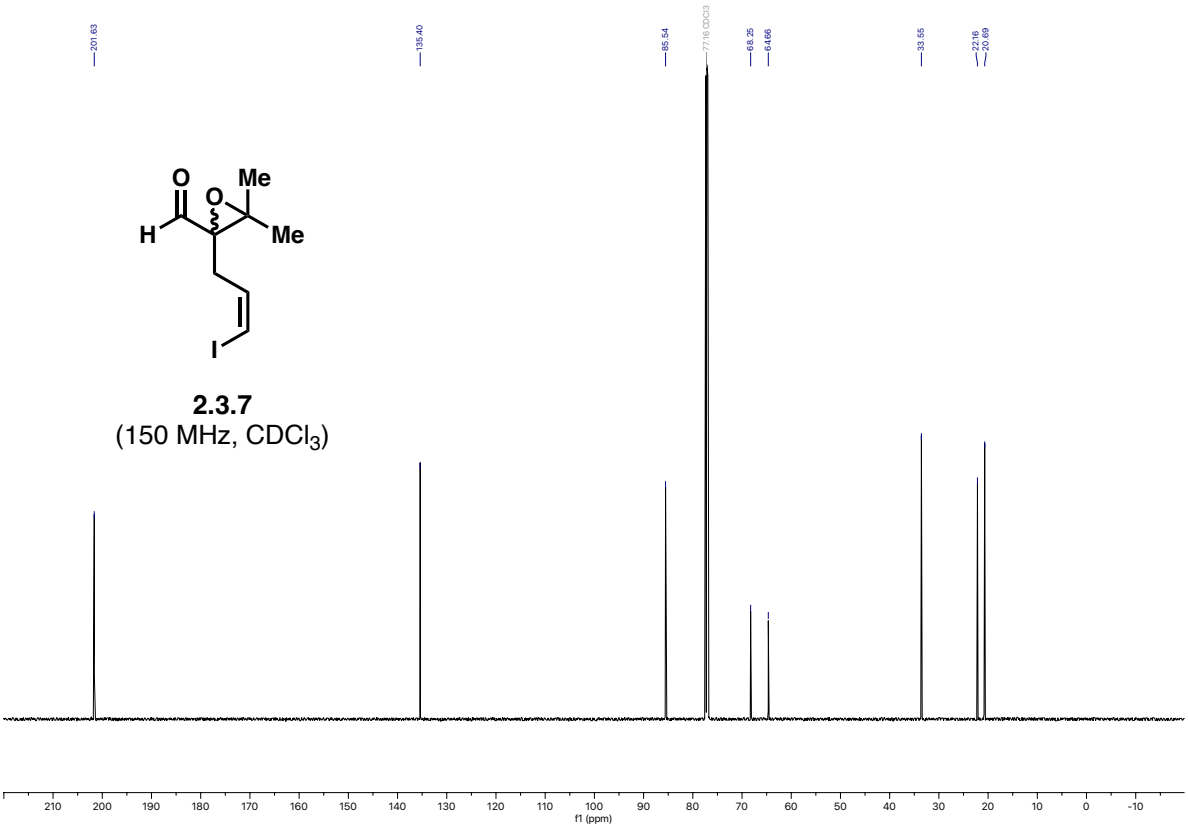
2.3.6
(400 MHz, $CDCl_3$)



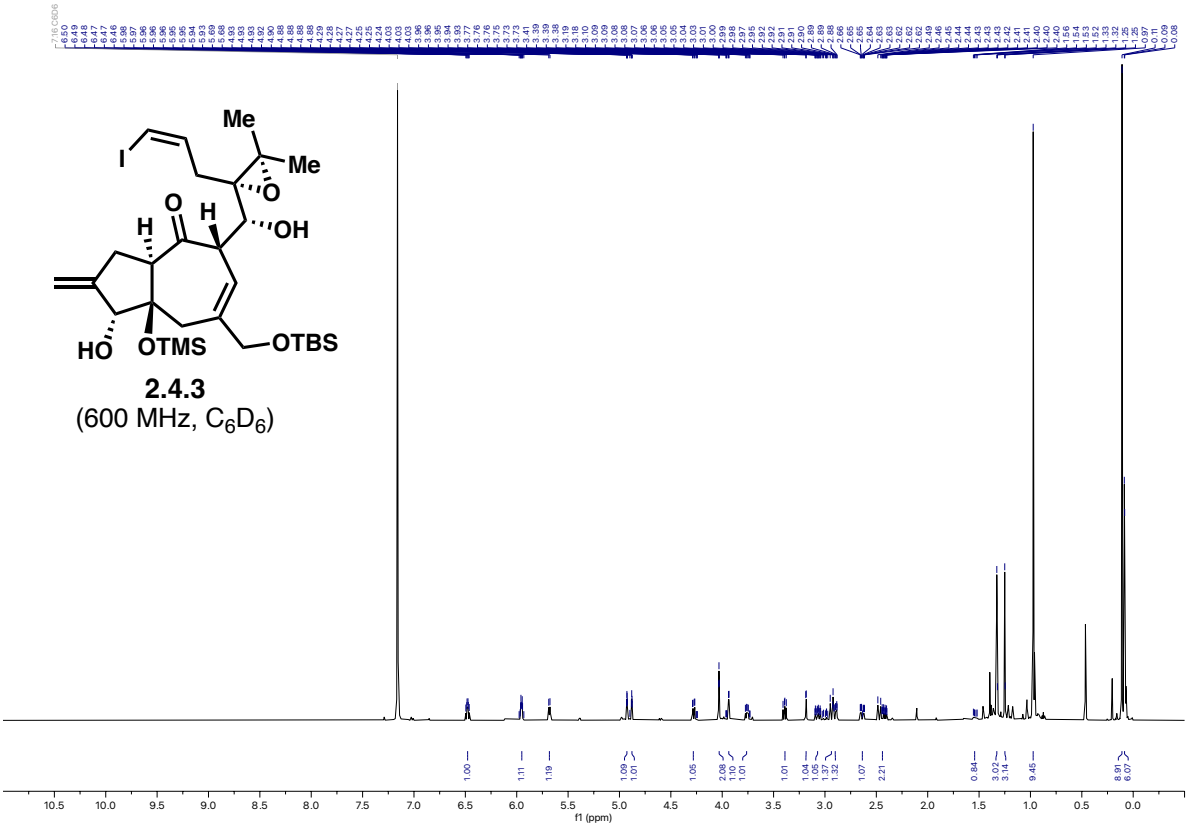
2.3.6
(150 MHz, $CDCl_3$)



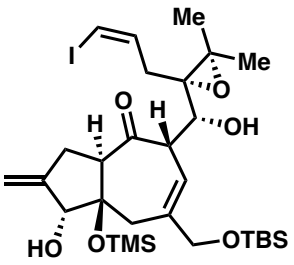
2.3.7
(700 MHz, $CDCl_3$)



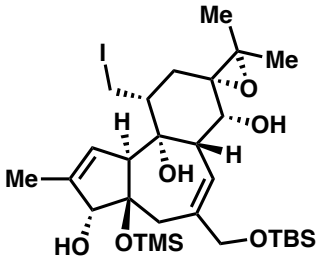
2.3.7
(150 MHz, $CDCl_3$)



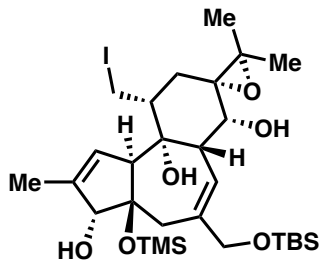
2.4.3
(600 MHz, C_6D_6)



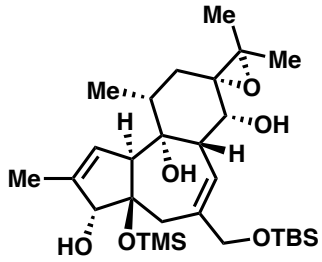
2.4.3
(150 MHz, C_6D_6)



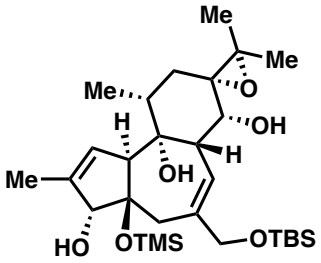
2.4.7
(600 MHz, C_6D_6)



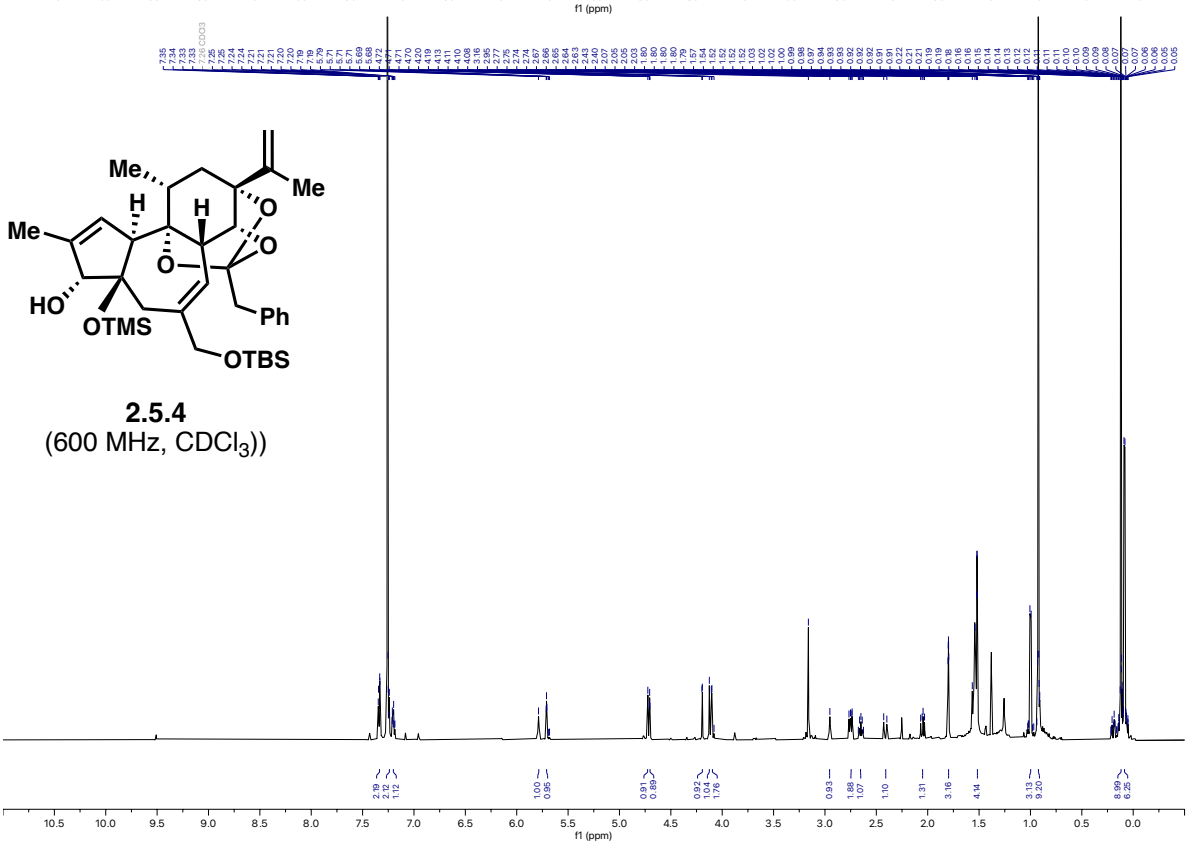
2.4.7
(150 MHz, C_6D_6)



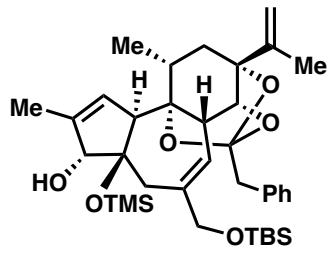
2.5.1
(600 MHz, $CDCl_3$))



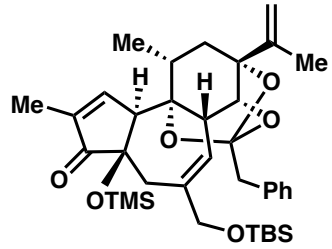
2.5.1
(150 MHz, $CDCl_3$)



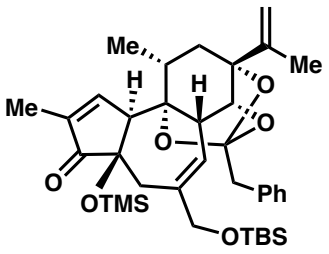
2.5.4
(600 MHz, $CDCl_3$))



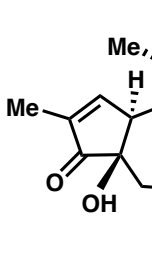
2.5.4
(150 MHz, $CDCl_3$))



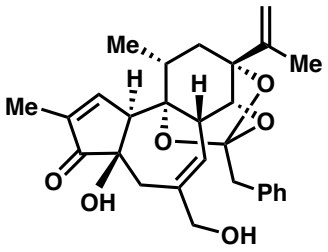
2.5.5
(600 MHz, $CDCl_3$))



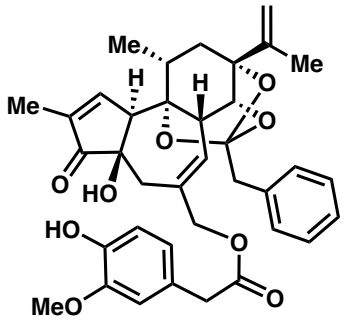
2.5.5
(150 MHz, $CDCl_3$))



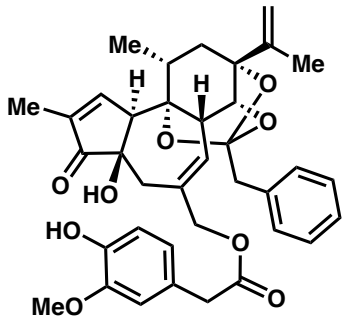
2.5.6
(600 MHz, $CDCl_3$))



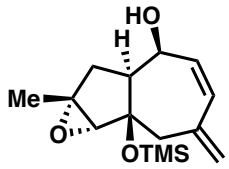
2.5.6
(150 MHz, $CDCl_3$))



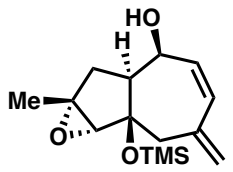
1.1.1
(600 MHz, $CDCl_3$))



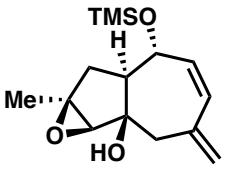
1.1.1
(150 MHz, $CDCl_3$))



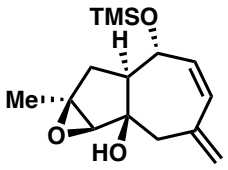
2.6.2
(600 MHz, C_6D_6)



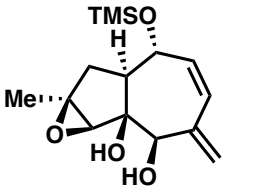
2.6.2
(150 MHz, C_6D_6)



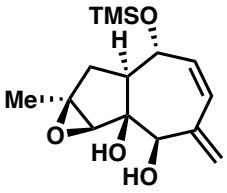
2.7.1
(600 MHz, C_6D_6)



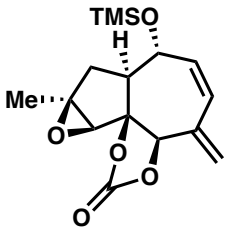
2.7.1
(150 MHz, C_6D_6)



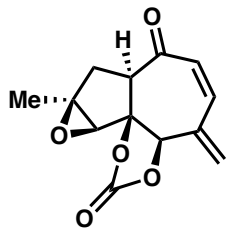
2.7.3
(600 MHz, C_6D_6)



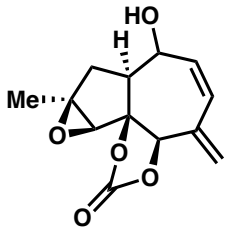
2.7.3
(150 MHz, C_6D_6)



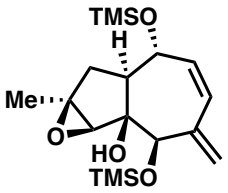
2.7.4
(700 MHz, C_6D_6)



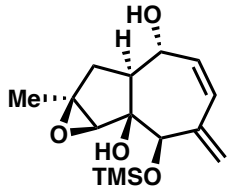
2.7.6
(700 MHz, C_6D_6)



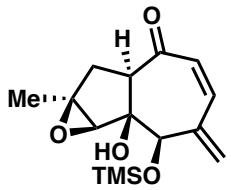
2.7.7
(700 MHz, C_6D_6)



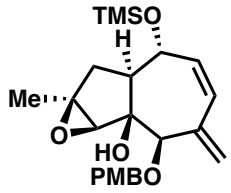
2.7.9
(500 MHz, C_6D_6)



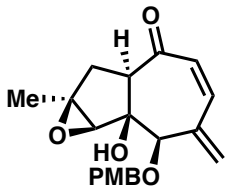
2.7.10
(500 MHz, C_6D_6)



2.7.11
(700 MHz, C_6D_6)



2.7.12
(700 MHz, C_6D_6)



2.7.14
(700 MHz, C_6D_6)