CHAPTER 3

Unified Approach to Daucane and Sphenolobane Bicyclo[5.3.0]decane core: Enantioselective Synthesis of Four Daucane Sesquiterpenes and Related Molecules[†]

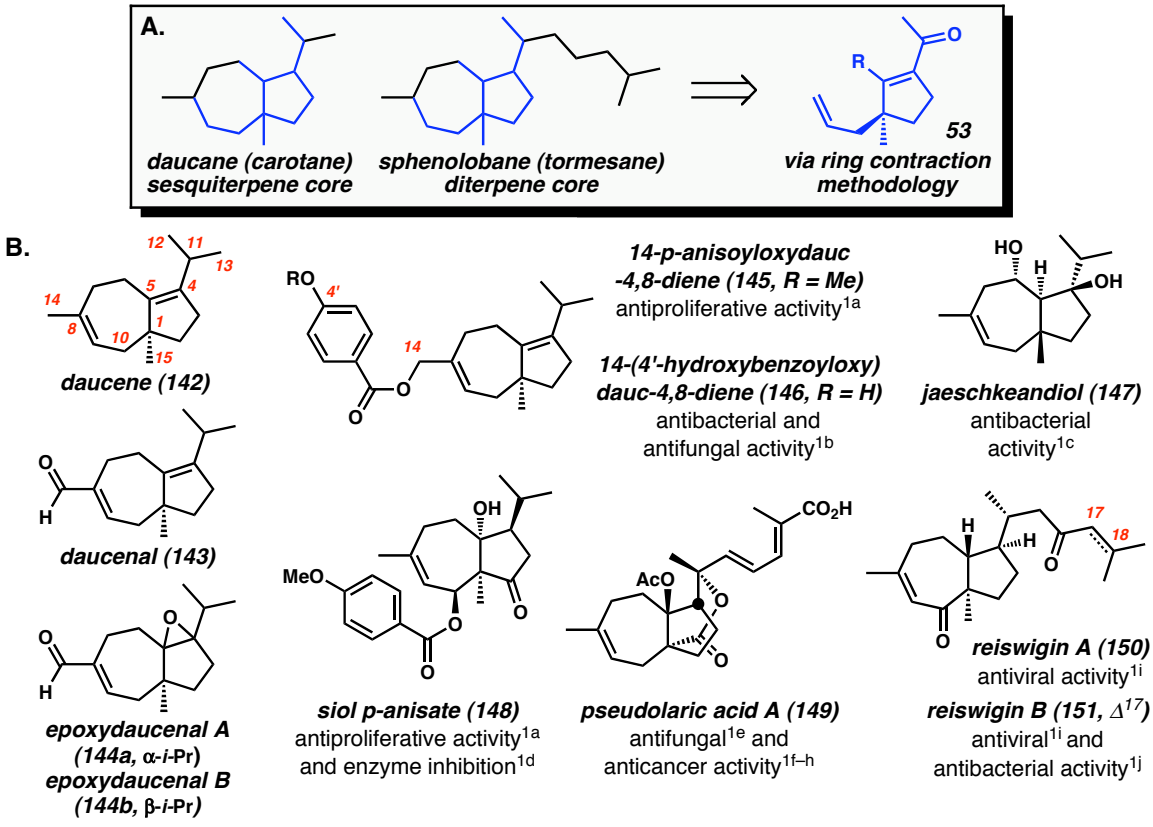
3.1 INTRODUCTION AND BACKGROUND

The daucane (carotane) sesquiterpenes and sphenolobane (tormesane) diterpenes are two structurally related families of natural products that share a hydroazulene (i.e., bicyclo[5.3.0]decane) core (Figure 3.1A). These terpenoids feature varied degrees of oxidation with diverse peripheral functionality and, as a group, exhibit a wide range of biological activity (Figure 3.1B).[1] As such, the synthetic community has reported several studies[2] and total syntheses[1i,3] of a number of these natural products. Central to our interest in these molecules is the cyclopentane motif, which we envisioned accessing from a γ-quaternary acylcyclopentene (**53**) generated by a combination of the palladium-catalyzed asymmetric enolate alkylation[4,5,6] and ring contraction chemistry that is

[†] The research has been submitted for publication.

discussed in the preceding chapter (Figure 3.1A).[7] As part of our ongoing efforts to apply this methodology,[8] we have developed a route to the sesquiterpene and diterpene carbocyclic scaffolds, explored functionalization of the hydroazulene skeleton to oxidized compounds including epoxydaucenal B (**144b**), and completed the first total syntheses of 14-*p*-anisoyloxydauc-4,8-diene (**145**) and daucenal (**143**) via the archetypal daucane sesquiterpene, daucene (**142**).

*Figure 3.1. Bicyclo[5.3.0]decane skeletons linked to acylcyclopentene **53** and examples of hydroazulene natural products.*



3.1.1 Isolation, Structural Determination, and Bioactivity of Relevant Daucane Sesquiterpenes

Feldmann reported the earliest study on a daucane sesquiterpene in 1865,[9] and since that time, numerous molecules in this class have been identified and investigated. The majority of the research on this family of natural products was performed in the 1950s–1970s, and an excellent review by Ghisalberti details the isolation, characterization, bioactivity, and biosynthesis of these sesquiterpenes.[10] The following section focuses on the daucane sesquiterpenes associated with our synthetic efforts and the reader is directed to the aforementioned review for further information.

The structurally simplest daucane we have prepared is daucene (**142**), which has been isolated from several sources[11] and is postulated to be the biosynthetic precursor to more functionalized derivatives.[11a,12] This natural product was originally obtained from *Daucus carotoa*[11a] in 1961 by Pigulevskii and has also more recently been found as a constituent of extracts from *Piptoporus betulinus*,[11b] *Gleophyllum odoratum*,[11b] x*Cupressocyparis leylandii*,[11c] *Ferula hermonis*,[11d] and *Matricaria chamomilla*.[11e] Interestingly, both enantiomers of daucene occur naturally. Pigulevskii first analyzed daucene with Raman and infrared (IR) spectroscopy, which suggested a hydroazulene structure with tri- and tetrasubstituted double bonds. A series of hydrogenation experiments were performed and the resulting reduced molecules were also examined. The structure of daucene was ultimately confirmed by several total syntheses, which are discussed in Section 3.2.

In 1991, Hashidoko et al. isolated daucenal (**143**) and epoxydaucenal A and B (**144a** and **b**) from the leaves of *Rosa rugosa*.[13] Initial analysis of daucenal by EI mass

spectrometry and $^{1}H/^{13}C$ NMR suggested the molecule contained either a [7–5] or [4–8] bicyclic skeleton. The bicyclo[5.3.0]decane structure that is characteristic of the daucane sesquiterpenes was ultimately confirmed by Correlation through Long-Range Coupling (COLOC) NMR.[14] The NMR spectra of epoxydaucenal A and B (**144a** and **b**) shared several related signals to daucenal, and mass spectrometry indicated each molecule contained an additional oxygen. The structural similarity was confirmed as daucenal (**143**) was oxidized with 3-chloroperbenzoic acid to provide a 70:30 mixture of the epoxidized molecules (**144a**:**144b**) in 58% yield. The relative stereochemistry of epoxy and isopropyl groups was determined by NOE experiments.

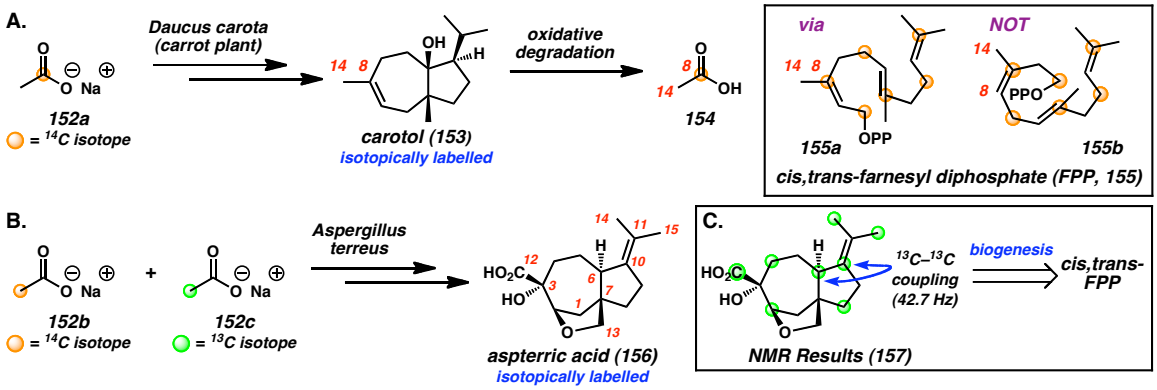
14-*p*-anisoyloxydauc-4,8-diene (**145**) was first isolated by Miski et al.[15] in 1986 from the roots of *Ferula tingitana*. The molecular structure of this sesquiterpene was elucidated by mass spectrometry and IR, ultraviolet (UV), and NMR spectroscopy. Viola and co-workers[1a] later isolated ester **145** from *Ferula communis* and found this molecule displays antiproliferative activity against HL-60, Jurkat, K562, RS 4;11, and SEM human tumor cells with IC_{50} values comparable or superior to many of the more oxygenated and complex daucane sesquiterpenes screened. Interestingly, the related 14-(4'-hydroxybenzoyloxy)dauc-4,8-diene (**146**), which was isolated from *Ferula hermonis*, displays antibacterial and antifungal activity.[1b]

Despite the earliest isolation occurring over twenty five years ago and this bioactivity, to our knowledge no total syntheses have been reported for any of these C(14) oxidized sesquiterpenes.

3.1.2 Biosynthetic Studies

Two main experiments have been performed to explore the biogenesis of the daucane sesquiterpene skeleton.[16] In 1962, Soucek fed ^{14}C-labeled sodium acetate (**152a**) to *Daucus carota* (carrot plant) to determine the positions of isotope incorporation in carotol (**153**, Scheme 3.1A).[17] The resulting ^{14}C-enriched carotol was oxidatively degraded to generate acetic acid (**154**) from the C(8) and C(14) positions of the molecule. The acetic acid formed through this process contained the ^{14}C-isotope, suggesting that the carbocyclic core arises through folding of *cis,trans*-farnesyl diphosphate (FPP, **155**) as depicted in intermediate **155a** instead of conformation **155b**. The latter arrangement would necessitate an additional methyl shift to obtain the carbon skeleton and consequently occlude ^{14}C-incorporation in the degradation product.

Scheme 3.1. ^{14}C- and ^{13}C-labeled sodium acetate feeding experiments.



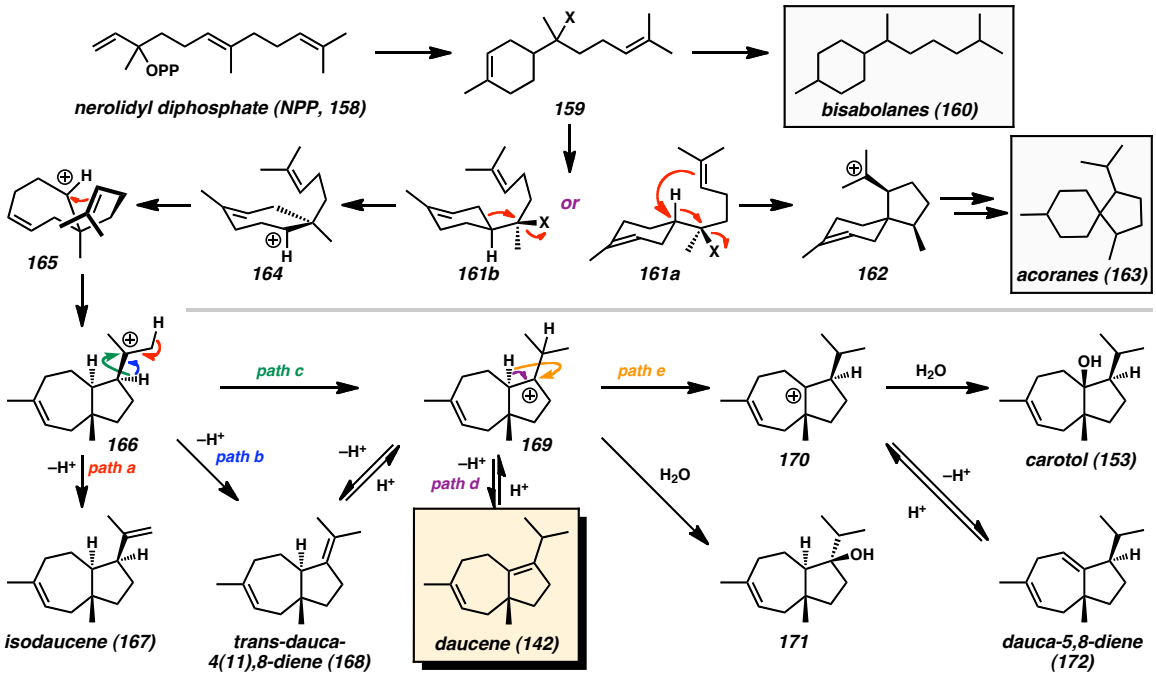
A second isotope study was performed by Tsuda et al. in 1976.[18] This publication details the first isolation of a daucane sesquiterpene from a source outside the Umbelliferae (Apiaceae) family. To gain insight into the biosynthetic pathway in the

fungus *Aspergillus terreus*, they simultaneously fed ^{14}C- and ^{13}C-labeled sodium acetate (**152b** and **152c**) to the organism and analyzed the resulting enriched aspterric acid (**156**, Scheme 3.1B). The mass of the enriched aspterric acid was obtained, and the extent of isotope incorporation was determined from the ^{14}C-isotope to be 1.32%. Analysis of the ^{13}C isotope by NMR revealed enrichment at multiple positions and a ^{13}C–^{13}C coupling between C(6) and C(10) (see **157**, Scheme 3.1C). Given these results, Tsuda and co-workers proposed that aspterric acid (**156**) also arises through a concerted cyclization of *cis,trans*-FPP (**155**) through a conformation like that described by Soucek.

Ghisalberti argues in his 1994 review that a concerted cyclization mechanism is plausible, but not necessarily operable, as such a pathway does not rationalize the formation of other sesquiterpenes that are co-isolated with daucanes.[10] To resolve this issue, he proposes an alternative stepwise biosynthesis that explains the co-occurrence of bisabolane (**160**)[19] and acorane (**163**)[11c,13,19] natural products (Scheme 3.2). Initial cyclization of nerolidyl diphosphate (NPP, **158**) generates carbocation **159**, which may be funneled to the bisabolanes directly or undergo a subsequent cyclization/1,2-hydride shift (**161a**) to afford the acorane sesquiterpenes. Alternatively, ring expansion of cyclohexane **161** and subsequent cyclization reveals daucane carbocation **166**, which may be converted to other cations through various 1,2-hydride shifts. Ultimately these carbocations may be neutralized through an elimination reaction or quenching with water. Ghisalberti's pathway is reasonable, but speculative. The only justification for this route beyond co-isolation is the observation of interconversion between the daucane and acorane scaffolds in synthetic efforts[20] and Naegeli and Kaiser's 1962 synthesis of daucene that also forms acoradiene (**173**) in the final acid-promoted cyclization (see

Section 3.2).[21] Further biological experiments are necessary to confirm the validity of this biosynthetic proposal.

*Scheme 3.2. Biosynthetic route that rationalizes co-isolation of bisabolane (**160**), acorane (**163**), and daucane sesquiterpenes.*

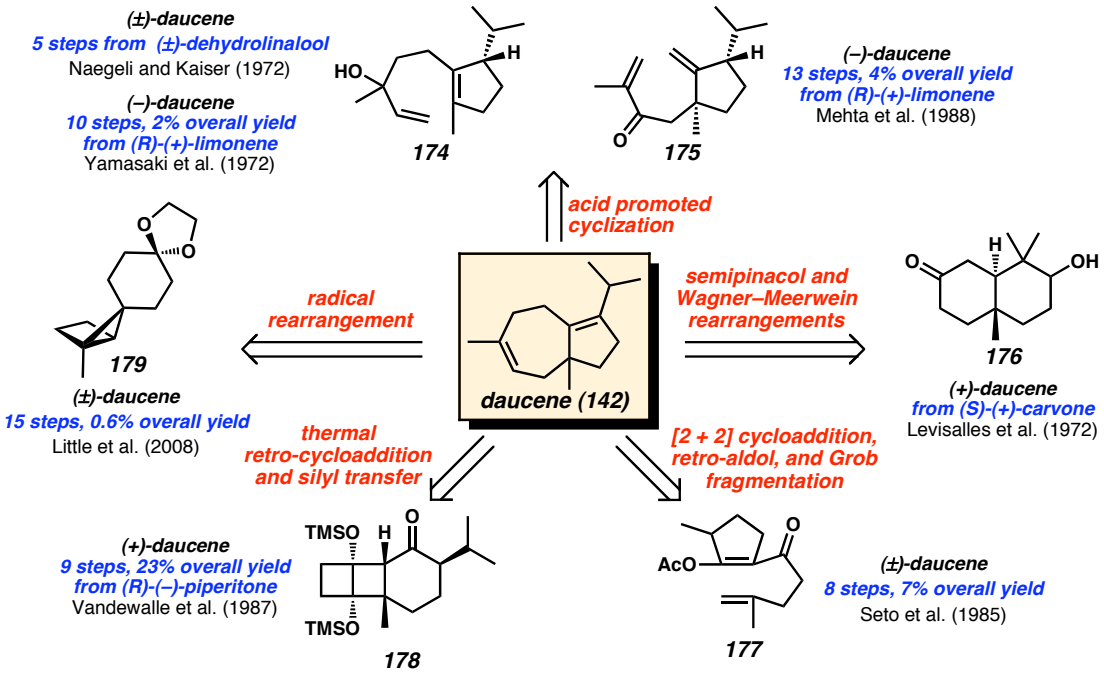


3.2 PREVIOUS TOTAL SYNTHESES OF DAUCENE

Of the daucane molecules we selected to target, only daucene (**142**) has been synthesized previously. Five main strategies have been employed to construct the [7–5] bicyclic core of this natural product (Scheme 3.3). Early efforts by Naegeli and Kaiser,[21] Yamasaki,[22] and Mehta[12,23] focus on acid-promoted cyclizations that append the seven-membered ring onto an existing cyclopentane scaffold. Around the same time, Levisalles reported a semipinacol and Wagner–Meerwein rearrangement sequence on *trans*-decalin **176** that expands the left half of the molecule to the cycloheptyl ring and contracts the

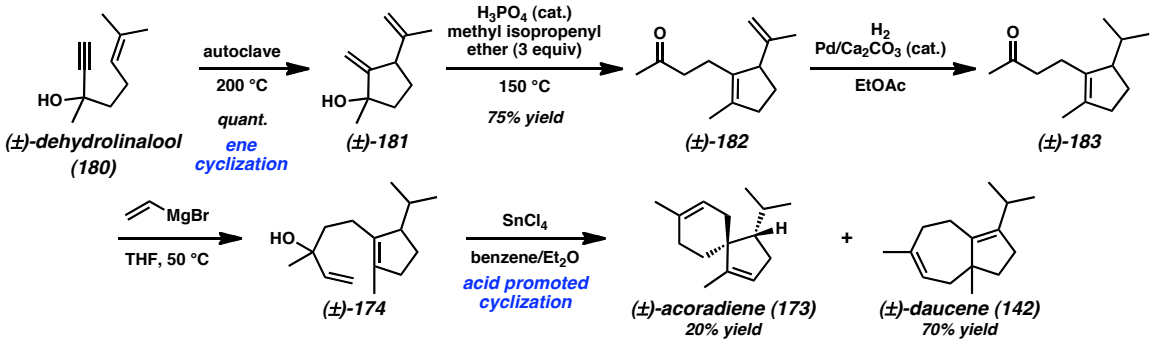
right portion to the isopropyl-accessorized cyclopentene motif.[24] In the 1980s, Seto[25] and Vandewalle[26] independently reported syntheses of daucene that include a [2 + 2] cycloaddition to prepare the bicyclic core. Seto cleaves the resulting cyclobutane with a retro-aldol fragmentation, while Vandewalle employs a thermally promoted retro-cycloaddition that triggers a silyl transfer reaction in situ. Most recently, Little has disclosed an electrochemically-induced radical ring expansion on cyclohexane **179**.[27] Overall, these past routes can only produce daucene racemically or rely on enantioenriched, naturally occurring starting materials to obtain the sesquiterpene asymmetrically. These approaches also suffer from low yields, poor enantiopurity, and/or extended preparation times (e.g., >30 days). Many of these syntheses also incorporate similar steps or strategies to arrive at key intermediates.

Scheme 3.3. Retrosynthetic analysis of previous routes to daucene.



Naegeli and Kaiser accomplished the first total synthesis of daucene (**142**) in 1972 (Scheme 3.4).[21] In their route, racemic dehydrolinalool (**180**) is cyclized to allylic alcohol **181** and subsequently treated with acid and methyl isopropenyl ether at elevated temperature to initiate a Claisen rearrangement that affords ketone **182**. Ketone **182** is hydrogenated with Lindlar's catalyst and converted to allylic alcohol **174** with vinylmagnesium bromide. Finally, a Lewis acid-induced cyclization with tin(IV) chloride completes the synthesis of daucene (**142**) and also produces the natural product acoradiene (**173**). This approach furnishes daucene quickly (5 steps), but prepares the racemic product, and does not indicate yields for several steps in the sequence.

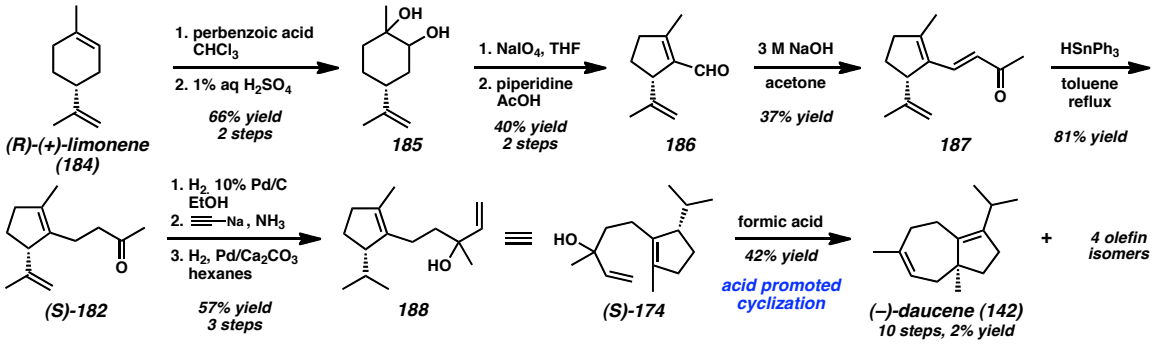
Scheme 3.4. First total synthesis by Naegeli and Kaiser in 1972.



Yamasaki and co-worker's synthesis also invokes an acid-promoted cyclization on allylic alcohol **174**, but affords the natural product in enantiopure form (Scheme 3.5).[22] Their approach starts with (*R*)-(+)-limonene (**184**), which is oxidized with perbenzoic acid to generate an epoxide that is opened with acid to furnish diol **185**. Diol **185** is contracted to acylcyclopentene **186** by sequential treatment with sodium periodate and piperidine in acetic acid. An aldol condensation on acylcyclopentene **186** produces

enone **187**, which is reduced to the corresponding ketone ((*S*)-**182**) with triphenyltin hydride. Conversion of ketone (*S*)-**182** to allylic alcohol **188** is accomplished through a three-step hydrogenation, acetylene addition, and Lindlar reduction sequence. It is unclear why the authors selected a two-step installation of the vinyl group instead of employing a vinyl organometallic reagent. Nevertheless, treatment of allylic alcohol (*S*)-**174** with formic acid results in the formation of five compounds, of which (–)-daucene (**142**) is isolated in 42% yield. The key disadvantage of Yamasaki's route is that several steps perform poorly and consequently provide the natural product in diminished overall yield.

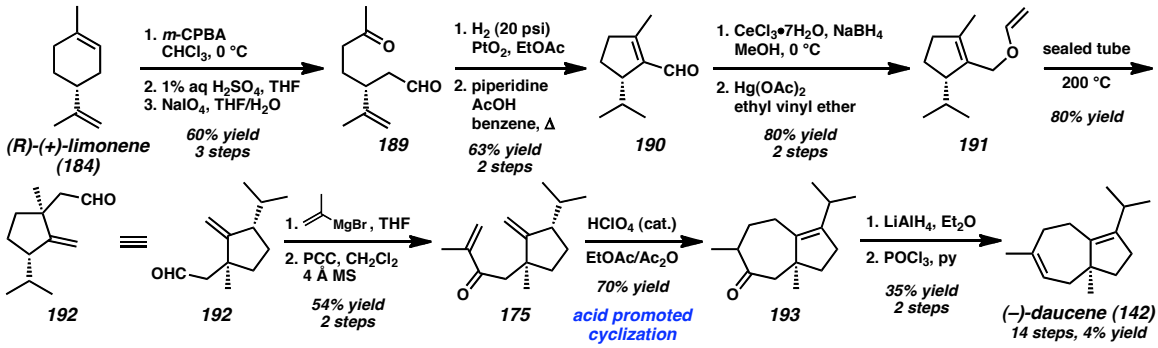
*Scheme 3.5. Yamasaki's 1972 route to enantioenriched allylic alcohol **182** and (–)-daucene (**142**).*



Mehta's synthesis[12,23] not only incorporates an acid-promoted cyclization, but also follows the same initial ring opening sequence from (*R*)-(+)-limonene (**184**) employed by Yamasaki. However, Mehta opts to hydrogenate the isopropenyl group earlier in the synthetic route, arriving at enal **190** instead of the dehydrated analog (**186**, Scheme 3.5). Luche reduction of enal **190** generates an allylic alcohol that is treated with mercury(II) acetate and ethyl vinyl ether to produce vinyl ether **191** (Scheme 3.6). Vinyl ether **191** is

heated in a sealed tube to initiate a Claisen rearrangement that affords aldehyde **192**, which is converted to enone **175** through Grignard addition and oxidation. Acid-catalyzed cyclization of enone **175** completes the cycloheptyl ring and furnishes ketone **193** as an inconsequential mixture of diastereomers. To install the remaining olefin and complete the synthesis, ketone **193** is reduced and the resulting alcohol is eliminated. However, the elimination step suffers from low yield due to the formation of other olefin isomers. In summary, Mehta's synthesis parallels Yamaski's efforts closely and again produces daucene in low overall yield.

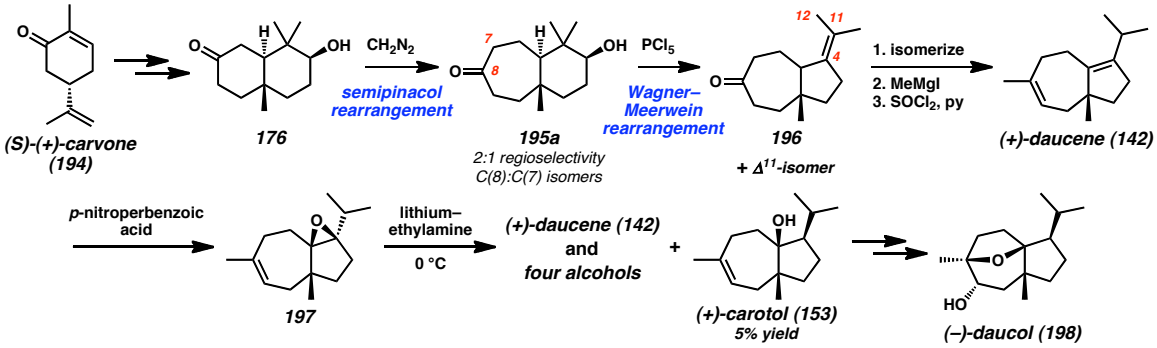
*Scheme 3.6. Mehta's 1988 acid-promoted cyclization approach to (–)-daucene (**142**).*



Shortly after the disclosure of Naegeli and Kaiser,[21] Levisalles et al. reported a route to daucene starting from (*S*)-(+)-carvone (**194**, Scheme 3.7).[24] Unfortunately, their report is vague and does not include yields for almost every transformation described, making it challenging to compare this work to other efforts in the area. The key sequence starts from the carvone-derived ketone **176**,[24] which is treated with diazomethane to effect a semipinacol rearrangement that generates a 2:1 inseparable mixture of ketone **195a** and the corresponding C(7) isomer. Purification of these alcohols is accomplished by

chromatographic separation of the corresponding acetates, after which hydrolysis again affords alcohol **195a**. A phosphorus pentachloride-initiated Wagner–Meerwein 1,2-rearrangement of alcohol **195a** produces alkene **196** as well as the Δ^{11}-isomer. (+)-Daucene (**142**) is subsequently obtained through isomerization of the C(4) olefin (conditions unspecified), Grignard addition to the ketone, and elimination of the resulting alcohol. Interestingly, Levisalle and co-workers also convert daucene to (+)-carotol (**153**) and (–)-daucol (**198**), although the process is extremely low yielding. Overall, this route is less desirable as several steps in the sequence have either poor regioselectivity or diastereoselectivity.

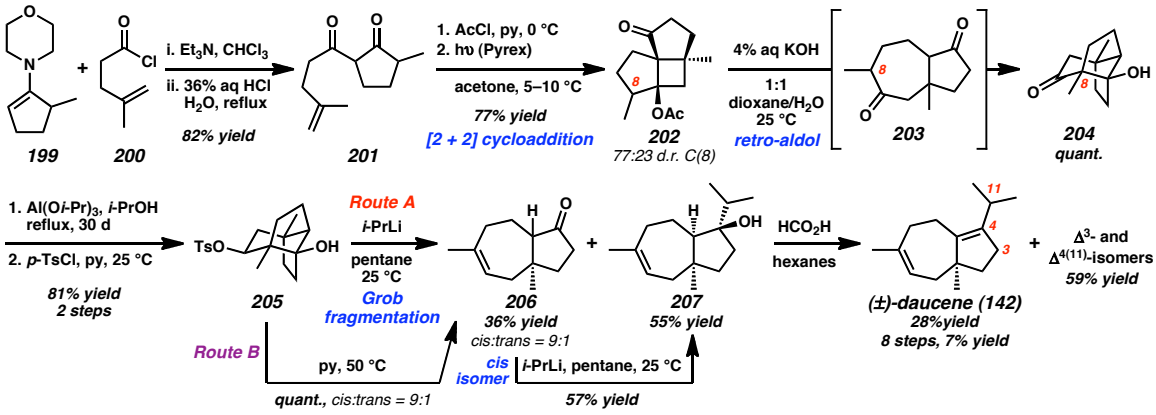
*Scheme 3.7. Synthesis of (+)-daucene (**142**), (+)-carotol (**153**), and (–)-daucol (**198**) by Levisalles in 1972.*



Seto and co-workers published an alternative strategy to racemic daucene in 1985.[25] In their route, enamine **199** is first treated with acid chloride **200** to afford dione **201**. Dione **201** is converted to the acetoxy enone and subsequently irradiated to furnish the [2 + 2] cycloaddition product, cyclobutane **202**. Fragmentation of cyclobutane **202** is accomplished through a base-mediated retro-aldol process that initially generates bicycle

203 en route to tricyclic ketone **204**. A Meerwein–Ponndorf–Verley reduction of ketone **204** forms the equatorial alcohol preferentially, although the process requires 30 days to complete. The resulting diol is selectively tosylated at the secondary position to afford sulfonic ester **205**. Isopropyllithium initiates Grob fragmentation of alcohol **205** and also diastereoselectively adds to the resulting ketone to produce a mixture of ketone **206** and alcohol **207** (Route A). Alternatively, a two-step sequence can be employed to obtain alcohol **207** (Route B). Elimination of the alcohol functionality with formic acid generates daucene (**142**) in low yield in conjunction with other olefin products. The early steps in Seto's synthesis proceed with good to excellent yields and install the necessary C(8)-C(9) olefin selectively due to the Grob fragmentation. However, the final steps in the sequence are low yielding and result in multiple isomers.

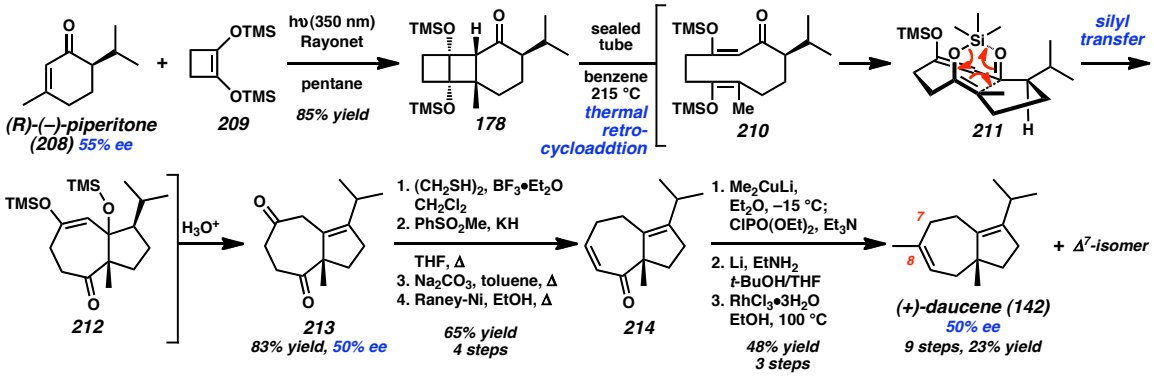
*Scheme 3.8. Seto's 1985 total synthesis of racemic daucene (**142**).*



Vandewalle's 1987 synthesis of (+)-daucene also incorporates a [2 + 2] cycloaddition, but arrives at the bicyclic core by fragmenting cyclobutane **178** through a thermally promoted retro-cycloaddition that initially generates siloxyenone **210** (Scheme

3.9).[26] Siloxyenone **210** is conformationally oriented such that a silyl transfer is triggered in situ. The resulting silyl ether (**212**) is hydrolyzed during work-up to reveal dione **213**. Vandewalle protects the more accessible ketone of dione **213** with ethane-1,2-dithiol, converts the sterically hindered ketone to the enone, and then removes the thioacetal functionality with Raney-Ni. Cuprate addition to enone **214** installs the C(14) methyl group and the reaction is quenched with diethyl phosphorochloridate to furnish a vinyl phosphate. Lithium reduction of this phosphate provides an alkene that is isomerized to (+)-daucene (**142**) and the Δ^7-isomer with Grieco's rhodium conditions.[28] Vandewalle's approach is elegant and produces daucene in good overall yield, but in poor enantiopurity due to the low natural enantioenrichment of the starting material.

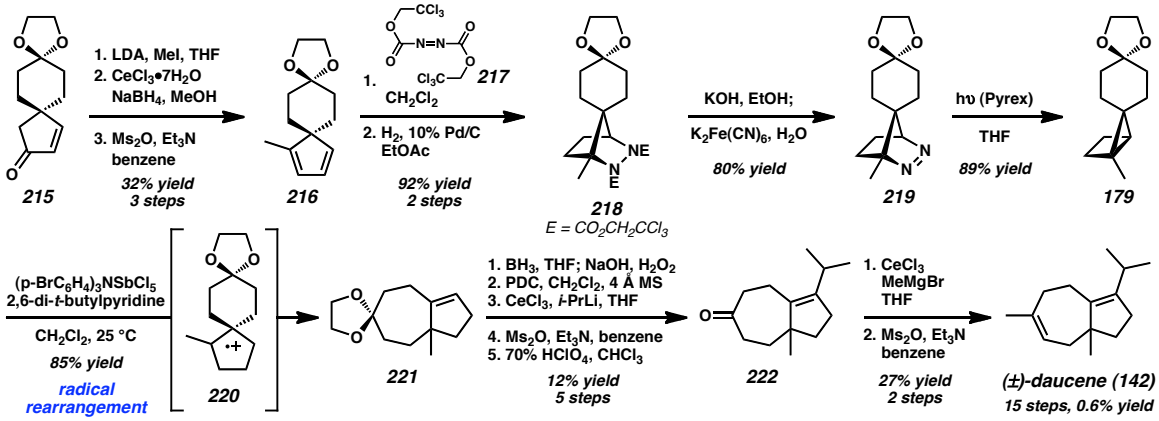
Scheme 3.9. Retro-cycloaddition/aldol approach to (+)-daucene by Vandewalle in 1987.



Twenty years elapsed following Vandewalle's and Mehta's 1980s syntheses before another approach to daucene was disclosed by Little and co-workers. Their publication focuses primarily on the development of an electrochemically-induced radical rearrangement, but also includes a low yielding synthesis of racemic daucene to

demonstrate application of the methodology. To this end, enone **215** is transformed into diene **216** through an alkylation, reduction, and elimination pathway. A [4 + 2] cycloaddition between diene **216** and azodicarboxylate **217** and ensuing reduction produce hydrazine **218**. The ester groups of hydrazine **218** are removed to generate diazene **219**, which is irradiated to liberate nitrogen and form cyclobutane **179**. Radical cleavage of the cyclobutane generates intermediate **220**, which undergoes a ring expansion rearrangement to ultimately afford alkene **221**. Alkene **221** is converted to a ketone, treated with isopropyllithium, and the resulting alcohol is eliminated to arrive at ketone **222**. Another organometallic addition and elimination sequence completes the synthesis, producing daucene in 15 steps and 0.6% overall yield. The middle portion of Little's synthesis is robust and well developed, but the early and late steps are low yielding. In particular, installation of the remaining functionality following the radical rearrangement is cumbersome. While the radical process provides an interesting and powerful alternative to previous approaches, Little's route needs optimization and could potentially also be improved by incorporating more of the necessary functionality earlier in the synthesis.

Scheme 3.10. Little's 2008 synthesis of racemic daucene.



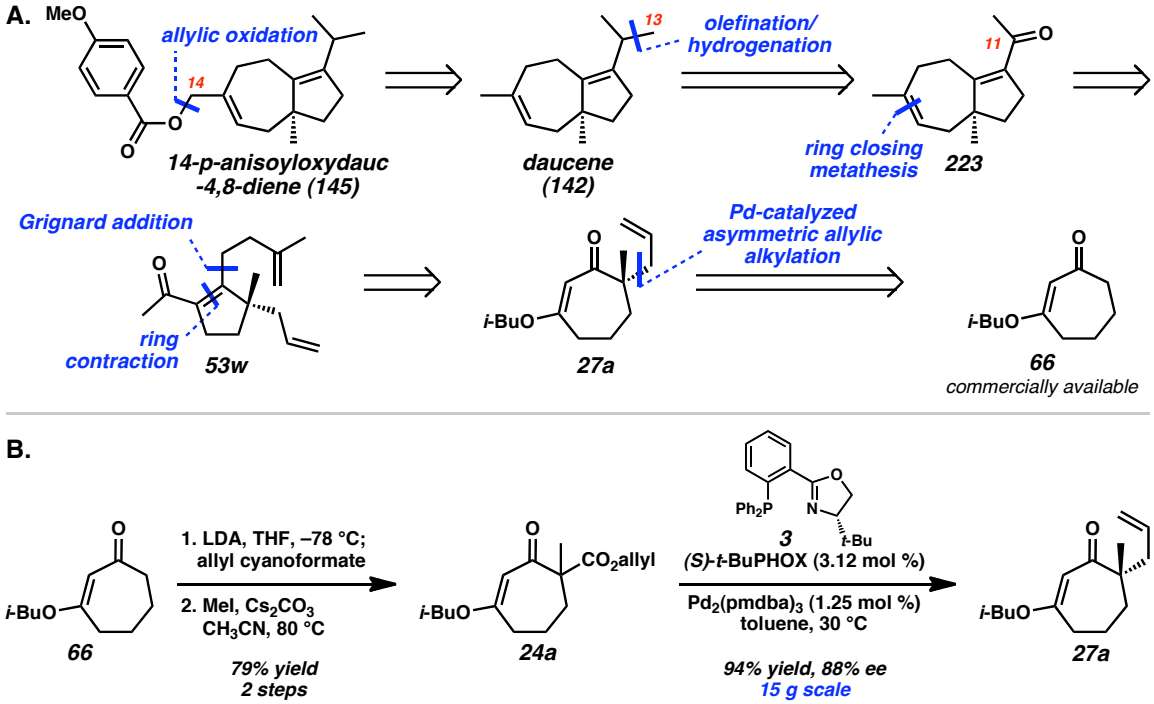
3.3 ENANTIOSELECTIVE SYNTHESIS OF BICYCLO[5.3.0]DECANE CARBOCYCLIC CORE AND DAUCANE SESQUITERPENES

3.3.1 Retrosynthetic Analysis

Our initial target was the biologically active sesquiterpene 14-*p*-anisoyloxydauc-4,8-diene (**145**). We retrosynthetically envisioned preparing this natural product via an allylic oxidation at the C(14) position of daucene (**142**, Scheme 3.11A). In contrast to previous efforts, we sought to access daucene by implementation of enantioselective catalysis in a manner that would avoid the formation of multiple olefin isomers. To this end, we planned a late-stage installation of the C(13) methyl group through olefination and hydrogenation of enone **223**. This key intermediate possesses the [7–5] bicyclic core and could potentially allow entry to either terpenoid series through incorporation of the appropriate sesquiterpene or diterpene chain at the C(11) position. We also anticipated that enone **223** may be converted to more oxidized members of the daucane family. Retrosynthetically, the cycloheptenyl portion of enone **223** would be formed through

ring-closing metathesis of acylcyclopentene **53w**, which could be generated by employing our retro-aldol/aldol ring contraction sequence[7] after Grignard addition to vinylogous ester **27a**. As described in Chapter 2, we have previously prepared vinylogous ester **27a**[7a] enantioselectively from vinylogous ester **66** using our palladium-catalyzed allylic alkylation methodology (Scheme 3.11B).[4]

*Scheme 3.11. (a) Retrosynthetic analysis and (b) synthesis of enantioenriched vinylogous ester **27a**.*

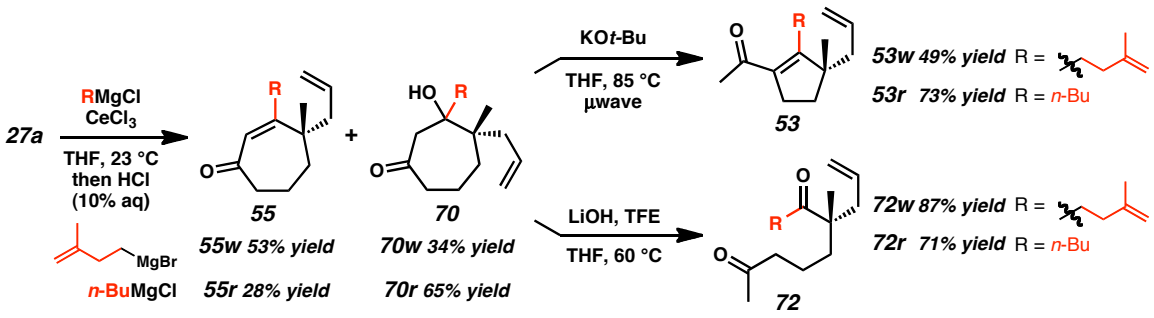


3.3.2 Challenges with Initial Approach

As we pursued this approach, we encountered two challenges. First, $CeCl_3$ assisted addition of (3-methylbut-3-en-1-yl)magnesium bromide to vinylogous ester **27a** results in poor selectivity for the desired β-hydroxyketone (**70w**), favoring formation of

cycloheptenone **55w** (Scheme 3). This product distribution contrasts with our previous work with *n*-butylmagnesium chloride,[7] where β-hydroxyketone **70r** is generated preferentially. Ultimately, this result directs considerable material to a less productive compound (vide infra), thus limiting our synthetic route. In addition, our optimized microwave-assisted ring contraction conditions proceed poorly to furnish acylcyclopentene **53w** also in diminished yield compared to the *n*-butyl analogue (**53r**, Scheme 3B). Alternatively, treatment of β-hydroxyketone **70w** with lithium hydroxide and trifluoroethanol (TFE) provides an excellent yield of acyclic dione **72w**, from which we envisioned installing the necessary cyclopentene ring in a later aldol reaction (see below). With an acceptable solution for the second issue, we turned our attention to resolve the first.

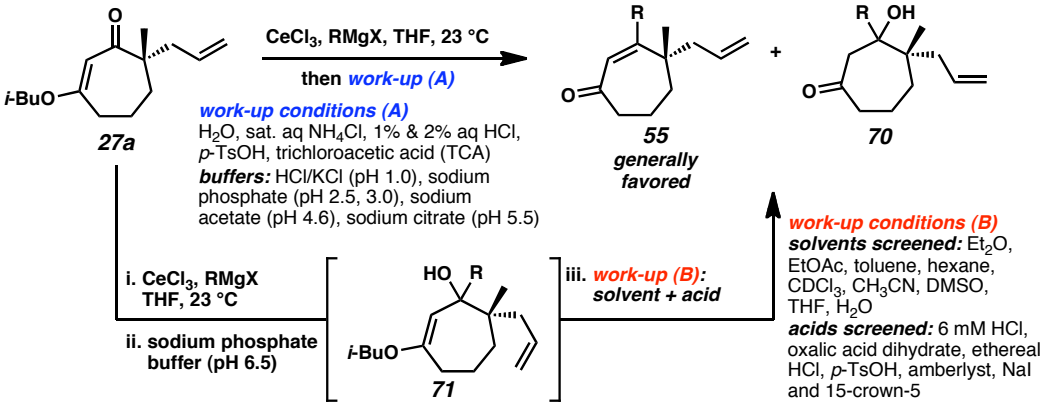
Scheme 3.12. Challenges with early steps.



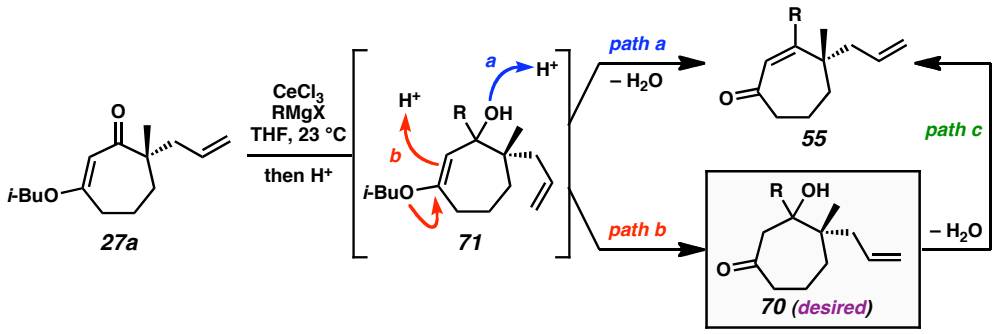
3.3.3 Efforts to Resolve Grignard Addition Selectivity and Siloxyenone Solution

In attempting to alter the Grignard addition product ratios, we first screened a series of work-up parameters.[29] Unfortunately, all other acidic quenching conditions investigated favor the cycloheptenone (**55**) or at best preferentially afford the β-hydroxyketone (**70**), but in lower yield (Scheme 3.13). We also examined several buffer solutions comprising a range of acidic pH, but the majority of these conditions provide similar results. The main exception is a sodium phosphate buffer (pH 6.5) quench, which leads to the transient formation of enol ether **71**.[30] A number of solvents and acids were probed for the selective hydrolysis of enol ether **71**, but the same trends were observed with this substrate. The propensity of elimination under a variety of acidic conditions is likely due to the stability of the carbocations generated with hydrolysis of tertiary alcohol **71** or **70** (i.e., path a/c favored over path b, Scheme 3.14). Although not necessarily the desired outcome, these efforts did identify conditions that enabled the development of our ketone transposition methodology toward γ-quaternary cycloheptenones (see Chapter 2, Section 2.6).[7b,30]

Scheme 3.13. Acidic work-up screen.



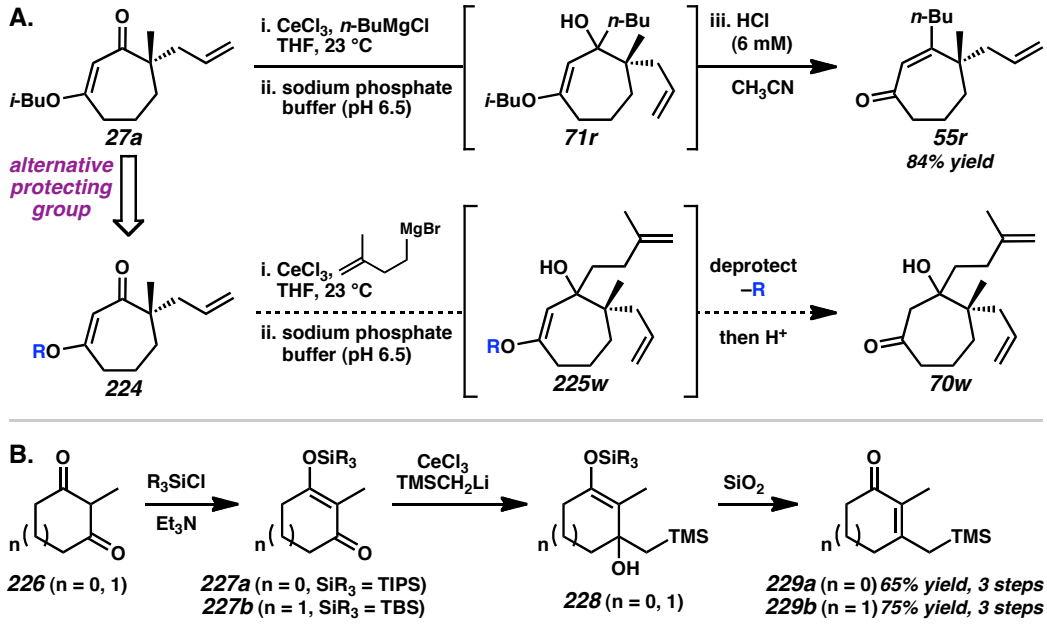
*Scheme 3.14. Elimination pathways to undesired product, cycloheptenone **55**.*



As varying the work-up parameters appeared ineffective at resolving this issue, we decided to redesign our electrophile and began examining alternative vinylogous systems. As mentioned above, our previous screening had indicated that a sodium phosphate buffer quench transiently provides enol ether **71** en route to cycloheptenone **55r** (Scheme 3.15A). We hypothesized that a related vinylogous molecule (**224**) with a more labile alkoxy group could be orthogonally removed after Grignard addition to afford β-hydroxyketone **70w** preferentially. Kuwajima has reported that the addition of lithium and cerium nucleophiles to five- and six-membered ring siloxyenones temporarily generates an α-hydroxy silyl enol ether (**228**) that eliminates to form β-substituted enones

(**229**) upon exposure to silica gel (Scheme 3.15B).[31,32] The initial lack of desilylation or Peterson olefination with these siloxyenone substrates suggests that the transformation is fairly mild. We consequently envisioned that the silyl enol ether analogue of intermediate **225w** (R = SiR_3) could be cleaved prior to chromatography with a fluoride source, prompting us to pursue siloxyenones as an alternative approach.

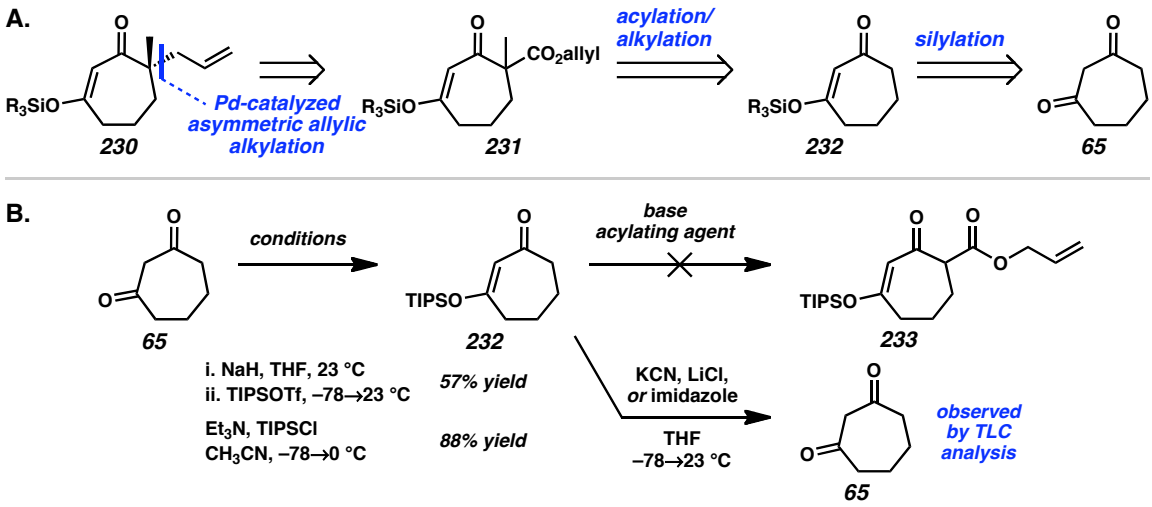
Scheme 3.15. Siloxyenone inspiration based on (a) previous results and (b) Kuwajima's precedence with Grignard addition to five- and six-membered siloxyenones.



Retrosynthetically, we planned to synthesize enantioenriched siloxyenone **230** through Pd-catalyzed asymmetric alkylation of β-ketoester **231** (Scheme 3.16A). β-Ketoester **231** would be derived from siloxyenone **232** through an acylation/alkylation pathway, as Kuwajima has shown that siloxyenones may be alkylated under standard LDA conditions.[31] Siloxyenone **232** can be obtained from dione **65** by treatment with

either sodium hydride[33] or Et_3N and a silylating agent (Scheme 3.16B), and we selected the TIPS substituted siloxyenone as it is amenable to flash column chromatography.[34] Although the silylation reaction proved effective, unfunctionalized siloxyenone **232** was unstable to a variety of acylating conditions. We screened several combinations of bases (LDA and LHMDS) and acylating agents (allyl cyanoformate, allyl chloroformate, allyl 1H-imidazole-1-carboxylate), but could never isolate β-ketoester **233**. A simple TLC experiment indicated that treatment of siloxyenone **232** with the acylating agent counterions results in loss of the silyl group (CN^- and imadazole > Cl^-) and production of dione **65** (Scheme 3.16B).

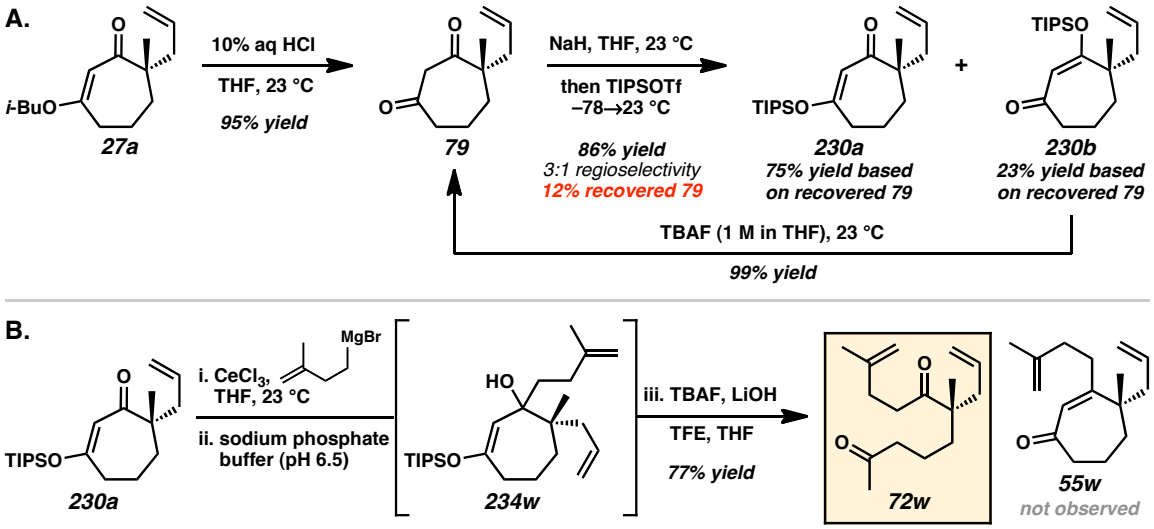
*Scheme 3.16. New retrosynthetic analysis and challenges with acylation of siloxyenone **232**.*



As such, we devised another approach from vinylogous ester **27a** that avoids these issues as the quaternary stereocenter is already incorporated in the molecule. To this end, vinylogous ester **27a** was hydrolyzed and the resulting dione (**79**) was treated with sodium hydride and triisopropylsilyl triflate[33] to produce siloxyenone **230a** in good

yield with 3:1 regioselectivity (Scheme 3.17). A number of other conditions were examined for the silylation; unfortunately, no improvements in reaction conversion or regioselectivity were observed with an amine base, multiple equivalents of reagents, other additives (i.e., 18-crown-6), or incremental warming of the reaction. However, siloxyenone **230b** can be converted to the desired isomer through iterative fluoride deprotection and silylation.

*Scheme 3.17. Synthesis and reactivity of siloxyenone **230a**.*



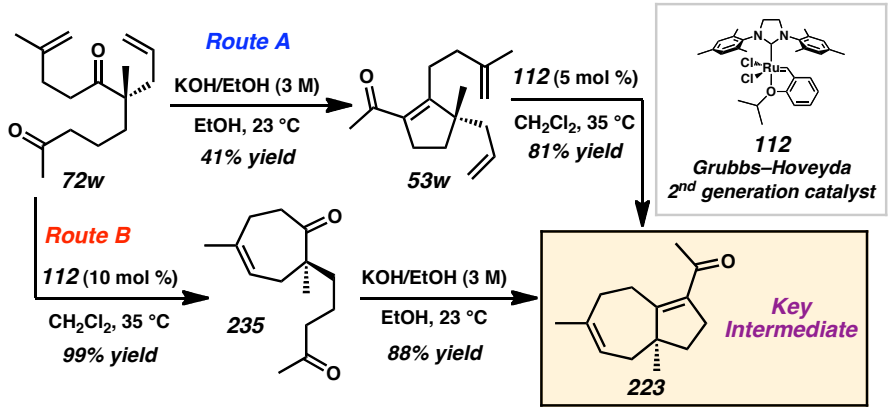
With this new vinylogous electrophile in hand, we tested our hypothesis by exposing siloxyenone **230a** to $CeCl_3$ promoted Grignard conditions with a buffer and fluoride quench. We were pleased to find that no cycloheptenone **55w** is observed and the reaction also incorporates the ring-opening step by directly producing acyclic dione **72w**. TLC analysis of the reaction after the fluoride quench indicates initial formation of both acyclic dione **72w** and β-hydroxyketone **70w**. The latter is converted to the dione

over time and the addition of LiOH/TFE expedites this retro-aldol process. A screen of other fluoride sources revealed that a TBAT quench only produces β-hydroketone **70w** even over extended exposure (determined by TLC analysis), [35] while a cesium fluoride and LiOH work-up also generates dione **72w**, albeit in a lower 70% yield. Overall, this new approach resolves the Grignard addition selectivity issues and provides the first example of interrupting the standard Stork-Danheiser ketone transposition process with a siloxyenone.

3.3.4 Completion of Key Intermediate Enone 223

Having developed an improved route to acyclic dione **72w**, we pursued preparation of our key intermediate, enone **223** (Scheme 3.18). Although this molecule can be synthesized from dione **72w** via acylcyclopentene **53w** (Route A), the sequence proceeds in higher yield when the ring-closing metathesis is performed first (Route B). Racemic dione **235** has previously been prepared from nerolidol by Urones and co-workers along several synthetic routes in 7–10 steps (13–33% yield), and these efforts are discussed in detail in the following section (Section 3.3.5).[36] By comparison, our route proceeding via enantioselective catalysis affords dione **235** in 7 steps with 40% overall yield. Applying Urones' potassium hydroxide aldol conditions generates enone **223** from dione **235** as reported.

Scheme 3.18. Two paths to [7–5] bicyclic enone ***223****.*

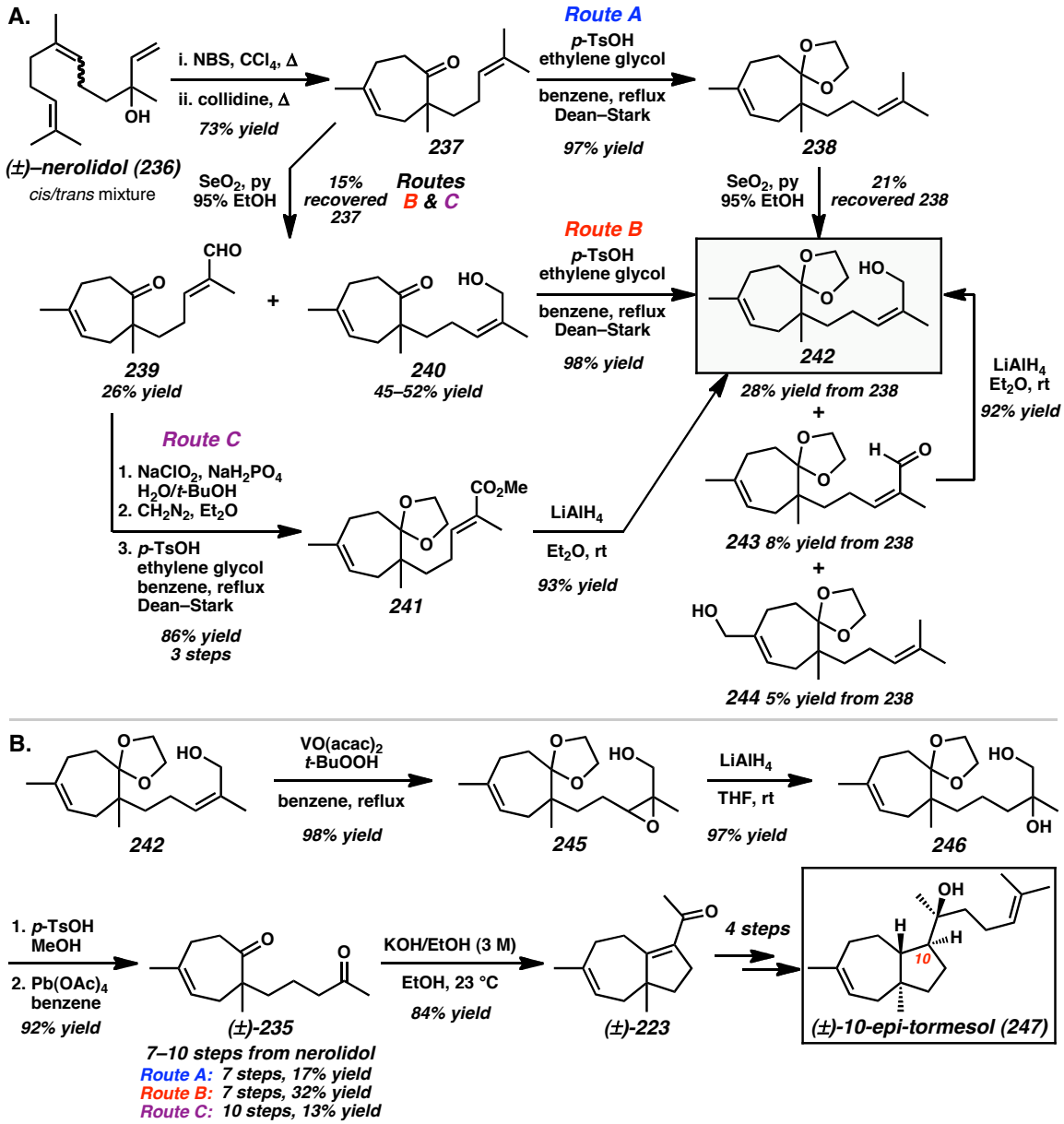


3.3.5 *Urones' Synthetic Route to Dione 235 and Enone 223*

During the 1990s, Urones and co-workers reported two papers on synthetic efforts toward tormesol (**248**) that incorporate dione (±)-**235** and enone (±)-**223** as key intermediates.[36] Their first publication investigates selenium oxidation of several cyclohepentyl molecules derived from nerolidol (**236**), including ketone **237** and ketal **238** (Scheme 3.19A).[36a] These oxidations generate a range of products in low to moderate yield that are sequentially moved on to alcohol **242**. The allylic olefin of alcohol **242** is selectively oxidized under vanadium-promoted conditions, and the resulting epoxide (**245**) is reduced to diol **246** with lithium aluminum hydride ($LiAlH_4$, Scheme 3.19B). Hydrolysis of ketal **246** reveals the ketone functionality and ensuing oxidative cleavage with $Pb(OAc)_4$ affords dione **235**. Along these routes, dione **235** is prepared in 7–10 steps and 13–33% overall yield. Urones' second report details efforts to obtain tormesol from enone **223**, which is derived from dione **235** as discussed previously.[36b] Ultimately, their approach is incapable of producing the desired diterpene

due to epimerization issues, but allows preparation of the non-natural isomer 10-epi-tormesol (**247**) from enone **223** in 4 steps.

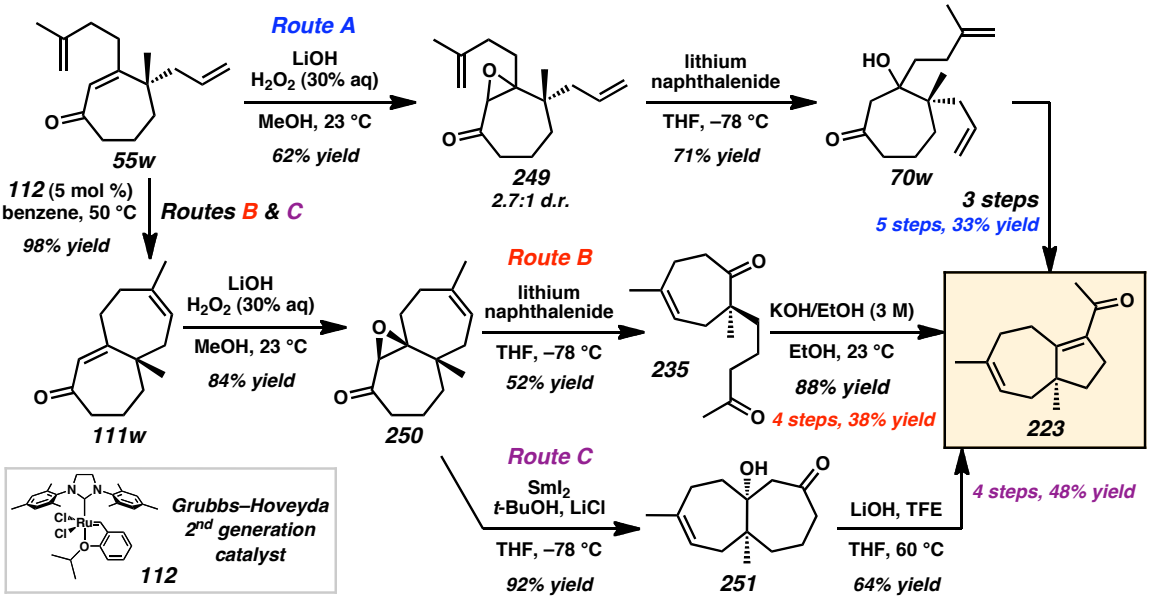
*Scheme 3.19. Urones' various routes to dione (±)-**235** and enone (±)-**223**.*



3.3.6 Alternative Routes to Enone 223 from Cycloheptenone 55w

As our early research on the addition of (3-methylbut-3-en-1-yl)magnesium bromide to vinylogous ester **27a** had generated a significant quantity of cycloheptenone **55w** (Scheme 3.12), we investigated means to direct this material back into our synthetic efforts. To this end, oxidation of cycloheptenone **55w** with lithium hydroxide and hydrogen peroxide generates epoxide **249** as an inconsequential 2.7:1 mixture of diastereomers (Route A, Scheme 3.20). Subsequent lithium naphthalenide reduction affords β-hydroxyketone **70w**, which may be conveyed onto enone **223** in 3 steps as discussed previously (Section 3.3.4). Unfortunately, the epoxidation step proceeds moderately, prompting us to examine alternative routes.

*Scheme 3.20. Epoxidation routes to key intermediate enone **223**.*



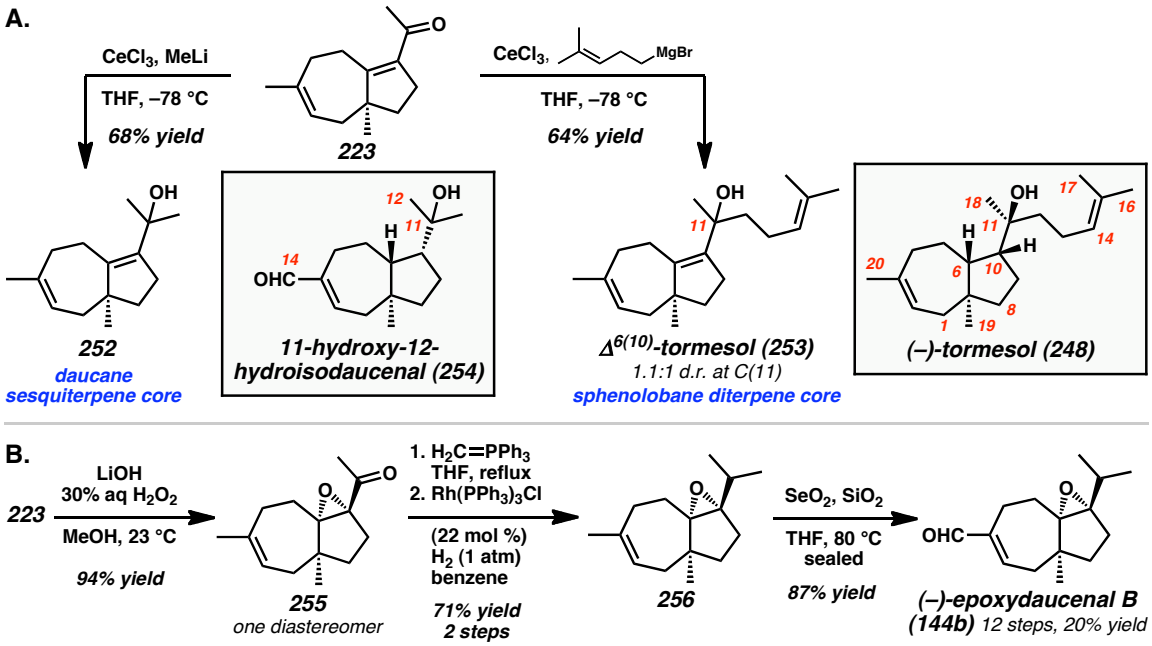
We consequently pursued two other approaches through bicyclic enone **111w** (Routes B and C), which can be formed from cycloheptenone **55w** via a nearly quantitative ring-closing metathesis. Gratifyingly, oxidation of enone **111w** under the same hydrogen peroxide conditions furnishes epoxide **250** in 84% yield. Reduction of epoxide **250** with lithium naphthalenide interestingly also promotes an in situ retro-aldol reaction that produces dione **235**, albeit in low yield (Route B). Dione **235** may be converted to enone **223** with Urones' aldol conditions (vide supra). Alternatively, reduction of epoxide **250** under milder samarium diiodide conditions with lithium chloride as an additive gives β-hydroxyketone **251** in 92% yield. Samarium diiodide reduction without lithium chloride or with HMPA as an additive also provides β-hydroxyketone **251**, but in lower yield or with additional side products.[37] Use of our standard ring contraction conditions (LiOH, TFE, THF, 65 °C) initiates both retro-aldol fragmentation of β-hydroxyketone **251** and ensuing aldol condensation to form enone **223**. Overall, route C provides enone **223** from cycloheptenone **55w** in the shortest sequence with the greatest overall yield.

As cycloheptenone **55w** may alternatively be prepared from vinylogous ester **27a** in 82% yield by a buffer quench (Chapter 2, Section 2.6), we also considered the relative merit of pursuing our daucane targets via this cycloheptyl molecule. Along this approach, the key intermediate enone **223** is produced in 8 steps from vinylogous ester **37a** with 29% overall yield. By comparison, our siloxyenone route also proceeds to enone **223** in 8 steps, but with a higher 35% overall yield. Further large-scale optimization of the cycloheptenone route may allow this alternative approach to become more competitive.

3.3.7 Derivatization of Enone 223 and Pursuit of Oxygenated Molecules

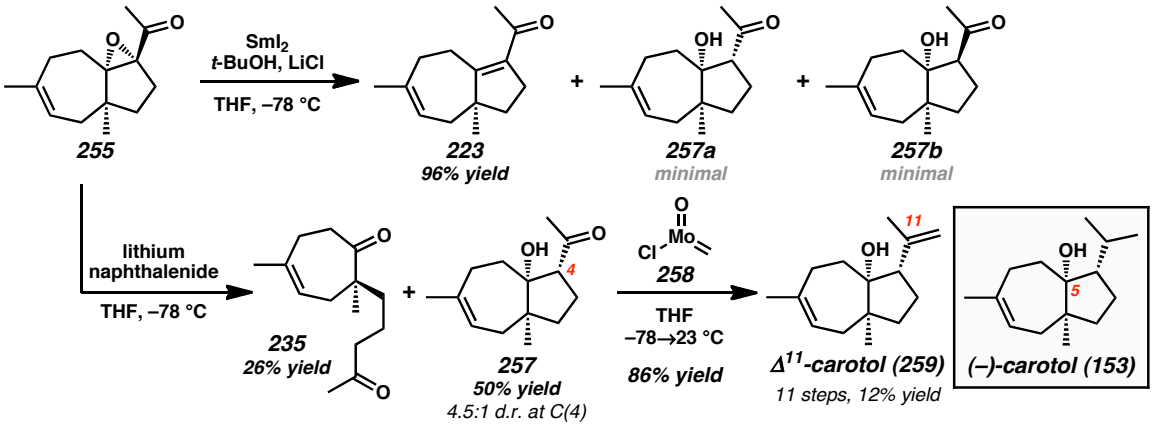
With several routes to enone **223** in hand, we converted this key intermediate to both terpenoid scaffolds and other oxygenated daucane molecules as part of our initial goals. Treatment of enone **223** with methyllithium or (4-methylpent-3-en-1-yl)magnesium bromide results in the formation of alcohols **23** and **24**, which contain the daucane and sphenolobane carbocyclic cores, respectively (Scheme 6A). This tertiary alcohol motif is present in natural products in both the daucane[38] and sphenolobane series, and alcohol **24** is the $\Delta^{6(10)}$-analogue of the diterpene (–)-tormesol (**25**).[39] Enone **223** can also be selectively epoxidized with lithium hydroxide and hydrogen peroxide to provide epoxyketone **255** in excellent yield as a single diastereomer (Scheme 3.21B). A few daucane sesquiterpenes incorporate an epoxide at this position, and of these, we decided to pursue epoxydaucenal B (**144b**).[13] Toward this target, Wittig olefination of epoxyketone **255** furnishes a diene that is selectively hydrogenated at the terminal alkene with Wilkinson's catalyst. The resulting isopropyl accessorized epoxide (**256**) is heated in a sealed vessel with selenium dioxide[40] to generate epoxydaucenal B (**144b**) in 12 steps and 20% overall yield from vinylogous ester **13** (longest linear sequence).

Scheme 3.21. Derivatization of enone ***223*** *to sesquiterpene/diterpene cores and conversion to (–)-epoxydaucenal B (****144b****).*



Having completed this natural product, we turned our attention to the carotol series, which contains a tertiary alcohol at C(5) (Scheme 3.22). We first explored samarium diiodide reduction of ketoepoxide **255** based on the previous success with epoxide **250** (Scheme 3.20), but surprisingly isolated enone **223** in 96% yield. The preference for elimination in the cyclopentyl, but not cycloheptyl system again suggests that the conformation of seven-membered ring compounds imparts unique reactivity to these molecules (see Chapter 2). Alternatively, lithium naphthalenide reduction opens ketoepoxide **255** to furnish tertiary alcohol **257** in 50% yield, favoring the desired C(4) isomer (**257a**) in 4.5:1 diastereoselectivity. Unfortunately, the reduction also produces dione **235** likely through an in situ retro-aldol process, but this material can be recycled through our route.

*Scheme 3.22. Efforts toward Δ^{11}-carotol (**259**).*



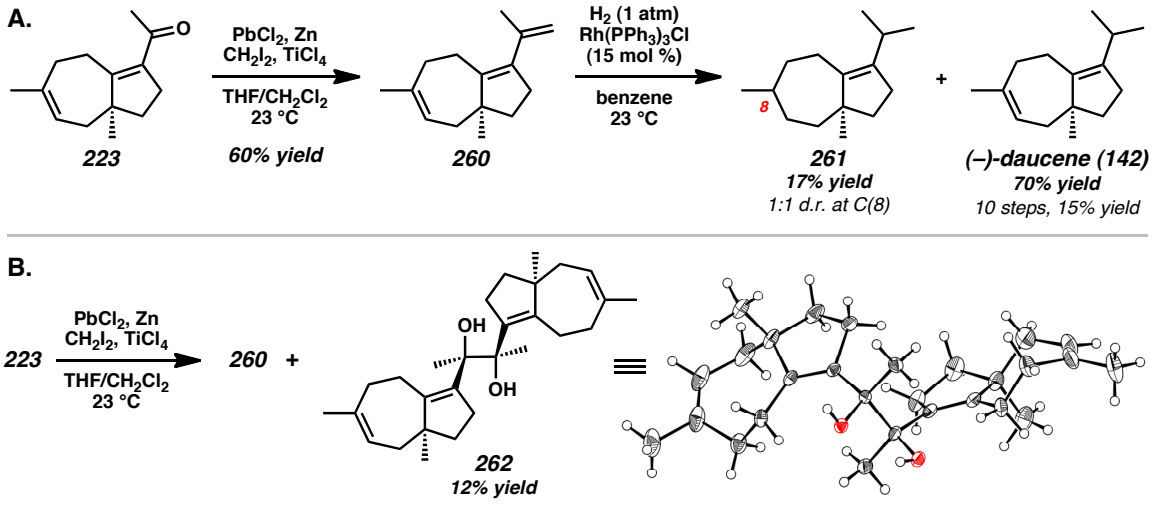
When considering olefination conditions for the installation of the C(13) carbon, we were drawn to the work of Kauffmann and co-workers,[41] who observed that methylene(oxo)molybdenum(V) chloride (**258**)[42] preferentially methylenates α- and β-hydroxyketones.[41c] Surprisingly, only the reports by Kauffmann on this molybdenum alkylidene exist and no synthetic applications with this system have been reported. Treatment of sterically hindered β-hydroxyketone **257a** with complex **258** proceeds in good yield to generate Δ^{11}-carotol (**259**), the dehydro analogue of (–)-carotol (**153**).

3.3.8 Endgame for Total Syntheses of Daucene, Daucenal, and 14-p-Anisoyloxydauc-4,8-diene

In addition to these transformations, we investigated conversion of enone **223** to daucene (**142**) and related C(14) oxidized natural products (Scheme 3.23A). Following our retrosynthetic plan, we attempted to olefinate enone **223** with the standard Wittig ylide, but unfortunately recovered starting material and observed poor conversion to triene **260**. Alternatively, methylenation with Lombardo conditions[43] generates triene

260 in moderate yield in conjunction with a number of more polar products. One of these polar molecules provided crystals suitable for X-ray analysis and was subsequently identified as diol **262** (Scheme 3.23B). Diol **262** likely arises under the reaction conditions from a titanium-mediated McMurry coupling.[44] With triene **260** in hand, we screened a series of hydrogenation conditions and found that Wilkinson's catalyst again preferentially reduces the terminal olefin to afford (–)-daucene (**142**) in 10 steps and 15% overall yield. Over hydrogenation to alkene **261** is also observed, especially with extended exposure to H_2.

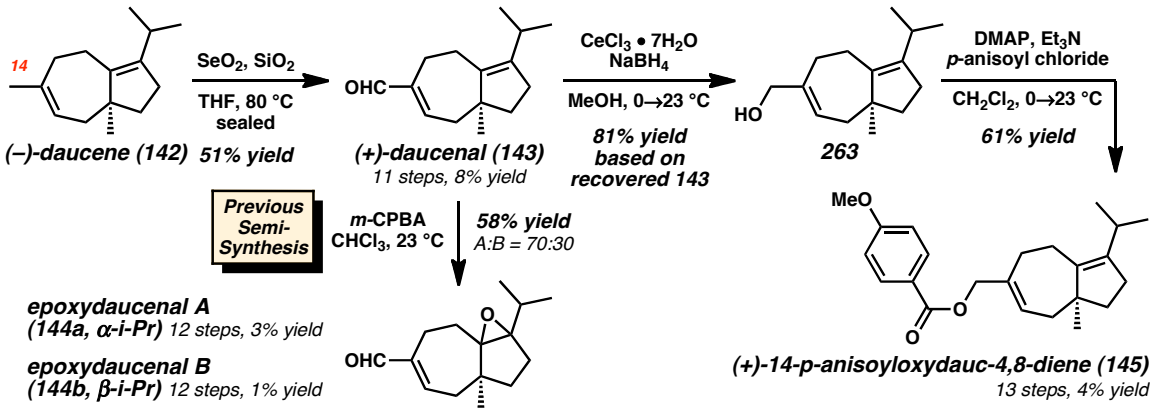
*Scheme 3.23. Olefination and hydrogenation steps toward (–)-daucene (**142**).*



We next examined allylic oxidation of daucene to access C(14) functionalized sesquiterpenes (Scheme 3.24). Gratifyingly, the selenium dioxide conditions employed previously also proved effective in the oxidation of daucene to generate (+)-daucenal (**143**) in 8% overall yield over 11 steps. As mentioned previously, Hashidoko completed a semi-synthesis of epoxydaucenal A and B (**144a** and **144b**) from daucenal as part of

their isolation efforts to confirm the structures of these epoxidized sesquiterpenes.[13] By comparison to our previous route, this formal synthesis of epoxydaucenal B (**144b**) also produces the natural product in 12 steps, albeit in much lower overall yield (1%). Continuing toward our initial goal, Luche reduction of daucenal (**143**) provides allylic alcohol **263**, which can be treated with base and *p*-anisoyl chloride to afford (+)-14-*p*-anisoyloxydauc-4,8-diene (**145**) in 13 steps with 4% overall yield. Given the bioactivity observed for esters **145** and **146** (Figure 3.1),[1a,b] we envision that exploration of other unnatural ester derivatives prepared from alcohol **263** may prove promising in structure-activity relationship studies and enable the subsequent preparation of more potent analogues.

*Scheme 3.24. Endgame for (+)-daucenal (**143**) and (+)-14-p-anisoyloxydauc-4,8-diene (**145**) and formal syntheses of epoxydaucenal A and B (**144a** and **144b**).*



3.4 CONCLUDING REMARKS

In summary, we have completed the first catalytic enantioselective total syntheses of epoxydaucenal B (**144b**), daucene (**142**), daucenal (**143**), and 14-*p*-anisoyloxydauc-

4,8-diene (**145**) in 10–13 steps with 20%, 15%, 8%, and 4% overall yields, respectively. Our route overcomes the challenge of accessing β-substituted acylcyclopentene **53w** by employing a siloxyenone to effect the Grignard addition and ring opening in a single step. Subsequent ring-closing metathesis and aldol reactions form the bicyclo[5.3.0]decane core. Derivatization of the key intermediate, enone **223**, allows access to either the daucane sesquiterpene or sphenobolane diterpene carbon skeletons, as well as other oxygenated scaffolds. Our efforts feature several olefination methods to install the C(13) carbon, including the underutilized molybdenum alkylidene developed by Kauffmann. Future directions are focused on biological evaluation of the molecules reported herein and application of the developed synthetic strategy to other daucane sesquiterpenes and sphenolobane diterpenes.

3.5 EXPERIMENTAL SECTION

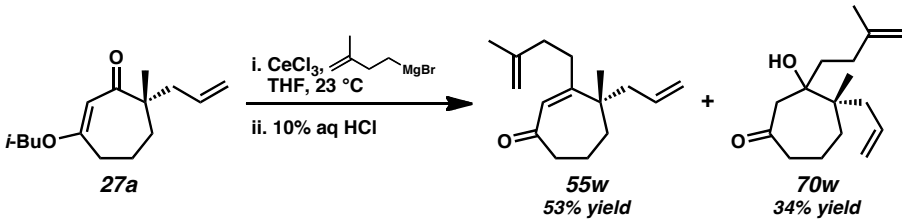
3.5.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[45] Methanol (MeOH) was distilled over Mg and I_2 according to the procedure of Lund and Bjerrum.[46] Brine solutions are saturated aqueous solutions of sodium chloride. Vinylogous ester **27a** was prepared following the method found in our previous report.[7a] Triisopropylsilyl triflate was distilled immediately before use. Oxotrischlorobis(tetrahydrofuran)molybdenum(V) was prepared according to the procedure of McUliffe.[42] All other reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, Alfa Aesar, or TCI America and used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator. Microwave-assisted reactions were performed in a Biotage Initiator 2.5 microwave reactor. Glove box manipulations were performed under a N_2 atmosphere. Reaction progress was monitored by thin-layer chromatography (TLC). TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde staining, and/or $KMnO_4$ staining. ICN silica gel (particle size 0.032-0.0653 mm) or Silicycle Silia*Flash* P60 Academic silica gel (particle size 0.040-0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Varian Inova 500 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm) or benzene-d_6 (C_6D_6, δ 7.16 ppm). ^{13}C NMR spectra are recorded on a Varian Inova 500 MHz

spectrometer (125 MHz) and are reported relative to $CDCl_3$ (δ 77.16 ppm) or benzene-d_6 (C_6D_6, δ 128.06 ppm). 2D NMR experiments were performed on a Varian Inova 400 MHz or Varian Inova 500 MHz spectrometer and are reported relative to residual solvent. Data for ^1H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, dm = doublet of multiplets, br = broad (e.g., br s = broad singlet), app = apparent. Data for ^{13}C are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility (EI+, GC-EI+, FAB+) or on an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent, *ee*).

3.5.2 Preparative Procedures

3.5.2.1 Procedures Associated with Initial Approach

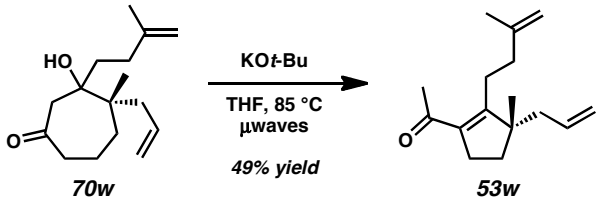


Cycloheptenone 55w and β-Hydroxyketone 70w. A flame-dried 250 mL round-bottom flask equipped with a stir bar was cycled into a glove box where the flask was loaded with anhydrous cerium chloride (2.66 g, 10.79 mmol, 2.54 equiv). The flask was removed from the glove box, connected to an Ar-filled manifold, and charged with THF (50 mL). After 24 h of stirring, (3-methylbut-3-en-1-yl)magnesium bromide[47] (0.24 M in THF, 52.85 mL, 12.69 mmol, 2.99 equiv) was added to the flask, causing the slurry to initially turn yellow and orange over time. After 3 h, the flask was charged with additional THF (20 mL), and vinylogous ester **27a** (1.00 g, 4.25 mmol, 1.00 equiv) was transferred from a conical flask to the round-bottom flask using several THF rinses (3 x 10 mL, total added = 106 mL, 0.04 M). TLC analysis indicated no starting material remained after 5 min. After 40 min, the reaction was quenched with HCl (10% w/w aq, 50 mL) and transferred to a separatory funnel where the aqueous layer was extracted five times with EtOAc. The combined organics were rinsed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 28 x 3 cm, 100% hexanes→5%→10%→20% EtOAc in hexanes) to afford cycloheptenone **55w** (473.0 mg, 2.04 mmol, 53% yield) as a

pale yellow oil and β-hydroxyketone **70w** (325.3 mg, 1.30 mmol, 34% yield) as a pale yellow oil.

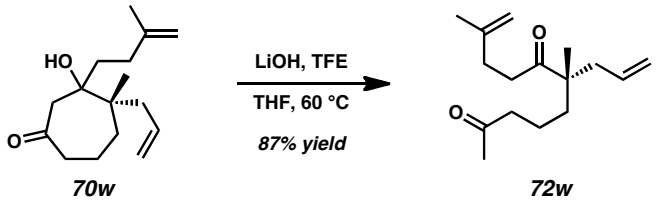
Cycloheptenone 55w. Characterization data matches that previously reported.[30]

β-hydroxyketone 70w. R_f = 0.55 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) mixture of two diastereomers, see Figure SI-1A; IR (Neat Film NaCl) 3464, 3072, 2965, 2936, 2866, 1694, 1647, 1638, 1452, 1375, 1342, 1299, 1229, 1186, 1110, 1073, 1029, 997, 967, 917, 884, 793 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{27}O_2$ $[M+H]^+$: 251.2006, found 251.2007.



Acylcyclopentene 53w. KO*t*-Bu (269.4 mg, 2.40 mmol, 1.65 equiv) and THF (10 mL, 0.10 M), were added to a flame-dried 20 mL microwave vial with a stir bar. β-hydroxyketone **70w** (364.9 mg, 1.46 mmol, 1.00 equiv) was transferred to the vial using benzene (200 μL) and THF (2 x 1 mL). Another portion of THF (3 mL, total added = 15 mL, 0.10 M) was added to the vial. The pale yellow solution was subjected to microwave irradiation in a Biotage Initiator microwave reactor (temperature: 85 °C, sensitivity: normal). After 5 min of irradiation, the crimp cap was removed and Na_2SO_4 was added to the vial. The reaction contents were transferred to a separatory funnel,

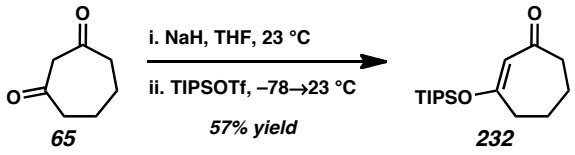
quenched with HCl (10% w/w aq, 10 mL), and extracted four times with Et_2O. The combined organics (300 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 28.5 x 3 cm, 100% pentane→5%→10%→15%→20% Et_2O in pentane) to afford acylcyclopentene **53w** (164.3 mg, 0.71 mmol, 49% yield) as a yellow oil; R_f = 0.75 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (dddd, J = 16.8, 10.3, 7.6, 7.0 Hz, 1H), 5.08–5.01 (m, 2H), 4.74 (dq, J = 2.2, 1.1 Hz, 1H), 4.73 (td, J = 1.4, 0.7 Hz, 1H), 2.61–2.52 (m, 3H), 2.33 (tdt, J = 12.2, 5.0, 1.1 Hz, 1H), 2.21 (s, 3H), 2.20–2.04 (m, 4H), 1.88 (ddd, J = 12.9, 7.5, 6.3 Hz, 1H), 1.80 (dd, J = 1.4, 1.0 Hz, 3H), 1.61–1.53 (m, 1H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 163.5, 146.3, 135.0, 134.9, 117.7, 109.9, 52.6, 43.7, 37.5, 35.0, 31.6, 30.4, 26.6, 24.7, 22.5; IR (Neat Film NaCl) 3074, 2957, 2929, 2864, 1676, 1648, 1602, 1453, 1373, 1355, 1313, 1273, 1252, 1208, 1113, 995, 960, 913, 885 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{25}O$ $[M+H]^+$: 233.1900, found 233.1903; $[\alpha]_D^{25.0}$ –7.12 (c 1.53, $CHCl_3$, 88% ee).



Dione 72w. β-Hydroxyketone **70w** (50.6 mg, 0.20 mmol, 1.00 equiv) was transferred to a flame-dried 15 mL round-bottom flask equipped with a stir bar and water condenser using several THF rinses (4 x 1 mL, total = 4 mL, 0.05 M). TFE (58 μL, 0.81 mmol, 4.00 equiv) and LiOH (14.2 mg, 0.59 mmol, 2.93 equiv) were added, generating a pale

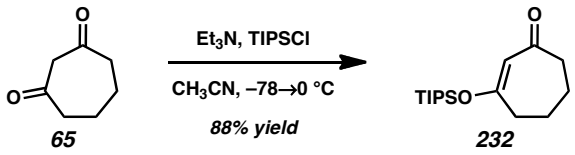
yellow solution. The flask was lowered into a preheated oil bath (60 °C) and heated for 2 h. After cooling to room temperature, the reaction was filtered through a short silica gel plug (2 x 10 cm) rinsing with Et_2O. The combined organics were concentrated under reduced pressure at 0 °C (ice/water) and purified by flash column chromatography (SiO_2, 25 x 2 cm, 100% pentane→2%→5%→10%→15% Et_2O in pentane) to afford dione **72w** (44.1 mg, 0.81 mmol, 87% yield) as a yellow oil; R_f = 0.56 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68–5.59 (m, 1H), 5.06–5.01 (m, 2H), 4.72 (dqt, J = 2.2, 1.5, 0.8 Hz, 1H), 4.67 (qq, J = 1.3, 0.8 Hz, 1H), 2.61–2.57 (m, 2H), 2.40 (dd, J = 7.3, 6.0 Hz, 2H), 2.33 (ddt, J = 14.0, 7.2, 1.2 Hz, 1H), 2.24 (t, J = 7.9 Hz, 2H), 2.21 (ddt, J = 14.0, 7.5, 1.2 Hz, 1H), 2.12 (s, 3H), 1.74 (dd, J = 1.4, 0.8 Hz, 3H), 1.63–1.54 (m, 1H), 1.52–1.33 (m, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.2, 208.6, 145.2, 133.9, 118.3, 110.2, 51.1, 44.0, 42.6, 37.4, 36.1, 31.5, 30.1, 22.9, 21.1, 18.7; IR (Neat Film NaCl) 3076, 2968, 2935, 1717, 1703, 1648, 1640, 1458, 1437, 1410, 1358, 1271, 1229, 1174, 1076, 996, 917, 889, 725 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{27}O_2$ $[M+H]^+$: 251.2006, found 251.2006; $[\alpha]_D^{25.0}$ 6.64 (c 0.96, $CHCl_3$, 88% ee).

3.5.2.2 Siloxyenone Efforts Toward Acyclic Dione 72w



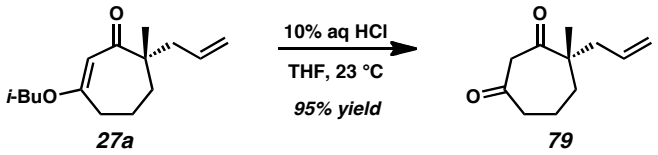
Siloxyenone 232. A flame-dried 50 mL round-bottom flask equipped with a stir bar was cycled into a glove box where the flask was loaded with sodium hydride (148.3 mg, 3.71 mmol, 1.06 equiv). The flask was removed from the glove box, connected to an Ar-filled manifold, and charged with THF (13 mL). Dione **65** (442.4 mg, 3.51 mmol, 1.00 equiv)

was transferred to the flask using several THF rinses (3 x 3 mL, total added = 22 mL, 0.16 M). The addition caused the reaction mixture to bubble vigorously and develop into an orange slurry. After 30 min, the flask was lowered into a –78 °C bath and TIPSOTf (990 μL, 3.68 mmol, 1.05 equiv) was added dropwise over several minutes. TLC analysis indicated no starting material remained after 1.5 h. Consequently, the reaction was transferred to a separatory funnel containing sat. aq $NaHCO_3$ and Et_2O and the aqueous layer was extracted three times with Et_2O. The combined organics (150 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 25.5 x 5 cm, 100% hexanes→5%→10% EtOAc in hexanes) to afford siloxyenone **232** (561.1 mg, 1.99 mmol, 57% yield) as an orange oil. Characterization data matches that reported previously by Corey et al.[48]



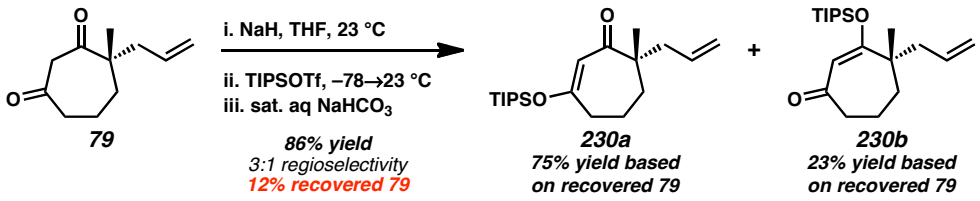
Siloxyenone 232. A flame-dried 50 mL round-bottom flask equipped with a stir bar and dione **65** (1.00 g, 7.93 mmol, 1.00 equiv) was charged with CH_3CN (79 mL, 0.10 M) and Et_3N (1.16 mL, 8.32 mmol, 1.05 equiv) and lowered into a –78 °C bath (dry ice/acetone). TIPSCl (1.87 mL, 8.74 mmol, 1.10 equiv) was added dropwise over 10 min and the reaction was moved to a 0 °C bath (ice/water). TLC analysis indicated no starting material remained after 2.5 h. Consequently, the reaction was quenched with sat. aq $NaHCO_3$ (10 mL) and transferred to a separatory funnel where the aqueous layer was

extracted three times with pentane. The combined organics (250 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. ^1H NMR analysis indicated that the resulting crude oil was sufficiently pure, affording siloxyenone **232** (1.96 g, 6.94 mmol, 88% yield) as an orange oil. Characterization data matches that reported previously by Corey et al.[48]



27a *79*

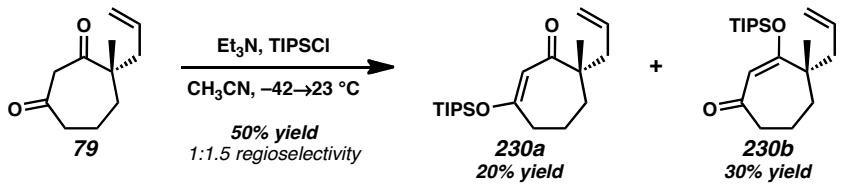
Dione 79. The following procedure affords a higher yield than our previous report.[7b] A flame-dried 50 mL round-bottom flask equipped with a stir bar was charged with vinylogous ester **27a** (1.83 g, 7.73 mmol, 1.00 equiv), THF (12.5 mL, 0.6 M), and hydrochloric acid (10% w/w aq = 2.87 M, 12.5 mL, 35.9 mmol, 4.64 equiv). The reaction mixture was initially a cloudy suspension that became a colorless solution over time. TLC analysis indicated no starting material remained after 4.5 h. Consequently, the reaction was transferred to a separatory funnel, diluted with water, and extracted six times with CH_2Cl_2. The combined organics (150 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 27 x 3 cm, 100% hexanes→15% EtOAc in hexanes) to afford dione **79** (1.33 g, 7.37 mmol, 95% yield) as a yellow oil. Characterization data matches that previously reported.[7b]



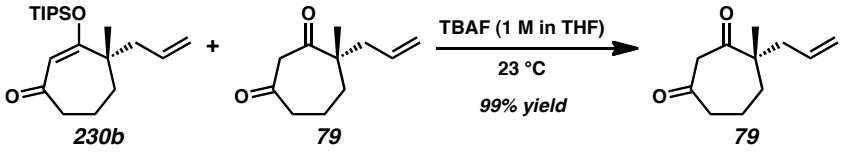
Siloxyenones 230a and 230b. A flame-dried 50 mL round-bottom flask equipped with a stir bar was cycled into a glove box where the flask was loaded with NaH (80.9 mg, 3.20 mmol, 1.05 equiv). The flask was removed from the glove box, connected to an Ar-filled manifold, and charged with THF (9 mL). Dione **79** (547.3 mg, 3.04 mmol, 1.00 equiv) was transferred via cannula from a scintillation vial to the round-bottom flask using several THF rinses (1 x 5 mL + 5 x 1 mL, total added = 19 mL, 0.16 M). The reaction was stirred at room temperature for 30 min before the flask was lowered into a –78 °C bath (dry ice/acetone) and TIPSOTf (850 μL, 3.16 mmol, 1.04 equiv) was added dropwise over 20 min. After the addition was complete, the bath was removed and the reaction was allowed to warm to room temperature. After 13 h of stirring, the reaction was poured into a separatory funnel containing Et_2O (20 mL), sat. aq $NaHCO_3$ (20 mL), and water (10 mL). The aqueous layer was extracted once with Et_2O and four times with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 26 x 3 cm, 100% hexanes→2%→15% EtOAc in hexanes) to afford siloxyenone **230a** (669.9 mg, 1.99 mmol, 66% yield, 75% yield based on recovered dione **79**) as a yellow oil, a mixed fraction of siloxyenone **230b** with dione **79** (206.5 mg total, 50:1 = **230b**:**79**, siloxyenone **230b**: 204.3 mg, 0.6069 mmol, 20% yield, 23% yield based on recovered dione **79**) as a yellow oil, and recovered dione **79** (66.0 mg, 0.366 mmol, 12% recovered) as a yellow oil.

Siloxyenone 230a. R_f = 0.76 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.87–5.74 (m, 1H), 5.78 (s, 1H), 5.06–5.00 (m, 2H), 2.51 (ddt, J = 13.5, 7.1, 1.3 Hz, 1H), 2.25 (ddt, J = 13.5, 7.7, 1.1 Hz, 1H), 2.21–2.16 (m, 2H), 1.67–1.59 (m, 1H), 1.44–1.37 (m, 2H), 1.34–1.28 (m, 1H), 1.20 (s, 3H), 1.13–1.00 (m, 21H); ^{13}C NMR (125 MHz, C_6D_6) δ 204.3, 167.5, 135.1, 117.8, 113.9, 51.8, 46.0, 38.2, 35.1, 25.4, 19.98, 18.1, 18.1, 12.9; IR (Neat Film NaCl) 3075, 2944, 2893, 2867, 1700, 1613, 1464, 1419, 1385, 1301, 1249, 1204, 1137, 1109, 1070, 1016, 996, 917, 883, 823, 782, 741 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{37}O_2Si$ $[M+H]^+$: 337.2557, found 337.2566; $[\alpha]_D^{25.0}$ –60.52 (c 1.01, $CHCl_3$, 88% ee).

Siloxyenone 230b. R_f = 0.64 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.72 (s, 1H), 5.78–5.65 (m, 1H), 5.06–4.98 (m, 2H), 2.54 (ddt, J = 13.6, 6.5, 1.5 Hz, 1H), 2.49 (dm, J = 18.0 Hz, 1H), 2.42 (ddd, J = 17.9, 9.4, 5.1 Hz, 1H), 2.05 (ddt, J = 13.6, 8.1, 1.1 Hz, 1H), 1.62 (ddd, J = 14.4, 9.9, 1.4 Hz, 1H), 1.44 (dtdd, J = 14.6, 9.8, 4.7, 1.4 Hz, 1H), 1.41–1.30 (m, 1H), 1.26 (ddt, J = 14.4, 9.0, 1.2 Hz, 1H), 1.19–1.06 (m, 3H), 1.11 (s, 3H), 1.04 (d, J = 3.1 Hz, 9H), 1.02 (d, J = 3.0 Hz, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 199.3, 172.1, 134.6, 118.1, 113.9, 46.3, 45.3, 44.5, 37.0, 25.9, 18.3, 18.3, 17.9, 13.1; IR (Neat Film NaCl) 2944, 2892, 2867, 1636, 1592, 1464, 1378, 1351, 1283, 1249, 1207, 1170, 1071, 1016, 996, 917, 883, 855, 782 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{20}H_{37}O_2Si$ $[M+H]^+$: 337.2557, found 337.2559; $[\alpha]_D^{25.0}$ –46.35 (c 1.35, $CHCl_3$, 88% ee).

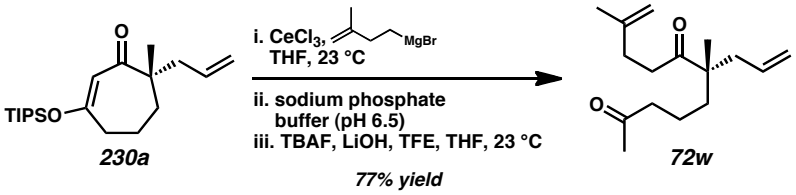


Siloxyenones 230a and 230b. A flame-dried 15 mL round-bottom flask equipped with a stir bar was charged with dione **79** (50.5 mg, 0.280 mmol, 1.00 equiv) and CH_3CN (2.8 mL, 0.1 M) and lowered into a –42 °C (dry ice/CH_3CN). Et_3N (40 μL, 0.287 mmol, 1.02 equiv) and TIPSCl (70 μL, 0.327 mmol, 1.17 equiv) were added dropwise to the reaction and the bath was allowed to expire over time. After 2 h, the reaction was quenched with water (5 mL) and transferred to a separatory funnel where the aqueous layer was extracted six times with hexanes. The combined organics (100 mL) were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 27 x 1.5 cm, 100% hexanes→2%→15% EtOAc in hexanes) to afford siloxyenone **230a** (19.2 mg, 0.0570 mmol, 20% yield) as a yellow oil and a mixed fraction of siloxyenone **230b** with dione **79** (31.0 mg total, 5.6:1 = **230b**:**79**, siloxyenone **230b**: 28.3 mg, 0.0840 mmol, 30% yield) as a yellow oil. (For characterization of siloxyenones **230a** and **230b**, see p. 739).



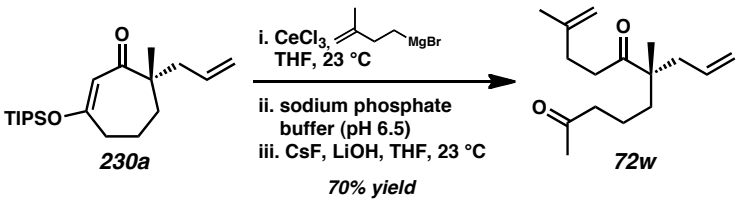
Dione 79. To a scintillation vial containing a mixed fraction of siloxyenone **230b** (262.6 mg, 0.780 mmol, 1.00 equiv) and dione **79** (12.0 mg, 0.0666 mmol) was added a stir bar and TBAF (1.0 M in THF, 2 mL, 2.00 mmol, 2.56 equiv). After 4 h, no siloxyenone

230b was observed by TLC. Consequently, the reaction was quenched with water (10 mL) and transferred to a separatory funnel where the aqueous layer was extracted six times with CH_2Cl_2. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 27.5 x 5 cm, 100% hexanes→5%→15% EtOAc in hexanes) to afford dione **79** (151.7 mg, 0.842 mmol, 99% yield) as a yellow oil. Characterization data matches that previously reported.[7b]



Dione 72w. A flame-dried 50 mL round-bottom flask equipped with a stir bar was cycled into a glove box where the flask was loaded with anhydrous cerium chloride (589.5 mg, 2.39 mmol, 2.50 equiv). The flask was removed from the glove box, connected to an Ar-filled manifold, placed under full vacuum, and lowered into an oil bath set to 140 °C. After 12.5 h, the flask was removed from the bath, allowed to cool to room temperature, and charged with THF (12 mL). After 3 h of stirring, (3-methylbut-3-en-1-yl)magnesium bromide[47] (0.59 M in THF, 4.86 mL, 2.87 mmol, 3.00 equiv) was added and the slurry initially turned yellow and then orange over time. After 40 min, siloxyenone **230a** (321.8 mg, 0.956 mmol, 1.00 equiv) was transferred from a scintillation vial to the round-bottom flask using several THF rinses (1 x 6 mL + 3 x 2 mL, total added = 24 mL, 0.04 M). TLC analysis indicated no starting material remained after 10 min. Consequently, the reaction was quenched with sodium phosphate buffer

(20 mM, pH 6.5, 20 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with Et_2O. The combined organics (150 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was transferred to a scintillation vial equipped with a stir bar and backfilled with Ar. The vial was charged with TBAF (1.0 M in THF, 1.43 mL, 1.43 mmol, 1.50 equiv), TFE (210 μL, 2.88 mmol, 3.01 equiv), and LiOH (34.4 mg, 1.44 mmol, 1.50 equiv). After 4 h, the reaction was quenched with water (10 mL) and transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified twice by flash column chromatography (SiO_2, 27.5 x 2 cm, 100% hexanes→5%→10% TBME in hexanes ***then*** SiO_2, 28 x 2 cm, 100% hexanes→2%→5%→20% TBME in hexanes) to afford dione **72w** (185.0 mg, 0.739 mmol, 77% yield) as a pale yellow oil. (For characterization data, see p. 734).

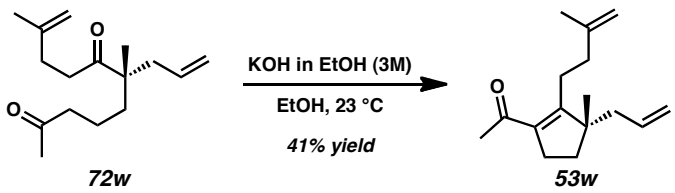


Dione 72w. A flame-dried 15 mL round-bottom flask equipped with a stir bar was cycled into a glove box where the flask was loaded with anhydrous cerium chloride (141.7 mg, 0.575 mmol, 2.50 equiv). The flask was removed from the glove box, connected to an Ar-filled manifold, placed under full vacuum, and lowered into an oil bath set to 140 °C. After 12 h, the flask was removed from the bath, allowed to cool to

room temperature, and charged with THF (1.7 mL). After 2 h of stirring, (3-methylbut-3-en-1-yl)magnesium bromide[47] (0.59 M in THF, 1.17 mL, 0.690 mmol, 3.01 equiv) was added and the slurry initially turned yellow and then orange over time. After 30 min, siloxyenone **230a** (77.3 mg, 0.230 mmol, 1.00 equiv) was transferred from a scintillation vial to the round-bottom flask using several THF rinses (1 x 2 mL + 2 x 1 mL, total added = 5.7 mL, 0.04 M). TLC analysis indicated no starting material remained after 5 min. Consequently, the reaction was quenched with sodium phosphate buffer (20 mM, pH 6.5, 5 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

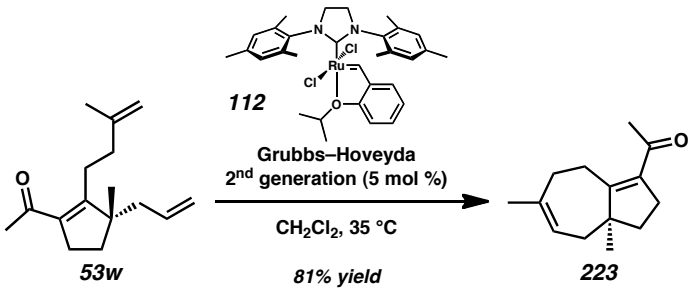
A separate flame-dried 10 mL round-bottom flask equipped with a stir bar was loaded with CsF (145.2 mg, 0.956 mmol, 4.16 equiv) and flame-dried again. Upon cooling, the crude oil from the previous step was transferred to the flask using several THF rinses (3 x 1 mL, total added = 3 mL, 0.08 M). As the reaction failed to progress by TLC analysis after 1 h, LiOH (18.5 mg, 0.772 mmol, 3.36 equiv) was added. TLC analysis indicated the desired product was mainly present after an additional 13 h. Consequently, the reaction was quenched with water (10 mL) and transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 28 x 1.5 cm, 100% hexanes→2%→5%→10% TBME in hexanes) to afford dione **72w** (40.4 mg, 0.161 mmol, 70% yield) as a pale yellow oil. (For characterization data, see p. 734).

3.5.2.3 Routes to Key Intermediate Enone 53w



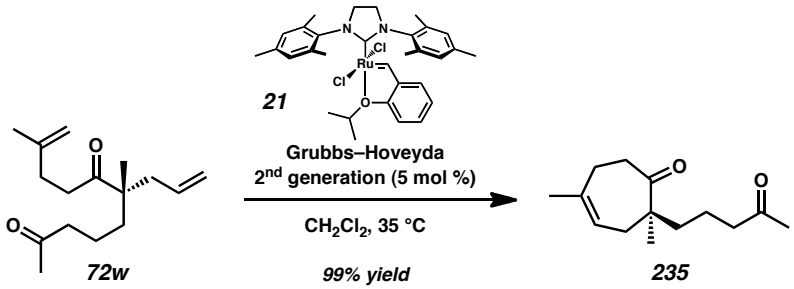
72w *53w*

Enone 53w. A scintillation vial equipped with a stir bar and dione **72w** (40.4 mg, 0.161 mmol, 1.00 equiv) was charged with EtOH (950 µL, 0.17 M) and KOH solution (3 M in EtOH, 140 µL, 0.420 mmol, 2.60 equiv). The resulting yellow solution was stirred vigorously. Over the course of the reaction, an additional portion of the KOH solution (2 d = 140 µL, 3 d = 280 µL, 4 d = 1.4 mL, 5 d = 5.0 mL, total added = 7.66 mL, 23.0 mmol, 142 equiv) was added. After 6 days, the reaction was quenched with water (10 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 28 x 1.5 cm, 100% hexanes→2%→5% EtOAc in hexanes) to afford enone **53w** (15.3 mg, 0.0660 mmol, 41% yield) as a yellow oil. (For characterization data, see p. 733).



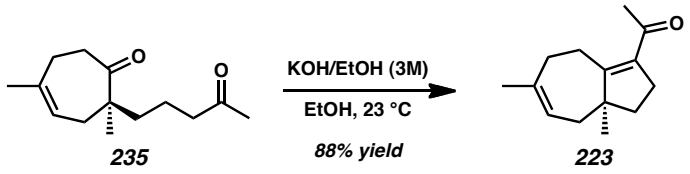
Enone 223. A flame-dried 25 mL round-bottom flask equipped with a stir bar and water condenser was charged with acylcyclopentene **53w** (1.0 M in benzene, 100 μL, 0.100 mmol, 1.00 equiv), CH_2Cl_2 (20 mL, 0.005 M, 30 min Ar sparge before use), and Grubbs–Hoveyda 2nd generation catalyst (**112**, 3.2 mg, 0.00511 mmol, 5 mol %), generating a pale green solution. The flask was lowered into a preheated oil bath (35 °C) and stirred for 5 h before the reaction was cooled to room temperature and quenched with ethyl vinyl ether. The reaction was filtered through a short silica gel plug rinsing with Et_2O and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 21.5 x 1.3 cm, 100% hexanes→2% Et_2O in pentane) to afford enone **223** (16.5 mg, 0.081 mmol, 81% yield) as a yellow oil. Spectral data for enone **223** matches that previously reported by Urones[36]: R_f = 0.73 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (ddt, J = 7.9, 6.7, 1.4 Hz, 1H), 3.21 (dt, J = 11.1, 5.9 Hz, 1H), 2.66–2.56 (m, 1H), 2.50 (ddd, J = 15.3, 8.7, 2.8 Hz, 1H), 2.29–2.16 (m, 1H), 2.21 (s, 3H), 2.17–2.11 (m, 3H), 2.02 (ddd, J = 14.4, 6.6, 1.2 Hz, 1H), 1.75–1.69 (m, 1H), 1.69 (d, J = 1.4 Hz, 3H), 1.64 (ddd, J = 12.3, 7.7, 2.8 Hz, 1H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 165.0, 139.4, 133.4, 121.1, 52.7, 37.8, 37.3, 33.2, 30.8, 30.4, 26.1, 24.2, 23.7; IR (Neat Film NaCl) 2926, 2852, 1675, 1653, 1612, 1437, 1356,

1301, 1262, 1204, 945, 825 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{20}O$ $[M+\bullet]^+$: 204.1514, found 204.1530; $[\alpha]_D^{25.0}$ –146.03 (c 0.98, $CHCl_3$, 88% ee).



Dione 235. To a flame-dried 250 mL Schlenk flask equipped with a stir bar and water condenser was added dione **72w** (422.6 mg, 1.69 mmol, 1.00 equiv) via several CH_2Cl_2 rinses (5 x 6 mL, 30 min Ar sparge before use). The flask was charged with additional CH_2Cl_2 (130 mL) and Hoveyda–Grubbs 2nd generation catalyst (**21**, 53.0 mg, 0.0846 mmol, 5.0 mol %), generating a pale green solution. The flask was rinsed with CH_2Cl_2 (10 mL, total added = 170 mL, 0.01 M) and lowered into a preheated oil bath (35 °C). After 22 h, the reaction was quenched with ethyl vinyl ether (3 mL), removed from the oil bath, and allowed to cool to room temperature. The reaction contents were filtered through a short silica gel plug, rinsing with TBME, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 27.5 x 2 cm, 100% hexanes→5%→10%→15%→20%→30% TBME in hexanes) to afford dione **235** (370.5 mg, 1.67 mmol, 99% yield) as a yellow oil. Spectral data for dione **235** matches that previously reported by Urones[36a]: R_f = 0.39 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 (dddd, J = 7.7, 6.2, 3.0, 1.5 Hz, 1H), 2.88 (ddd, J = 11.5, 9.5, 5.7 Hz, 1H), 2.59 (ddd, J = 11.5, 6.9, 5.4 Hz, 1H), 2.43

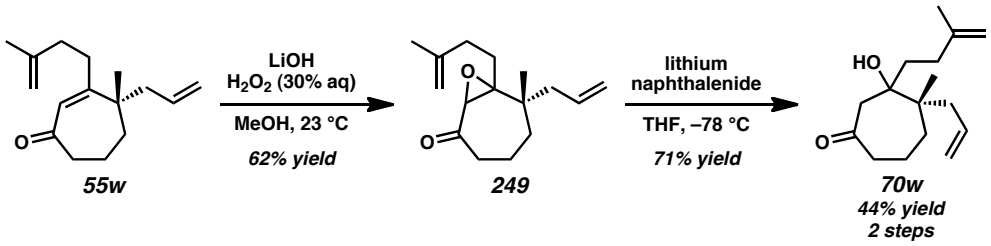
(dddd, J = 15.2, 6.1, 2.7, 1.3 Hz, 1H), 2.38 (t, J = 6.9 Hz, 2H), 2.34–2.20 (m, 2H), 2.11 (s, 3H), 2.08 (ddq, J = 15.4, 7.3, 1.0 Hz, 1H), 1.66 (q, J = 1.1 Hz, 3H), 1.56–1.38 (m, 4H), 1.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.0, 208.8, 137.0, 121.5, 53.8, 44.2, 38.0, 37.9, 34.7, 32.1, 30.1, 25.4, 22.4, 18.7; IR (Neat Film NaCl) 2963, 2931, 1714, 1705, 1436, 1360, 1314, 1215, 1173, 1123, 1071, 1011, 894, 826 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{23}O_2$ $[M+H]^+$: 223.1693, found 223.1696; $[\alpha]_D^{25.0}$ 52.49 (c 0.93, $CHCl_3$, 88% ee).



Enone 223. Procedure adapted from report by Urones.[36a] A flame-dried 25 mL round-bottom flask equipped with a stir bar was charged with dione **235** (255.6 mg, 1.15 mmol, 1.00 equiv), EtOH (6.74 mL, 0.17 M), and KOH solution (3 M in EtOH, 1.02 mL, 3.06 mmol, 2.66 equiv), generating a yellow solution that transitioned to orange over time. After 9 h, an additional portion of KOH (3 M in EtOH, 0.90 mL, total added = 1.92 mL, 5.76 mmol, 5.01 equiv) was added. After 22 h, no starting material remained by TLC. Consequently, the reaction was diluted with water (15 mL) and transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (100 mL) were rinsed with HCl (0.5 M, 15 mL) and water (15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 26 x 2 cm, 100% hexanes→5% TBME in hexanes) to afford enone **223** (205.6 mg, 1.01 mmol, 88% yield)

as a yellow oil. Spectral data for enone **223** matches that previously reported by Urones.[36a] (For characterization data, see p. 745).

3.5.2.4 Routes to Reincorporate Cycloheptenone 55w into Synthetic Efforts

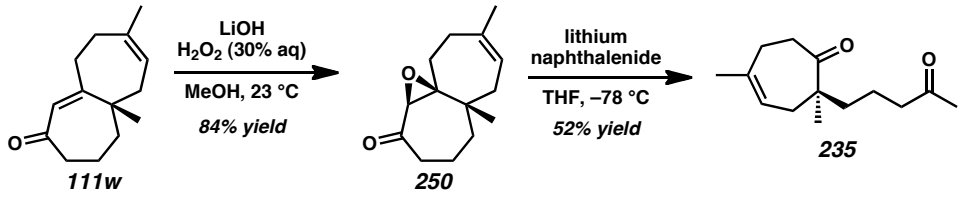


Epoxide 249. Procedure adapted from report by Stoltz.[7a] To a scintillation vial containing a stir bar and cycloheptenone **55w** (216.6 mg, 0.932 mmol, 1.00 equiv) was added MeOH (3.6 mL), LiOH (56.1 mg, 2.34 mmol, 2.51 equiv), H_2O_2 (30% w/w aq, 950 µL, 9.30 mmol, 9.98 equiv), and additional MeOH (1.0 mL, total added = 4.6 mL, 0.2 M). During the course of the reaction, additional LiOH (7 h = 56.5 mg, 22 h = 55.8 mg, 31 h = 56.0 mg, 95.5 h = 55.9 mg, 142 h = 56.2 mg, total added = 336.5 mg, 14.0 mmol, 15.0 equiv) and H_2O_2 (950 µL more at 7 h, 22 h, 31 h, 71.5 h, 142 h, 151 h, total added = 7.6 mL, 74.4 mmol, 80 equiv) were added to the flask. The solvent level decreased over time and so more MeOH (47.5 h = 3 mL, 71.5 h = 2 mL, 77.5 h = 3 mL) was added when appropriate. After 10 days, TLC analysis indicated minor starting material remaining. Consequently, the reaction was diluted with CH_2Cl_2 (10 mL) and water (20 mL), quenched with sat. $NaHCO_3$ solution (10 mL), and transferred to a separatory funnel where the aqueous layer was extracted six times with CH_2Cl_2. The combined organics (125 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 28 x 2 cm,

100% hexanes→2%→5%→10%→20% EtOAc in hexanes) to afford recovered cycloheptenone **55w** (22.1 mg, 0.0951 mmol, 10% recovered) and epoxide **249** (142.8 mg, 0.575 mmol, 62% yield, 69% yield based on recovered cycloheptenone **55w**) as a cloudy yellow oil; R_f = 0.75 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) mixture of two diastereomers, see Figure SI-2A; IR (Neat Film NaCl) 3075, 2970, 2936, 1703, 1649, 1639, 1457, 1395, 1376, 1339, 1291, 1261, 1206, 1169, 1121, 996, 919, 890, 848 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{16}H_{25}O_2$ $[M+H]^+$: 249.1855, found 249.1851.

β-Hydroxyketone 70w. Procedure adapted from report by Liu.[49] A flame-dried 25 mL round-bottom flask equipped with a stir bar was loaded with epoxide **249** (50.0 mg, 0.201 mmol, 1.00 equiv) and THF (5.8 mL, 0.10 M) and lowered into a –78 °C bath (dry ice/acetone). A lithium naphthalenide solution[50] (1.0 M in THF, 3.6 mL, 3.60 mmol, 6.26 equiv) was added dropwise to the flask, generating a dark green solution. During the course of the reaction, an additional portion of lithium naphthalenide (1.0 M in THF, 1 h = 1.0 mL, 5 h = 2.0 mL, 2.5 h = 0.58 mL, total added = 6.60 mL, 6.60 mmol, 11.5 equiv) was added. After 9 h, the reaction was quenched with water (10 mL), diluted with EtOAc, and stirred for 12 h. The reaction contents were transferred to a separatory funnel where the aqueous layer was extracted four times with CH_2Cl_2. The combined organics (125 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified twice by flash column chromatography (SiO_2, 27.5 x 2 cm, 100% hexanes→5%→10%→20% EtOAc in hexanes ***then*** SiO_2, 27.5 x 2 cm, 100% hexanes→2%→5%→10%→15% EtOAc in hexanes) to afford β-

hydroxyketone **70w** (102.6 mg, 0.410 mmol, 71% yield) as a yellow oil. (For characterization data, see p. 733).

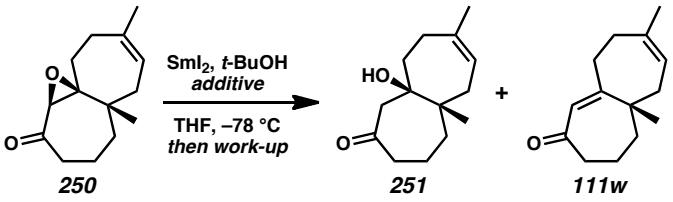


Epoxide 250. A flame-dried 25 round-bottom flask equipped with a stir bar was charged with enone **111w** (110.3 mg, 0.540 mmol, 1.00 equiv), MeOH (4.8 mL, 0.11 M), LiOH (32.4 mg, 1.35 mmol, 2.50 equiv), and H_2O_2 (30% w/w aq, 550 μL, 5.38 mmol, 10.0 equiv). After 30.5 h, no starting material remained by TLC analysis. Consequently, the reaction was quenched with sat. aq $NaHCO_3$ (10 mL) and water (10 mL) and was transferred to a separatory funnel where the aqueous layer was extracted five times with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 28 x 1.5 cm, 100% hexanes→2%→5%→20% EtOAc in hexanes) to afford epoxide **250** (99.5 mg, 0.452 mmol, 84% yield) as a yellow oil that solidified upon freezing; R_f = 0.68 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.20 (ddt, J = 8.6, 5.1, 1.8 Hz, 1H), 3.18 (d, J = 1.3 Hz, 1H), 2.45 (td, J = 11.5, 5.3 Hz, 1H), 2.24–2.14 (m, 1H), 2.07 (ddd, J = 13.3, 12.4, 2.9 Hz, 1H), 2.00–1.89 (m, 1H), 1.82 (ddt, J = 14.9, 4.9, 1.8 Hz, 1H), 1.68 (ddd, J = 15.7, 5.6, 2.9 Hz, 1H), 1.67–1.58 (m, 1H), 1.56 (q, J = 1.4 Hz, 3H), 1.46 (dd, J = 14.8, 8.6 Hz, 1H), 1.29–1.20 (m, 1H), 1.13–1.04 (m, 2H), 0.97 (s, 3H), 0.78 (ddd, J = 13.3, 5.5, 3.2 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 207.8, 138.0, 121.7, 72.0, 67.5, 40.6, 40.6, 40.1, 36.3, 33.8, 31.2, 26.1, 25.7, 18.1; IR

(Neat Film NaCl) 2961, 2928, 2843, 1698, 1452, 1437, 1330, 1270, 841 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{20}O_2$ $[M+\bullet]^+$: 220.1463, found 220.1496; $[\alpha]_D^{25.0}$ –78.43 (c 1.06, $CHCl_3$, 88% ee).

Dione 235. To a 15 mL round-bottom flask equipped with a stir bar was loaded with epoxide **250** (35.6 mg, 0.162 mmol, 1.00 equiv) and THF (1.6 mL, 0.10 M) and lowered into a –78 °C bath (dry ice/acetone). A lithium naphthalenide solution[50] (1.0 M in THF, 680 μL, 0.680 mmol, 4.2 equiv) was added dropwise to the flask, generating a dark green solution. After 1.5 h, the reaction was quenched with water (5 mL), allowed to warm to room temperature, and transferred to a separatory funnel where the aqueous layer was extracted six times with CH_2Cl_2. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified twice by flash column chromatography (SiO_2, 29 x 1.5 cm, 100% hexanes→5%→10%→15%→20%→50% EtOAc in hexanes ***then*** SiO_2, 25.5 x 1.5 cm, 100% hexanes→10%→15% EtOAc in hexanes) to afford enone **235** (18.7 mg, 0.0842 mmol, 52% yield) as a yellow oil. (For characterization data, see p. 746).

Table 3.1. Samarium diiodide reduction of epoxide ***250****.*



250 ***251*** ***111w***

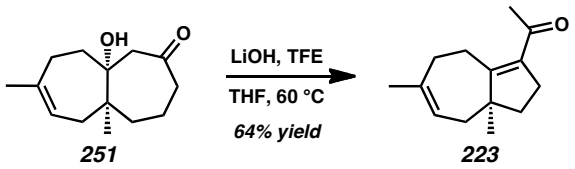
entry	additive	equiv.	work-up	yield (%)[b] *251*	*111w*
1	–	–	sat. aq. NH_4Cl	75[c]	–
2	HMPA	5.7	sat. aq. NH_4Cl	90[d]	8
3	LiCl	7.1	sat. aq. NH_4Cl	76	–
4	LiCl	8.6	H_2O	92	–[e]

[a] *Conditions*: epoxide **250** (1.0 equiv), SmI_2 (1.8–2.1 equiv.), *t*-BuOH (1.1–1.4 equiv.), and additive in THF (0.1 M) at –78 °C. [b] Isolated yield. [c] 95% purity. [d] 86% purity. [e] Observed, but not isolated.

Samarium Diiodide Reduction Screen on Epoxide 250. A series of samarium diiodide conditions were investigated in the reduction of epoxide **250**. A general procedure is provided below and related reactions were performed analogously with appropriate changes in additive and work-up conditions.

β-Hydroxyketone 251 (*LiCl Additive and H_2O quench*: Table 3.1, entry 4). A flame-dried 10 mL round-bottom flask equipped with a stir bar was cycled into a glove box where the flask was loaded with lithium chloride (52.6 mg, 1.24 mmol, 8.57 equiv). The flask was removed from the glove box and connected to an Ar-filled manifold. Epoxide **250** (31.9 mg, 0.145 mmol, 1.00 equiv) was transferred to the flask using several THF rinses (30 min Ar sparge before use, 3 x 0.5 mL, total added = 1.5 mL), *t*-BuOH (20 μL, 0.209 mmol, 1.44 equiv) was added, and the flask was lowered into a –78 °C bath (dry ice/acetone). A samarium diiodide solution[51] (0.1 M in THF, 3.04 mL, 0.304 mmol, 2.10

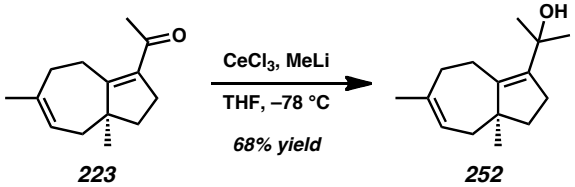
equiv) was added dropwise over 5 min down the side of the flask, generating a dark blue solution. TLC analysis indicated that no starting material remained after 5 min. After an additional 5 min, the reaction was quenched with water (2 mL), allowed to warm to room temperature, and transferred to a separatory funnel where the aqueous layer was extracted four times with EtOAc. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 25 x 1.5 cm, 100% hexanes→20% EtOAc in hexanes) to afford β-hydroxyketone **251** (29.7 mg, 0.133 mmol, 92% yield) as a yellow oil that solidified upon freezing; R_f = 0.26 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (tdd, J = 6.2, 2.6, 1.4 Hz, 1H), 3.10 (br s, 1H), 2.67 (br m, 1H), 2.43–2.32 (m, 2H), 2.20 (br m, 1H), 2.13 (br m, 1H), 2.04 (br m, 1H), 1.90 (dd, J = 15.4, 10.7 Hz, 1H), 1.84–1.76 (m, 2H), 1.73 (d, J = 1.3 Hz, 3H), 1.77–1.67 (m, 2H), 1.62 (br s, 1H), 1.57 (dd, J = 14.3, 10.5 Hz, 1H), 1.47 (ddd, J = 13.8, 8.9, 1.8 Hz, 1H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.0, 140.0, 122.5, 77.3, 54.2, 43.1, 42.4, 40.1, 38.3, 36.4, 28.0, 25.4, 23.0, 18.2; IR (Neat Film NaCl) 3510, 2958, 2926, 2859, 1692, 1445, 1402, 1284, 1023, 903, 851, 828 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{22}O_2$ $[M+\bullet]^+$: 222.1620, found 222.1629; $[\alpha]_D^{25.0}$ –39.67 (c 0.85, $CHCl_3$, 86% ee).



251 *223*

Enone 223. A 20 mL scintillation vial equipped with a stir bar and β-hydroxyketone **251** (13.6 mg, 0.0612 mmol, 1.00 equiv) was connected to an Ar-filled manifold and flushed with Ar. The vial was loaded with THF (1.5 mL, 0.04 M), TFE (10 μL, 0.137 mmol, 2.24 equiv), and LiOH (2.2 mg, 0.0919 mmol, 1.50 equiv) and lowered into a preheated oil bath (60 °C). After 72 h, the solvent had evaporated, and so the vial was charged with additional THF (1.5 mL). TLC analysis of the reaction after 75 h indicated no starting material or dione **235**. Consequently, the reaction was removed from the oil bath, allowed to cool to room temperature, filtered through a celite plug rinsing with Et_2O, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO2, 23 x 1.5 cm, 100% hexanes hexanes→5% TBME in hexanes) to afford enone **223** (8.0 mg, 0.0392 mmol, 64% yield) as a yellow oil. (For characterization data, see p. 745).

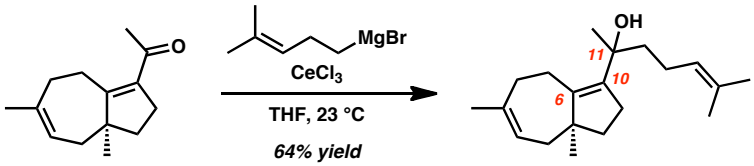
3.5.2.5 Derivatization of Enone 223 and Synthesis of (–)-Epoxydaucenal B (144b) and Δ[11]-Carotol (259)



223 *252*

Alcohol 252. A flame-dried 15 mL round-bottom flask equipped with a stir bar was cycled into a glove box where the flask was loaded with anhydrous cerium chloride (76.4

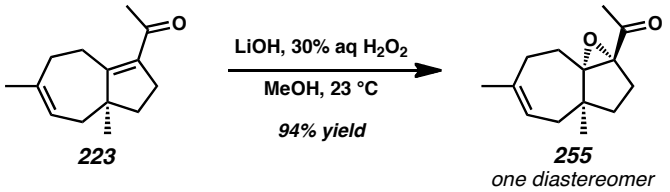
mg, 0.310 mmol, 2.53 equiv). The flask was removed from the glove box, connected to an Ar-filled manifold, placed under full vacuum, and lowered into an oil bath set to 140 °C. After 13 h, the flask was removed from the bath, allowed to cool to room temperature, and charged with THF (3 mL). After 3 h of stirring, methyllithium (1.6 M in pentane, 310 μL, 0.496 mmol, 4.05 equiv) was added and the flask was lowered into a –78 °C bath (dry ice/acetone). The resulting slurry initially turned yellow and then orange over time. After 10 min, enone **223** (25.0 mg, 0.122 mmol, 1.00 equiv) was added neat. TLC analysis indicated no starting material remained after 5 min. Consequently, the reaction was quenched after 10 min with sat. NH_4Cl solution (20 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 27.5 x 2 cm, 100% hexanes→5% TBME in hexanes) to afford alcohol **252** (18.3 mg, 0.0829 mmol, 68% yield) as a pale yellow oil; R_f = 0.65 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (tp, J = 6.5, 1.5 Hz, 1H), 3.00 (ddd, J = 13.6, 4.9, 3.9 Hz, 1H), 2.37–2.26 (m, 1H), 2.21 (dddd, J = 15.6, 8.6, 3.4, 1.2 Hz, 1H), 2.14 (dt, J = 15.2, 4.6 Hz, 1H), 2.11–2.04 (m, 1H), 2.01 (dt, J = 7.0, 1.1 Hz, 2H), 1.99–1.94 (m, 1H), 1.71 (t, J = 1.3 Hz, 4H), 1.62–1.51 (m, 2H), 1.36 (s, 3H), 1.34 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.1, 139.3, 139.0, 122.0, 72.5, 51.3, 39.3, 37.8, 34.1, 31.2, 30.7, 30.5, 26.1, 24.1, 23.3; IR (Neat Film NaCl) 3373, 2965, 2924, 2850, 1455, 1367, 1331, 1259, 1172, 1138, 1083, 1043, 1012, 984, 945, 887, 822 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{15}H_{23}O$ $[(M+H)–H_2]^+$: 219.1749, found 219.1743; $[\alpha]_D^{25.0}$ –33.73 (c 1.83, $CHCl_3$, 88% ee).



223 ***Δ$^{6(10)}$-tormesol (253)***
1:1 d.r. at C11

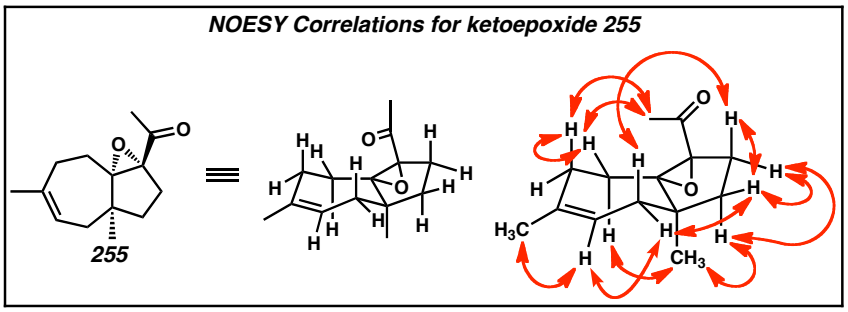
Δ$^{6(10)}$-tormesol (253). A flame-dried 15 mL round-bottom flask equipped with a stir bar was cycled into a glove box where the flask was loaded with anhydrous cerium chloride (91.2 mg, 0.370 mmol, 2.52 equiv). The flask was removed from the glove box, connected to an Ar-filled manifold, placed under full vacuum, and lowered into an oil bath set to 140 °C. After 12 h, the flask was removed from the bath, allowed to cool to room temperature, and charged with THF (1.6 mL). After 3 h of stirring, (4-methylpent-3-en-1-yl)magnesium bromide (0.39 M in THF, 1.13 mL, 0.441 mmol, 3.00 equiv) was added and the slurry turned yellow. After 45 min, enone **223** (30.0 mg, 0.147 mmol, 1.00 equiv) was transferred from a scintillation vial to the round-bottom flask using several THF rinses (1 x 1.5 mL + 3 x 0.5 mL, total added = 4.6 mL, 0.03 M). TLC analysis indicated no starting material remained after 5 min. Consequently, the reaction was quenched with sat. NH_4Cl solution (3 mL) at –78 °C and allowed to warm to room temperature. The reaction contents were transferred to a separatory funnel where the aqueous layer was extracted four times with CH_2Cl_2 and three times with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 28 x 1.5 cm, 5% TBME in hexanes) to afford Δ$^{6(10)}$-tormesol (**253**, 27.1 mg, 0.0941 mmol, 64% yield) as a yellow oil; R_f = 0.75 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) mixture of two diastereomers, see Figure SI-10A; IR (Neat

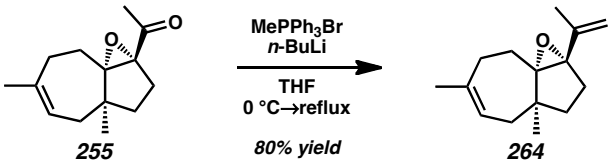
Film NaCl) 3460, 2964, 2925, 2853, 1668, 1645, 1449, 1375, 1330, 1310, 1261, 1238, 1192, 1111, 1063, 1006, 983, 924, 825 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{20}H_{32}O$ $[M+\bullet]^+$: 288.2453, found 288.2451.



Ketoepoxide 255. Procedure adapted from report by Stoltz.[7a] A flame-dried 25 mL round-bottom flask equipped with a stir bar and enone **223** (100.4 mg, 0.491 mmol, 1.00 equiv) was backfilled with Ar and charged with MeOH (3 mL), LiOH (29.5 mg, 1.23 mmol, 2.50 equiv), and H_2O_2 (30% w/w aq, 500 μL, 4.90 mmol, 10.0 equiv). Over the course of the reaction, additional LiOH (29.5 mg at 33 h, 46 h, 73 h and 29.6 mg at 80.5 h, total added = 147.6 mg, 6.15 mmol, 12.5 equiv) and H_2O_2 (500 μL at 33 h, 46 h, 73 h, 80.5 h, total added = 2.5 mL, 24.5 mmol, 50 equiv) were added. After 4 days, no starting material remained by TLC analysis. Consequently, CH_2Cl_2 (10 mL), water (10 mL), and sat. $NaHCO_3$ solution (10 mL) was added. The reaction contents were transferred to a separatory funnel where the aqueous layer was extracted four times with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 28.5 x 1.5 cm, 100% hexanes→2%→5% TBME in hexanes) to afford ketoepoxide **255** (101.8 mg, 0.462 mmol, 94% yield) as a yellow oil; R_f = 0.70 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.31 (ddq, J = 8.7, 5.2, 1.7 Hz, 1H), 2.22 (ddd, J = 13.8, 11.1, 8.2 Hz, 1H), 2.07 (dddd, J = 13.6, 3.8, 1.9, 1.0 Hz, 1H), 2.03–1.93 (m, 1H), 1.97 (s,

3H), 1.77 (tdd, J = 12.8, 2.0, 1.1 Hz, 1H), 1.73 (ddt, J = 13.8, 8.2, 0.9 Hz, 1H), 1.56 (td, J = 1.8, 0.7 Hz, 3H), 1.52 (dddd, J = 14.4, 6.6, 2.0, 1.2 Hz, 1H), 1.47 (dd, J = 14.4, 8.6 Hz, 1H), 1.41 (dddd, J = 12.4, 6.2, 5.5, 0.7 Hz, 1H), 1.37 (ddd, J = 12.4, 11.1, 8.2 Hz, 1H), 1.00 (ddt, J = 12.4, 8.2, 0.8 Hz, 1H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 204.9, 139.9, 122.8, 78.3, 74.7, 44.5, 35.9, 35.8, 29.1, 27.9, 26.8, 26.1, 25.2, 19.4; IR (Neat Film NaCl) 2962, 2930, 2868, 1701, 1446, 1354, 1266, 1178, 1136, 1128, 1079, 1020, 994, 975, 954, 934, 882, 833 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{21}O_2$ $[M+H]^+$: 221.1536, found 221.1530; $[\alpha]_D^{25.0}$ –50.64 (c 1.24, $CHCl_3$, 88% ee).

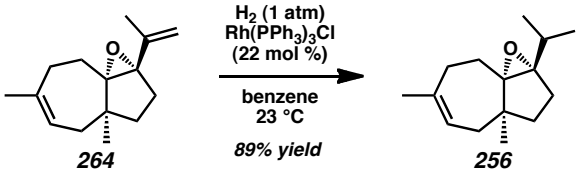




Diene 264. A flame-dried 25 mL round-bottom flask equipped with a stir bar was cycled into a glove box and loaded with methyltriphenylphosphonium bromide (121.1 mg, 0.339 mmol, 1.54 equiv). The flask was removed from the glove box, connected to an Ar-filled manifold, charged with THF (1.4 mL), and lowered into a 0 °C bath (ice/water). *n*-BuLi (2.5 M in hexanes, 110 µL, 0.275 mmol, 1.25 equiv) was added dropwise to the flask, generating a bright yellow solution. After 15 min, ketoepoxide **255** (48.5 mg, 0.220

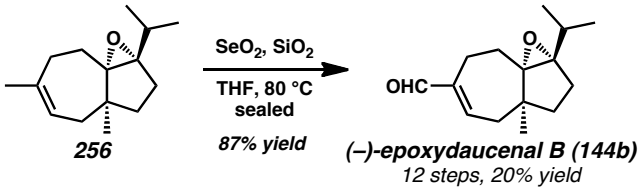
mmol, 1.00 equiv) was transferred via cannula to the flask using several THF rinses (3 x 1 mL, total added = 4.4 mL, 0.05 M) and the bath was allowed to warm to room temperature over time. After 1 h, significant starting material persisted by TLC analysis. Consequently, an additional solution (15 min prestir at 0 °C) of methyltriphenylphosphonium bromide (353.5 mg, 0.990 mmol, 4.50 equiv) and *n*-BuLi (2.5 M in hexanes, 330 μL, 0.275 mmol, 1.25 equiv) in THF (2 mL) was prepared and cannula transferred to the 25 mL flask. After 17 h, starting material was still present by TLC analysis, so a water condenser was attached to the flask and the reaction was heated to reflux. After 45 h, starting material was still observed by TLC analysis. Consequently, another solution (15 min prestir at 0 °C) of methyltriphenylphosphonium bromide (356.7 mg, 0.999 mmol, 4.53 equiv) and *n*-BuLi (2.5 M in hexanes, 330 μL, 0.275 mmol, 1.25 equiv) in THF (2 mL) was prepared and cannula transferred to the 25 mL flask. The solvent level decreased over time and more THF (2 mL at 47 h and 65 h) was added when appropriate. After 4 days, no starting material was observed by TLC analysis. Consequently, the reaction was quenched with H_2O (5 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with Et_2O. The combined organics (75 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 26.5 x 1.5 cm, 100% hexanes→2%→10% TBME in hexanes) to afford diene **264** (38.5 mg, 0.176 mmol, 80% yield) as a yellow oil; R_f = 0.76 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.47 (ddp, J = 8.6, 5.1, 1.6 Hz, 1H), 4.98 (q, J = 1.2 Hz, 2H), 2.14 (dddt, J = 14.2, 4.5, 1.8, 0.9 Hz, 1H), 2.06 (ddd, J = 13.7, 10.8, 8.3 Hz, 1H), 2.00 (br t, J = 13.8 Hz, 1H), 1.87 (t, J = 1.2 Hz, 3H), 1.87–1.83

(m, 1H), 1.82 (ddt, J = 13.8, 8.3, 1.0 Hz, 1H), 1.80–1.72 (m, 1H), 1.76 (td, J = 1.8, 0.6 Hz, 3H), 1.67 (dddd, J = 14.0, 13.0, 2.1, 1.1 Hz, 1H), 1.41 (ddd, J = 12.7, 10.8, 8.3 Hz, 1H), 1.39 (dddd, J = 13.7, 6.5, 1.9, 0.6 Hz, 1H), 1.23 (dd, J = 12.4, 8.2 Hz, 1H), 0.99 (d, J = 0.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 139.9, 123.0, 112.9, 78.6, 74.1, 43.9, 36.2, 36.1, 29.9, 28.4, 25.4, 24.6, 20.8, 19.7; IR (Neat Film NaCl) 2962, 2929, 2868, 2851, 1646, 1444, 1373, 960, 903, 831 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{15}H_{22}O$ $[M+\bullet]^+$: 218.1671, found 218.1672; $[\alpha]_D^{25.0}$ –55.99 (c 1.11, $CHCl_3$, 88% ee).



Epoxide 256. A flame-dried 10 mL round-bottom flask equipped with a stir bar was cycled into a glove box and loaded with Wilkinson's catalyst (13.1 mg, 0.0142 mmol, 15.0 mol %). The flask was removed from the glove box, connected to an Ar-filled manifold, and charged with benzene (30 min Ar sparge before use, 0.15 mL). Diene **264** (20.6 mg, 0.0944 mmol, 1.00 equiv) was transferred to the flask via a cannula using several benzene rinses (3 x 1 mL, total added = 3.15 mL, 0.03 M). The reaction was disconnected from the manifold, connected to a hydrogen balloon, and flushed with hydrogen, generating an orange solution. After 4 h, no starting material was observed by TLC, so the stir bar was removed and rinsed with CH_2Cl_2, and the reaction was concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 24.5 x 1.5 cm, 100% hexanes→1% TBME in hexanes) to afford an oil that contained both epoxide **256** and residual starting

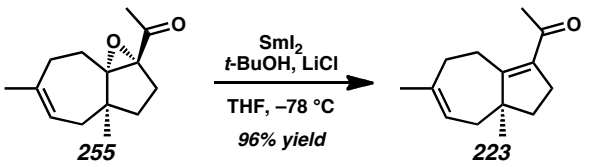
material (~10%). The reaction was set up again following the above procedure (Wilkinson's catalyst: 6.3 mg, 0.00681 mmol, 7 mol %; benzene: 3.15 mL, 0.03 M). After 3 h, a reaction aliquot was removed and ^{1}H NMR analysis revealed no starting material. Consequently, the stir bar was removed and rinsed with CH_2Cl_2, and the reaction was concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 27 x 1.5 cm, 100% hexanes→1% TBME in hexanes) to afford epoxide **256** (18.4 mg, 0.0835 mmol, 89% yield) as a yellow oil; R_f = 0.69 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46 (ddq, J = 8.7, 5.3, 1.7 Hz, 1H), 2.17 (ttt, J = 13.3, 1.8, 0.8 Hz, 1H), 2.08 (dd, J = 14.7, 4.5 Hz, 1H), 1.94 (dddd, J = 14.4, 6.6, 1.9, 1.3 Hz, 1H), 1.82–1.74 (m, 1H), 1.77 (td, J = 1.8, 0.7 Hz, 3H), 1.76–1.66 (m, 4H), 1.43 (ddd, J = 14.1, 6.6, 1.9 Hz, 1H), 1.31 (ddd, J = 12.5, 10.5, 8.6 Hz, 1H), 1.15 (ddd, J = 12.3, 8.0, 1.0 Hz, 1H), 1.07 (d, J = 6.9 Hz, 6H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 123.2, 77.5, 76.3, 44.1, 36.2, 35.4, 30.1, 28.6, 25.5, 25.4, 22.9, 19.7, 19.5, 19.0; IR (Neat Film NaCl) 2961, 2930, 2869, 1709, 1454, 1368, 1022, 964, 828 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{15}H_{24}O$ $[M+\bullet]^+$: 220.1827, found 220.1820; $[\alpha]_D^{25.0}$ –50.57 (c 1.25, $CHCl_3$, 88% ee).



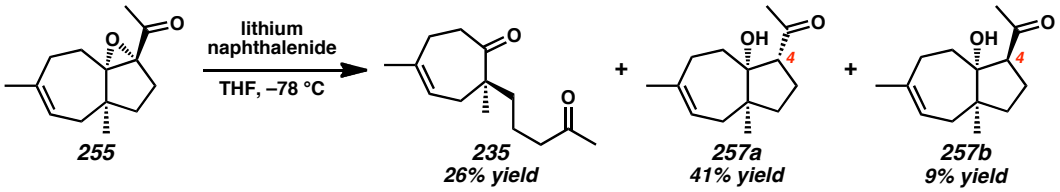
256 ***(–)-epoxydaucenal B (144b)***
12 steps, 20% yield

(–)-Epoxydaucenal B (144b). Adapted from a procedure by Wood.[40] A 20 mL scintillation vial equipped with a stir bar and epoxide **256** (10.8 mg, 0.0490 mmol, 1.00 equiv) was connected to an Ar-filled manifold and flushed with Ar. The vial was charged

with THF (5.13 mL) and premixed selenium dioxide (10.9 mg, 0.0982 mmol, 2.00 equiv) and silica gel (117.8 mg, 1.96 mmol, 40.0 equiv). The vial was rinsed with THF (1 mL, total added = 6.13 mL, 0.008 M), sealed with a teflon cap, and lowered into a preheated sand bath (80 °C). After 30 min, starting material persisted by TLC analysis, so the vial was resealed and lowered back into the sand bath. After an additional 15 min, no starting material remained by TLC analysis. Consequently, the reaction was filtered through a short celite pad rinsing with Et_2O and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 26 x 1.5 cm, 100% hexanes$\rightarrow$2%$\rightarrow$5%$\rightarrow$10% TBME in hexanes) to afford epoxydaucenal B (**144b**, 10.0 mg, 0.0427 mmol, 87% yield) as a yellow oil; R_f = 0.58 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 9.22 (s, 1H), 6.03 (dddd, J = 8.7, 5.1, 2.2, 1.2 Hz, 1H), 3.11–3.03 (m, 1H), 1.85 (ddtd, J = 14.0, 5.1, 1.5, 0.8 Hz, 1H), 1.69–1.60 (m, 1H), 1.62–1.52 (m, 3H), 1.51 (sept, J = 7.0 Hz, 1H), 1.44–1.40 (m, 1H), 1.41–1.33 (m, 2H), 1.03 (d, J = 6.8 Hz, 3H), 0.96–0.86 (m, 1H), 0.83 (s, 3H), 0.77 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 191.9, 152.5, 146.3, 75.7, 75.1, 44.3, 37.1, 35.7, 28.5, 25.4, 22.9, 20.1, 19.8, 19.6, 19.0; IR (Neat Film NaCl) 2961, 2931, 2869, 1687, 1683, 1644, 1455, 1444, 1378, 1229, 1149, 1023, 1003, 965, 876 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{15}H_{22}O_2$ $[M+\bullet]^+$: 234.1620, found 234.1630; $[\alpha]_D^{25.0}$ –20.52 (c 1.00, $CHCl_3$, 88% ee).



Enone 223. A flame-dried 10 mL round-bottom flask equipped with a stir bar was cycled into a glove box where the flask was loaded with lithium chloride (77.0 mg, 1.82 mmol, 8.59 equiv). The flask was removed from the glove box and connected to an Ar-filled manifold. Epoxide **255** (46.6 mg, 0.212 mmol, 1.00 equiv) was transferred to the flask using several THF rinses (60 min Ar sparge before use, 1 x 0.6 mL + 3 x 0.5 mL, total added = 2.1 mL, 0.1 M), *t*-BuOH (20 μL, 0.209 mmol, 0.99 equiv) was added, and the flask was lowered into a –78 °C bath (dry ice/acetone). A samarium diiodide solution[51] (0.1 M in THF, 4.5 mL, 0.450 mmol, 2.13 equiv) was added dropwise over 5 min down the side of the flask, generating a dark blue solution. TLC analysis indicated that no starting material remained after 8 min. Consequently, the reaction was quenched with sat. NH_4Cl solution (2 mL), allowed to warm to room temperature, and transferred to a separatory funnel where the aqueous layer was extracted four times with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (SiO_2, 26 x 1.5 cm, 100% hexanes→5%→10%→15%→30%→50% TBME in hexanes) to afford enone **223** (41.5 mg, 0.203 mmol, 96% yield) as a yellow oil. (For characterization data, see p. 745).

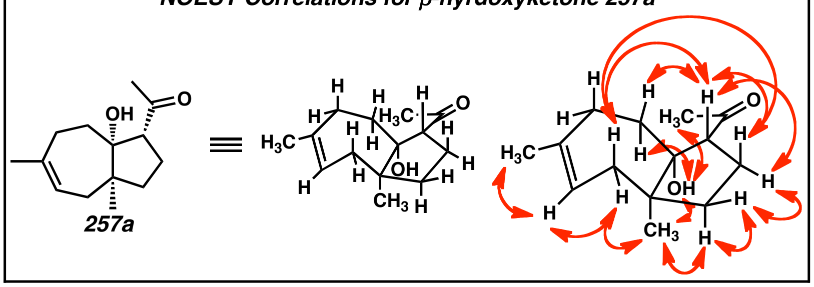


β-hydroxyketone 257a and b. Procedure adapted from report by Liu.[49] A flame-dried 15 mL round-bottom flask equipped with a glass stir bar and ketoepoxide **255** (50.2 mg, 0.228 mmol, 1.00 equiv) was charged with THF (2.3 mL, 0.1 M) and lowered into a –78 °C bath (acetone/dry ice). A lithium naphthalenide solution[50] (1.0 M, 680 μL, 0.680 mmol, 2.98 equiv) was added dropwise and the reaction mixture turned dark green. Over the course of the reaction, an additional portion of lithium naphthalenide was added (680 μL at 1.5 h, 3 h, 4.5 h, total added = 2.72 mL, 2.72 mmol, 11.9 equiv). After 9 h, the reaction was quenched with H_2O and allowed to warm to room temperature. The reaction was transferred to a separatory funnel where the aqueous layer was extracted six times with CH_2Cl_2. The combined organics (50 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 28 x 1.5 cm, 100% hexanes→2%→5%→10%→20%→40% TBME in hexanes) to afford dione **235** (13.1 mg, 0.0588 mmol, 26% yield), β-hydroxyketone **257a** (20.7 mg, 0.0933 mmol, 41% yield) as a yellow oil, and β-hydroxyketone **257b** (4.6 mg, 0.0206 mmol, 9% yield) as a yellow oil. (For characterization data of dione **235**, see p. 746).

β-hydroxyketone 257a. R_f = 0.57 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.34 (ddt, J = 8.5, 4.5, 1.5 Hz, 1H), 3.95 (s, 1H), 2.77 (dd, J = 10.2, 9.1 Hz, 1H), 2.00

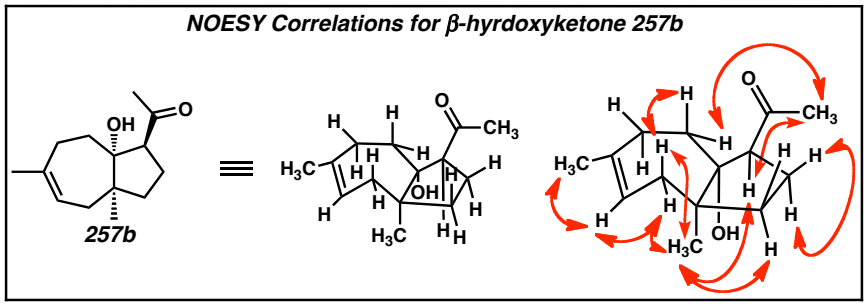
(dddd, J = 12.2, 3.4, 1.7, 0.9 Hz, 1H), 1.96 (dt, J = 8.6, 1.6 Hz, 1H), 1.90 (ddd, J = 12.3, 10.1, 5.1 Hz, 1H), 1.87–1.74 (m, 3H), 1.69 (ddd, J = 14.4, 10.7, 1.9 Hz, 1H), 1.68 (s, 3H), 1.63 (t, J = 1.7 Hz, 3H), 1.53 (ddd, J = 17.5, 12.4, 5.1 Hz, 1H), 1.57–1.47 (m, 1H), 1.24–1.15 (m, 1H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 212.8, 139.5, 122.6, 84.1, 56.3, 48.7, 40.4, 38.3, 34.2, 31.0, 29.4, 25.4, 25.3, 20.5; IR (Neat Film NaCl) 3479, 2959, 2925, 2853, 1694, 1446, 1394, 1362, 1307, 1260, 1243, 1175, 1105, 1077, 1051, 1010, 832 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{23}O_2$ [M+H]$^+$: 223.1693, found 223.1692; $[\alpha]_D^{25.0}$ –193.24 (c 0.57, $CHCl_3$, 88% ee).

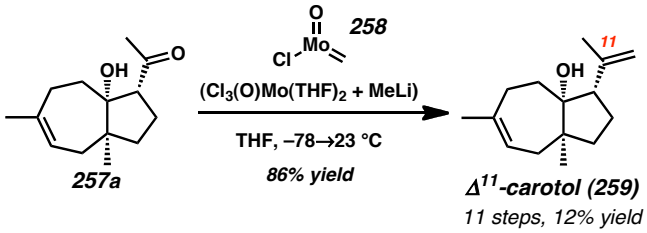
NOESY Correlations for β-hyrdoxyketone 257a



β-hydroxyketone 257b. R_f = 0.36 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.21 (dddd, J = 8.6, 6.4, 3.2, 1.6 Hz, 1H), 2.83 (t, J = 9.6 Hz, 1H), 2.24 (br t, J = 14.2 Hz, 1H), 2.18 (dddd, J = 13.7, 10.5, 9.7, 5.4 Hz, 1H), 2.04 (dd, J = 15.1, 6.4 Hz, 1H), 1.98 (s, 3H), 1.85 (dd, J = 15.0, 7.4 Hz, 1H), 1.69–1.57 (m, 4H), 1.53 (dt, J = 1.7, 0.8 Hz, 3H), 1.45 (dtd, J = 13.7, 9.4, 6.1 Hz, 1H), 1.26 (ddd, J = 14.9, 6.5, 2.6 Hz, 1H), 1.15 (ddd, J = 13.0, 9.3, 5.4 Hz, 1H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 208.2, 140.4, 122.2, 84.2, 62.7, 47.5, 35.6, 34.2, 31.5, 31.1, 28.1, 25.2, 24.8, 20.6; IR (Neat Film NaCl) 3501, 2962, 2927, 2874, 1694, 1457, 1363, 1213, 1069, 1027, 833, 819 cm^{-1}; HRMS (EI+) *m/z*

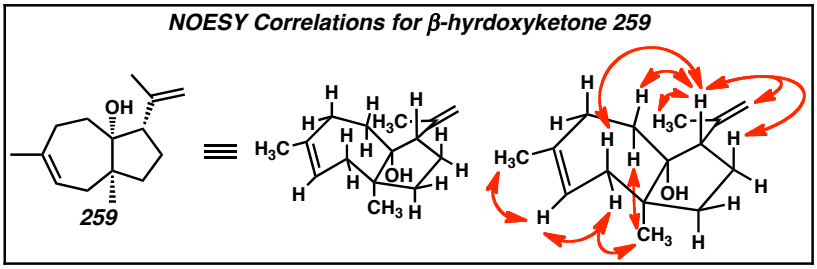
calc'd for $C_{14}H_{22}O_2$ $[M+\bullet]^+$: 222.1620, found 222.1623; $[\alpha]_D^{25.0}$ 67.43 (c 0.46, $CHCl_3$, 88% ee).



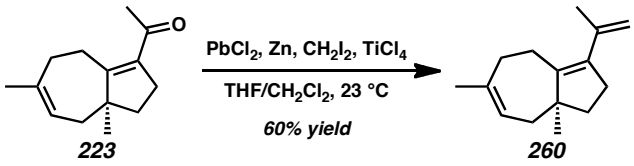


Δ^{11}-carotol (259). A flame-dried 25 mL round-bottom flask equipped with a stir bar was cycled into a glove box, loaded with oxotrischlorobis(tetrahydrofuran)molybdenum(V)[42] (139.0 mg, 0.383 mmol, 4.11 equiv), removed from the glove box, and connected to an Ar-filled manifold. The flask was charged with THF (2 mL) and lowered into a –78 °C bath (dry ice/acetone). Methyllithium (1.58 M in Et_2O, 240 µL, 0.379 mmol, 4.06 equiv) was added dropwise to the flask causing the reaction mixture to transition from a bright green solution to a dark red/purple solution. After 1 h, β-hydroxyketone **257a** (20.7 mg, 0.0933 mmol, 1.00 equiv) was transferred to the flask via cannula using several THF rinses (2 x 1.5 mL + 1 mL, total added = 6 mL), and the bath was allowed to expire over time. After 29 h, starting material persisted by TLC analysis. Consequently, an additional solution (1 h prestir at –78 °C) of oxotrischlorobis(tetrahydrofuran)-

molybdenum(V) (138.7 mg, 0.383 mmol, 4.10 equiv) and methyllithium (1.58 M in Et_2O, 240 μL, 0.275 mmol, 1.25 equiv) in THF (1 mL) was prepared and transferred via cannula to the 25 mL flask at –78 °C. The bath was once again allowed to expire over time. As starting material was still observed by TLC analysis after 40 h and 53 h, two additional solutions (*vide supra*) were prepared at –78 °C and transferred via cannula to the 25 mL flask at these times ($Cl_3(O)Mo(THF)_2$ total added = 556.1 mg, 1.52 mmol, 16.4 equiv; MeLi total added = 0.96 mL, 1.52 mmol, 16.3 equiv; THF total added = 9 mL). After 65 h, starting material was completely consumed by TLC analysis. The reaction was subsequently quenched with water (5 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with Et_2O. The combined organics (50 mL) were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 25.5 x 1.5 cm, 100% hexanes→2% TBME in hexanes) to afford Δ^{11}-carotol (**259**, 17.6 mg, 0.0799 mmol, 86% yield) as a yellow oil; R_f = 0.75 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.32 (ddp, J = 8.8, 4.5, 1.5 Hz, 1H), 5.04 (p, J = 1.5 Hz, 1H), 4.86 (dq, J = 1.7, 0.9 Hz, 1H), 2.77 (dd, J = 11.0, 7.7 Hz, 1H), 2.32 (ddd, J = 15.7, 4.3, 2.1 Hz, 1H), 2.18–2.01 (m, 2H), 1.84 (dd, J = 1.5, 0.8 Hz, 3H), 1.87–1.75 (m, 2H), 1.76–1.62 (m, 3H), 1.69 (t, J = 1.7 Hz, 3H), 1.51 (ddd, J = 14.2, 9.1, 2.5 Hz, 1H), 1.47 (br s, 1H), 1.35 (dd, J = 12.3, 8.0 Hz, 1H), 1.01 (d, J = 0.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.8, 139.0, 122.2, 113.3, 83.2, 53.4, 48.3, 40.4, 39.3, 34.6, 29.5, 26.8, 25.4, 25.2, 21.9; IR (Neat Film NaCl) 3545, 3069, 2963, 2924, 2867, 1636, 1448, 1374, 1006, 898, 825 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{24}O$ $[M+\bullet]^+$: 220.1827, found 220.1834; $[\alpha]_D^{25.0}$ 17.49 (c 1.05, $CHCl_3$, 88% ee).

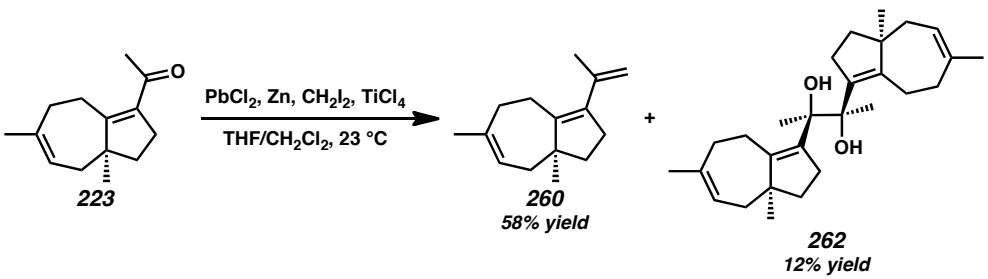


3.5.2.6 Synthesis of (–)-Daucene (142), (+)-Daucenal (143), and (+)-14-p-Anisoyloxydauc-4,8-diene (145)



Triene 260. A flame-dried two-neck 25 mL round-bottom flask equipped with a stir bar and water condenser was loaded with lead(II) chloride (20.6 mg, 0.0740 mmol, 0.16 equiv) and zinc dust (437.5 mg, 6.69 mmol, 14.4 equiv) and backfilled with argon. The flask was charged with THF (6.5 mL) and diiodomethane (300 μL, 3.72 mmol, 8.02 equiv) and lowered into a preheated oil bath (70 °C). After 15 min, the bath was removed, the reaction was cooled to room temperature over 15 min and then lowered into a 0 °C bath (ice/water). Premixed titanium(IV) chloride (100 μL, 0.912 mmol, 1.96 equiv) and CH_2Cl_2 (830 μL) were added quickly, the bath was removed, and the reaction was allowed to warm to room temperature. After 1 h, enone **223** (94.9 mg, 0.464 mmol, 1.00 equiv) was transferred to the flask via cannula using several THF rinses (3 x 1 mL, total added = 9.5 mL, 0.05 M). No starting material remained after 1.5 h by TLC analysis, so the reaction was quenched with a sat. $NaHCO_3$ solution (10 mL) and filtered

through a celite plug into a separatory funnel rinsing with Et_2O. The aqueous layer was extracted four times with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 28 x 1.5 cm, 100% hexanes) to afford triene **260** (56.5 mg, 0.279 mmol, 60% yield) as a pale yellow oil; R_f = 0.73 (0.3% Et_2O in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (ddp, J = 7.4, 5.9, 1.5 Hz, 1H), 4.90 (dq, J = 2.9, 1.5 Hz, 1H), 4.71 (dq, J = 2.5, 0.8 Hz, 1H), 2.65 (ddd, J = 13.8, 5.1, 3.6 Hz, 1H), 2.40 (dtd, J = 15.2, 8.3, 2.9 Hz, 1H), 2.29 (dddd, J = 15.4, 7.4, 4.7, 1.3 Hz, 1H), 2.11–2.04 (m, 3H), 2.01 (dd, J = 13.9, 7.6 Hz, 1H), 1.92 (ddddd, J = 16.7, 10.6, 4.7, 2.9, 1.4 Hz, 1H), 1.85 (dd, J = 1.5, 0.8 Hz, 3H), 1.74 (t, J = 1.5 Hz, 3H), 1.64–1.60 (m, 2H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.4, 142.6, 139.9, 135.2, 122.4, 112.8, 50.5, 40.1, 38.4, 33.7, 32.6, 26.1, 23.7, 23.6, 22.8; IR (Neat Film NaCl) 3078, 2962, 2924, 2846, 1627, 1443, 1368, 891, 829 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{15}H_{22}$ $[M+\bullet]^+$: 202.1721, found 202.1703; $[\alpha]_D^{25.0}$ –76.62 (c 0.94, $CHCl_3$, 88% ee).



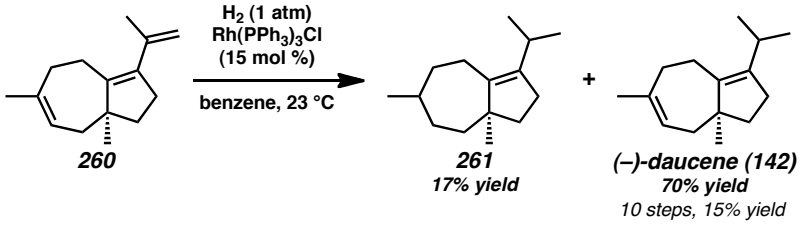
Triene 260 and Diol 262. A flame-dried two-neck 50 mL round-bottom flask equipped with a stir bar and water condenser was loaded with lead(II) chloride (30.9 mg, 0.111 mmol, 0.16 equiv) and zinc dust (640.0 mg, 9.79 mmol, 14.4 equiv) and backfilled with argon. The flask was charged with THF (10 mL) and diiodomethane (440 µL, 5.46

mmol, 8.04 equiv) and lowered into a preheated oil bath (80 °C). After 20 min, the bath was removed, the reaction was cooled to room temperature over 10 min, and then lowered into a 0 °C bath (ice/water). Premixed titanium(IV) chloride (150 μL, 1.37 mmol, 2.01 equiv) and dichloromethane (1.22 mL) were added quickly, the bath was removed, and the reaction was allowed to warm to room temperature. After 50 min, enone **223** (138.9 mg, 0.680 mmol, 1.00 equiv) was transferred to the flask via cannula using several THF rinses (1 x 1.6 mL + 2 x 1 mL, total added = 13.6 mL, 0.05 M). TLC analysis indicated no starting material remained after 1.5 h. Consequently, the reaction was quenched with a sat. aq $NaHCO_3$ (13 mL) and filtered through a celite plug into a separatory funnel rinsing with Et_2O. The aqueous layer was extracted four times with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 29 x 1.5 cm, 100% hexanes) to afford triene **260** (79.9 mg, 0.395 mmol, 58% yield) as a pale yellow oil, diol **262** (15.3 mg, 0.03735 mmol, 12% yield) as a white solid, and several other polar organics.

Triene 260. For characterization data, see p. 768.

Diol 262. R_f = 0.57 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42 (ddt, J = 7.5, 4.5, 1.3 Hz, 2H), 3.30–3.20 (m, 2H), 2.36 (dddd, J = 15.6, 10.5, 7.5, 3.1 Hz, 2H), 2.17–2.00 (m, 12H), 1.98 (dd, J = 14.3, 7.5 Hz, 2H), 1.73 (t, J = 1.3 Hz, 6H), 1.52 (ddd, J = 12.0, 7.5, 1.7 Hz, 2H), 1.46 (ddd, J = 12.1, 10.3, 8.4 Hz, 2H), 1.40 (s, 6H), 0.93 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 140.4, 135.7, 122.2, 80.2, 50.1, 40.0, 38.4, 33.2,

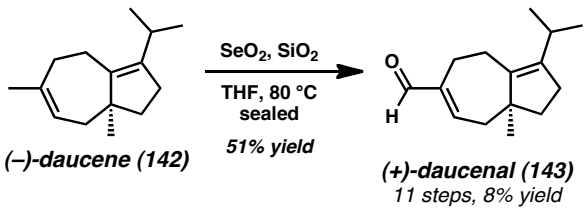
31.9, 25.5, 25.5, 24.1, 23.1; IR (Neat Film NaCl) 3339, 2965, 2942, 2924, 2849, 1439, 1368, 1184, 1097, 1057, 977, 914, 828 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{28}H_{41}O$ $[M–OH]^+$: 393.3152, found 393.3029; $[\alpha]_D^{25.0}$ –58.15 (c 1.53, $CHCl_3$, 88% ee).



(–)-Daucene (142). A flame-dried 25 mL round-bottom flask equipped with a stir bar was cycled into a glove box and loaded with Wilkinson's catalyst (48.0 mg, 0.0519 mmol, 15.0 mol %). The flask was removed from the glove box, connected to an Ar-filled manifold, and charged with benzene (30 min Ar sparge before use, 3 mL). Triene **260** (70.0 mg, 0.346 mmol, 1.00 equiv) was transferred to the flask via cannula using several benzene rinses (1 x 2.5 mL + 3 x 2 mL, total added = 11.5 mL, 0.03 M). The flask was disconnected from the manifold, connected to a hydrogen balloon, and flushed with hydrogen, generating an orange solution. After 8 h, minimal starting material remained by TLC, so the stir bar was removed and rinsed with CH_2Cl_2 and the reaction was concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was loaded onto a silica gel column[52] using hexanes and minimal CH_2Cl_2 and purified by flash column chromatography (SiO_2, 27.5 x 2 cm, 100% hexanes) to afford alkene **261** (11.9 mg, 0.0576 mmol, 17% yield) as a clear colorless oil and daucene (**142**, 49.5 mg, 0.242 mmol, 70% yield) as a clear colorless oil.

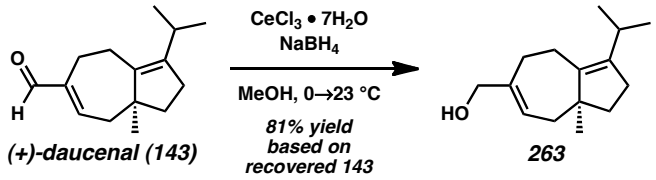
Alkene 261. R_f = 0.92 (0.3% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) mixture of two diastereomers, see Figure SI-19A; IR (Neat Film NaCl) 2955, 2923, 2856, 1457, 1379, 1369, 1360 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{15}H_{26}$ $[M+\bullet]^+$: 206.2034, found 206.2040.

(–)-Daucene (142). R_f = 0.84 (0.3% Et_2O in hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 5.42 (ddt, J = 9.2, 5.6, 1.5 Hz, 1H), 2.66 (sept, J = 6.8 Hz, 1H), 2.44–2.36 (m, 1H), 2.17 (ddt, J = 8.7, 6.7, 2.2 Hz, 2H), 2.08–2.03 (m, 1H), 2.05–1.99 (m, 2H), 1.94 (dd, J = 14.1, 7.8 Hz, 1H), 1.86–1.78 (m, 1H), 1.74 (t, J = 1.6 Hz, 3H), 1.62–1.48 (m, 2H), 0.98 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H), 0.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.0, 139.9, 138.8, 122.8, 49.7, 40.5, 38.7, 33.7, 27.3, 26.6, 26.1, 23.7, 22.7, 22.0, 21.4; IR (Neat Film NaCl) 2959, 2932, 2845, 1444, 1366, 1330, 1303, 1202, 828 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{15}H_{24}$ $[M+\bullet]^+$: 204.1878, found 204.1878; $[\alpha]_D^{25.0}$ –24.95 (c 1.37, $CHCl_3$, 86% ee).



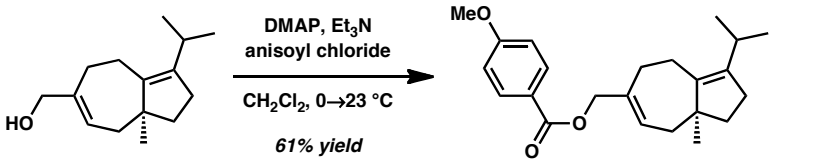
(+)-Daucenal (143). Adapted from a procedure by Wood.[40] A 20 mL scintillation vial equipped with a stir bar and daucene (**142**, 9.6 mg, 0.047 mmol, 1.00 equiv) was connected to an Ar-filled manifold and flushed with Ar. The vial was charged with THF (4.87 mL) and premixed selenium dioxide (10.4 mg, 0.0937 mmol, 2.00 equiv) and silica gel (113.9 mg, 1.896 mmol, 40.4 equiv). The vial was sealed with a teflon cap and

lowered into a preheated sand bath (80 °C). After 20 min, starting material persisted by TLC analysis, so the vial was resealed and lowered back into the sand bath. After an additional 10 min, no starting material remained by TLC analysis. Consequently, the reaction was filtered through a short celite pad rinsing with Et_2O and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 27.5 x 1.5 cm, 100% hexanes→5%→10%→ 20% TBME in hexanes) to afford daucenal (**143**, 5.2 mg, 0.0238 mmol, 51% yield) as a yellow oil; R_f = 0.77 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (d, J = 1.1 Hz, 1H), 6.10 (dddd, J = 8.4, 5.2, 2.0, 1.1 Hz, 1H), 3.05 (ddd, J = 15.2, 5.4, 2.7 Hz, 1H), 2.51 (sept, J = 6.7 Hz, 1H), 2.33 (ddd, J = 14.1, 5.5, 3.1 Hz, 1H), 2.13 (ddd, J = 8.5, 5.1, 1.9 Hz, 2H), 2.05 (dd, J = 14.3, 5.2 Hz, 1H), 1.94 (ddd, J = 14.3, 8.2, 1.1 Hz, 1H), 1.76 (br tdd, J = 14.2, 3.4, 1.6 Hz, 1H), 1.62 (br ddt, J = 14.5, 10.1, 2.4 Hz, 1H), 1.55 (dtd, J = 12.6, 6.8, 1.2 Hz, 1H), 1.47 (dtd, J = 12.4, 7.7, 1.1 Hz, 1H), 0.90 (dd, J = 6.9, 1.1 Hz, 3H), 0.88 (dd, J = 6.9, 1.1 Hz, 3H), 0.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 152.8, 146.8, 141.0, 140.3, 49.8, 41.7, 39.2, 27.4, 26.7, 24.2, 24.0, 22.4, 21.9, 21.3; IR (Neat Film NaCl) 2956, 2930, 2863, 1685, 1636, 1453, 1378, 1245, 1144, 929 cm^{-1}; HRMS (GC-EI+) *m/z* calc'd for $C_{15}H_{22}O$ $[M+\bullet]^+$: 218.1671, found 218.1680; $[\alpha]_D^{25.0}$ 33.65 (c 0.50, $CHCl_3$, 86% ee).



Allylic Alcohol 263. A 20 mL scintillation vial equipped with a stir bar and daucenal (**143**, 10.2 mg, 0.0467 mmol, 1.00 equiv) was connected to an Ar-filled manifold and flushed with Ar. The vial was charged with MeOH (930 μL) and cerium chloride heptahydrate (20.9 mg, 0.0561 mmol, 1.20 equiv). After 10 min of stirring, the cerium chloride heptahydrate had dissolved, generating a yellow solution. The vial was subsequently lowered into a 0 °C bath (ice/water) and sodium borohydride (4.1 mg, 0.108 mmol, 2.32 equiv) was added. The bath was allowed to expire over time. Additional sodium borohydride (35 min = 11.9 mg, 2 h 25 min = 12.3 mg, 6 h = 12.9 mg, 8 h = 50.2 mg; total added = 91.5 mg, 2.42 mmol, 51.8 equiv) and cerium chloride heptahydrate (8 h = 22.7 mg; total added = 43.6 mg, 0.117 mmol, 2.51 equiv) were added. After 20 h, the reaction was quenched with a sat. NH_4Cl solution (5 mL) and transferred to a separatory funnel where the aqueous layer was extracted four times with Et_2O. The combined organics were rinsed with 5% w/w HCl (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure at 0 °C (ice/water). The resulting crude oil was purified by flash column chromatography (SiO_2, 29 x 1.5 cm, 100% hexanes→5%→10%→20% TBME in hexanes) to afford recovered daucenal (**143**, 3.4 mg, 0.0156 mmol, 33% recovered) and alcohol **263** (5.6 mg, 0.0253 mmol, 54% yield, 81% yield based on recovered **143**) as a yellow oil; R_f = 0.42 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (ddtd, J = 8.0, 5.2, 2.0, 0.9 Hz, 1H), 4.03 (t, J = 1.5 Hz, 2H), 2.68 (sept, J = 6.8 Hz, 1H), 2.48 (ddd, J = 13.9, 5.7, 2.9 Hz, 1H), 2.22–2.16 (m,

4H), 2.14 (dd, J = 14.1, 5.3 Hz, 1H), 2.04 (dd, J = 14.1, 8.0 Hz, 1H), 2.05–1.95 (m, 1H), 1.86–1.77 (m, 1H), 1.62 (dt, J = 12.3, 6.2 Hz, 1H), 1.55 (dt, J = 12.3, 8.2 Hz, 1H), 0.98 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 141.6, 139.4, 124.7, 68.9, 49.4, 40.4, 38.8, 29.6, 27.3, 26.6, 23.8, 23.2, 22.0, 21.3; IR (Neat Film NaCl) 3325, 2957, 2930, 2859, 1710, 1455, 1380, 1367, 1360, 1261, 1055, 997, 841, 803 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{24}O$ $[M+\bullet]^+$: 220.1827, found 220.1830; $[\alpha]_D^{25.0}$ –13.28 (c 0.56, $CHCl_3$, 86% ee).



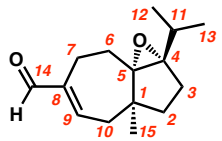
263 ***(+)-14-p-anisoyloxydauc-4,8-diene (145)***
13 steps, 4% yield

14-*p*-Anisoyloxydauc-4,8-diene (145). A scintillation vial equipped with allylic alcohol **263** (5.6 mg, 0.0253 mmol, 1.00 equiv), a stir bar, and a Teflon cap was flushed with Ar and connected to an Ar-filled manifold. The vial was charged with CH_2Cl_2 (2 mL, 0.01 M) and lowered into a 0 °C bath (ice/water). DMAP (0.5 mg, 0.0041 mmol, 16 mol %), Et_3N (10 μL, 0.072 mmol, 2.8 equiv), and *p*-anisoyl chloride (10 μL, 0.074 mmol, 2.9 equiv) were added to the vial and the bath was allowed to expire over time. TLC analysis indicated starting material remained after 4 h, so additional Et_3N (10 μL, total added = 20 μL, 0.14 mmol, 5.7 equiv) and *p*-anisoyl chloride (10 μL, total added = 20 μL, 0.15 mmol, 5.8 equiv) were added. TLC analysis indicated no residual starting material after 18 h, so the reaction was loaded directly onto a column, and the crude material was purified by flash column chromatography (SiO_2, 28.5 x 2 cm, 100% hexanes→2% TBME

in hexanes) to afford 14-p-anisoyloxydauc-4,8-diene (**145**, 5.5 mg, 0.0155 mmol, 61% yield) as a yellow oil that solidified upon freezing; R_f = 0.70 (30% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (dm, J = 8.9 Hz, 2H), 6.92 (dm, J = 8.9 Hz, 2H), 5.85 (ddp, J = 7.3, 5.0, 1.1 Hz, 1H), 4.70 (d, J = 1.1 Hz, 2H), 3.86 (s, 3H), 2.67 (sept, J = 6.9 Hz, 1H), 2.49 (ddd, J = 13.9, 5.7, 2.8 Hz, 1H), 2.25 (ddd, J = 14.6, 5.8, 2.8 Hz, 1H), 2.19 (ddd, J = 8.2, 6.0, 2.2 Hz, 2H), 2.20–2.14 (m, 1H), 2.07 (dd, J = 14.1, 8.1 Hz, 1H), 2.07 (tm, J = 13.5 Hz, 1H), 1.88 (dddd, J = 14.6, 12.3, 5.0, 2.5 Hz, 1H), 1.64 (dt, J = 12.3, 6.1 Hz, 1H), 1.56 (dt, J = 12.4, 8.3 Hz, 1H), 0.98 (d, J = 6.9 Hz, 3H), 0.95 (s, 3H), 0.93 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 163.4, 141.5, 139.5, 138.6, 131.8, 128.4, 123.0, 113.7, 70.3, 55.6, 49.4, 40.5, 38.8, 29.9, 27.3, 26.6, 23.8, 23.0, 22.0, 21.3; IR (Neat Film NaCl) 2956, 2928, 2854, 1716, 1607, 1582, 1456, 1421, 1368, 1315, 1271, 1256, 1167, 1100, 1032, 846, 770 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{23}H_{30}O_3$ $[M+\bullet]^+$: 354.2195, found 354.2193; $[\alpha]_D^{25.0}$ 2.27 (c 0.55, $CHCl_3$, 86% ee).

3.5.3 Comparison of Data for Synthetic and Reported Natural Products

Spectral data for synthetic (–)-epoxydaucenal B (**144b**), (–)-daucene (**142**), (+)-daucenal (**143**), and (+)-14-*p*-anisoyloxydauc-4,8-diene (**145**) (^{1}H NMR, ^{13}C NMR, $[\alpha]_D^T$) were compared with available reported spectral data for either natural or synthetic samples. Tables comparing compound data are shown in Tables 3.2–3.9.

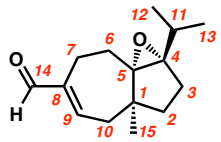


(–)-epoxydaucenal B (144b)

*Table 3.2. Comparison of ^{1}H NMR data for synthetic and natural epoxydaucenal B (**144b**).[a–b]*

Assignment	Synthetic 144b (ppm)[c]	Multiplicity, *J* (Hz)	Natural[13] 144b (ppm)[d]	Multiplicity, *J* (Hz)
C1	—	—	—	—
C2	1.41–1.33	m		
	0.96–0.86	m		
C3	1.69–1.60	m		
	1.41–1.33	m		
C4	—	—	—	—
C5	—	—	—	—
C6	1.62–1.52	m		
	1.44–1.40	m		
C7	3.11–3.03	m	3.068	m
	1.62–1.52	m		
C8	—	—	—	—
C9	6.03	dddd, 8.7, 5.1, 2.2, 1.2	6.028	m
C10	1.85	ddtd, 14.0, 5.1, 1.5, 0.8	1.840	dd, 14.1, 5.0
	1.62–1.52	m		
C11	1.51	sept, 7.0	1.522	sept, 6.9
C12	1.03	d, 6.8	1.028	d, 6.9
C13	0.77	d, 7.0	0.763	d, 6.9
C14	9.22	s	9.211	s
C15	0.83	s	0.828	s

[a] See Figure 5.16.1 for ^{1}H NMR spectra. [b] Blank spaces in table represent neglected or unreported signals. [c] ^{1}H NMR spectra was obtained at 500 MHz in C_6D_6 and standardized to residual C_6H_6. [d] ^{1}H NMR spectra was obtained at 500 MHz in C_6D_6 and standardized to TMS.

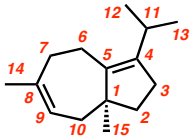


(–)-epoxydaucenal B (144b)

*Table 3.3. Comparison of ^{13}C NMR data for synthetic and natural epoxydaucenal B (**144b**).*[a]

Assignment	**Synthetic 144b** (ppm)[b]	**Natural**[13] **144b** (ppm)[c]
C1	44.3	44.2
C2	35.7	35.7
C3	22.9	22.8[d]
C4	75.1	75.0
C5	75.7	75.7
C6	25.4	25.4[d]
C7	20.1	20.1
C8	146.3	146.3
C9	152.5	152.3
C10	37.1	37.1
C11	28.5	28.5
C12	19.0	18.9[e]
C13	19.6	19.5[e]
C14	191.9	191.8
C15	19.8	19.7

[a] See Figure 5.16.3 for ^{13}C NMR spectra. [b] ^{13}C NMR spectra was obtained at 125 MHz in C_6D_6 and standardized to residual C_6H_6. [c] ^{13}C NMR spectra was obtained at 125 MHz in C_6D_6 and standardized to TMS. [d] C(3) and C(6) were misassigned, see HSQC spectra, Figure SI-14D. [e] C(12) and C(13) were misassigned, see HSQC spectra, Figure 5.16.4.

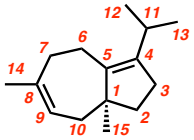


(–)-daucene (142)

*Table 3.4, Part 1. Comparison of ^{1}H NMR Data for synthetic and reported[53] daucene (**142**).[a–b]*

Assignment	**Synthetic 142** (ppm)[b]	**Multiplicity, *J*** (Hz)	**Little[27] 142** (ppm)[d]	**Multiplicity, *J*** (Hz)	**Seto[25] 142** (ppm)[e]	**Multiplicity, *J*** (Hz)
C1	—	—	—	—	—	—
C2	1.59	ddd, 11.9, 6.7, 5.1	1.65–1.48[f]	m		
	1.52	dt, 12.2, 8.5				
C3	2.17	ddt, 8.7, 6.7, 2.2	2.21–2.12	m		
C4	—	—	—	—	—	—
C5	—	—	—	—	—	—
C6	2.44–2.36	m	2.39	m		
	1.86–1.78	m	1.81	m		
C7	2.05–1.99	m	2.05–1.90	m		
C8	—	—	—	—	—	—
C9	5.42	ddt, 9.2, 5.6, 1.5	5.42	m	5.43	br t, 6.6
C10	2.08–2.03	m	2.05–1.90	m		
	1.94	dd, 14.1, 7.8				
C11	2.66	sept, 6.8	2.66	sept, 6.75	2.67	sept, 6.8
C12	0.98	d, 6.9	0.98	d, 6.75	0.98	d, 6.8
C13	0.92	d, 6.9	0.93	d, 6.75	0.92	d, 6.8
C14	1.74	t, 1.6	1.74	s	1.74	br s
C15	0.91	s	0.91	s	0.91	s

[a] See Figure 5.22.1 for ^{1}H NMR spectra. [b] Blank spaces in table represent neglected or unreported signals. [c] ^{1}H NMR spectra was obtained at 500 MHz in $CDCl_3$ and standardized to residual $CHCl_3$. [d] ^{1}H NMR spectra was obtained at 400 MHz in $CDCl_3$ and standardized to residual $CHCl_3$. [e] ^{1}H NMR was obtained in $CDCl_3$ at unknown MHz. [f] Little reports this signal as 3H, however HSQC data indicates only 2H for this range (see Figure 5.22.4).

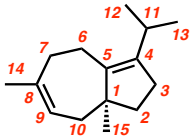


(–)-daucene (142)

*Table 3.4, Part 2. Comparison of ^{1}H NMR Data for synthetic and reported[53] daucene (**2**).[a–b]*

Assignment	Synthetic **142** (ppm)[b]	Multiplicity, ***J*** (Hz)	Yamasaki[22] **142** (ppm)[e]	Multiplicity, ***J*** (Hz)	Naegeli[21] **142** (ppm)[e]	Multiplicity, ***J*** (Hz)
C1	—	—	—	—	—	—
C2	1.59	ddd, 11.9, 6.7, 5.1				
	1.52	dt, 12.2, 8.5				
C3	2.17	ddt, 8.7, 6.7, 2.2				
C4	—	—	—	—	—	—
C5	—	—	—	—	—	—
C6	2.44–2.36	m				
	1.86–1.78	m				
C7	2.05–1.99	m				
C8	—	—	—	—	—	—
C9	5.42	ddt, 9.2, 5.6, 1.5	5.37	t, 5	5.44	t, 6.5
C10	2.08–2.03	m				
	1.94	dd, 14.1, 7.8				
C11	2.66	sept, 6.8				
C12	0.98	d, 6.9	0.99	d, 5	1.00	d, 6.5
C13	0.92	d, 6.9	0.92	d, 5	0.92	d, 6.5
C14	1.74	t, 1.6	1.73	s	1.75	br s
C15	0.91	s	0.94	s	0.91	s

[a] See Figure 5.22.1 for ^{1}H NMR spectra. [b] Blank spaces in table represent neglected or unreported signals. [c] ^{1}H NMR spectra was obtained at 500 MHz in $CDCl_3$ and standardized to residual $CHCl_3$. [d] ^{1}H NMR spectra was obtained at 400 MHz in $CDCl_3$ and standardized to residual $CHCl_3$. [e] ^{1}H NMR was obtained in $CDCl_3$ at unknown MHz.

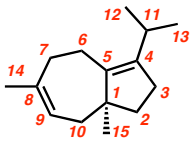


(–)-daucene (142)

*Table 3.5. Comparison of ^{13}C NMR data for synthetic and reported daucene (**142**).*[a]

Assignment	**Synthetic 142** (ppm)[b]	**Little[27] 142** (ppm)[c]	**Seto[25] 142** (ppm)[d]
C1	49.7	49.7	49.7
C2	38.7	38.7	38.7
C3	27.3	27.3	27.3
C4	138.8	138.9	138.8
C5	142.0	142.1	142.0
C6	22.7	22.7	22.6
C7	33.7	33.7	33.6
C8	139.9	140.0	139.7
C9	122.8	122.9	122.8
C10	40.5	40.6	40.5
C11	26.6	26.6	26.5
C12	22.0	22.1	21.9
C13	21.4	21.4	21.2
C14	26.1	26.2	25.9
C15	23.7	23.7	23.6

[a] See Figure 5.22.3 for ^{13}C NMR spectra. [b] ^{13}C NMR spectra was obtained at 125 MHz in $CDCl_3$ and standardized to residual $CHCl_3$. [c] ^{13}C NMR spectra was obtained at 100 MHz in $CDCl_3$ and standardized to residual $CHCl_3$. [d] ^{13}C NMR was obtained in $CDCl_3$ at unknown MHz

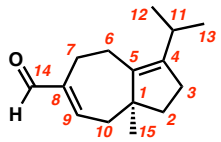


(–)-daucene (142)

*Table 3.6. Comparison of optical rotation data for synthetic and reported daucene (**142**).*[a]

Synthetic 142	**(+)-Natural[11a] 142**	**Yamasaki[22] 142**	**Mehta[23] 142**
$[\alpha]_D^{25} = -24.95$ (c 1.37, $CHCl_3$, 86% ee)	$[\alpha]_D^{25} = +23.32$ (c unspecified)	$[\alpha]_D^{25} = -21.5$ (c 0.8, EtOH)	$[\alpha]_D^{25} = -20$ (c 1.00)

[a] Daucene has been isolated from a number of sources.[11] Both (+)-[11] and (–)-daucene[11b–c] have been isolated from nature, however the optical rotation has only been determined for natural (+)-daucene. Yamasaki and Mehta, though, have reported rotations for synthetic (–)-daucene.

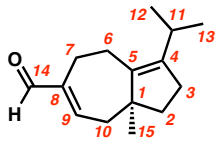


(+)-daucenal (143)

*Table 3.7. Comparison of ^{1}H NMR data for synthetic and natural daucenal (**143**).*[a]

Assignment	**Synthetic 143** (ppm)[b]	**Multiplicity, *J*** (Hz)	**Natural**[13] **143** (ppm)[c]	**Multiplicity, *J*** (Hz)
C1	—	—	—	—
C2	1.55	dtd, 12.6, 6.8, 1.2	1.550	dd, 12.4, 7.4
	1.47	dtd,12.4, 7.7, 1.1	1.471	dd, 12.4, 7.4
C3	2.13	ddd, 8.5, 5.1, 1.9	2.125	br ddd, 7.7, 7.4, 2.9
C4	—	—	—	—
C5	—	—	—	—
C6	2.33	ddd, 14.1, 5.5, 3.1	2.330	ddd, 14.0, 5.4, 3.0
	1.62	br ddt, 14.5, 10.1, 2.4	1.616	br ddd, 14.5, 14.0, 2.9
C7	3.06	ddd, 15.2, 5.4, 2.7	3.049	ddd, 14.9, 15.4, 2.9
	1.76	br tdd, 14.2, 3.4, 1.6	1.763	br dddd, 14.9, 14.5, 3.0, 2.0
C8	—	—	—	—
C9	6.10	dddd, 8.4, 5.2, 2.0, 1.1	6.101	ddd, 8.2, 5.2, 2.0
C10	2.05	dd, 14.3, 5.2	2.053	br dd, 14.3, 5.2
	1.94	ddd, 14.3, 8.2, 1.1	1.935	dd, 14.3, 8.2
C11	2.51	sept, 6.7	2.512	sept, 6.9
C12	0.90	dd, 6.9, 1.1	0.897	d, 6.9
C13	0.88	dd, 6.9, 1.1	0.869	d, 6.9
C14	9.26	d, 1.1	9.263	s
C15	0.81	s	0.811	s

[a] See Figure 5.24.1 for ^{1}H NMR spectra. [b] ^{1}H NMR spectra was obtained at 500 MHz in C_6D_6 and standardized to residual C_6H_6. [c] ^{1}H NMR spectra was obtained at 500 MHz in C_6D_6 and standardized to TMS.

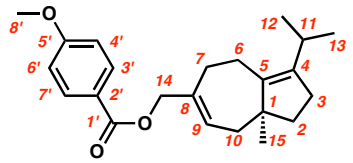


(+)-daucenal (143)

*Table 3.8. Comparison of ^{13}C NMR data for synthetic and natural daucenal (**143**).*[a]

Assignment	**Synthetic 143** (ppm)[b]	**Natural[13] 143** (ppm)[c]
C1	49.8	49.8
C2	39.2	41.7[d]
C3	27.4	27.4
C4	140.3	141.0
C5	141.0	146.7[e]
C6	22.4	24.0
C7	24.0	22.4
C8	146.8	140.2[e]
C9	152.8	152.8
C10	41.7	39.2[d]
C11	26.7	26.7
C12	21.9	21.7
C13	21.3	21.2
C14	193.0	193.0
C15	24.2	24.2

[a] See Figure 5.24.3 for ^{13}C NMR spectra. [b] ^{13}C NMR spectra was obtained at 125 MHz in C_6D_6 and standardized to residual C_6H_6. [c] ^{13}C NMR spectra was obtained at 125 MHz in C_6D_6 and standardized to TMS. [d] C2 and C10 were misassigned, see 2D NMR spectra, Figures 5.24.4–6. [e] C5 and C8 were misassigned, see 2D NMR spectra, Figures 5.24.4–6.



(+)-14-p-anisoyloxydauc-4,8-diene (145)

*Table 3.9. Comparison of ^{1}H NMR data for synthetic and natural[15,1a] 14-p-anisoyloxydauc-4,8-diene (**145**).[a–b]*

Assignment	Synthetic **145** (ppm)[c]	Multiplicity, ***J*** (Hz)	Natural[15] **145** (ppm)[d]	Multiplicity, ***J*** (Hz)
C1	—	—	—	—
C2	1.64	dt, 12.3, 6.1		
	1.56	dt, 12.4, 8.3		
C3	2.19	ddd, 8.2, 6.0, 2.2		
C4	—	—	—	—
C5	—	—	—	—
C6	2.49	ddd, 13.9, 5.7, 2.8		
	1.88	dddd, 14.6, 12.3, 5.0, 2.5		
C7	2.25	ddd, 14.6, 5.8, 2.8		
	2.07	tm, 13.5		
C8	—	—	—	—
C9	5.85	ddp, 7.3, 5.0, 1.1	5.86	br t, 6.5
C10	2.20–2.14	m		
	2.07	dd, 14.1, 8.1		
C11	2.67	sept, 6.9	2.69	sept
C12	0.98	d, 6.9	0.98	d, 7.2
C13	0.93	d, 6.8	0.93	d, 7.2
C14	4.70	d, 1.1	4.70	br s
C15	0.95	s	0.95	s
C1'	—	—	—	—
C2'	—	—	—	—
C3'/ C7'	6.92	dm, 8.9	6.93	d, 9.1
C4'/C6’	8.01	dm, 8.9	8.01	d, 9.1
C5'	—	—	—	—
C8'	3.86	s	3.86	s

[a] See Figure 5.26.1 for ^{1}H NMR spectra. [b] Blank spaces in table represent neglected or unreported signals. [c] ^{1}H NMR spectra was obtained at 500 MHz in $CDCl_3$ and standardized to residual $CDCl_3$. [d] ^{1}H NMR spectra was obtained at 200 MHz in $CDCl_3$ and standardized to TMS.

3.6 NOTES AND REFERENCES

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(51) Example procedure for the preparation of a samarium diiodide solution: A flame-dried 50 mL Schlenk tube equipped with a stir bar was connected to an Ar-filled manifold, loaded with samarium metal (311.3 mg, 2.07 mmol, 1.45 equiv), and backfilled with Ar three times. The flask was charged with THF (1 h Ar sparge before use, 14.3 mL, 0.1 M) and lowered into a 0 °C bath (ice/water). 1,2-Diiodoethane was added in two portions (203.0 mg and 30 min = 200.2 mg, total added = 403.2 mg, 1.43 mmol, 1.00 equiv), the ice bath was removed, and the reaction was allowed to warm to room temperature. After 1 h of vigorous stirring, the reaction had developed into a dark blue solution and was administered as a 0.1 M solution.

(52) Use of benzene to load the crude oil onto the column prohibits clean separation of the nonpolar products (i.e., alkene **261** and daucene (**142**)).

(53) Mehta also reports several ^{1}H NMR signals for daucene, but neglects to include J values for most signals (Ref. 23). Mehta indicates that they compared data with an authentic sample provided by the Seto group (Ref. 25). Consequently, Mehta's data has been neglected from the table.