CHAPTER TWO

Enantioselective Formal Total Syntheses of Natural Products Using Palladium-Catalyzed Decarboxylative Alkylation

2.1 Introduction

The enantioselective generation of all-carbon quaternary stereocenters is a challenge for the modern organic chemist.[1] A recent tool added to the arsenal of methods in this field has been palladium-catalyzed decarboxylative alkylation.[2] This method has allowed for the preparation of diverse cyclic α-quaternary allyl ketones and vinylogous esters, with high functional group tolerance. Recently, we developed three methods for generating enantioenriched α-quaternary ketones in the presence of a Pd(0) source and a chiral phosphinooxazoline ligand. The first two methods utilize silyl enol ether and enol carbonate substrates, respectively,[3] while the third method employs racemic allyl β-ketoesters.[4] Since the enantioenriched products prepared are well suited for further synthetic elaboration, we sought to advance them to intermediates reported in total syntheses of classic molecules. Herein we disclose catalytic enantioselective formal syntheses of an array of challenging natural products bearing at least one all-carbon quaternary stereocenter.

2.2 Formal Total Synthesis of (–)-Thujopsene[†]

2.2.1 *Background*

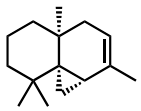
The Japanese Hiba tree, *Thujopsis dolabrata*, has been used for centuries as decoration and within traditional architecture.[5] The plant is a member of the order

[†] This work on (–)-thujopsene was done in collaboration with Jacqueline Malette.

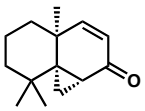
Cupressaceae, and its fragrant wood oil contains many sesquiterpene natural products, including mayurone (**90**),[6] α-cadinol (**91**),[7] and (–)-thujopsene (**92**)[8] (Figure 2.1). The wood oil has been shown to have potent deterent effects against dust mites; thus, in addition to its ornamental value, the hiba tree also provides an environmentally benign means of pest control.[9]

Figure 2.1 Natural Products from *Thujopsis dolabrata*

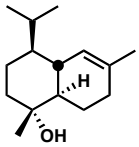
Japanese Hiba Tree



(–)-Thujopsene *(92)*



Mayurone *(90)*



α-Cadinol *(91)*

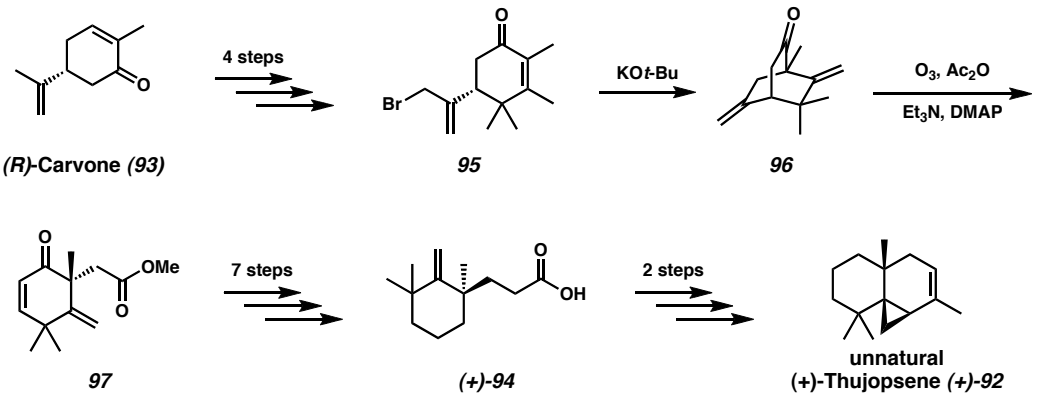
2.2.2 *Structural Analysis of Thujopsene*

(–)-Thujopsene (**92**) bears many features that have made it an attractive target to synthetic chemists. In addition to its tricyclo[5.4.0.0^{1,3}]undecane skeleton, the compound contains three contiguous all-carbon quaternary centers, two of which are stereogenic, and one that is also part of a cyclopropane (Scheme 2.1).[10] Additionally, the natural product is a hydrocarbon with few functional group handles for retrosynthetic analysis.

Inspired by the interesting structure of (–)-thujopsene (**92**), several groups have reported racemic approaches to the natural product.[11] In addition, at least two enantioselective routes have been completed.[12] Srikrishna and Anebouselvy reported an enantiospecific route to the (+)-thujopsene **(+)-92** from (*R*)-carvone (**93**).[13] During their total synthesis, the authors prepare carboxylic acid **(+)-94** over 13 steps (Scheme 2.1).

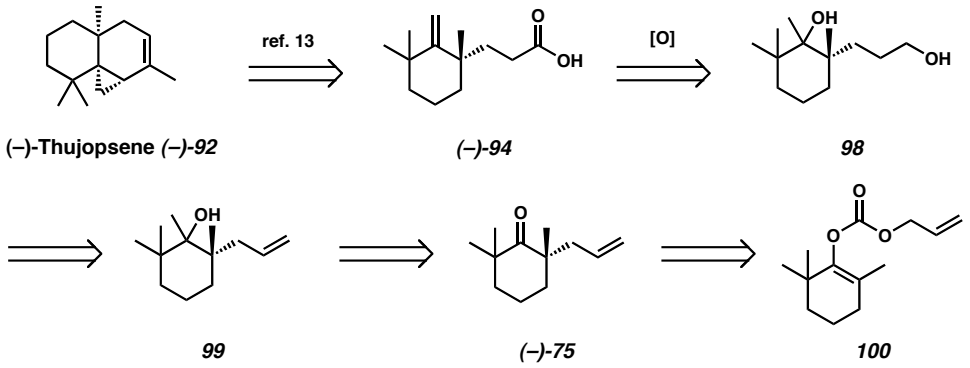
We anticipated that we could intercept this intermediate in an efficient manner using our enantioselective decarboxylative allylation chemistry.

Scheme 2.1 Srikrishna and Anebouselvy's Approach to (–)-Thujopsene



We designed a retrosynthesis of the carboxylic acid **(–)-94** (Scheme 2.2). It was anticipated that the acid functionality might arise via selective oxidation of diol **98**. We believed the olefinic moiety present in **(–)-94** might be installed by acid-mediated elimination concomitant with primary alcohol oxidation. The terminal alcohol could be installed by hydroboration-oxidation of the olefin **99**. This bis-homoallylic alcohol could potentially come from allyl ketone **(–)-75**, available in 91% ee from enol carbonate **100**. This allyl enol carbonate is readily prepared from 2,2,6-trimethylcyclohexanone (**101**).

Scheme 2.2 Retrosynthetic Analysis of (–)-Thujopsene

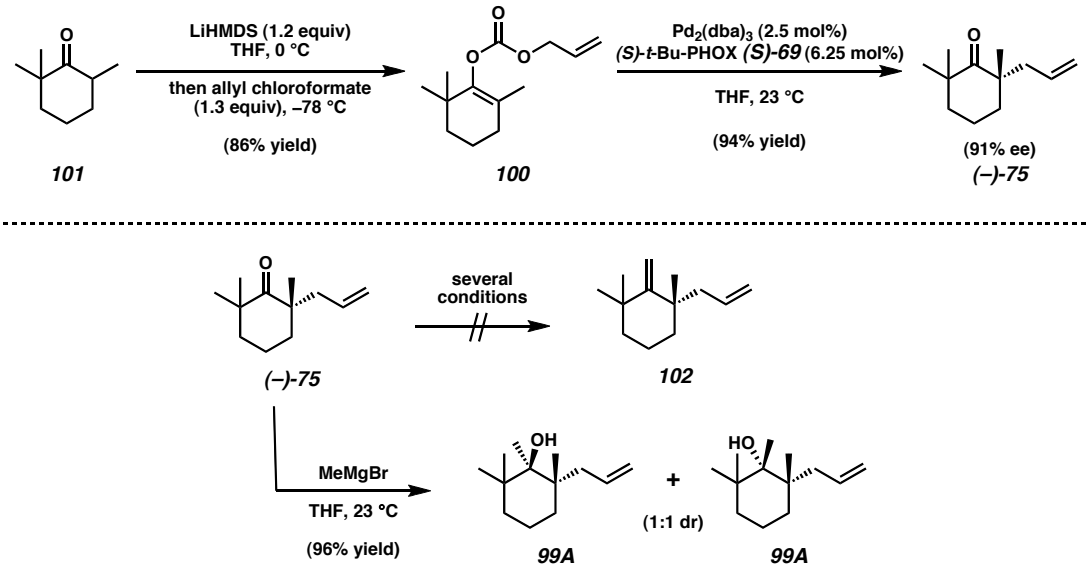


2.2.3 *Formal Total Synthesis of (–)-Thujopsene*

We commenced our formal total synthesis of (–)-thujopsene (**(–)-92**) by treatment of **101** with LiHMDS in THF followed by allyl chloroformate, furnishing known enol carbonate **100** in excellent yield (Scheme 2.3). This substrate smoothly underwent Pd-catalyzed enantioselective decarboxylative allylation in the presence of (*S*)-*t*-Bu PHOX (***(S)*-69**), giving allyl ketone **(–)-75** in 94% yield and 91% ee.[14] Rigorous exclusion of air and moisture was crucial for obtaining high yield and enantioselectivity.[15]

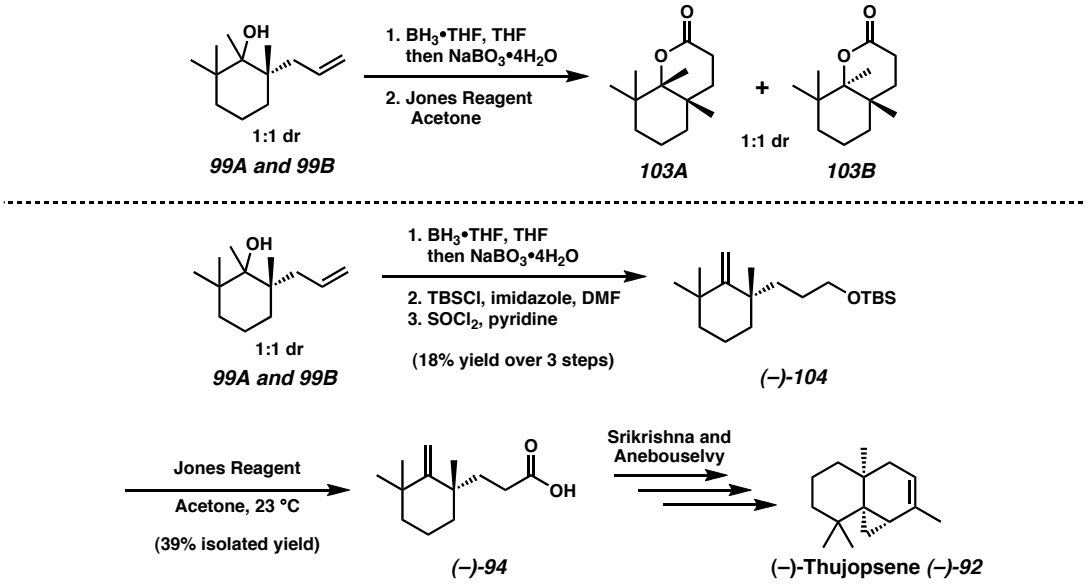
The next task was the installation of the exocyclic methylene of **(–)-94**. Attempted Wittig olefination failed to produce bis-olefin **102**, presumably due to the steric congestion proximal to the ketone. Although direct methylenation of ketone **(–)-75** was not workable, addition of methyl magnesium bromide at 23 °C gave a 1:1 mixture of homoallylic alcohols **99A** and **99B** in excellent yield.

Scheme 2.3 Preparation of Diastereomeric Alcohols



The **99A**/**99B** mixture was carried through a two-step sequence of hydroboration/oxidation and Jones oxidation (Scheme 2.4). It was anticipated that under highly acidic oxidizing conditions, the tertiary alcohols present would be eliminated, removing a stereocenter and installing the requisite exocyclic olefin present in **(–)-94**. Oxidation of the primary alcohol (installed during the hydroboration) to a carboxylic acid was also anticipated. In the event, two diastereomeric lactones **103A** and **103B** were obtained as the sole isolated products in 1:1 dr. Apparently, primary alcohol oxidation is more rapid than any tertiary alcohol elimination.

Scheme 2.4 Completion of the Carboxylic Acid



The formation of the lactones **103A** and **103B** necessitated revision of our synthetic plan. We subjected the mixture of diastereomeric alcohols **99A** and **99B** to hydroboration, followed by oxidative workup with $NaBO_3•4H_2O$ (Scheme 2.4). The product mixture was purified, then treated with TBSCl and imidazole in dry DMF. This resulted in selective protection of the primary alcohol installed during the hydroboration/oxidation sequence. The combined, purified monoprotected diols were treated with thionyl chloride in pyridine, affecting a net dehydration reaction, providing silyl ether **(–)-104** in 18% yield over three steps from the mixture of **99A** and **99B**. The purified TBS ether was exposed briefly to the Jones reagent, accomplishing silyl ether cleavage *and* primary alcohol oxidization to a carboxylic acid. This oxidative transformation furnished **(–)-94**, thus completing the formal total synthesis of (–)-thujopsene (**(–)-92**).

2.3 Formal Total Synthesis of (–)-Dysidiolide

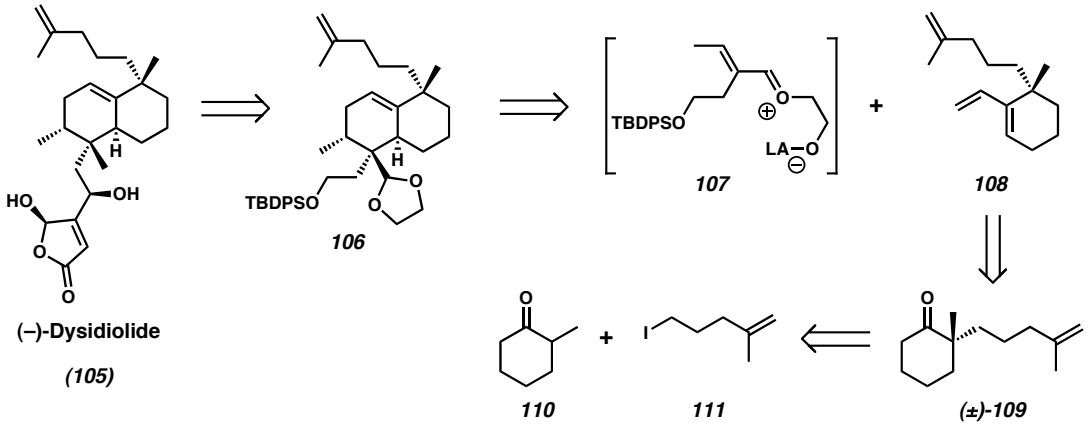
2.3.1 *Background*

Dysidiolide (**105**) was isolated from the marine sponge *Dysidea etheria* and found to have inhibitory activity toward the protein phosphatase cdc25, with an IC_{50} value of 9.4 μM (Scheme 2.5).[16] This enzyme belongs to a protein family involved in dephosphorylation of cyclin-dependent kinases.[17] Thus, inhibitors of cdc25 might allow for targeted cell-cycle disruption in cancer cell lines.[16]

Initial investigations into the structure of the natural product were made using NMR techniques; however, many of the signals in the ^{13}C NMR spectrum were broad.[16] Fortuitously, the relative stereochemistry of the sesterterpene **105** was determined via single-crystal X-ray diffraction. Dysidiolide (**105**) was found to have a butenolide ring and six stereocenters, two that were of the all-carbon quaternary variety. Several groups have reported total syntheses of this natural product,[18] three of which are enantioselective.[18a,18b,18h,18l,19]

In Danishefsky's racemic approach, the cyclohexene ring of **106** was installed via diastereoselective Diels-Alder reaction of a transient dioxolenium dienophile (**107**) with a chiral vinylcyclohexene (**108**) (Scheme 2.5).[18j] Diene **108** was prepared from α-quaternary ketone **(±)-109** in racemic form. This keto-olefin was synthesized via alkylation of the thermodynamic lithium enolate of 2-methylcyclohexanone (**110**) with 5-iodo-2-methyl-1-pentene (**111**). We believed that our catalytic decarboxylative alkylation chemistry might allow for an enantioselective synthesis of **(–)-109**, constituting a formal total synthesis of (–)-dysidiolide (**105**).

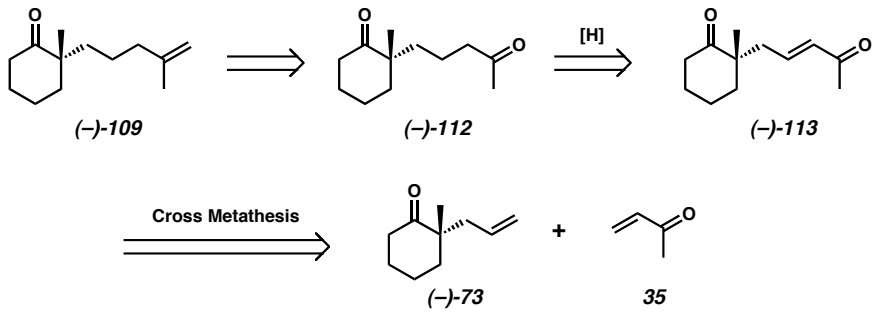
Scheme 2.5 Danishefsky's Approach to (±)-Dysidiolide



2.3.2 *Retrosynthetic Analysis*

Looking at the target keto-olefin **(–)-109**, we reasoned that the geminally di-substituted olefin could be prepared from a diketone **(–)-112** (Scheme 2.6). Based on steric arguments, we believed selective olefination of the less-hindered distal ketone moiety would be possible. Diketone **(–)-112** could easily arise from keto-enone **(–)-113** via olefin reduction. Retrosynthetically, **(–)-113** could come from methyl vinyl ketone (**35**) and the α-quaternary cyclohexanone **(–)-73**, readily available in enantioenriched form through our enantioselective decarboxylative allylation chemistry.

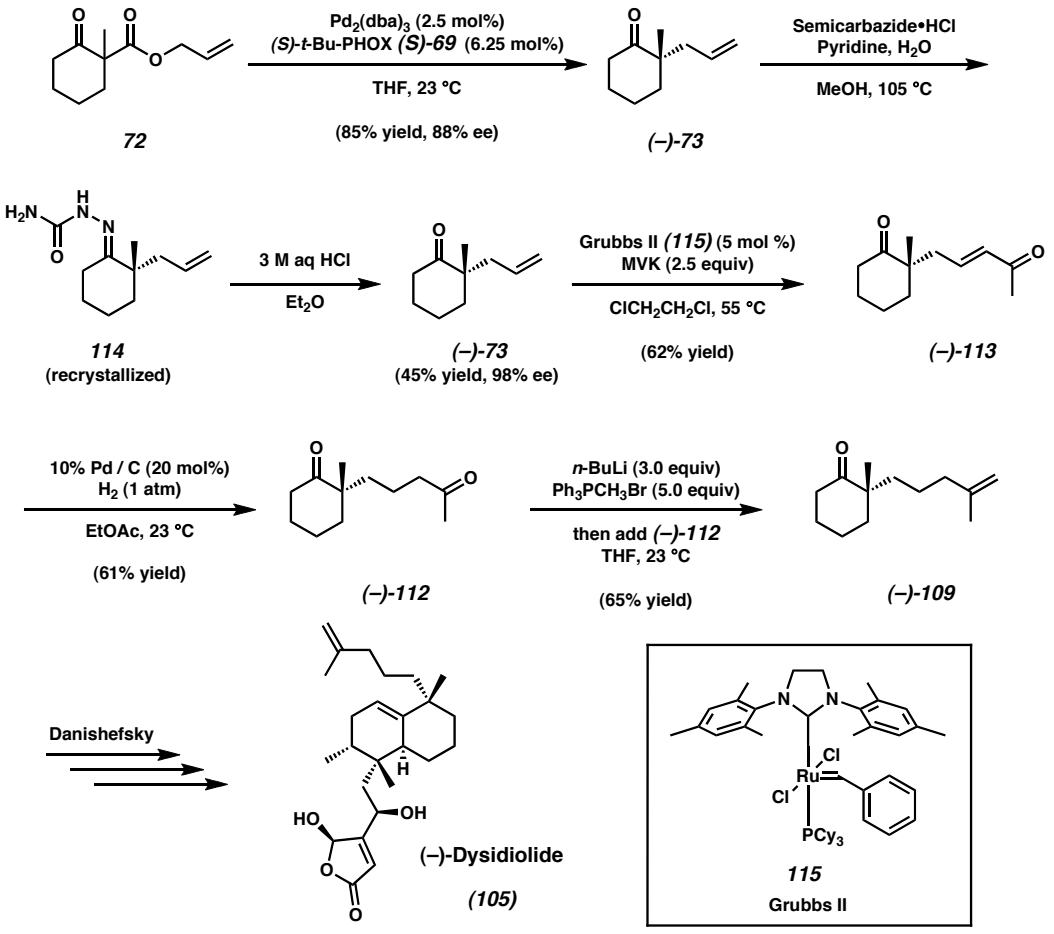
Scheme 2.6 Retrosynthetic Analysis of the Keto-Olefin



2.3.3 *Formal Total Synthesis of (–)-Dysidiolide*

Our synthesis commenced by treating known allyl β-ketoester **72** with catalytic $Pd_2(dba)_3$ and (*S*)-*t*-Bu-PHOX (***(S)*-69**), furnishing 2-allyl-2-methylcyclohexanone (**(–)-79**) in 85% yield and 88% ee (Scheme 2.7).[4] The allyl ketone was enriched to 98% ee via the semicarbazone **114**.[3] Using the Grubbs 2nd generation metathesis catalyst (**115**), allyl ketone **(–)-73** was crossed with methyl vinyl ketone (**35**) in reasonable yield. The keto-enone **(–)-113** was then reduced to diketone **(–)-112** using Pd/C and H_2.

Scheme 2.7 Formal Synthesis of (–)-Dysidiolide



A Wittig reaction seemed ideal for installation of the geminally disubstituted olefin. However, it was critical that the methyl triphenyl phosphonium salt be completely deprotonated because any unreacted base led to side reactions of the starting material.[20] Due to their limited solubility, NaH and KO*t*-Bu failed to react completely with the phosphonium salt. However, *n*-BuLi reacted completely for preparation of the phosphorus ylide. Treatment of the ylide with **(–)-112** resulted in chemoselective methylenation of the distal ketone. This completed **(–)-109** and thus our formal synthesis of (–)-dysidiolide (**(–)-105**).

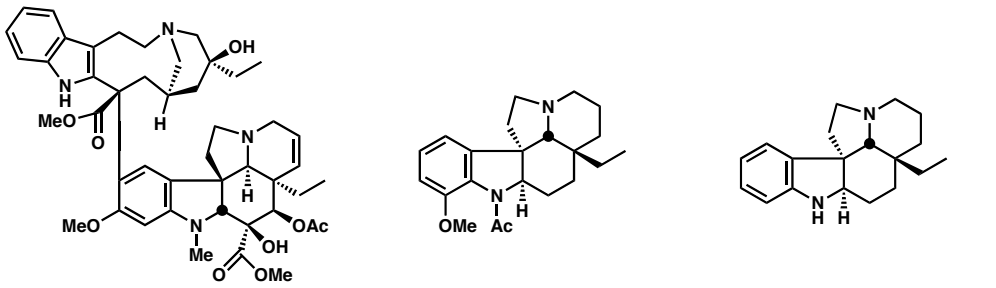
2.4 Formal Total Synthesis of (–)-Aspidospermine[†]

2.4.1 *Background*

The aspidosperma alkaloids have garnered much attention over the years as targets for synthetic chemists. Most of the 250 compounds in this large class share a common pentacyclic core, from the complex vinca alkaloids such as vinblastine (**116**) (used as a chemotherapeutic) to the simpler aspidospermidine (**117**) (Figure 2.2).[21] To address the challenging synthetic features of the aspidosperma alkaloids, many clever synthetic approaches have been reported, highlighted by the seminal work of Stork and Dolfini[22] along with Ban and co-workers.[23]

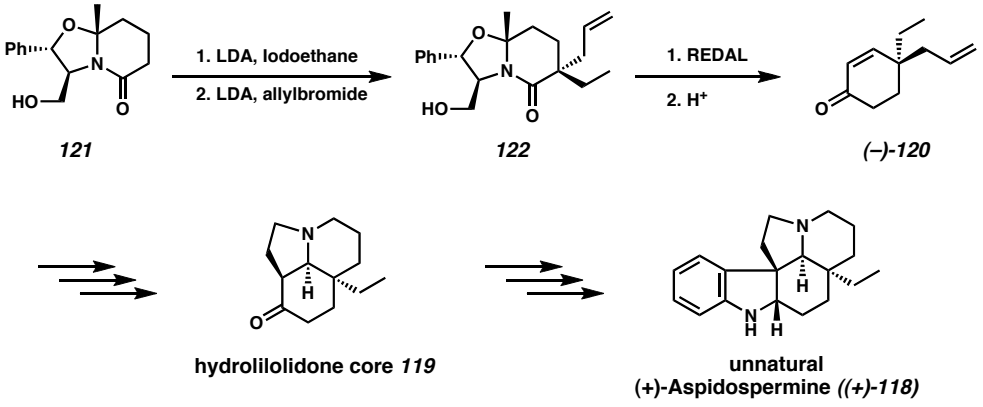
[†] This work on (–)-aspidospermine was done in collaboration with David E. White and Michael R. Krout.

Figure 2.2 Representative Aspidosperma Alkaloids



One popular target within this natural product family is aspidospermine (**(–)-118**). Although not as medicinally potent as certain other members of the aspidosperma class, it has served as a testing ground for chemists venturing into this alkaloid realm. In 1989, Meyers reported an enantioselective synthesis of the (4a*S*,8a*R*,8*S*)-hydrolilolidone core **119**[22,23,24] present in aspidospermine (**(+)-118**), and thus a formal synthesis of the alkaloid itself (Scheme 2.8).[25] One of the precursors to the core structure, prepared in enantioenriched form, was enone **(–)-120**. Contrasting Meyers' approach, which employed a chiral auxiliary, we thought a catalytic enantioselective alkylative strategy would be ideal for a formal total synthesis of aspidospermine (**(–)-118**).

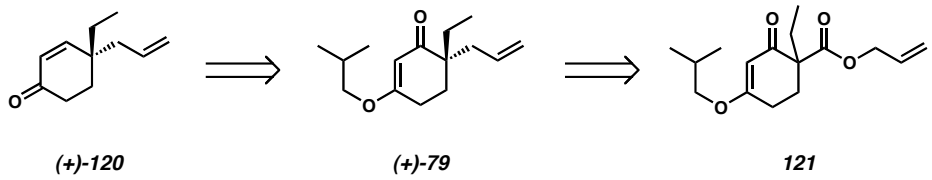
Scheme 2.8 Meyers' Approach to Unnatural (+)-Aspidospermine



2.4.2 *Retrosynthetic Analysis*

One challenge associated with **(+)-120** was its γ-stereogenicity. To address this issue retrosynthetically, we installed oxygenation at the β-carbon (Scheme 2.9). A reasonable retron was vinylogous ester **(+)-79**. This retrosynthetic plan simplified the problem of γ-chirality to one of α-stereogenicity. The allyl vinylogous ester could potentially arise from α-allyloxycarbonyl vinylogous ester **121** via enantioselective allylation. One goal during this formal synthesis was to finish the target compound (**(+)-120**) with an ee of at least 90%. Overall, our proposed forward synthetic sequence is an enantioselective form of Stork-Danheiser chemistry.[26]

Scheme 2.9 Retrosynthetic Analysis of the γ-Allyl Enone



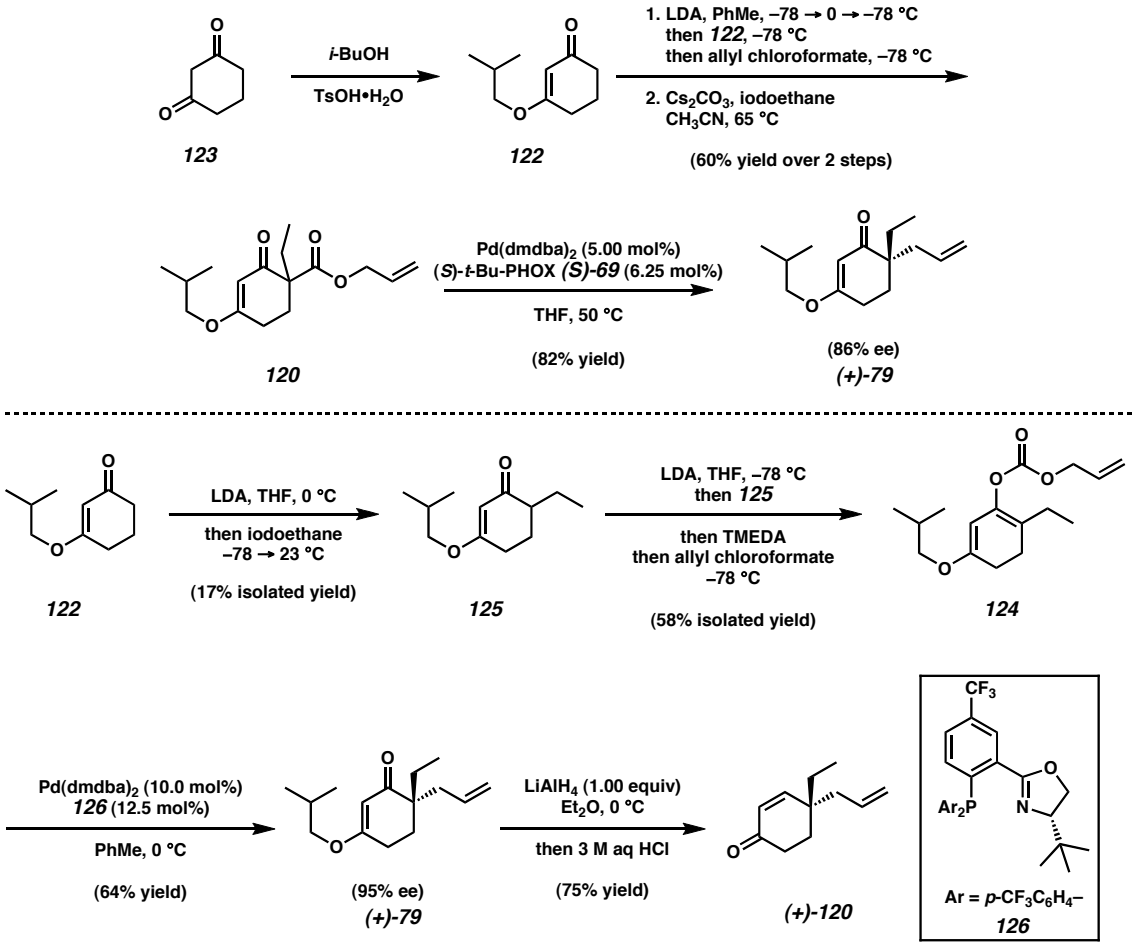
(+)-120 *(+)-79* *121*

2.4.3 *Two Routes to the Alkylated Vinylogous Ester: Formal Synthesis of Aspidospermine*

We started our formal synthesis with the known isobutyl vinylogous ester **122**, readily available from 1,3-cyclohexanedione (**123**) (Scheme 2.10). Compound **122** was selectively acylated on carbon with allylchloroformate, furnishing a vinylogous β-diester as a tautomeric mixture. This composite was immediately subjected to alkylation with iodoethane in acetonitrile under basic conditions, providing **120** in good yield. When we performed the decarboxylative allylation, we obtained allyl vinylogous ester **(+)-79** in

82% yield and 86% ee. The higher temperature used was necessary to achieve complete conversion, but it came with the cost of lowered enantioselectivity.

Scheme 2.10 Two Decarboxylative Alkylation Methods Tested



An alternative route to **(+)-79** was developed, demonstrating the versatility of our decarboxylative alkylation chemistry. We discovered it was possible to prepare **124** in reasonable yield from **125** (Scheme 2.10).[27] Using the tris-trifluoromethyl PHOX ligand **126** at reduced temperatures in toluene allowed for the synthesis of **(+)-79** in 64% isolated yield and 95% ee. The product allyl vinylogous ester **(+)-79** was then treated

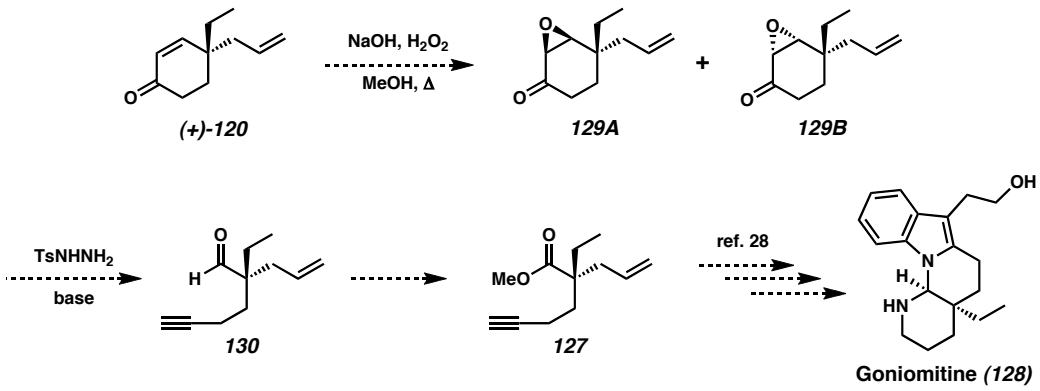
with $LiAlH_4$ in Et_2O, giving selective 1,2-reduction. Hydrolysis of the crude porduct with 3 M aqueous HCl gave rise to enone **(+)-120**, resulting in a formal synthesis of (–)-aspidospermine.

2.5 Other Targets for Formal Total Synthesis

2.5.1 *Goniomitine*

Some of the intermediates we prepared during our formal synthesis endeavors might find use in other contexts. For instance, ester **127** has been reported as an intermediate in the total synthesis of goniomitine (**128**) (Scheme 2.11).[28] We envision that enone **(+)-120** might be elaborated to ester **127**, constituting a formal total synthesis of goniomitine (**128**). The enone **(+)-120** could undergo nucleophilic epoxidation to give **129A** and **129B**. These diastereomeric epoxides, when condensed with *p*-toluenesulfonhydrazide and treated with base, are anticipated to undergo an Eschenmoser-Tanabe fragmentation. This transformation would lead to alknye **130**, which could be oxidized and esterified to give the desired ester **127**.

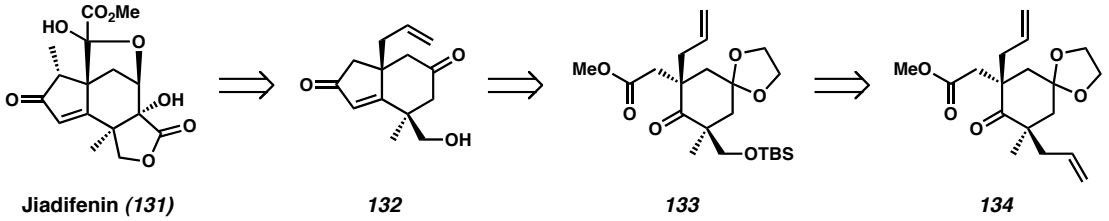
Scheme 2.11 A Possible Formal Synthesis of Goniomitine



2.5.2 *Jiadifenin*

The neurotrophic natural product jiadifenin (**131**) is another structurally interesting target, which has been synthesized in racemic form by Danishefsky.[29] This synthesis proceeds through a chiral, racemic tetrasubstituted cyclohexanone **133**. Considering the possibility of performing two stereoselective alkylations on a single molecule, it might be possible to intercept Danishefsky's intermediate **133** in enantioenriched form (Scheme 2.12).

Scheme 2.12 Danishefsky's Intermediates in the Jiadifenin Synthesis

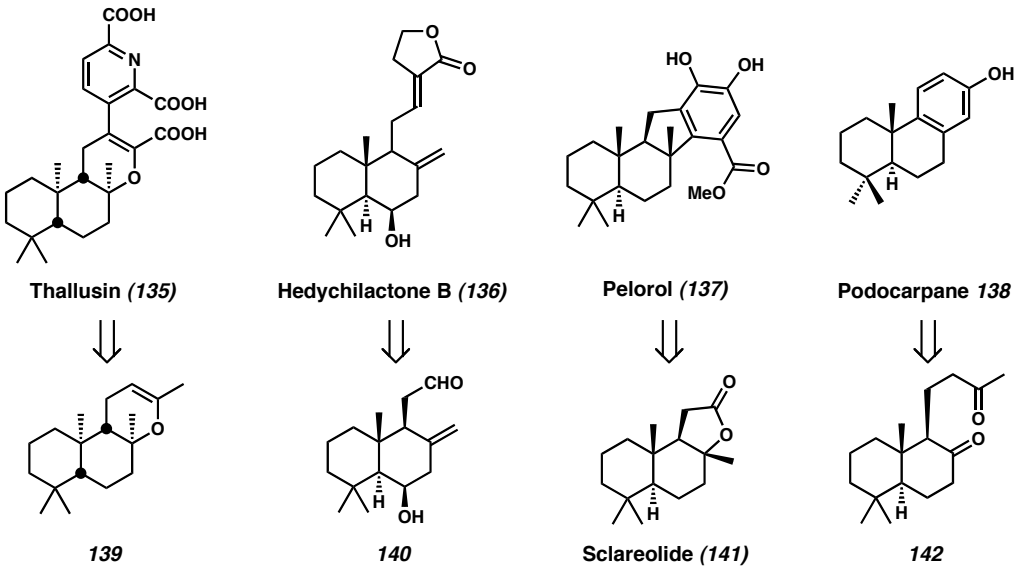


Jiadifenin *(131)* ***132*** ***133*** ***134***

2.5.3 *Other Natural Products*

There are many other potential uses for chiral non-racemic quaternary compounds available through our chemistry. Formal syntheses of natural products including, but not limited to, (–)-thallusin (**135**),[30] hedychilactone (**136**),[31] (–)-pelorol (**137**),[32] and podocarpane **138**[33] could all be envisioned (Scheme 2.13). Yang's synthesis of Pelorol itself even began with another natural product, sclareolide (**141**).[32] Our enantioselective decarboxylative alkylation chemistry is anticipated to find widespread use in the synthesis of functionally diverse quaternary-carbon entities.

Scheme 2.13 Other Natural Products Targeted for Formal Synthesis



2.6 Concluding Remarks

The development of a Pd-catalyzed method for generating all-carbon quaternary stereocenters has set the stage for formal total syntheses of an array of natural products including terpenes and alkaloids. An efficient route to the sesquiterpene (–)-thujopsene (**(–)-92**)[13] has been delineated, featuring the installation of a sterically congested exocyclic olefin. We have also intercepted a key intermediate in Danishefsky's synthesis of dysidiolide (**(–)-105**),[18j] demonstrating chemoselective modification of the allyl group installed during the palladium catalysis. Finally, we have shown that the various starting materials utilized in our alkylation method can provide great flexibility in overall synthetic design, allowing us to overcome obstacles associated with enantioselectivity. The use of an allyl enol carbonate (**124**) derived from a vinylogous ester (**125**), as opposed to an allyl vinylogous β-diester (**120**), allowed for the highly enantioselective synthesis of a quaternary allyl vinylogous ester (**(+)-79**). Using traditional Stork-

Danheiser chemistry, a formal total synthesis of (–)-Aspidospermine (**(–)-118**) was achieved.[25] We anticipate that formal total syntheses of other natural products are soon to follow, lending us additional insight into synthetic elaborations of compounds with all-carbon quaternary stereocenters.

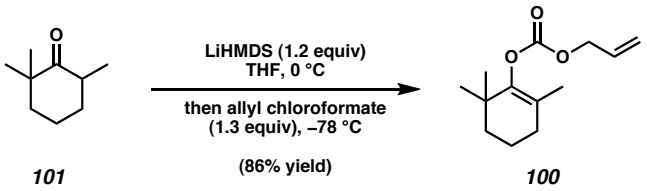
2.7 Experimental Procedures

2.7.1 *Materials and Methods*

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (either freshly distilled or passed through activated alumina columns). Chloroform, stabilized with ethanol, was stored in the dark over oven-dried 4Å molecular sieves. Absolute ethanol, methanol, and *N,N*-dimethyl acetamide were used as purchased. 2,2,6-Trimethylcyclohexanone **(101)** was used as received. TMEDA and *i*-Pr_2NH were distilled from CaH_2. All other commercially obtained reagents were used as received unless specified otherwise. (*S*)-*t*-Bu-PHOX ligand ***(S)*-69** was prepared according to known methods.[3,34] (*S*)-2-(tris-*p*-trifluoromethylphenylphosphin-2′-yl)-4-*t*-butyloxazoline (**126**) was also prepared according to the published procedure.[3,34b] Reaction temperatures were controlled using an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized using UV at 254 nm, *p*-anisaldehyde, potassium permanganate, and iodine vapor over sand. TLC data include R_f, eluent, and method of visualization. ICN silica gel (particle size 0.032-0.063 mm), SilliaFlash P60 Academic silica gel (0.040-0.063 mm), or Florisil (Aldrich) was

used for flash column chromatography. Analytical chiral HPLC analyses were performed with an Agilent 1100 Series HPLC using a chiralcel OD or AD normal-phase column (250 x 4.6 mm) employing 2.0-3.0% ethanol in hexane isocratic elution and a flow rate of 0.1 mL/min with visualization at 254nm. Analytical chiral GC analysis was performed with an Agilent 6850 GC using a GT-A column (0.25m x 30.00m) employing an 80 °C isotherm and a flow rate of 1.0 mL/min. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) or a Varian Inova 500 (at 500 MHz) and are reported relative to the residual solvent peak (δ 7.26 for $CDCl_3$ and δ 7.16 for C_6D_6). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz),[35] and integration. ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz) or a Varian Inova 500 (at 125 MHz) and are reported relative the residual solvent peak (δ 77.2 for $CDCl_3$ and δ 128.4 for C_6D_6). Data for ^{13}C NMR spectra are reported in terms of chemical shift, and integration (where appropriate). IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrometer and are reported in frequency of absorption (cm^{-1}). IR samples were thin films deposited on sodium chloride plates by evaporation from a solvent (usually $CDCl_3$), which is recorded. Optical rotations were measured with a Jasco P-1010 polarimeter, using a 100 mm path-length cell. High-resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

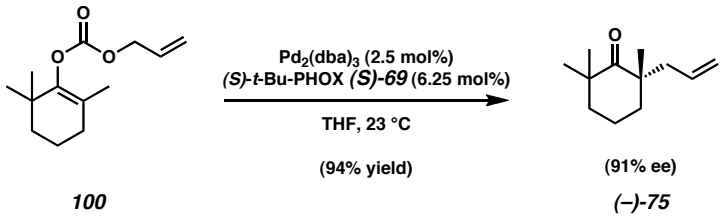
2.7.2 *Syntheses of Compounds Related to Thujopsene*



101 ***100***

Enol Carbonate 100. A solution of LiHMDS (1.0 M in THF, 57.5 mL, 57.5 mmol) was added to THF (300 mL), then cooled to 0 °C. A solution of 2,2,6-trimethylcyclohexanone (**101**) (6.67 g, 47.6 mmol) in THF (10 mL) was added. The reaction was stirred at 0 °C for 1 h, then cooled to –78 °C and fitted with an addition funnel, which was charged with a solution of allyl chloroformate (6.56 mL, 61.8 mmol) in THF (200 mL). The solution was added dropwise over 30 min. Then the reaction was warmed to 23 °C. After 13 h, the reaction was poured into a mixture of sat. aq NH_4Cl (100 mL), water (100 mL), and hexane (100 mL). After 10 min, the organic phase was collected and the aqueous phase extracted with Et_2O (3 x 75 mL). All organic layers were combined, washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (2:98 Et_2O/hexane eluent), affording enol carbonate **100** (9.19 g, 86% yield) as a clear oil. R_f 0.43 (1:9 EtOAc/hexane), (*p*-Anisaldehyde, blue spot); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.96 (app. ddt, J_{d1} = 17.1 Hz, J_{d2} = 10.7 Hz, J_t = 5.8 Hz, 1H), 5.38 (app. ddq, J_{d1} = 17.3 Hz, J_{d2} = 8.3 Hz, J_q = 1.4 Hz, 1H), 5.28 (app. ddq, J_{d1} = 10.5 Hz, J_{d2} = 4.4 Hz, J_q = 1.1 Hz, 1H), 4.65 (app. ddt, J_{d1} = 10.2 Hz, J_{d2} = 5.7 Hz, J_t = 1.4 Hz, 2H), 2.05 (t, J = 5.5 Hz, 2H), 1.77-1.52 (m, 4H), 1.50 (s, 3H), 1.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.5, 148.1, 131.8, 120.9, 119.1, 68.7, 39.4, 35.1, 31.4, 26.9, 19.3, 16.7; IR (NaCl/$CDCl_3$): 2965, 2934, 2868, 2838, 1759, 1459, 1363, 1271, 1238,

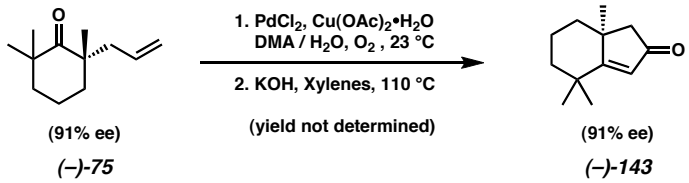
1138, 1025, 993, 937 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{13}H_{20}O$, 224.1413; found, 224.1408.



100 ***(–)-75***

Allyl Ketone (–)-75. A round bottom flask was flame-dried under argon and cycled into the glovebox. It was charged with $Pd_2(dba)_3$ (242 mg, 0.264 mmol, 6.25 mol%) and (*S*)-*t*-Bu-PHOX (***(S)*-69**) (256 mg, 0.661 mmol, 2.5 mol%). Then, THF (317 mL) was introduced. The red mixture was stirred for 20 min at 25 °C. Then, enol carbonate **100** (2.37 g, 10.57 mmol, 1.00 equiv) in THF (10 mL) was added. After the reaction was gauged complete using TLC analysis, it was removed from the glovebox, then concentrated. PhH (~20 mL) was added. After concentrating a second time, more PhH (~20 mL) was added. The solution was purified by flash chromatography on silica gel (2:98 Et_2O/hexane eluent), affording allyl ketone **(–)-75** (1.72 g, 94% yield) as a clear oil in 91% ee as determined by chiral HPLC analysis. R_f 0.48 (1:9 EtOAc/hexane), (I_2/sand, brown spot); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.64 (dddd, J = 17.1 Hz, 10.5 Hz, 7.7 Hz, 6.9 Hz, 1H), 5.05 (app. ddt, J_{d1} = 6.3 Hz, J_{d2} = 2.2 Hz, J_t = 1.1 Hz, 1H), 4.98 (app. ddt, J_{d1} = 13.8 Hz, J_{d2} = 2.5 Hz, J_t = 1.4 Hz, 1H), 2.32 (app. ddt, J_{d1} = 13.8 Hz, J_{d2} = 6.9 Hz, J_t = 1.4 Hz, 1H), 2.16 (app. ddt, J_{d1} = 13.8 Hz, J_{d2} = 6.9 Hz, J_t = 1.4 Hz, 1H) 1.87-1.47 (m, 6H), 1.15 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 219.8, 134.7, 118.0, 47.7, 44.6, 44.0, 39.9, 37.0, 28.0, 27.3, 25.7, 17.9; IR (NaCl/$CDCl_3$): 3077, 2979,

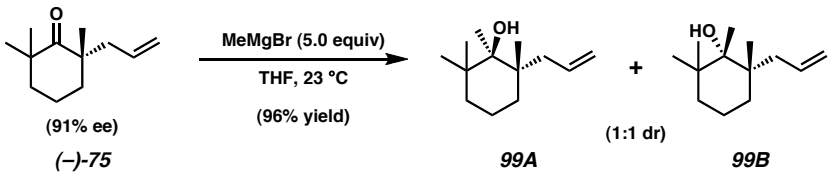
2964, 2933, 2869, 1697, 1463, 1382, 999, 914 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{12}H_{20}O$, 180.1514; found, 180.1506; $[\alpha]^{24}_D$ –36.3° (*c* 0.140, $CHCl_3$), 91% ee.



Bicyclic Enone (–)-143. A round-bottom flask was charged with $PdCl_2$ (10 mg, 56 μmol), $Cu(OAc)_2•H_2O$ (30 mg, 0.16 mmol), *N*,*N*-dimethylacetamide (3.0 mL), and water (0.5 mL). Then, allyl ketone **(–)-75** (20 mg, 0.11 mmol) was introduced. The system was cooled to –78 °C and evacuated with vacuum and back-filled with O_2 from a balloon (3 x). The mixture was warmed to 23 °C and stirred vigorously for 40 h under a balloon of O_2. The reaction was then diluted with H_2O (50 mL) and extracted with hexanes (3 x 25 mL). All organic phases were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (15:85 EtOAc:hexane eluent), affording a diketone as a clear oil, which was immediately used in the next reaction.

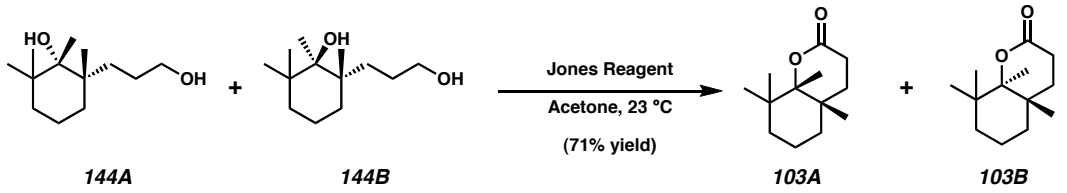
To a solution of this diketone (10 mg, 51 μmol) in xylenes (1.0 mL) was added freshly powdered KOH (3.0 mg, 54 μmol). The reaction was heated to 110 °C for 16 h. The reaction was cooled to 23 °C and directly loaded onto a preparative TLC plate (20:80 EtOAc/hexane eluent), affording bicyclic enone **(–)-143** (yield not determined) as a clear, fragrant oil in 91% ee as determined by chiral HPLC assay. R_f 0.37 (1:4 EtOAc/hexane), (UV, 254 nm); mp 9-11 °C (Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.82 (s, 1H), 2.29 (app. s, 2.29, 2H), 1.93 (app. dq, J_d = 10.5 Hz, J_q = 2.8 Hz, 1H), 1.83 (app. tt, *J* = 13.5 Hz, 3.3 Hz, 1H), 1.71-1.54 (m, 2H), 1.40 (app. ddd, *J* = 12.4 Hz, 8.0 Hz, 3.9 Hz, 1H),

1.36 (app. ddd, J = 8.0 Hz, 3.3 Hz, 2.0 Hz, 1H), 1.35 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.1, 194.4, 126.4, 54.7, 44.3, 41.5, 40.6, 36.5, 31.3, 27.4, 26.2, 19.1; IR (NaCl/$CDCl_3$): 2997, 2987, 2960, 2929, 2868, 2847, 1712, 1696, 1600, 1459, 1261, 1166 cm^{-1}; HRMS-EI$^+$ (m/z): $[M]^+$ calc'd for $C_{12}H_{18}O$, 178.1358; found, 178.1356; $[\alpha]^{25}_D$ –87.2° (*c* 0.280, $CHCl_3$), 91% ee.



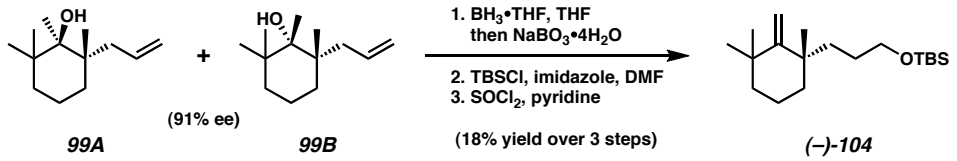
Alcohols 99A and **99B**. A round-bottom flask was charged with a solution of allyl ketone **(–)-75** (1.02 g, 5.65 mmol, 1.00 equiv, 91% ee) and THF (55.5 mL). Then, methyl magnesium bromide (3.0 M in Et_2O, 9.25 mL, 27.8 mmol, 5.00 equiv) was gradually introduced at 23 °C. After 24 h, the reaction was carefully quenched at 0 °C with sat. aq NH_4Cl (30 mL). Then H_2O (50 mL) was added, along with hexanes (50 mL). The biphasic mixture was extracted with Et_2O (2 x 30 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The wet residue was taken up in $CHCl_3$ and dried again with Na_2SO_4, then filtered. The filtrate was concentrated, giving a 1:1 mixture of diastereomeric alcohols **99A** and **99B** (1.04 g, 94% yield) as a colorless oil. R_f 0.59 (10:90 EtOAc/hexane), (*p*-Anisaldehyde, violet spot); ^{1}H NMR (300 MHz, $CDCl_3$) (both diastereomers): δ 5.84 (app. dddd, J = 19.4 Hz, 14.6 Hz, 7.4 Hz, 7.2 Hz, 2H), 5.01 (app. d, J = 11.1 Hz, 2H), 5.00 (app. d, J = 14.6 Hz, 2H), 2.44 (app. ddd, J = 12.6 Hz, 11.1 Hz, 7.5 Hz, 2H), 2.07 (app. ddd, J = 19.4 Hz, 13.6 Hz, 7.7 Hz, 2H), 1.62-1.46 (m, 4H), 1.44-1.36 (m, 4H), 1.28-1.10 (m, 2H), 1.14 (app. s, 6H), 1.07 (s, 3H), 1.06 (s, 3H), 1.10 (s,

3H), 0.99 (s, 3H), 0.98-0.86 (m, 2H), 0.97 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) (both diastereomers): δ 136.8, 136.4, 117.0, 116.8, 78.2, 77.9, 43.8, 42.0, 41.6, 41.2, 39.2, 39.0, 37.2, 36.9, 33.6, 33.0, 28.3, 28.2, 26.6, 25.8, 22.9, 22.2, 18.6, 18.5, 18.3, 18.1; IR (NaCl/$CDCl_3$): 3504 (broad), 3074, 2930, 2867, 1638, 1454, 1378, 1305, 1071, 998, 910 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{13}H_{24}O$, 196.1827; found, 196.1803.



Lactones 103A and **103B**. A round-bottom flask containing a mixture of diastereomeric diols **144A** and **144B** (50.0 mg, 0.234 mmol) was charged with acetone (ACS grade, 5 mL). Jones reagent (1.0 M aq CrO_3 and 4.0 M aq H_2SO_4) was added dropwise at 23 °C until a red coloration persisted. The reaction was carefully quenched with sat. aq Na_2SO_3 (excess), followed by 6 M aq HCl (10 mL). The reaction was then extracted with Et_2O (8 x 15 mL). All organic layers were combined, washed with brine (2 x 15 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo, giving lactones **103A** and **103B** (34.7 mg, 71% combined yield) as a mixture of diastereomers that were not separated. The mixture is a yellow, fragrant oil. R_f 0.20 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, blue spot); ^{1}H NMR (300 MHz, $CDCl_3$)(major diastereomer only): δ 2.71-2.42 (m, 2H), 2.07-1.84 (m, 1H), 1.72-1.63 (m, 1H), 1.58-1.26 (m, 3H), 1.33 (s, 3H), 1.26-0.95 (m, 3H), 1.12 (s, 3H), 1.05 (app. s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$)(major diastereomer only): δ 172.4, 91.2, 39.0, 36.3, 35.3, 33.2, 32.6, 27.3, 26.1, 25.6, 24.9, 18.2, 17.8; IR (NaCl/$CDCl_3$): 2934,

2874, 1770, 1732, 1463, 1398, 1382, 1349, 1274, 1254, 1175, 1112, 1073, 1047, 965 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{13}H_{22}O_2$, 210.1619; found, 210.1620.

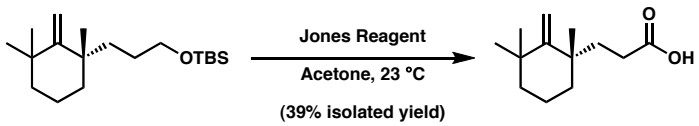


Methylene Cyclohexane (–)-104. A round-bottom flask containing a mixture of diastereomeric alcohols **99A** and **99B** (900 mg, 4.59 mmol, 1.00 equiv, 91% ee) and THF (25 mL) was cooled to 0 °C and treated with BH_3•THF (1.0 M in THF, 11.5 mL, 11.5 mmol, 2.5 equiv). The reaction was warmed to 23 °C and stirred for 6 h. Then the reaction was cooled to 0 °C, and H_2O (25 mL) was carefully added, followed by $NaBO_3$•$4H_2O$ (3.05 g, 19.82 mmol, 4.32 equiv). The biphasic reaction was stirred vigorously at 23 °C for 28 h and 6 M aq HCl (10 mL) was added. The reaction was diluted with hexanes, and the organic phase was collected. The aqueous layer was extracted with EtOAc (3 x 20 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (10:90 EtOAc:hexane → 30:70 EtOAc:hexane → 50:50 EtOAc:hexane eluent), giving an oil containing two diastereomeric products, which was immediately used in the next reaction.

This mixture was transferred to a round-bottom flask, and imidazole (recrystallized, 344 mg, 5.05 mmol) was introduced, followed by a solution of TBSCl (726 mg, 4.82 mmol) in anhydrous, argon-degassed DMF (5.0 mL) at 23 °C. After 2.5 h, the reaction was diluted with H_2O (50 mL). The mixture was extracted with Et_2O (3 x 50

mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (10:90 EtOAc:hexane eluent), affording a diastereomeric mixture of silyl ethers. This composite was carried on to the next reaction without further characterization.

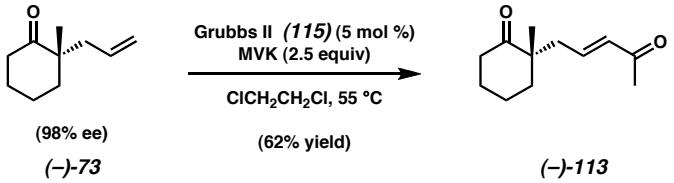
The mixture of silyl ethers was transferred to a round-bottom flask, which was charged with pyridine (freshly distilled from CaH_2, 5.0 mL). After cooling to 0 °C, $SOCl_2$ (192 μL, 2.64 mmol) was slowly introduced. After 1 h, H_2O (50 mL) was carefully added, followed by Et_2O (50 mL). The organic phase was collected, and the aqueous layer was extracted with Et_2O (2 x 20 mL). All organic layers were combined, washed with 1.0 M aq $CuSO_4$ (6 x 10 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (1:99 Et_2O:hexane → 5:95 Et_2O:hexane eluent), giving pure methylene cyclohexane **(–)-104** (306.3 mg, 18% yield from **99A** and **99B**) as a colorless oil. R_f 0.71 (10:90 EtOAc/hexane), (*p*-Anisaldehyde, blue spot); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.00 (app. s, 1H), 4.79 (app. s, 1H), 3.57 (app. t, J = 6.6 Hz, 2H), 1.80-1.64 (m, 2H), 1.62-1.16 (m, 8H), 1.11 (s, 3H), 1.10 (s, 3H), 1.04 (s, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.5, 108.7, 64.1, 41.8, 40.8, 39.4, 36.6, 36.5, 32.8, 29.9, 29.8, 28.4, 26.2 (3C), 18.7, 18.6, 5.0 (2C); IR (NaCl/$CDCl_3$): 3100, 2955, 2929, 2858, 1623, 1472, 1382, 1361, 1255, 1100, 940, 900, 836, 774 cm^{-1}; HRMS-EI$^+$ (*m/z*): [M]$^+$ calc'd for $C_{19}H_{38}SiO$, 310.2692; found, 310.2689. $[\alpha]^{24}_D$ –18.8° (*c* 1.90, $CHCl_3$), 91% ee.



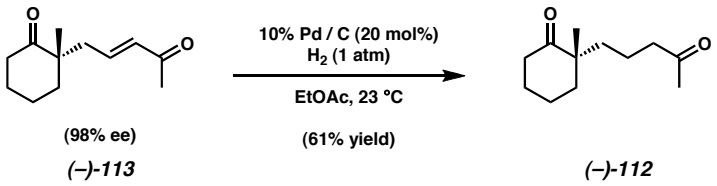
(–)-104 *(–)-94*

Carboxylic Acid (–)-94. A vessel containing methylene cyclohexane **(–)-104** (90.2 mg, 0.291 mmol) was charged with acetone (ACS grade, 5.0 mL), then treated with Jones reagent (1.0 M CrO_3, 4.0 H_2SO_4 in H_2O)(1.0 mL, dropwise from a glass pipet) at 23 °C. After 10 min, the reaction was carefully quenched with sat. aq Na_2SO_3 (2 mL). $CHCl_3$ (10 mL) was added, followed by 6 M aq HCl (5.0 mL). After 10 min, the reaction was diluted with H_2O (15 mL) and extracted with $CHCl_3$ (3 x 25 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (20:80 EtOAc:hexane eluent), giving carboxylic acid **(–)-94** (24.1 mg, 39% yield) as a colorless oil. R_f 0.17 (10:90 EtOAc/hexane), (*p*-Anisaldehyde, blue spot); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.06 (app. s, 1H), 4.80 (app. s, 1H), 2.36-2.04 (m, 3H), 1.82-1.66 (m, 2H), 1.60-1.30 (m, 5H), 1.11 (s, 3H), 1.10 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 109.6, 41.5, 40.6, 39.2, 36.5, 34.7, 32.7, 29.61, 29.56, 18.6; IR (NaCl/$CDCl_3$): 3000 (broad), 2927, 1708, 1462, 1414, 1380, 1296, 1095, 902 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{13}H_{22}O$, 210.1620; found, 210.1618. $[\alpha]^{24}_D$ –27.8° (*c* 1.205, $CHCl_3$), 91% ee.

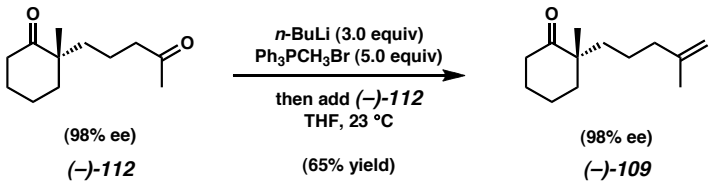
2.7.3 *Syntheses of Compounds Related to Dysidiolide*



Keto-Enone (–)-113. A vial was charged with allyl ketone **(–)-73** (45.2 mg, 0.297 mmol, 1.0 equiv, 98% ee), followed by a solution of methyl vinyl ketone (61.8 μL, 0.743 mmol, 2.5 equiv) in 1,2-dichloroethane (1.5 mL). Then, Grubbs 2nd generation catalyst (12.6 mg, 14.9 μmol, 5 mol%) was added. The vessel was sealed and warmed to 55 °C for 24 h. The reaction transitioned from maroon to deep green. The reaction was cooled to 23 °C and concentrated. The residue was purified by flash chromatography on silica gel (hexane → 20:80 EtOAc:hexane eluent), giving keto-enone **(–)-113** (35.7 mg, 62% yield) as a pale brown oil. R_f 0.23 (20:80 EtOAc/hexane), (UV, 254 nm); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (app. dt, J_d = 15.9 Hz, J_t = 7.4 Hz, 1H), 6.03 (app. d, J = 15.9 Hz, 1H), 2.50-2.26 (m, 2H), 2.40 (app. d, J = 6.9 Hz, 1H), 2.39 (app. d, J = 6.9 Hz, 1H), 2.22 (s, 3H), 1.91-1.81 (m, 2H), 1.80-1.60 (m, 4H), 1.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.6, 198.4, 144.1, 134.2, 48.7, 41.0, 38.9, 38.7, 27.4, 26.9, 23.1, 21.1; IR (NaCl/$CDCl_3$): 2935, 2866, 1704, 1672, 1626, 1426, 1361, 1254, 1124, 986 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{12}H_{18}O_2$, 194.1307; found, 194.1336. $[\alpha]^{22}_D$ –1.14° (*c* 1.415, $CHCl_3$), 98% ee.



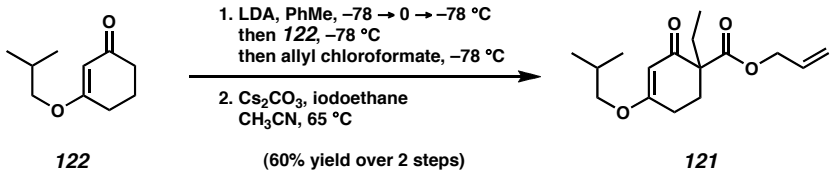
Diketone (–)-112. A round-bottom flask containing keto-enone **(–)-113** (28.0 mg, 0.144 mmol, 1.0 equiv) in EtOAc (3.0 mL) was sparged with argon for 2 min. Pd/C (10% w/w) (30.6 mg, 28.8 μmol, 20 mol) was introduced, and the reaction was cooled to –78 °C. It was purged/backfilled with vacuum/H_2 (1 atm) (3 x) and warmed to 23 °C and stirred under H_2 (1 atm) for 12 h. More EtOAc (5 mL) was added, and the reaction was sparged with argon to remove residual H_2. The material was filtered through a plug of silica gel with the aide of EtOAc. The filtrate was concentrated, affording diketone **(–)-112** (17.3 mg, 61% yield) as a pale yellow oil. R_f 0.26 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, peach spot); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (app. t, J = 6.6 Hz, 2H), 2.36 (app. t, J = 5.5 Hz, 2H), 2.11 (s, 3H), 1.90-1.44 (m, 9H), 1.36 (app. d, J = 7.7 Hz, 1H), 1.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.0, 208.8, 48.6, 44.0, 39.2, 38.9, 37.0, 30.1, 27.6, 22.7, 21.2, 18.2; IR (NaCl/$CDCl_3$): 2936, 2865, 1705, 1452, 1360, 1167, 1123, 1099 cm^{-1}; HRMS-EI$^+$ (*m/z*): [M]$^+$ calc'd for $C_{12}H_{20}O_2$, 196.1463; found, 196.1469. $[\alpha]^{22}_D$ –42.3° (*c* 0.865, $CHCl_3$), 98% ee.



Keto-Olefin (–)-109. A round-bottom flask was charged with methyl triphenyl phosphonium bromide (weighed in glovebox, 260 mg, 0.688 mmol, 5.0 equiv). THF (5.5

mL) was introduced, followed by *n*-BuLi (2.5 M in hexane, 165 μL, 0.413 mmol, 3.0 equiv) at 23 °C. After stirring for 1 h, a solution of diketone **(–)-112** (27.0 mg, 0.138 mmol, 1.0 equiv) in THF (2.0 mL) was added. 30 min later, the reaction was quenched with sat. aq NH_4Cl (4.0 mL). Then, the reaction was diluted with H_2O (20 mL) and hexane (15 mL). The biphasic mixture was extracted with EtOAc (4 x 20 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexane → 2:98 EtOAc:hexane eluent), giving keto-olefin **(–)-109** (17.3 mg, 65% yield) as a colorless oil. R_f 0.75 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, blue spot); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.70 (app. s, 1H), 4.65 (app. s, 1H), 2.46-2.26 (m, 2H), 1.98 (app. t, *J* = 7.1 Hz, 2H), 1.94-1.84 (m, 1H), 1.82-1.50 (m, 5H), 1.68 (s, 3H), 1.47-1.39 (m, 1H), 1.38 (app. ddd, *J* = 26.4 Hz, 12.6 Hz, 4.1 Hz, 1H), 1.22-1.10 (m, 2H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.3, 145.7, 110.3, 48.7, 39.6, 39.0, 38.4, 37.2, 27.7, 22.8, 22.5, 21.7, 21.2; IR (NaCl/$CDCl_3$): 3074, 2936, 2865, 1707, 1650, 1452, 1376, 1260, 1096, 1020, 886, 804 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{13}H_{22}O$, 194.1671; found, 194.1680. $[\alpha]^{21}_D$ –49.8° (*c* 0.865, $CHCl_3$), 98% ee.

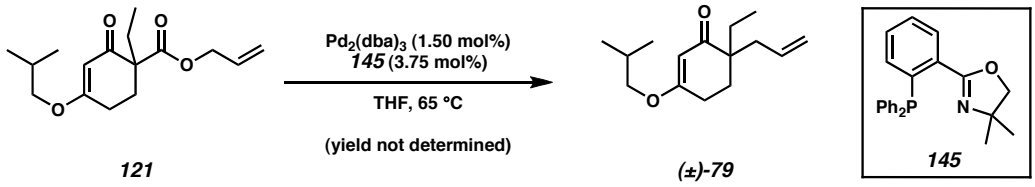
2.7.4 *Syntheses of Compounds Related to Aspidospermine*



α–Ethyl–α–Allyloxycarbonyl Vinylogous Ester 121. A round-bottom flask was flamedried under argon and charged with dry PhMe (320 mL). Then, *i*-Pr_2NH (12.81 mL, 91.3 mmol, 2.05 equiv) was introduced. The reaction was cooled to –78 °C, and *n*-BuLi (2.5 M in hexane, 35.68 mL, 89.2 mmol, 2.00 equiv) was added slowly. The reaction was warmed to 0 °C for 15 min, then promptly cooled back to –78 °C. Then, a solution of vinylogous acid **122** (7.50 g, 44.6 mmol, 1.00 equiv) in PhMe (20 mL) was added at –78 °C over a 5 min period. After 40 min had passed, the reaction was treated with allyl chloroformate (4.97 mL, 46.8 mmol, 1.05 equiv) over a 5 min timeframe at –78 °C. After 15 min, the reaction was warmed to 23 °C and stirred for 1 h, during which the reaction went from yellow to orange. Then, 1.0 M aq $KHSO_4$ (127 mL) was added with vigorous stirring, causing the reaction to turn yellow. The organic phase was collected. The aqueous layer was extracted with Et_2O (2 x 50 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated, giving a crude α–allyloxycarbonyl vinylogous ester as an orange oil, which was immediately used in the next reaction.

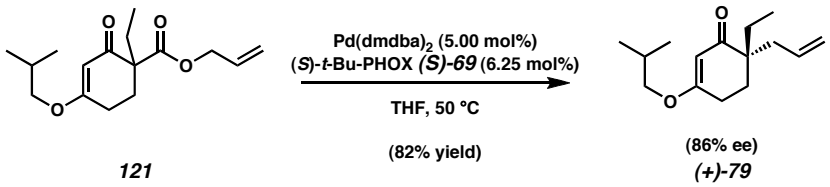
A round-bottom flask containing the crude vinylogous ester was charged with CH_3CN (45 mL), followed by iodoethane (14.26 mL, 178.4 mmol, 4.0 equiv relative to **122**). Anhydrous Cs_2CO_3 (29.06 g, 89.2 mmol, 2.0 equiv relative to **122**) was introduced, and the reaction was stirred vigorously at 65 °C for 12 h. The reaction was cooled to 23 °C and filtered over glass frits. The filtrate was concentrated in vacuo, and the residue

was purified by flash column chromatography on silica gel (hexane → 15:85 EtOAc:hexane eluent), giving semipure **121**. The product-containing fractions were combined and concentrated, and the resulting residue was purified on a second silica gel flash column (5:95 EtOAc:CH_2Cl_2 eluent), giving pure α–ethyl–α–allyloxycarbonyl vinylogous ester **121** (7.47 g, 60% yield over 2 steps) as a yellow oil. R_f 0.44 (20:80 EtOAc/hexane), (*p*-Anisaldehyde, brownish-blue spot); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.83 (ddt, J_{d1} = 16.2 Hz, J_{d2} = 10.7 Hz, J_t = 5.7 Hz, 1H), 5.31 (s, 1H), 5.24 (app. ddd, J = 16.2 Hz, 2.9 Hz, 1.5 Hz, 1H), 5.15 (app. ddd, J = 10.7 Hz, 2.9 Hz, 1.5 Hz, 1H), 4.56 (app. dt, J_d = 5.4 Hz, J_t = 1.5 Hz, 2H), 3.54 (d, J = 6.7 Hz, 2H), 2.68-2.28 (m, 2H), 2.42-2.26 (m, 1H), 1.99 (dq, J_d = 22.2 Hz J_q = 7.4 Hz, 1H), 1.97-1.85 (m, 2H), 1.78 (dq, J_d = 22.2 Hz, J_q = 7.4 Hz, 1H), 0.92 (d, J = 6.9 Hz, 6H), 0.86 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.8, 176.8, 171.6, 131.9, 118.2, 102.2, 74.9, 65.5, 56.3, 27.77, 27.76, 27.0, 26.4, 19.1, 9.1; IR (NaCl/$CDCl_3$): 3083, 2963, 2939, 2879, 1731, 1664, ,1610, 1470, 1384, 1236, 1195, 1178, 1119, 998, 919 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{16}H_{24}O_4$, 280.1687; found, 280.1687.



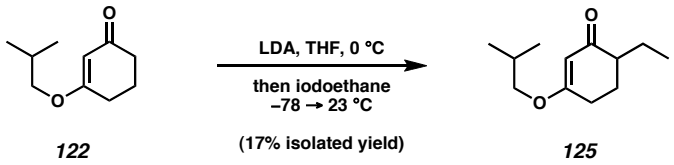
Racemic Allyl Vinylogous Ester (±)-79. In the glovebox, a vial was charged with $Pd_2(dba)_3$ (2.5 mg, 2.68 μmol, 1.50 mol%), then removed from the glovebox. Phosphinooxazoline **145** (2.4 mg, 6.71 μmol, 3.75 mol%) was then added, followed by THF (800 μL). The reaction was stirred for 30 min at 23 °C. Then, a solution of

α–ethyl–β–allyloxycarbonyl vinylogous ester **120** (50.0 mg, 0.179 mmol, 1.00 equiv) in THF (1.0 mL) was introduced. The vial was sealed and heated to 65 °C for 24 h. The reaction was cooled to 23 °C and split into two portions. Both portions were concentrated and purified on separate preparative silica gel TLC plates (20:80 EtOAc:hexane eluent), giving racemic allyl vinylogous ester **(±)-79** (yield not determined) as a colorless oil. The material was used for chiral HPLC assay development. Characterization is reported on pages 52 and 53 below.



Allyl Vinylogous Ester (+)-79 (86% ee). In the glovebox, a flamedried round-bottom flask was charged with $Pd(dmdba)_2$ (40.8 mg, 50.0 μmol, 5.00 mol%) and (*S*)-*t*-butyl phosphinooxazoline (24.2 mg, 62.5 μmol, 6.25 mol%) and removed from the glovebox. THF (30 mL) was added, and the reaction stirred at 23 °C for 30 min. Then, a solution of α–ethyl–β–allyloxycarbonyl vinylogous ester **121** (280 mg, 1.00 mmol, 1.00 equiv) in THF (3.0 mL) was added. The reactor was quickly fitted with a reflux condenser, and the reaction was heated to 50 °C under N_2 for 24 h. During this time the reaction went from orange to green. The reaction was cooled to 23 °C and concentrated. The residue was purified by flash chromatography on silica gel (hexane → 5:95 EtOAc:hexane eluent), giving allyl vinylogous ester **(+)-79** (193.4 mg, 82% yield) in 86% ee (as determined by chiral HPLC assay) as a yellow oil. R_f 0.58 (20:80 EtOAc/hexane), (UV, 254 nm); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.73 (app. dddd, J = 17.0 Hz, 10.5 Hz, 7.7 Hz, 6.9 Hz, 1H), 5.24 (s, 1H), 5.08-5.04 (m, 1H), 5.04-5.00 (m, 1H), 3.57 (d, J = 6.6 Hz, 2H), 2.42 (app.

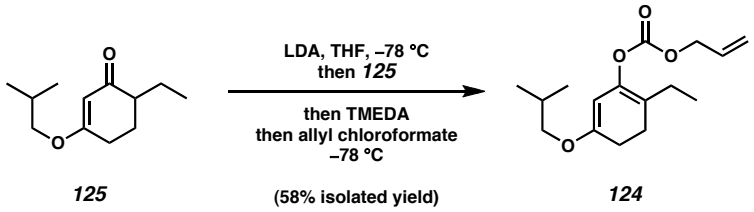
td, J_t = 6.6 Hz, J_d = 2.5 Hz, 2H), 2.38 (app. dd, J = 14.0 Hz, 7.1 Hz, 1H), 2.19 (app. dd, J = 14.0 Hz, 7.1 Hz, 1H), 1.85 (app. t, J = 6.6 Hz, 2H), 2.01 (app. septuplet, J = 6.6 Hz, 1H), 1.61 (dq, J_d = 22.2 Hz, J_q = 7.4 Hz, 1H), 1.55 (dq, J_d = 22.2 Hz, J_q = 7.4 Hz, 1H), 0.97 (d, J = 6.6 Hz, 6H), 0.84 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.0, 176.0, 134.8, 117.8, 102.0, 74.8, 46.6, 39.4, 29.0, 27.9, 27.6, 25.8, 19.2, 8.5; IR (NaCl/$CDCl_3$): 3074, 2963, 2936, 2878, 1652, 1612, 1384, 1193, 1178, 1003 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{15}H_{24}O_2$, 236.1776; found, 236.1788. $[\alpha]^{24}_D$ +10.4° (*c* 0.675, $CHCl_3$), 86% ee.



122 **(17% isolated yield)** ***125***

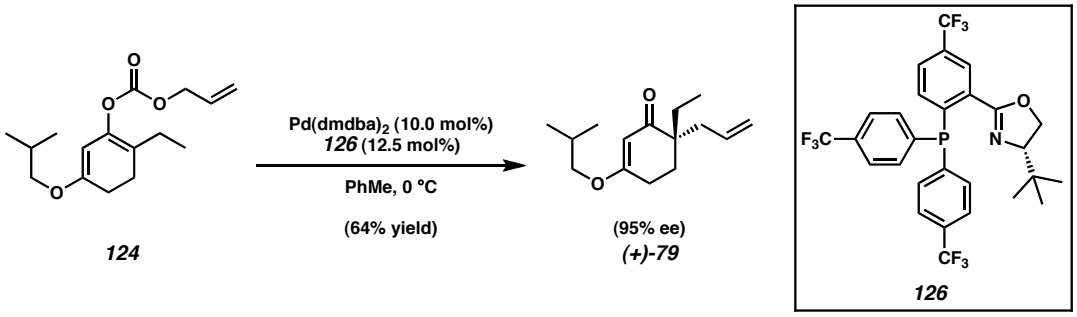
Ethyl Vinylogous Ester 125. A round-bottom flask was charged with THF (90 mL), and *i*-Pr_2NH (4.55 mL, 32.7 mmol, 1.10 equiv) was introduced. The reaction was cooled to 0 °C, and *n*-BuLi (2.5 M in hexane, 12.48 mL, 31.2 mmol, 1.05 equiv) was added slowly. 30 min later, a solution of vinylogous ester **122** (5.00 g, 29.7 mmol, 1.00 equiv) in THF (10 mL) was introduced. After 1 h, the reaction was cooled to –78 °C, and iodoethane (4.75 mL, 59.4 mmol, 2.00 equiv) was rapidly added. The reaction was allowed to warm to 23 °C over 4 h, during which it turned deep orange. The reaction was then quenched with sat. aq NH_4Cl (20 mL). Then, the reaction was diluted with H_2O (50 mL) and hexane (30 mL). The organic phase was collected, and the aqueous layer extracted with EtOAc (2 x 30 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (5:95 EtOAc:hexane → 20:80 EtOAc:hexane eluent), giving two sets of fractions. The first

contained impure **125** (which was not factored into the yield calculation), but the second set was combined and concentrated, affording pure ethyl vinylogous ester **125** (1.00 g, 17% isolated yield) as a pale yellow oil. R_f 0.43 (20:80 EtOAc/hexane), (UV, 254 nm); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.23 (s, 1H), 3.42 (d, J = 6.6 Hz, 2H), 2.37 (app. t, J = 6.2 Hz, 2H), 2.10-1.96 (m, 2H), 1.98 (septuplet, J = 6.6 Hz, 1H), 1.88-1.72 (m, 1H), 1.76-1.60 (m, 1H), 1.38 (app. dq, J_d = 22.2 Hz J_q = 7.4 Hz, 1H), 0.91 (d, J = 6.6 Hz, 6H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.6, 177.0, 102.3, 74.7, 46.6, 27.9, 27.8, 25.7, 22.5, 19.1, 11.5; IR (NaCl/$CDCl_3$): 2961, 2875, 1659, 1610, 1470, 1384, 1368, 1239, 1222, 1194, 990 cm^{-1}; HRMS-EI$^+$ (*m/z*): [M]$^+$ calc'd for $C_{12}H_{20}O_2$, 196.1463; found, 196.1461.



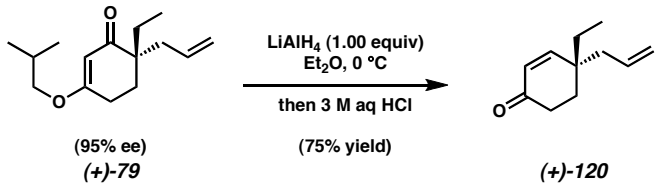
Enol Carbonate 124. A flamedried round-bottom flask under argon was charged with THF (28 mL), and *i*-Pr_2NH (858 μL, 6.12 mmol, 1.20 equiv) was introduced. The reaction was cooled to 0 °C, and *n*-BuLi (2.5 M in hexane, 2.20 mL, 5.51 mmol, 1.08 equiv) was added slowly. After 30 min, the reaction was cooled to –78 °C, and a solution of ethyl vinylogous ester **125** (1.00 g, 5.10 mmol, 1.00 equiv) in THF (3.0 mL) was added dropwise. After 30 min, TMEDA (918 μL, 6.12 mmol, 1.20 equiv) was added slowly below the solvent interface. Once 1 h had passed, a solution of allyl chloroformate (595 μL, 5.61 mmol, 1.10 equiv) in THF (3.0 mL) was added slowly below the solvent level. White precipitate began to form and the reaction was yellow. After 35 min,

conversion had reached 65% (as determined by ^{1}H NMR), and sat. aq $NaHCO_3$ (20 mL) was added at –78 °C. The reaction was warmed to 23 °C and diluted with hexanes (30 mL) and H_2O (30 mL). The organic phase was collected. The aqueous layer was extracted with EtOAc (3 x 30 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was concentrated from PhH, and then purified by rapid flash chromatography on florisil (5:95 EtOAc:hexane eluent), giving enol carbonate **124** (823 mg, 59% yield, 89% yield based on starting material consumption) as a yellow oil. R_f 0.65 (20:80 EtOAc/hexane), (UV, 254 nm); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.95 (app. ddt, J_{d1} = 17.1 Hz, J_{d2} = 10.4 Hz, J_t = 5.8 Hz, 1H), 5.37 (app. d, J = 17.1 Hz, 1H), 5.27 (app. d, J = 10.4 Hz, 1H), 4.72 (s, 1H), 4.65 (app. d, J = 5.8 Hz, 2H), 3.44 (d, J = 6.6 Hz, 2H), 2.30 (app. t, J = 4.4 Hz, 1H), 2.04 (app. q, J = 7.4 Hz, 2H), 1.94 (septuplet, J = 6.6 Hz, 1H), 0.95 (t, J = 7.4 Hz, 3H), 0.92 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 153.6, 140.1, 131.6, 119.1, 117.1, 91.8, 74.0, 68.8, 28.0, 27.3, 25.7, 22.4, 19.4, 12.4; IR (NaCl/$CDCl_3$): 3086, 2963, 2936, 2876, 2832, 1759, 1677, 1635, 1471, 1383, 1368, 1244, 1200, 1156, 1120, 1090, 1042, 993, 948 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{16}H_{24}O_4$, 280.1675; found, 280.1676.



Allyl Vinylogous Ester (+)-79 (95% ee). A flamedried round-bottom flask in the glovebox was charged with $Pd(dmdba)_2$ (40.8 mg, 50.0 μmol, 10.0 mol%) and

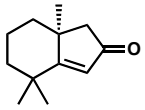
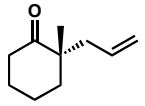
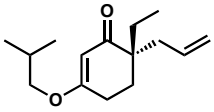
phosphinooxazoline **126** (37.0 mg, 62.5 μmol, 12.5 mol%) and removed from the glovebox. PhMe (14.7 mL) was introduced, and the reaction was stirred at 23 °C for 30 min and cooled to 0 °C. A solution of enol carbonate **124** (140 mg, 0.5 mmol, 1.00 equiv) in PhMe (2.0 mL) was introduced. After 9 h, the reaction was concentrated in vacuo to a total volume of ~3 mL, and the solution was directly loaded onto a silica gel flash column, then purified chromatographically (5:95 EtOAc:hexane eluent), giving allyl vinylogous ester **(+)-79** (75.1 mg, 64% yield) as a yellow oil in 95% ee as determined by chiral HPLC assay. $[\alpha]^{24}_{D}$ +10.7° (*c* 1.502, $CHCl_3$), 95% ee. Other characterization data can be found on pages 52 and 53 above.



γ-Ethyl-γ-Allyl Enone (+)-120. A round-bottom flask was charged with allyl vinylogous ester **(+)-79** (50.0 mg, 0.212 mmol, 95% ee, 1.00 equiv), and the reactor was purged with vacuum/argon (1 x). Et_2O (10.0 mL) was introduced, and the reaction was cooled to 0 °C. $LiAlH_4$ (8.0 mg, 0.212 mmol, 1.00 equiv) was then added, and the reaction was stirred for 1 h. The 3 M aq HCl (10.0 mL) was very cautiously added at 0 °C. Once the addition was complete, the reaction was warmed to 23 °C and stirred vigorously for 5 h. The reaction was transferred to a separatory funnel and extracted with Et_2O (3 x 10 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue, which contained some H_2O, was dissolved in $CHCl_3$ and dried with Na_2SO_4. The mixture was filtered, and the filtrate was concentrated, affording γ-ethyl-γ-allyl enone **(+)-120**

(26.2 mg, 75% yield) as a colorless, volatile oil. R_f 0.57 (20:80 EtOAc/hexane), (UV, 254 nm) ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.69 (d, J = 10.4 Hz, 1H), 5.91 (d, J = 10.4 Hz, 1H), 5.74 (app. ddt, J_{d1} = 16.7 Hz, J_{d2} = 9.9 Hz, J_t = 7.4 Hz, 1H), 5.10 (app. d, J = 9.9 Hz, 1H), 5.08 (app. d, J = 16.7 Hz, 1H), 2.42 (app. t, J = 6.9 Hz, 2H), 2.21 (app. d, J = 7.4 Hz, 2H), 1.86 (app. t, J = 6.9 Hz, 2H), 1.53 (dq, J_d = 22.2 Hz, J_q = 7.4 Hz, 1H), 1.47 (dq, J_d = 22.2 Hz, J_q = 7.4 Hz, 1H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.9, 158.3, 133.7, 128.4, 118.7, 41.9, 38.7, 34.0, 30.6, 30.4, 8.5; IR (NaCl/$CDCl_3$): 3077, 2966, 2929, 2880, 1682, 1452, 1387, 916, 800 cm^{-1}; HRMS-EI$^+$ (*m/z*): $[M]^+$ calc'd for $C_{11}H_{16}O$, 164.1201; found, 164.1207. $[\alpha]^{25}_D$ +27.5° (*c* 0.524, $CHCl_3$), 95% ee.

2.7.5 *Methods for the Determination of Enantiomeric Excess*

Entry	Substrate	Assay	Column	Method	Retention Time (min)	
1.	 (***S*)-(–)-143**	*Enantiomeric Excess*	Chiral HPLC	3%EtOH/Hex monitor@254nm	Minor (***R***)	9.1
			Chiralcel AD Column	20 min	Major (***S***)	10.2
2.	 (***S*)-(–)-73**	*Enantiomeric Excess*	Chiral GC	100 °C isotherm	Major (***S***)	11.1
			Agilent GT-A Column	40 min	Minor (***R***)	12.7
3.	 (***S*)-(+)-79**	*Enantiomeric Excess*	Chiral HPLC	2%EtOH/Hex monitor@254nm	Major (***S***)	7.4
			Chiralcel OD Column	20 min	Minor (***R***)	8.2

2.8 Notes and Citation

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(1) For reviews on catalytic enantioselective methods for quaternary stereocenter generation, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388-401. (b) Christoffers, J.; Mann A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591-4597. (c) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363-5367.

(2) For a review of enantioselective decarboxylative alkylations, see: Mohr, J. T.; Stoltz, B. M. *Chem. Asian J.* **2007**, (In Press: DOI: 10.1002/asia.200700183).

(3) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044-15045.

(4) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924-6927.

(5) The famous Japanese building Konjiki-do, a structure within the Chuson-ji Temple of Iwate Prefecture, was constructed of wood from *Thujopsis dolabrata.* It is speculated that the terpenes in the wood oil, which have antifungal and insecticidal properties, have preserved the wood. For this reason, the temple lasted around 840 years without significant restoration. For an account, see: Yoshihiko, I.; Yasuhiro, M.; Yoshikazu, S.; Toshihoro, O.; Nakao, I. *Biocontrol science* **2006**, *11*, 49-54.

(6) Mayurone was originally isolated from *Mayur pankhi*, see: (a) Chetty, G. L.; Dev, S. *Tetrahedron Lett.* **1965**, *6*, 3773-3776. It was later found in *Thujopsis dolabrata*, see: (b) Ito, S.; Endo, K.; Honma, H.; Ota, K. *Tetrahedron Lett.* **1965**, *6*, 3777-3781.

(7) α-Cadinol has been implicated as an active contributor to the disease-resistance of *Thujopsis dolabrata*, see: Yatagai, M. *Aroma Res.* **2007**, *8*, 88-93.

(8) (a) Yano, M. *J. Soc. Chem. Ind. Jpn.* **1913**, *16*, 443. (b) Uchida, S. *J. Soc. Chem. Ind. Jpn.* **1928**, *31*, 501.

(9) (a) Miyazaki, Y. *Mokuzai Gakkaishi* **1996**, *42*, 624-626. (b) Yatagai, M. *Curr. Top. Phytochem.* **1997**, *1*, 85-97. (c) Hiramatsu, Y.; Miyazaki, Y. *J. Wood. Sci.* **2001**, *47*, 13-17.

(10) For the establishment of the relative stereochemistry of thujopsene, see: (a) Nozoe, T.; Takeshita, H.; Ito, S.; Ozeki, T.; Seto, S. *Chem. Pharm. Bull.* **1960**, *8*, 936-938. (b) Norin, T. *Acta Chem. Scand.* **1961**, *15*, 1676-1694. (c) Sisido, K.; Nozaki, H.; Imagawa, T. *J. Org. Chem.* **1961**, *26*, 1964-1967. (d) Norin, T. *Acta Chem. Scand.* **1963**, *17*, 738-748.

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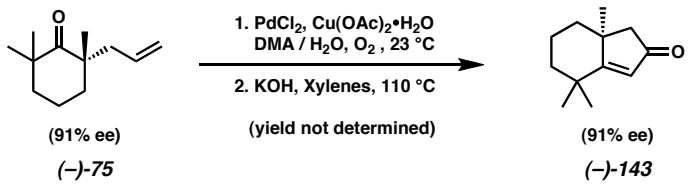

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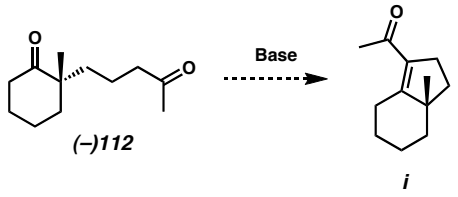
(20) The side products appeared to arise via intramoleclar aldol consensation:



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(27) Unreacted starting material (**125**) could be recovered at the end of the reaction.

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(35) When a subscript is shown with the coupling constant, it indicates what type of splitting the constant is associated with. For example (td, J_t = 5.0 Hz, J_d = 3.3 Hz, 1H) indicates that the triplet splitting has a 5.0 Hz coupling constant and the doublet has a 3.3 Hz coupling constant.