CHAPTER 3

Formal Synthesis of Classical Natural Product Target Molecules via Palladium-Catalyzed Enantioselective Alkylation[÷]

3.1 Introduction

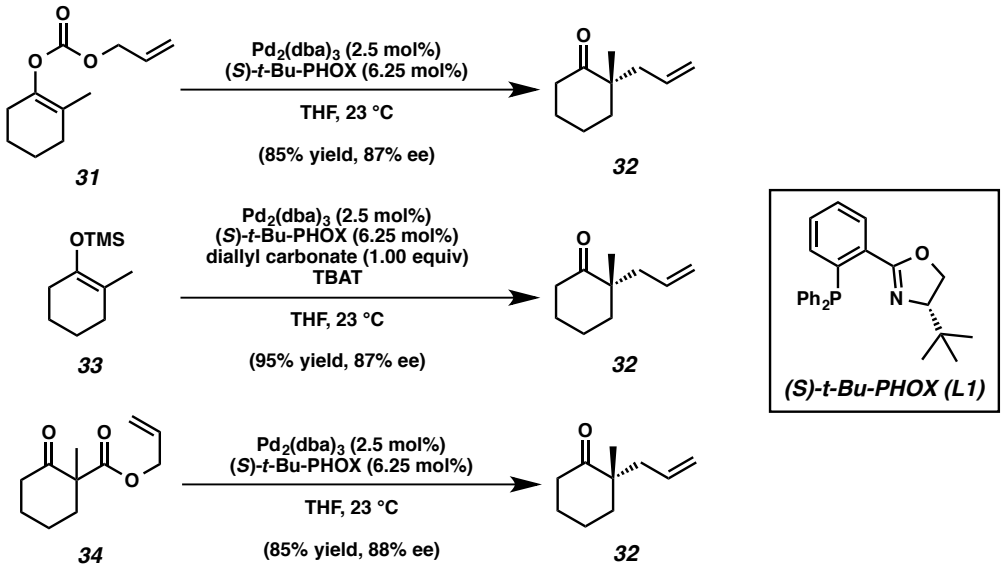
Catalytic enantioselective allylic alkylation has emerged as a powerful method for the construction of building blocks bearing quaternary carbon and fully substituted tertiary centers.[1,2] A recent addition developed by our laboratory is the allylic alkylation of nonstabilized enolate precursors to form α-quaternary carbonyl compounds (Scheme 3.1).[3] Once the key stereocenter is set by this chemistry, further elaboration allows access to many bioactive small molecules. In our lab alone, this palladium-catalyzed

---

[÷] This work was performed in collaboration with Dr. Marc Liniger. Drs. Ryan M. McFadden and Jenny L. Roizen also contributed significantly to this work. This chapter was partially adapted from the publication: Liu, Y.; Liniger, M.; McFadden, R. M.; Roizen, J. L.; Malette, J.; Reeves, C. M.; Behenna, D. C.; Seto, M.; Kim, J.; Mohr, J. T.; Virgil, S. C.; Stoltz, B. M. *Beilstein J. Org. Chem.* **2014**, *10*, 2501–2512. Open Access 2014 Beilstein-Institut.

alkylation has enabled the enantioselective total syntheses of dichroanone,[4] elatol,[5] cyanthiwigins,[6,7,8] carissone,[9] cassiol,[10] chamigrenes,[11] and liphagal.[12] Other labs have also utilized our method in natural products total synthesis.[13,14] Often, it is the case that a new technology that allows the synthesis of building blocks will open up new avenues to complex structures of long standing interest.[15,16] Herein we detail the application of this asymmetric chemistry in formal total syntheses of "classic" natural product targets across a range of compound families by strategic selection of allylic alkylation substrates and subsequent product transformations.

Scheme 3.1 Three classes of Pd-catalyzed enantioselective allylic alkyations

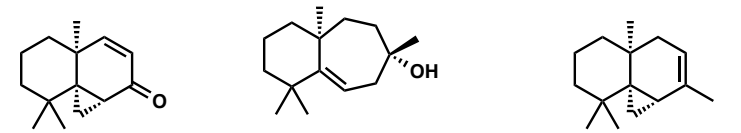


3.2 Thujopsene

The Japanese hiba tree, *Thujopsis dolabrata* has been used for centuries as decoration and within traditional architechture.[17] The plant is a member of the order *Cupressaceae*, and its fragrant wood oil contains numerous sesquiterpenes including

mayurone (**35**),[18,19] widdrol (**36**),[20] and (–)-thujopsene (**37**) (Figure 3.1).[21,22] The wood oil is a potent dust mite deterrent; thus, in addition to its ornamental value, the hiba tree also provides and environmentally benign means of pest control.[23,24]

Figure 3.1 Selected natural products from Thujopsis dolabrata

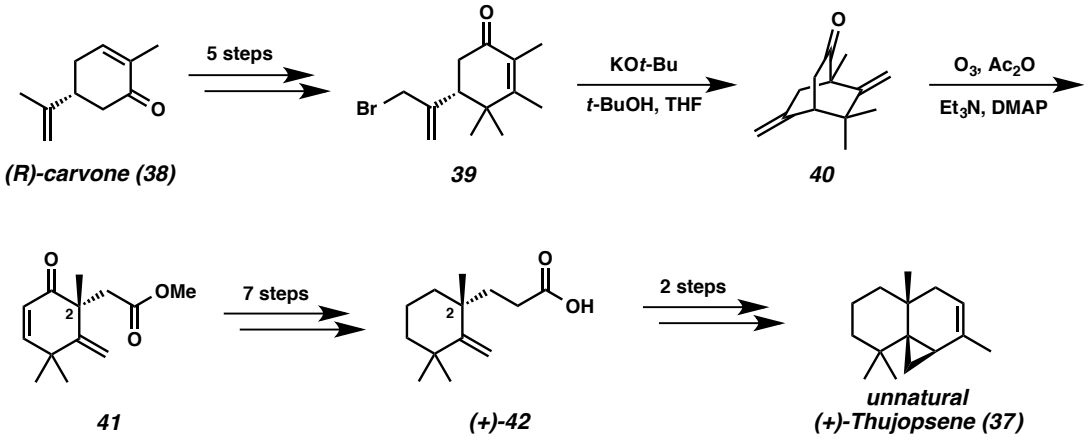


Mayurone (35) ***Widdrol (36)*** ***(–)-Thujopsene (37)***

(–)-Thujopsene (**37**) has attractive features to the synthetic chemist. Its tricyclo[5.4.0.0^{1,3}]undecane skeleton contains three contiguous all-carbon quaternary centers, two of which are stereogenic. Being a hydrocarbon, (–)-thujopsene (**37**) has few natural handles for retrosynthetic analysis. Inspired by the complexity of this relatively small natural product, several total syntheses of racemic **37** have been reported[25,26,27,28,29] along with at least two enantioselective routes.[30,31,32]

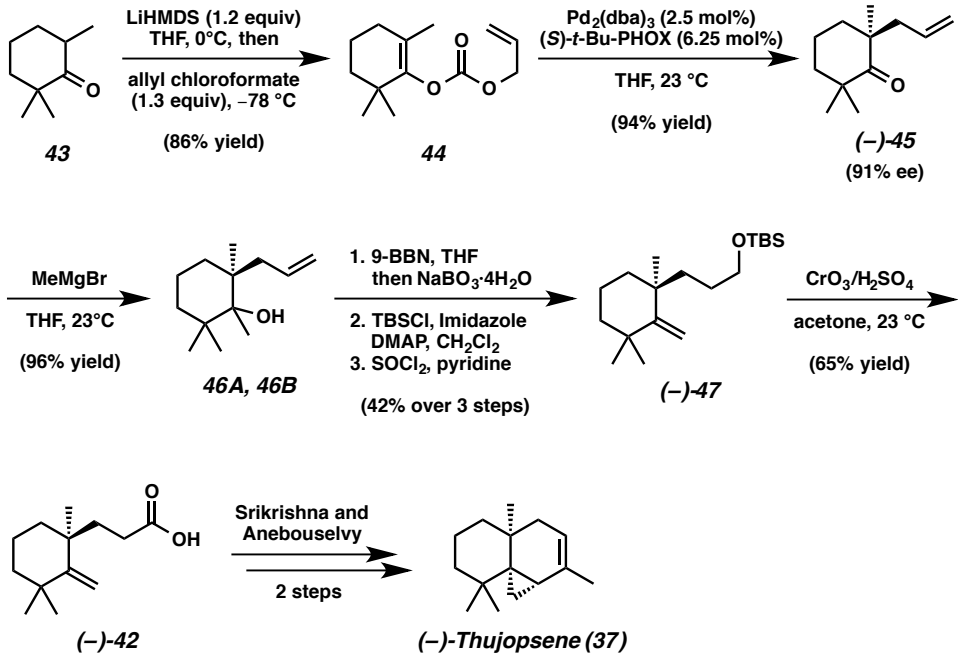
One enantiospecific total synthesis of (+)-thujopsene (**37**) by Srikrishna and Anebouselvy began with (*R*)-carvone (**38**) (Scheme 3.2).[33] During the total synthesis, the authors prepared carboxylic acid (+)-**42** over a 14-step sequence. We planned to intercept the antipode of (+)-**42** using the palladium-catalyzed enantioselective alkylation chemistry described above.

Scheme 3.2 Srikrishna and Anebouselvy's approach to thujopsene



We commenced a formal total synthesis of (–)-Thujopsene (**37**) with the goal of improved efficiency compared to the Srikrishna/Anebouselvy route and to use enantioselective palladium catalysis to install the initial stereocenters (Scheme 3.3). Treatment of **43** with LiHMDS in THF, followed by allyl chloroformate, furnished the known carbonate **44** in high yield.[34] This substrate smoothly undergoes palladium-catalyzed enantioselective decarboxylative allylation in the presence of (*S*)-*t*-Bu-PHOX (**L1**), giving allyl ketone (–)-**45** in 94% yield and 91% ee.[34] Treatment of the ketone (–)-**45** with MeMgBr at 23 ºC provided a mixture of two diastereomeric alcohols **46A** and **46B** in 96% yield. Without separation, the diastereomers were rapidly carried through a three-step sequence of hydroboration/oxidation, terminal alcohol silylation, and tertiary alcohol dehydration, affording methylene cyclohexane (–)-**47**. Treatment of this silyl ether with Jones reagent simultaneously cleaved the silyl group and oxidized the resulting alcohol, furnishing carboxylic acid (–)-**42** in 65% yield. With this enantioenriched acid in hand, the formal total synthesis of (–)-thujopsene (**37**) is completed in only 9 steps from trimethylcyclohexanone (**43**).

Scheme 3.3 Formal total synthesis of (–)-thujopsene

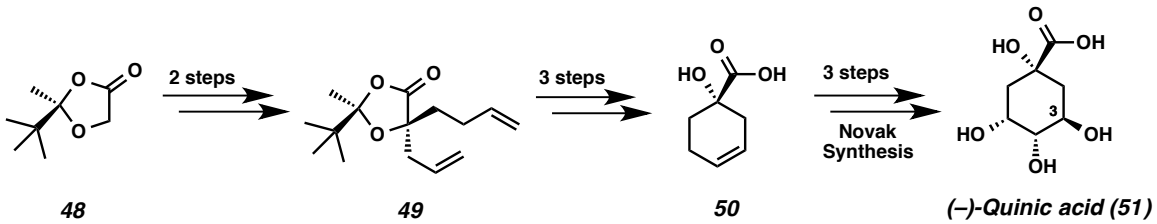


3.3 Quinic Acid

(–)-Quinic acid (**51**)[35,36] serves as a useful chiral building block that has been employed in numerous syntheses,[37] including our own syntheses of (+)- and (–)-dragmacidin F,[38,39,40,41] and the initial commercial-scale synthesis of Tamiflu.[42] In Renaud's formal total synthesis of (–)-quinic acid (**51**),[35] a key carboxylic acid **50** was accessed, intercepting Novak's older synthesis of the natural product (Scheme 3.4).[36] To begin, Renaud transformed the chiral glycolic acid ketal **48** (enantioenriched to 80% ee) to the more elaborate diene **49** via two diastereoselective alkylations. After a sequence of three reactions including removal of the pinacolone portion of the auxiliary, carboxylic acid **50** could be accessed. Novak's synthesis applied a bromolactonization of **50** to build

in the requisite syn relationship between the carboxylate group and the 3-hydroxyl group, ultimately leading to quinic acid.

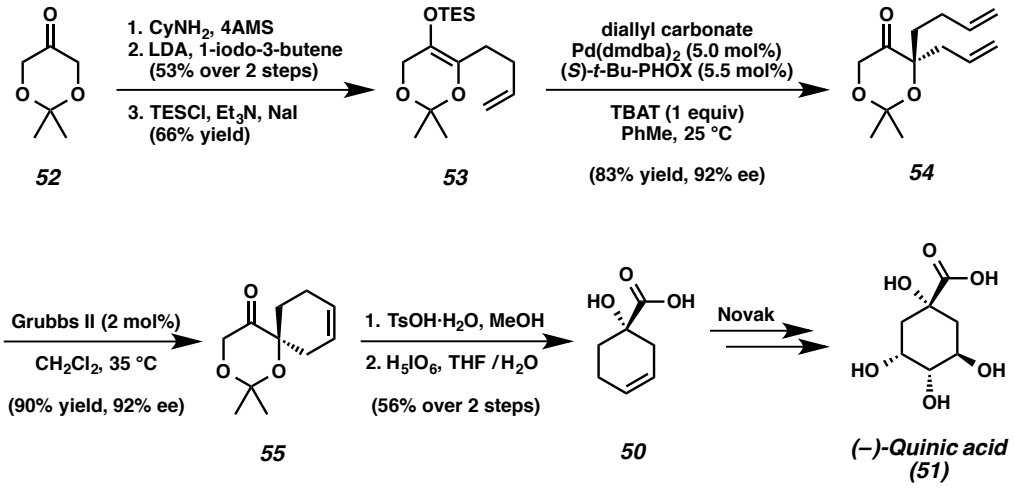
Scheme 3.4 Renaud's formal total synthesis of quinic acid



Unlike the allylic alkylations in Scheme 3.1, which form all-carbon stereocenters, we envisioned a unique modification of the silyl enol ether version to access nonracemic tertiary alcohols (Scheme 3.5).[43] The planned modification would involve the use of dioxanone-derived substrates instead of the prototypical cycloalkanone-derived ones. To demonstrate this new technology in the context of formal total synthesis, we chose to intercept the acid **50** in the Renaud and Novak routes to quinic acid (**51**). Conversion of dioxanone **52** to a cyclohexylimine enabled alkylation via a metalloenamine. On acidic work-up, imine hydrolysis furnished an alkylated dioxanone in good yield. The targeted silyl enol ether **53** was prepared by thermodynamic silylation in 66% yield.[43] Optimal conversions and enantioselectivities were achieved from triethylsilyl enol ether **53** on exposure to $Pd(dmdba)_2$ (5 mol%), (*S*)-*t*-BuPHOX (**L1**, 5.5 mol%), and diallyl carbonate (1.05 equiv) at 25 °C, in PhMe with an equivalent of $Bu_4NPh_3SiF_2$ (TBAT).[43] Recognizing that enantioenriched α,ω-dienes could be transformed into cycloalkenes with a stereocenter remote to the olefin,[44] chiral diene **54** was submitted to ring closing metathesis to generate **55** in 90% yield and 92% ee.[43] Cyclohexene **55** readily undergoes

acetonide cleavage and periodic acid oxidation to provide carboxylic acid (*S*)-**50**,[43] completing the formal synthesis of (–)-quinic acid (**51**). Additionally, one could in principle also access the less commercially abundant antipode (+)-quinic acid (**51**) using the catalyst (*R*)-*t*-Bu-PHOX.

Scheme 3.5 Formal total synthesis of (–)-quinic acid

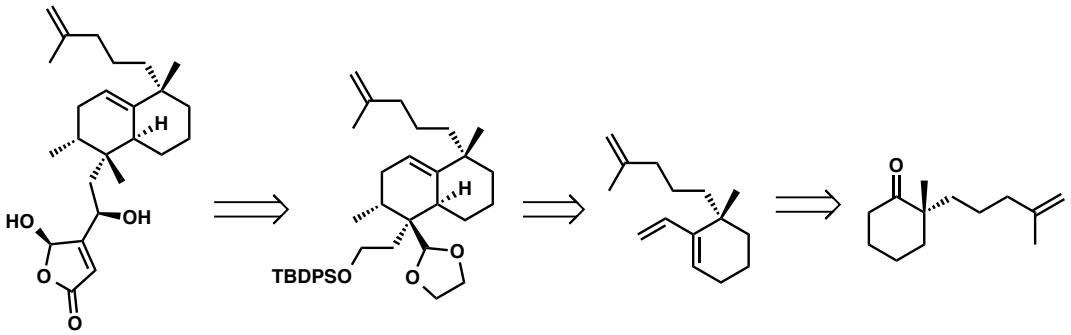


3.4 Dysidiolide

Dysidiolide (**56**, Scheme 3.6) was isolated from the marine sponge *Dysidea etheria* and found to have inhibitory activity toward protein phosphatase cdc25, with an IC_{50} value of 9.4 μM.[45] This enzyme is a member of the protein family responsible for dephosphorylation of cyclin-dependent kinases.[46] Thus, inhibitors of cdc25 might allow for targeted cell-cycle disruption.[45] The relative stereochemistry of dysidiolide (**56**) was determined via single-crystal X-ray diffraction analysis, revealing a molecule with six stereocenters, one of which is a quaternary carbon.[45] Several groups have reported total syntheses of this natural product,[47,48,49,50,51,52,53] three of which are enantioselective.[54,55,56]

In Danishefsky's approach to racemic dysidiolide, the cyclohexene ring of **57** was installed via diastereoselective Diels-Alder reaction of a transient dioxolenium dienophile and chiral vinylcyclohexene **58**.[48] Triene **58** was prepared from α-quaternary ketone (±)-**59** in racemic form. We anticipated the interception of (–)-**59** in Danishefsky's route using enantioselective palladium-catalyzed allylic alkylation to set the quaternary stereocenter.

Scheme 3.6 Danishefsky's approach to (±)-dysidiolide

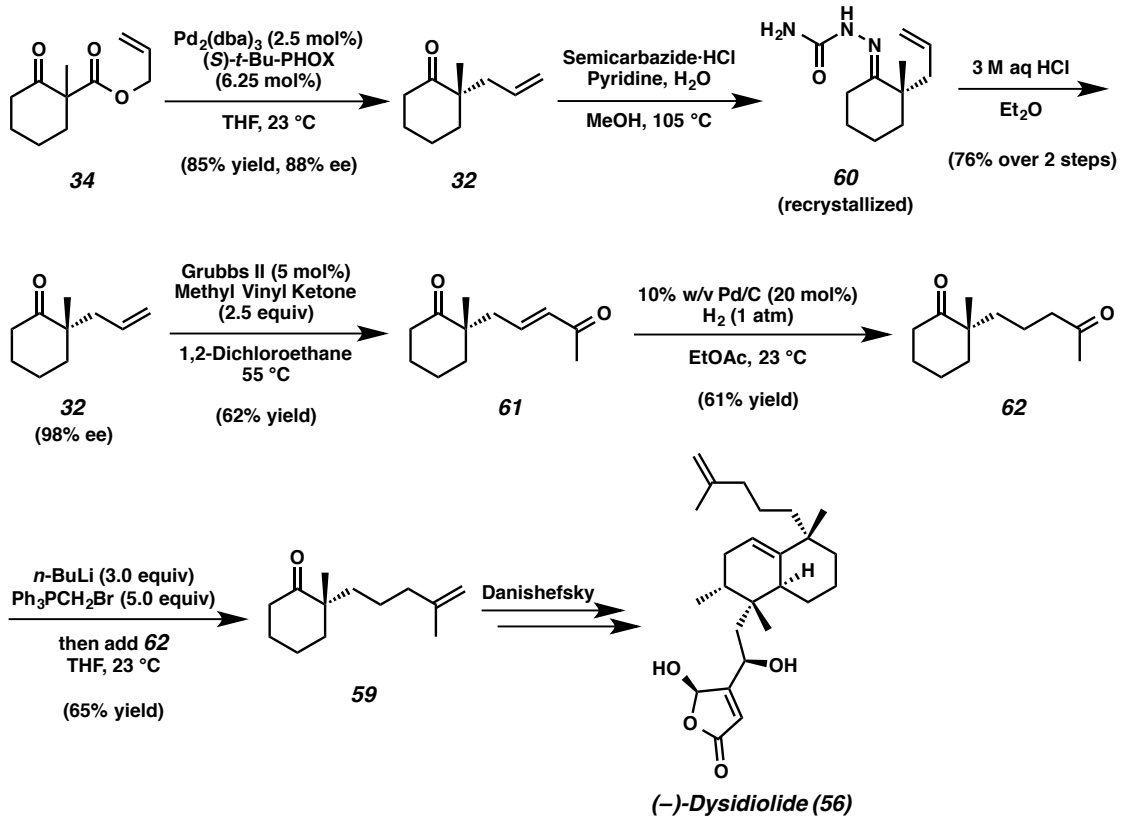


(–)-Dysidiolide (56) ***57*** ***58*** ***59***

The formal total synthesis of (–)-Dysidiolide (**56**) commenced with known allyl β-ketoester **34** (Scheme 3.7), which was converted to 2-allyl-2-methylcyclohexanone (**32**) in 85% yield and 88% ee[57] with a catalytic amount of Pd_2dba_3 and (*S*)-*t*-BuPHOX (**L1**, Scheme 3.1). The allyl ketone was enriched to 98% ee via the semicarbazone **60**.[58] Using the Grubbs 2nd generation metathesis catalyst, allyl ketone (–)-**32** was crossed with methyl vinyl ketone in 62% yield.[34] Reduction of enone **61** was achieved in the presence of Pd/C with H_2 in EtOAc to furnish diketone **62**.[34] Chemoselective Wittig mono-olefination of **62** provided ω-enone (–)-**59**, spectroscopically identical to the material in Danishefsky's racemic synthesis. This formal synthesis shows the power of the

enantioselective allylic alkylation to access formerly racemic constructs as single enantiomers; Danishefsky's synthesis is now rendered enantioselective.

Scheme 3.7 Formal total synthesis of (–)-dysidiolide



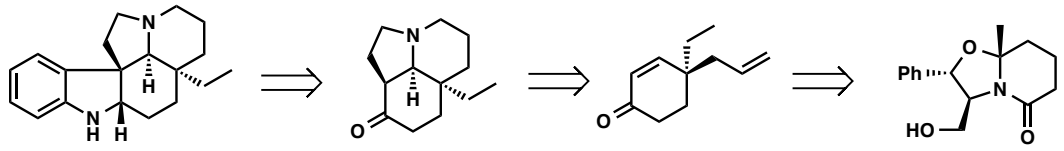
3.5 Aspidospermine

The aspidosperma alkaloids have garnered much attention as beautiful targets for the synthetic chemist. Most of the 250-plus compounds in this class share a pentacyclic core, from the clinical anti-cancer therapeutics vincristine and vinblastine to the simpler aspidospermidine.[59] To address the challenging synthetic features of the aspidosperma alkaloids, many clever synthetic approaches have been reported.[60,61] One popular target in this family is aspidospermine (**63**, Scheme 3.8). Although its medicinal potency is

inferior to other members of the class, this alkaloid has served as a proving ground for many synthetic chemists.

In 1989, Meyers reported an enantioselective synthesis of the (4a*S*,8a*R*,8*S*)-hydrolilolidone core **64**[60,62] present in aspidospermine (**63**), and thus a formal total synthesis of the alkaloid itself,[63] intercepting Stork's classic route.[64] One precursor described in the core synthesis is enone (–)-**65**, which bears the quaternary stereocenter of the natural product. Contrasting Meyers' approach, which employed a chiral auxiliary as part of **66**, we thought a catalytic enantioselective alkylation strategy would be ideal for a formal total synthesis of natural (–)-aspidospermine (**63**) via the antipode of (–)-**65**.

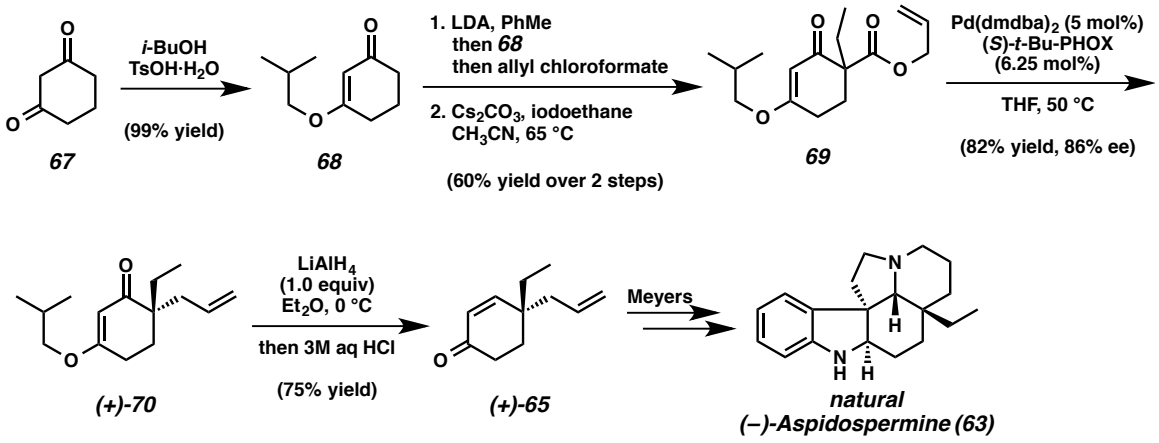
Scheme 3.8 Meyers' approach to unnatural (+)-aspidospermine



The formal synthesis began with 1,3-cyclohexanedione (**67**), which was converted to isobutyl vinylogous ether **68** under acid promotion (Scheme 3.9).[65] The β-ketoester **69** was prepared using a two-step sequence of acylation and alkylation, then treated with the (*S*)-*t*-Bu-PHOX catalyst system (with $Pd(dmdba)_2$) to generate (+)-**70** in 86% ee. The challenge of installing the γ-stereocenter of the target (+)-**65** was addressed as follows: $LiAlH_4$ treatment of (+)-**70** gave exclusive 1,2-reduction. When the crude product was hydrolyzed, β-elimination gave the desired enone (+)-**65**. The overall formal synthesis

represents a previously rare but now readily accessible example of enantioselective Stork-Danheiser chemistry.[66,67]

Scheme 3.9 Formal total synthesis of (–)-aspidospermine



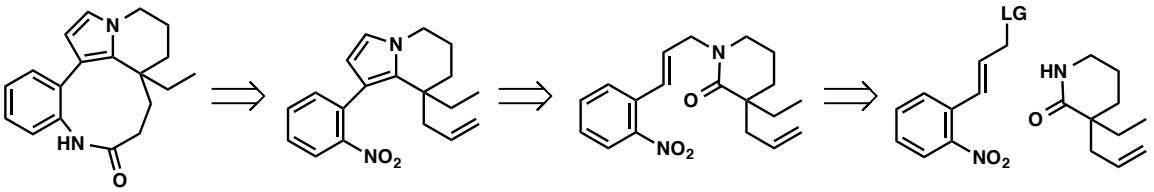
3.6 Rhazinilam

(–)-Rhazinilam (**71**) has been isolated from various plants including *Rhazya strica decaisne*,[68] *Melodinus australis*,[69] and *Kopsia singapurensis*.[70] Shortly after the first isolation, its structure was elucidated by single crystal X-ray diffraction analysis.[71] It features a tetracyclic scaffold with a nine-membered ring and an all-carbon quaternary stereocenter. This alkaloid is a microtubule-disrupting agent that displays similar cellular effects to paclitaxel.[72,73] Because of its biological activities and potential pharmaceutical use, many groups have pursued its total synthesis,[74,75,76,77] including a number of enantioselective syntheses.[78,79,80,81,82]

In 2001, Magnus and Rainey reported a total synthesis of rhazinilam in racemic form (Scheme 3.10).[83] In their approach, the first retrosynthetic disconnection of the amide C–N bond in the nine-membered ring led to tricyclic compound **72**. The pyrrole

ring of **72** was formed by intramolecular condensation of cinnamyl amide **73**, which is prepared via union of quaternary piperidinone **25** and cinnamyl electrophile **74**. We envisioned that our allylic alkylation of lactam enolates would furnish enantioenriched piperidinone **25**, and thus a single enantiomer of rhazinilam may be prepared.

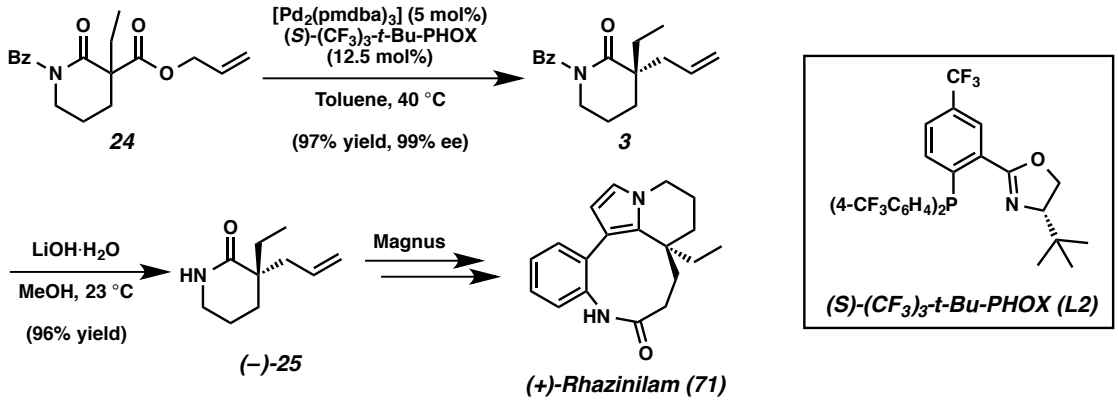
Scheme 3.10 Magnus' approach to rhazinilam



Rhazinilam (71) ***72*** ***73*** ***74*** ***(±)-25***

The formal synthesis of (+)-rhazinilam commenced with palladium-catalyzed decarboxylative allylic alkylation of known carboxy-lactam **24** to afford benzoyl-protected piperidinone **3** in 97% yield and 99% ee (Scheme 3.11).[84] Cleavage of the benzoyl group under basic conditions furnished piperidinone (–)-**25**,[84] which can be advanced to (+)-rhazinilam via Magnus' route. This formal synthesis demonstrates the utility of our recently developed asymmetric lactam alkylation chemistry.

Scheme 3.11 Formal total synthesis of (+)-rhazinilam

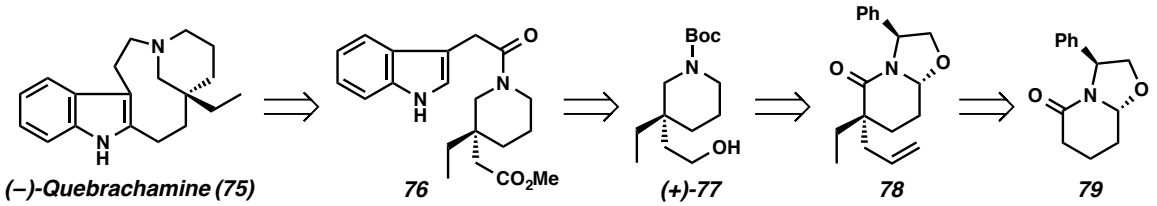


3.7 Quebrachamine

Quebrachamine (**75**) is an indole alkaloid isolated from the *Aspidosperma quebracho* tree bark.[85] It has been found to possess adrenergic blocking activities for a variety of urogenital tissues.[86] Structurally, it features a tetracycle including an indole nucleus, a 9-membered macrocycle, and an all-carbon quaternary stereocenter. Due to its structural complexity and biological activities, quebrachamine has received considerable attention from the chemistry community. A number of total syntheses have been reported,[87,88,89] with several examples of asymmetric syntheses.[90,91,92]

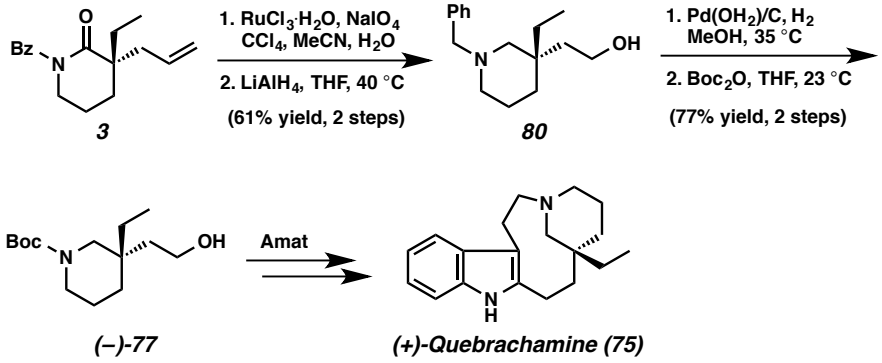
In 2007, Amat reported an enantioselective total synthesis of quebrachamine (Scheme 3.12).[93] In their planning, disconnection at the macrocycle led to amide **76**, which was prepared from 3,3-disubstituted piperidine (+)-**77**. The all-carbon quaternary stereocenter in **78** was installed by double alkylation of lactam **79**, using an auxiliary to control the stereoselectivity. We envisioned that an alternative way of constructing this motif would again make use of our recently developed palladium-catalyzed asymmetric alkylation of lactam enolates.

Scheme 3.12 Amat's approach to quebrachamine



The formal synthesis of (+)-quebrachamine commenced with benzoyl lactam **3** (Scheme 3.13), which was prepared in excellent yield and ee by alkylation of carboxy-lactam **24** (see Scheme 3.11).[84] Oxidative cleavage of the terminal double bond and subsequent reduction with $LiAlH_4$ afforded *N*-benzyl piperidine-alcohol **80**.[84] Hydrogenolysis of the *N*-benzyl group and re-protection with di-*tert*-butyl dicarbonate furnished *N*-boc piperidine-alcohol (–)-**77**,[84] thus intercepting an intermediate in Amat's synthesis of quebrachamine.

Scheme 3.13 Formal total synthesis of (+)-quebrachamine



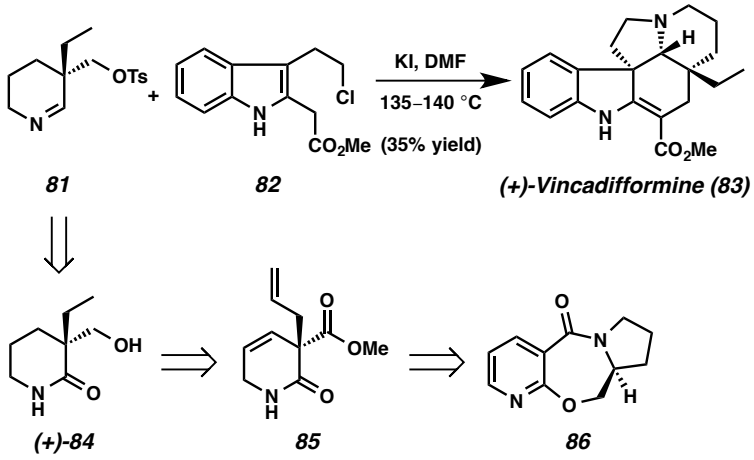
3.8 Vincadifformine

Vincadifformine (**83**) was isolated in both enantioenriched and racemic forms from the leaves and roots of *Rhazya stricta* in 1963.[94] Not only is it a representative

member of the *Aspidosperma* alkaloid family, but it also holds particular significance as a valuable precursor to pharmaceutically important vincamine, vincamone, and cavinton.[95,96,97,98] The molecule has a fused pentacyclic framework with three contiguous stereocenters, two of which are all-carbon quaternary centers. The medicinal relevance and structural complexity of vincadifformine have led to a large number of total syntheses,[99,100,101,102,103,104,105] including several enantioselective examples.[106,107,108,109]

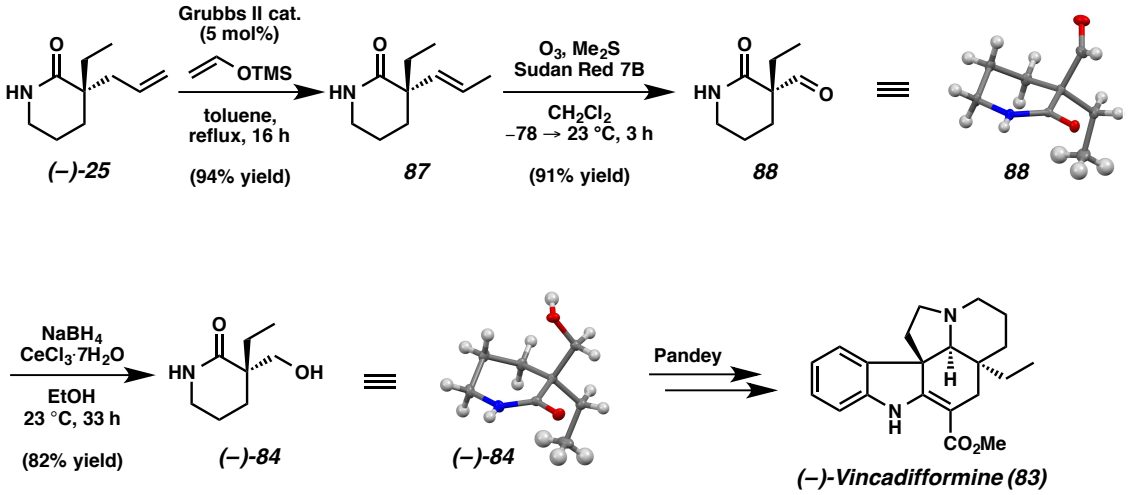
Recently, Pandey reported a highly efficient synthesis of (+)-vincadifformine (Scheme 3.14).[107] The key step in the synthesis was an iminium ion cascade reaction that formed the fused ring systems by coupling 3,3-disubstituted tetrahydropyridine **81** with indole derivative **82**. The former coupling partner was derived from chiral α-quaternary lactam (+)-**84**, which was constructed using a chiral auxiliary strategy. We envisioned that chiral lactam **84** could again be readily accessed by our palladium-catalyzed enantioselective alkylation chemistry.

Scheme 3.14 Pandey's approach to (+)-vincadifformine



The formal synthesis of (–)-vincadifformine commenced with ruthenium-catalyzed isomerization of the terminal olefin moiety in unprotected piperidinone (–)-**25** to produce internal olefin **87** (Scheme 3.15).[110] Ozonolysis of the double bond furnished aldehyde **88**, which was reduced under Luche conditions to alcohol (–)-**84**, a compound identical in structure and enantiomeric to the intermediate employed by Pandey in the synthesis of (+)-vincadifformine.

Scheme 3.15 Formal total synthesis of (–)-vincadifformine

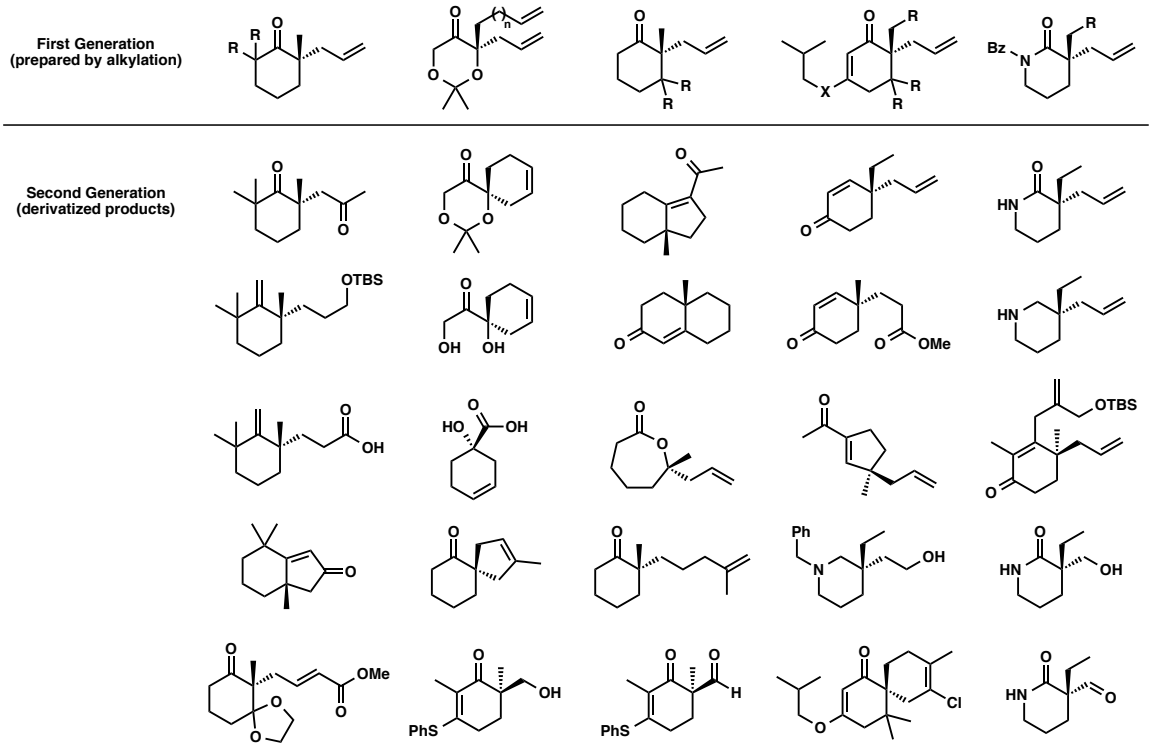


3.9 Conclusions

The development of a series of Pd-catalyzed methods for constructing stereogenic quaternary carbons has provided two generations of building blocks (Figure 3.2). The described derivatization enabled the formal total syntheses of an array of classic natural products including sugar derivatives, terpenes, and alkaloids, adding significantly to the growing list of uses for this powerful C–C bond construction. An efficient route to the sesquiterpenoid (–)-thujopsene (**37**) has been delineated, allowing access to the

compound's natural antipode. Our lab's novel approach to quinic acid (**51**) allowed access to either enantiomer of this important substance. We have also intercepted a key intermediate in Danishefsky's synthesis of dysidiolide (**56**), rendering the former racemic route enantioselective. Additionally, a rapid approach to a compound in Meyers' formal synthesis of aspidospermine (**63**) granted access to the natural product without the use of a chiral auxiliary. Finally, we have demonstrated the application of lactam alkylation products in the catalytic asymmetric syntheses of rhazinilam (**71**), quebrachamine (**75**), and vincadifformine (**83**). The powerful catalytic enantioselective allylic alkylation will undoubtedly enable new synthetic endeavors in the context of both academic and industrial research.

Figure 3.2 Two generations of building blocks



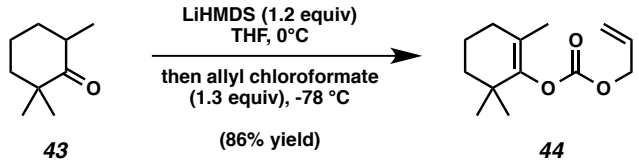
3.10 Experimental Section

3.10.1 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 (**43**) 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 **L1** was prepared according to known methods.[111] 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. ^1H 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 ^1H NMR spectra are reported as follows: chemical shift (d ppm), multiplicity, coupling constant (Hz),[112] 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.

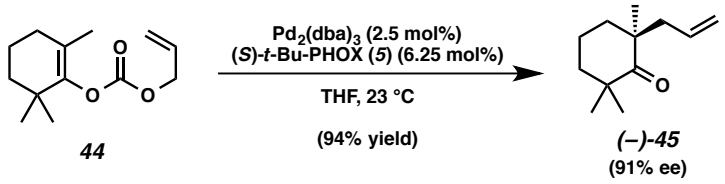
3.10.2 Syntheses of Compounds Related to Thujopsene



43 ***44***

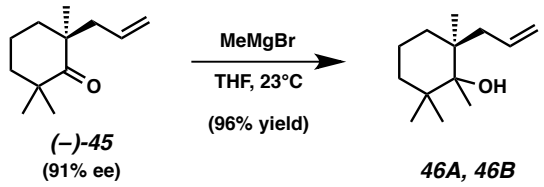
Enol Carbonate 44.[113] A solution of LiHMDS (1.0 M in THF, 57.5 mL, 57.5 mmol) was added to THF (300 mL), then cooled to 0 °C. A solution of 2,2,6-trimethylcyclohexanone (**43**) (6.67 g, 47.6 mmol) in THF (10 mL) was added. The reaction was stirred at 0 °C for 1 h, then cooled to –78 °C and fitted 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 **44** (9.19 g, 86% yield) as a clear oil. R_f = 0.43 (10% EtOAc in hexanes); ^{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 (Neat Film NaCl) 2965, 2934, 2868, 2838, 1759, 1459, 1363, 1271, 1238, 1138, 1025, 993, 937 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{20}O$ $[M]^+$: 224.1413, found 224.1408.



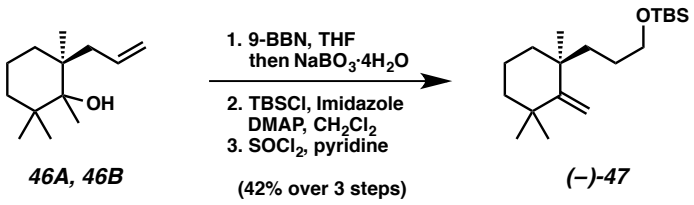
Allyl Ketone (–)-45. A round bottom flask was flame-dried under argon and cycled into the glovebox. It was charged with $Pd_2(dba)_3$ (242 mg, 0.264 mmol, 6.25 mol%) and (*S*)-*t*-Bu-PHOX (**L1**, 256 mg, 0.661 mmol, 2.5 mol%). Then, THF (317 mL) was introduced. The red mixture was stirred for 20 min at 25 °C. Then, enol carbonate **44** (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 (–)-**45** (1.72 g, 94% yield) as a clear oil in 91% ee as determined by chiral HPLC analysis. R_f = 0.48 (10% EtOAc in hexanes); ^{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 (Neat Film NaCl) 3077, 2979, 2964, 2933, 2869, 1697, 1463, 1382, 999, 914 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{20}O$ $[M]^+$: 180.1514, found 180.1506; $[\alpha]_D^{24}$ –36.3° (*c* 0.140, $CHCl_3$, 91% ee).



Alcohols 46A and **46B**. A round-bottom flask was charged with a solution of allyl ketone (–)-**45** (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 **46A** and **46B** (1.04 g, 94% yield) as a colorless oil. R_f = 0.59 (10% EtOAc in hexanes); ^{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 (Neat Film NaCl) 3504 (broad), 3074, 2930, 2867, 1638, 1454, 1378, 1305, 1071, 998, 910 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{24}O$ $[M]^+$: 196.1827, found 196.1803.



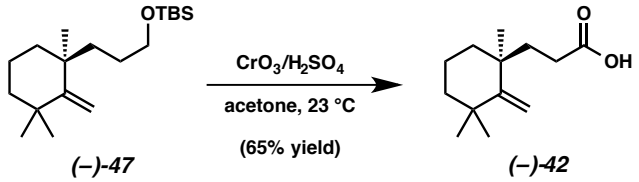
Methylene Cyclohexane (–)-47. A 20 mL scintillation vial containing a mixture of diastereomeric alcohols **46A** and **46B** (72 mg, 0.367 mmol, 1.00 equiv, 91% ee) was treated with a solution of 9-borabicyclo[3.3.1]nonane in THF (0.5 M, 0.90 mL, 0.45 mmol, 1.23 equiv) at 23 °C. The reaction was stirred for 2.5 h. Then the reaction was cooled to 0 °C, and H_2O (1 mL) was carefully added, followed by $NaBO_3$•$4H_2O$ (219 g, 1.42 mmol, 3.88 equiv). The biphasic reaction mixture was stirred vigorously at 23 °C for 2 h, diluted with water, and extracted with CH_2Cl_2 (4 x 1 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash

chromatography on silica gel (25% → 33% → 50% EtOAc in hexanes), giving an oil containing two diastereomeric products, which was immediately used in the next reaction.

This mixture was transferred to a 20 mL scintillation vial. Imidazole (39 mg, 0.57 mmol), 4-dimethylaminopyridine (1 mg, 0.00885 mmol), and anhydrous CH_2Cl_2 (1.0 mL) were introduced, followed by a solution of TBSCl (48 mg, 0.314 mmol) in anhydrous CH_2Cl_2 (1.0 mL) at 23 °C. A white precipitate quickly formed. After 10 min, the reaction was diluted with hexanes (4 mL), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (5:95 EtOAc:hexane eluent), affording a diastereomeric mixture of silyl ethers. This composite was carried on to the next reaction without further characterization.

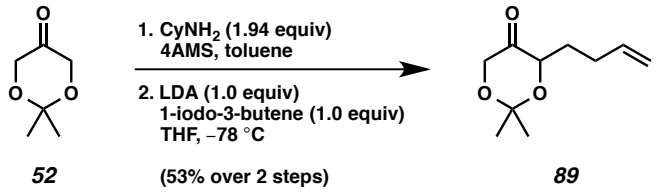
The mixture of silyl ethers was transferred to a 20 mL scintillation vial, which was charged with pyridine (freshly distilled from CaH_2, 1.5 mL). After cooling to 0 °C, $SOCl_2$ (36 μL, 0.50 mmol) was slowly introduced. After stirring 1 h at 0 °C and another 1 h at 23 °C, H_2O (5 mL) was carefully added, followed by Et_2O (8 mL). The organic phase was collected, and the aqueous layer was extracted with Et_2O (2 x 10 mL). All organic layers were combined and washed with 1.0 M aq $CuSO_4$ (4 x 5 mL). The aqueous washings were back-extracted with Et_2O (1 x 10 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (1% → 2% Et_2O in hexanes), giving pure methylene cyclohexane (–)-**47** (48 mg, 42% yield from **46A** and **46B**) as a colorless oil. R_f = 0.71 (10% EtOAc in hexanes); ^{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 (Neat Film NaCl) 3100, 2955, 2929, 2858, 1623, 1472, 1382, 1361, 1255, 1100, 940, 900, 836, 774 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{19}H_{38}SiO$ $[M]^+$: 310.2692, found 310.2689; $[\alpha]_D^{24}$ –18.8° (*c* 1.90, $CHCl_3$, 91% ee).



Carboxylic Acid (–)-42. A vessel containing methylene cyclohexane (–)-**47** (48 mg, 0.154 mmol) was charged with acetone (ACS grade, 2.5 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 15 min, the reaction was carefully quenched with sat. aq Na_2SO_3 (2 mL). $CHCl_3$ (5 mL) was added, followed by H_2O (5 mL) and 6 M aq HCl (4 mL). After 5 min, the reaction was extracted with $CHCl_3$ (3 x 10 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (6% → 14% Et_2O in CH_2Cl_2), giving carboxylic acid (–)-**42** (21 mg, 65% yield) as a colorless oil. R_f = 0.17 (10% EtOAc in hexanes); ^{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 (Neat Film NaCl) 3000 (broad), 2927, 1708, 1462, 1414, 1380, 1296, 1095, 902 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{22}O$ $[M]^+$: 210.1620, found 210.1618; $[\alpha]_D^{24}$ –27.8° (*c* 1.205, $CHCl_3$, 91% ee).

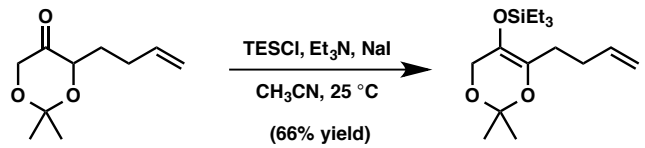
3.10.3 Syntheses of Compounds Related to Quinic Acid



Dioxanone 89.[114] To a solution of 2,2-dimethyl-1,3-dioxan-5-one **52** (5.0 g, 38.4 mmol, 1.0 equiv) in toluene (125 mL, 0.3 M) were added 4Å molecular sieves (5.0 g) and cyclohexylamine (8.50 mL, 74.3 mmol, 1.94 equiv) at room temperature (ca. 25 °C). The mixture was stirred for 14 h, before the molecular sieves were removed by filtration. The filtrate was concentrated under reduced pressure to give crude imine (7.95 g).

Lithium diisopropylamine was prepared in a separate flask by dropwise addition of *n*-BuLi (2.50 M in hexanes, 15.4 mL, 38.5 mmol, 1.0 equiv) via syringe to a solution of diisopropylamine (5.40 mL, 38.5 mmol, 1.0 equiv) in THF (60 mL, 0.64 M) at 0 °C. The solution was stirred at 0 °C for 10 min, and then cooled to –78 °C. A solution of the imine (7.95 g) in THF (40.0 mL) was added dropwise via syringe to the resulting LDA solution at –78 °C. The reaction mixture was warmed to –35 °C, and stirred for 2 h, after which it was re-cooled to –78 °C, and 1-iodo-3-butene (7.00 g, 38.4 mmol, 1.0 equiv) was added. The reaction was warmed to room temperature (ca. 25 °C) over 3 h. Saturated aq NH_4Cl (60 mL) was added to the reaction mixture, and the mixture was stirred at room temperature overnight. The mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and filtered. Solvent was removed under reduced pressure, and the residue was purified by flash chromatography (20% Et_2O in pentane on silica gel) to give dioxanone **89** (3.75 g, 53% yield over 2 steps) as a colorless oil. R_f = 0.38 (20% Et_2O in hexanes); ^{1}H NMR

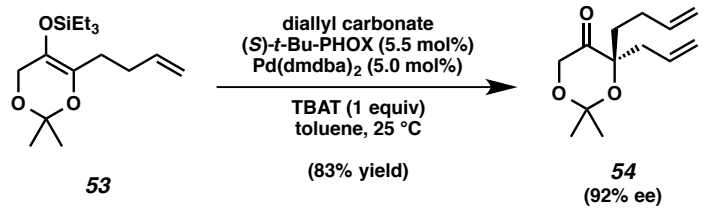
(300 MHz, $CDCl_3$) δ 5.85–5.72 (m, 1H), 5.09–4.98 (m, 2H), 4.29–4.21 (m, 2H), 3.98 (d, J = 16.8 Hz, 1H), 2.30–2.08 (m, 2H), 2.03–1.92 (m, 1H), 1.70–1.58 (m, 1H), 1.45 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.0, 137.7, 115.8, 101.0, 73.8, 66.8, 29.3, 27.6, 24.1, 23.9; IR (Neat Film NaCl) 2988, 2938, 2884, 1748, 1642, 1434, 1376, 1251, 1225, 1175, 1103, 1071, 916, 864 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{10}H_{16}O_3$ $[M]^+$: 184.1100, found 184.1131.



89 ***53***

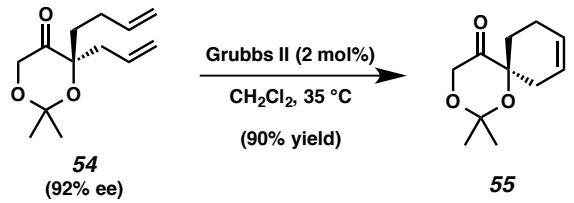
Triethylsilyl Enol Ether 53.[114] To a solution of dioxanone **89** (0.58 g, 3.16 mmol, 1.0 equiv), Et_3N (0.71 mL, 5.09 mmol, 1.6 equiv) and sodium iodide (0.62 g, 4.14 mmol, 1.3 equiv) in acetonitrile (5.0 mL, 0.63 M) was added triethylsilyl chloride (0.69 mL, 4.11 mmol, 1.3 equiv) at room temperature (ca. 25 °C). After the mixture was stirred for 20 h, pentane (10 mL) was added. The mixture was stirred at room temperature for 2 min, before the pentane was decanted. After additional pentane extractions (5 x 10 mL), the combined pentane extracts were washed with water (20 mL) and then with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (1% Et_2O in petroleum ether on silica gel) to give triethylsilyl enol ether **53** (0.623 g, 66% yield) as a colorless oil. R_f = 0.58 (10% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.90–5.77 (m, 1H), 5.07–5.0 (m, 1H), 5.0–4.93 (m, 1H), 4.05 (s, 2H), 2.30–2.13 (m, 4H), 1.43 (s, 6H), 0.98 (t, J = 7.8 Hz, 9H), 0.65 (q, J = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 137.2, 125.7, 114.8, 98.2, 61.1, 30.9, 27.0,

24.3, 6.9, 5.6; IR (Neat Film NaCl) 2995, 2957, 2914, 2878, 2838, 1383, 1369, 1277, 1223, 1198, 1147, 1085, 1006, 857, 745, 730 cm^{-1}; HRMS (EI+) *m*/*z* calc'd for $C_{16}H_{30}O_3Si$ $[M]^+$: 298.1964, found 298.1967.

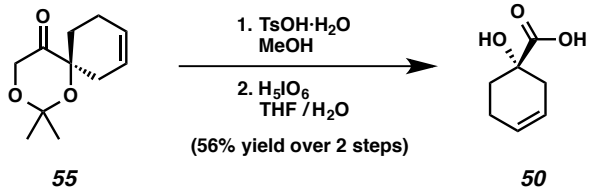


Diene 54.[114] A 100 mL round-bottom flask was flame dried under vacuum and back-filled with argon. $Pd(dmdba)_2$ (20.3 mg, 0.025 mmol, 0.05 equiv), (*S*)-*t*-Bu-PHOX (10.6 mg, 0.027 mmol, 0.055 equiv), and TBAT (270 mg, 0.50 mmol, 1.0 equiv) were added to the flask. The system was evacuated under vacuum and backfilled with argon (3 x). Toluene (15 mL, 0.033 M) was added by syringe and the mixture was stirred at room temperature (ca. 25 °C) for 30 min. Diallyl carbonate (75.2 μL, 0.52 mmol, 1.05 equiv) and triethylsilyl enol ether **53** (149 mg, 0.50 mmol, 1.0 equiv) were added sequentially. When the reaction was complete by TLC (after ca. 9 h), the reaction mixture was loaded onto a silica gel column and eluted with 2% Et_2O in petroleum ether to give diene **54** (93.0 mg, 83% yield, 92% ee) as a colorless oil. R_f = 0.33 (10% Et_2O in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.86–5.70 (m, 2H), 5.11–4.92 (m, 4H), 4.19 (d, *J* = 18.0 Hz, 2H), 4.15 (d, *J* = 18.0 Hz, 2H), 2.60–2.45 (m, 2H), 2.27–1.95 (m, 2H), 1.93–1.69 (m, 2H), 1.51 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.5, 138.2, 132.4, 119.1, 115.0, 100.1, 84.5, 67.4, 41.9, 36.1, 27.7, 27.3, 26.5; IR (Neat Film NaCl) 3079, 2987, 2941, 1738 1642, 1427, 1382 1372, 1232, 1209, 1168, 1148, 1098, 998, 915 cm^{-1}; HRMS

(EI+) *m*/*z* calc'd for $C_{13}H_{20}O_3$ $[M]^+$: 224.1412, found 224.1416; $[\alpha]_D^{20.2}$ +7.04° (*c* 1.030, CH_2Cl_2, 92% ee).

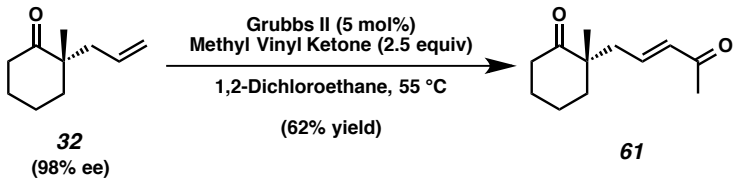


Cyclohexene 55.[114] To a solution of diene **54** (60 mg, 0.268 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added Grubbs second generation catalyst (4.6 mg, 0.0054 mmol, 0.02 equiv) at room temperature. After the mixture was stirred at 35 °C for 40 h, it was concentrated under reduced pressure. The residue was purified by flash chromatography (2% Et_2O in petroleum ether on silica gel) to give the cyclohexene **55** (47.3 mg, 90% yield) as a colorless oil. R_f = 0.24 (10% Et_2O in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80–5.70 (m, 1H), 5.67–5.58 (m, 1H), 4.27 (s, 2H), 2.60–2.47 (m, 1H), 2.38–2.18 (m, 2H), 2.17–1.81 (m, 3H), 1.51 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.1, 126.4, 122.8, 100.5, 79.9, 66.6, 33.5, 29.9, 27.7, 26.3, 21.8; IR (Neat Film NaCl) 3030, 2991, 2938, 2911, 1739, 1429, 1382, 1372, 1259, 1230, 1200, 1155, 1099, 1062, 999, 886, 836, 778, 651 cm^{-1}; HRMS (EI+) *m*/*z* calc'd for $C_{11}H_{16}O_3$ $[M]^+$: 196.1100, found 196.1139; $[\alpha]_D^{20.2}$ –20.9° (*c* 1.045, CH_2Cl_2, 92% ee).

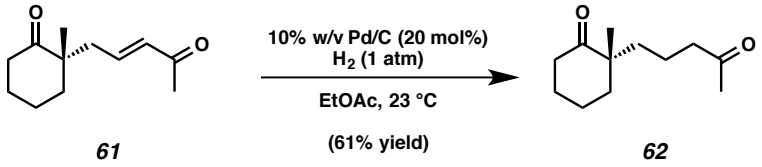


Carboxylic Acid 50.[114] To a solution of cyclohexene **55** (40 mg, 0.20 mmol, 1.0 equiv) in MeOH (4 mL, 0.05 M) was added *p*-toluenesulfonic acid monohydrate (3.9 mg, 0.02 mmol, 0.1 equiv) at room temperature (24 °C). After the mixture was stirred for 3 h, Et_3N (0.1 mL) was added. The mixture was concentrated under reduced pressure to give a yellow oil. The oil was diluted with EtOAc (10 mL), filtered through SiO_2 (1 mL), and concentrated under reduced pressure to furnish a white solid (35 mg). The solid was dissolved in THF (0.4 mL) and water (0.2 mL), and the colorless solution was cooled to 0 °C (ice water bath). H_5IO_6 (46 mg, 0.20 mmol, 1 equiv) was added to the solution. The mixture was allowed to warm to room temperature (26 °C) over 10 minutes, and then stirred for 2 h. The reaction was diluted with water (0.5 mL), and extracted with EtOAc (4 x 15 mL). Extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The white solid was purified by column chromatography over silica gel (ca. 9 mL) with 2:1 Hexanes:EtOAc to give carboxylic acid **50** (16.3 mg, 56% yield, 92% ee) as a white solid: mp 79–81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88–5.79 (m, 1H), 5.72–5.61 (m, 1H), 2.79–2.62 (m, 1H), 2.37–2.11 (m, 4H), 1.95–1.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.5, 126.6, 122.6, 72.6, 34.9, 30.6, 21.4; IR (Neat Film NaCl) 3432, 3032, 2929, 2624, 1736, 1443, 1370, 1356, 1318, 1253, 1216, 1092, 1064, 982, 939, 886, 773, 746, 650, 736 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_8H_{12}O_3$ $[M]^+$: 143.0708, found 143.0708; $[\alpha]_D^{20.7}$ +31.7° (*c* 0.310, CH_2Cl_2, 92% ee).

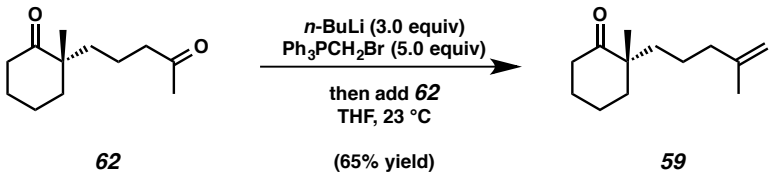
3.10.4 Syntheses of Compounds Related to Dysidiolide



Keto-Enone 61.[113] A vial was charged with allyl ketone **32** (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 (hexanes → 20% EtOAc in hexanes), giving keto-enone **61** (35.7 mg, 62% yield) as a pale brown oil. R_f = 0.23 (20% EtOAc in hexanes); ^{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 (Neat Film NaCl) 2935, 2866, 1704, 1672, 1626, 1426, 1361, 1254, 1124, 986 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{18}O_2$ $[M]^+$: 194.1307, found 194.1336; $[\alpha]_D^{22}$ –1.14° (*c* 1.415, $CHCl_3$, 98% ee).



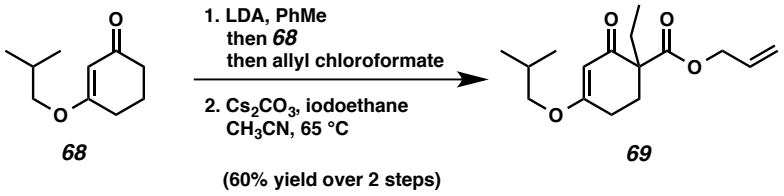
Diketone 62.[113] A round-bottom flask containing keto-enone **61** (28.0 mg, 0.144 mmol, 1.0 equiv) in EtOAc (3.0 mL) was sparged with argon for 2 min. Pd/C (10% w/w) (30.6 mg, 28.8 μmol, 20 mol) was introduced, and the reaction was cooled to –78 °C. It was purged/backfilled with vacuum/H_2 (1 atm) (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 **62** (17.3 mg, 61% yield) as a pale yellow oil. R_f = 0.26 (20% EtOAc in hexanes); ^{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 (Neat Film NaCl) 2936, 2865, 1705, 1452, 1360, 1167, 1123, 1099 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{20}O_2$ $[M]^+$: 196.1463, found 196.1469; $[\alpha]_D^{22}$ –42.3° (*c* 0.865, $CHCl_3$, 98% ee).



Keto-Olefin 59. 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 **62** (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 (hexanes → 2% EtOAc in hexanes), giving keto-olefin **59** (17.3 mg, 65% yield) as a colorless oil. R_f = 0.75 (20% EtOAc in hexanes); ^{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 (Neat Film NaCl) 3074, 2936, 2865, 1707, 1650, 1452, 1376, 1260, 1096, 1020, 886, 804 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{22}O$ $[M]^+$: 194.1671, found 194.1680; $[\alpha]_D^{21}$ –49.8° (*c* 0.865, $CHCl_3$, 98% ee).

3.10.5 Syntheses of Compounds Related to Aspidospermine

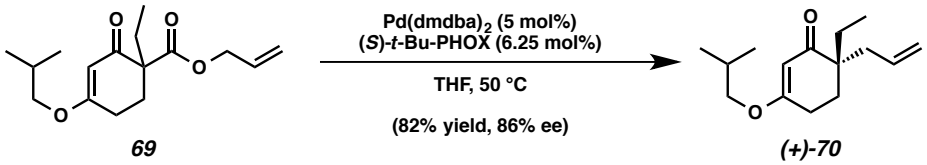


α-Ethyl-α-Allyloxycarbonyl Vinylogous Ester 69. A round-bottom flask was flamedried under argon and charged with dry PhMe (320 mL). Then, *i*-Pr_2NH (12.81 mL, 91.3 mmol, 2.05 equiv) was introduced. The reaction was cooled to –78 °C, and *n*-BuLi (2.5 M in hexane, 35.68 mL, 89.2 mmol, 2.00 equiv) was added slowly. The reaction was warmed to 0 °C for 15 min, then promptly cooled back to –78 °C. Then, a solution of vinylogous ester **68** (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.

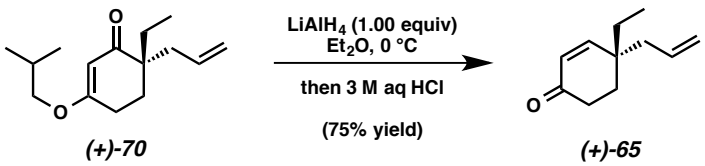
A round-bottom flask containing the crude vinylogous ester was charged with CH_3CN (45 mL), followed by iodoethane (14.26 mL, 178.4 mmol, 4.0 equiv relative to **68**. Anhydrous Cs_2CO_3 (29.06 g, 89.2 mmol, 2.0 equiv relative to **68**) was introduced, and the reaction was stirred vigorously at 65 °C 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% EtOAc in hexanes), giving semipure **69**. The product-containing fractions were combined and concentrated, and the resulting residue was purified on a second silica gel flash column (5% EtOAc in CH_2Cl_2), giving pure α-ethyl-α-allyloxycarbonyl vinylogous ester **69** (7.47 g, 60% yield over 2 steps) as a yellow oil. R_f = 0.44 (20% EtOAc in hexanes); ^{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 (Neat Film NaCl) 3083, 2963, 2939, 2879, 1731, 1664, 1610, 1470, 1384, 1236, 1195, 1178, 1119, 998, 919 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{24}O_4$ $[M]^+$: 280.1687, found 280.1687.



Allyl Vinylogous Ester (+)-70. 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-α-allyloxycarbonyl vinylogous ester **69** (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 (hexanes → 5% EtOAc in hexanes), giving allyl vinylogous ester (+)-**70** (193.4 mg, 82% yield) in 86% ee (as determined by chiral HPLC assay) as a yellow oil. R_f = 0.58 (20% EtOAc in hexanes); ^{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,

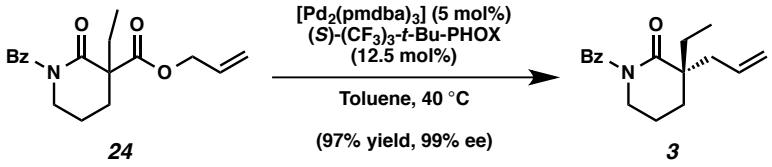
J_d = 22.2 Hz, J_q = 7.4 Hz, 1H), 1.55 (dq, J_d = 22.2 Hz, J_q = 7.4 Hz, 1H), 0.97 (d, J = 6.6 Hz, 6H), 0.84 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 176.0, 134.8, 117.8, 102.0, 74.8, 46.6, 39.4, 29.0, 27.9, 27.6, 25.8, 19.2, 8.5; IR (Neat Film NaCl) 3074, 2963, 2936, 2878, 1652, 1612,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



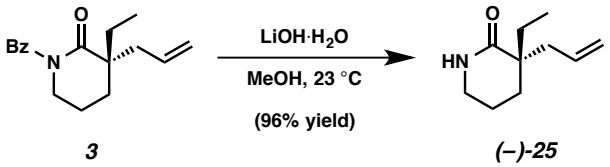
γ-Ethyl-γ-Allyl Enone (+)-65. A round-bottom flask was charged with allyl vinylogous ester (+)-**70** (50.0 mg, 0.212 mmol, 95% ee, 1.00 equiv), and the reactor was purged with vacuum/argon (1 x). Et_2O (10.0 mL) was introduced, and the reaction was cooled to 0 °C. $LiAlH_4$ (8.0 mg, 0.212 mmol, 1.00 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 (+)-**65** (26.2 mg, 75% yield) as a colorless, volatile oil. R_f = 0.57 (20% EtOAc in hexanes); ^{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 (Neat Film NaCl) 3077, 2966, 2929, 2880, 1682, 1452, 1387, 916, 800 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{16}O$ $[M]^+$: 164.1201, found 164.1207; $[\alpha]_D^{25}$ +27.5° (*c* 0.524, $CHCl_3$, 95% ee).

3.10.6 Syntheses of Compounds Related to Rhazinilam

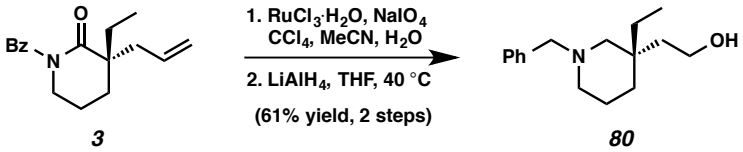


Benzoyl Lactam 3.[115] See Chapter 2 for synthetic procedure and characterization data of benzoyl lactam **3**.



Piperidin-2-one (–)-25.[115] See Chapter 2 for synthetic procedure and characterization data of piperidin-2-one (–)-**25**.

3.10.7 Syntheses of Compounds Related to Quebrachamine

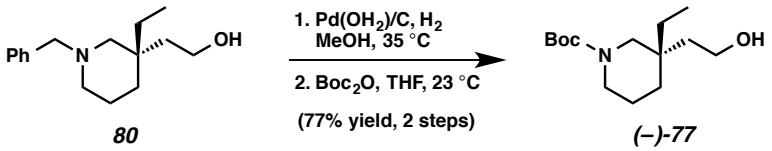


3 ***80***

Alcohol 56.[115] To a vigorously stirred mixture of benzoyl lactam **3** (291 mg, 1.07 mmol, 1.00 equiv) and $NaIO_4$ (915 mg, 4.28 mmol, 4.00 equiv) in CCl_4 (4.3 mL), MeCN (4.3 mL), and H_2O (6.5 mL) was added $RuCl_3•H_2O$ (11.0 mg, 0.053mmol, 0.05 equiv). After 28 h, the reaction mixture was diluted with half-saturated brine (30 mL) and extracted with CH_2Cl_2 (5 x 25 mL). The combined organics were washed with half-saturated brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was suspended in Et_2O (30 mL) and filtered through a pad of celite. The celite pad was washed with Et_2O (2 x 15 mL), and the combined filtrate was concentrated under reduced pressure. This crude residue was used in the next step without further purification.

With cooling from a room temperature bath, the above residue was dissolved in THF (19 mL) and then treated with lithium aluminum hydride (487 mg, 12.9 mmol, 12.0 equiv) *(Caution: Gas evolution and exotherm)*. The reaction mixture was stirred at ambient temperature for 12 h and then warmed to 40 °C for an addition 12 h. The reaction mixture was then cooled (0 °C) and dropwise treated with brine (20 mL, *Caution: Gas evolution and exotherm*). Once gas evolution had ceased the reaction mixture was diluted with half-saturated brine (20 mL) and EtOAc (20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (5 x 50 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (3 x 12 cm SiO_2, 35 to 70% EtOAc in hexanes) to afford alcohol **80** as a colorless oil (162 mg, 61% yield for

two steps). R_f = 0.36 (75% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.24 (m, 5H), 3.80–3.72 (m, 1H), 3.71–3.60 (m, 2H), 3.31 (br s, 1H), 2.85–2.70 (br s, 2H), 2.00–1.70 (br s, 4H), 1.66–1.45 (m, 3H), 1.35–1.10 (m, 3H), 0.81 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 129.5, 128.4, 127.4, 63.9, 63.4, 59.4, 52.9, 39.9, 35.9, 35.1, 33.4, 22.4, 7.5; IR (Neat Film NaCl) 3345 (br), 2933, 2793, 1453, 1350, 1115, 1040, 1028, 739 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{16}H_{26}NO$ $[M+H]^+$: 248.2009, found 248.2016.



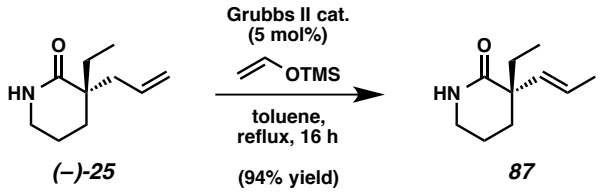
80 ***(–)-77***

Alcohol (–)-77.[115] A mixture of alcohol **80** (162.3 mg, 0.656 mmol, 1.00 equiv) and 20% $Pd(OH)_2/C$ (50 mg) in MeOH (15 mL) was stirred under an H_2 atmosphere for 3.5 h. The reaction mixture was filtered through a pad of celite. The celite pad was washed with MeOH (2 x 15 mL), and the combined filtrate was concentrated under reduced pressure. This crude residue was used in the next step without further purification.

To a solution of the above residue in THF (10 mL) was added Boc_2O (150 mg, 0.689 mmol, 1.05 equiv). After stirring for 24 h, the reaction mixture was concentrated under reduced pressure and partitioned between CH_2Cl_2 (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (2 x 20 cm SiO_2, 15 to 35% EtOAc in hexanes) to afford alcohol (–)-**77** as a colorless oil (130 mg, 77% yield for two steps). R_f = 0.34 (35% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74–3.60 (m, 2H), 3.48 (br s, 1H), 3.31 (br s, 1H), 3.20 (br s, 1H), 2.96 (br s,

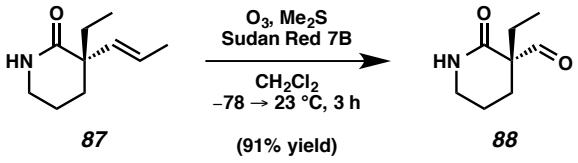
1H), 2.16 (br s, 1H), 1.66–1.55 (m, 1H), 1.55–1.42 (m, 3H), 1.44 (s, 9H), 1.40–1.27 (m, 2H), 1.25–1.15 (m, 1H), 0.83 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.2, 79.4, 58.7, 52.5, 44.5, 36.1, 35.3, 34.6, 28.4, 27.6, 21.2, 7.4; IR (Neat Film NaCl) 3439 (br), 2967, 2934, 2861, 1693, 1670, 1429, 1365, 1275, 1248, 1162, 1045, 865, 767 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{14}H_{28}NO_3$ $[M+H]^+$: 258.2064, found 258.2069; $[\alpha]_D^{25}$ –7.0° (c 1.13, $CHCl_3$, 96% ee).

3.10.8 Syntheses of Compounds Related to Vincadifformine



Disubstituted Alkene 87.[116] To a solution of (–)-**25** (108 mg, 0.65 mmol, 1.0 equiv) and vinyloxytrimethylsilane (0.96 mL, 6.46 mmol, 10 equiv) in toluene (34 mL) was added at rt Grubbs 2nd generation catalyst (27.4 mg, 5 mol%). The purple reaction mixture was immersed in an oil bath (125 °C) (color changed to yellow) and refluxed for 16 h. The reaction mixture was then concentrated under reduced pressure and the residue was purified by column chromatography (50% EtOAc in hexanes → EtOAc) to afford **87** (102 mg, 93% conv., 94%) as a brown oil. R_f = 0.20 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (brs, 1H), 5.55–5.42 (m, 2H), 3.31–3.22 (m, 2H), 1.91–1.66 (m, 5H), 1.69 (d, J = 5.4 Hz, 3H), 1.64–1.54 (m, 1H), 0.84 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 134.8, 124.7, 48.1, 42.7, 31.5, 29.3, 19.1, 18.1, 8.4; IR (Neat Film NaCl) 3203, 3074, 2936, 2876, 1654, 1489, 1447, 1354, 1298, 1209, 979, 852 cm^{-1};

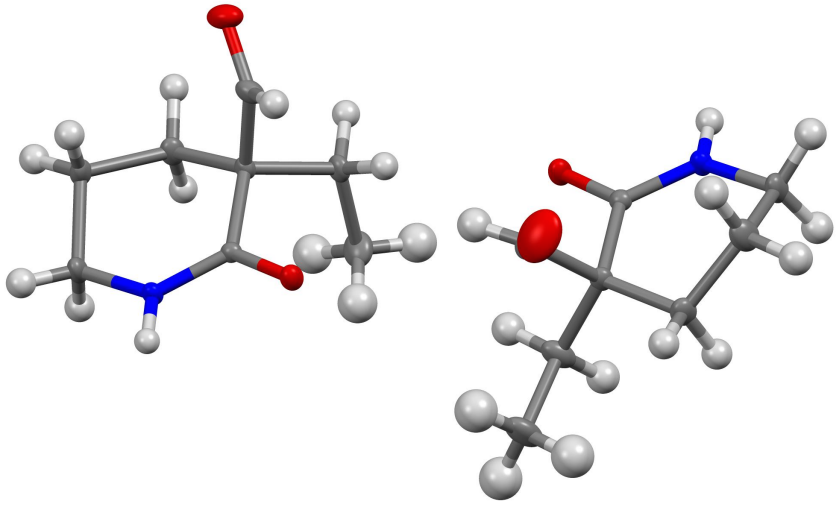
HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{10}H_{17}NO$ $[M+H]^+$: 168.1383, found 168.1385; $[\alpha]_D^{24}$ +10.2° (*c* 1.270, $CHCl_3$).

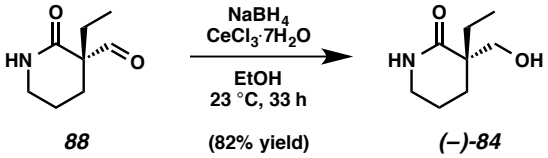


Aldehyde 88. Ozone was bubbled through a cooled (–78 °C) solution of **87** (100 mg, 0.60 mmol, 1.0 equiv) in CH_2Cl_2 (6.0 mL with one drop of sat. Sudan Red 7B CH_2Cl_2 solution) until the reaction mixture turned from bright purple to colorless. Then, the ozone generator was turned off and oxygen was bubbled through for a few minutes. Then, the argon flow was turned on and dimethylsulfide (0.88 mL, 12.0 mmol, 20 equiv) was added dropwise at –78 °C. After stirring for 30 min at that temperature, the reaction mixture was allowed to warm to rt over 2.5 h. The reaction mixture was then concentrated under reduced pressure and the residue was purified by column chromatography (67% EtOAc in hexanes → EtOAc) to afford **88** (84.7 mg, 91%) as beige crystalline solid. X-ray quality crystals sublimed under high vacuum at rt. R_f = 0.36 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.63 (s, 1H), 6.54 (brs, 1H), 3.34–3.20 (m, 2H), 2.33–2.20 (m, 1H), 2.05–1.93 (m, 1H), 1.89–1.75 (m, 2H), 1.73–1.62 (m, 1H), 1.62–1.52 (m, 1H), 0.87 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.2, 171.1, 58.9, 42.5, 27.3, 24.1, 20.2, 8.2; IR (Neat Film NaCl) 3290, 2941, 2877, 1727, 1660, 1488, 1462, 1450, 1353, 1323 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_8H_{13}NO_2$ $[M+H]^+$: 156.1019, found 156.1021; $[\alpha]_D^{24}$ –54.6° (*c* 1.305, $CHCl_3$); mp: 63–65 °C. X-

ray structure has been deposited in the Cambridge Database (CCDC) under the deposition number 1000826.

*Figure 3.3 Crystal structure of **88** (ellipsoids, 50% probability level)*





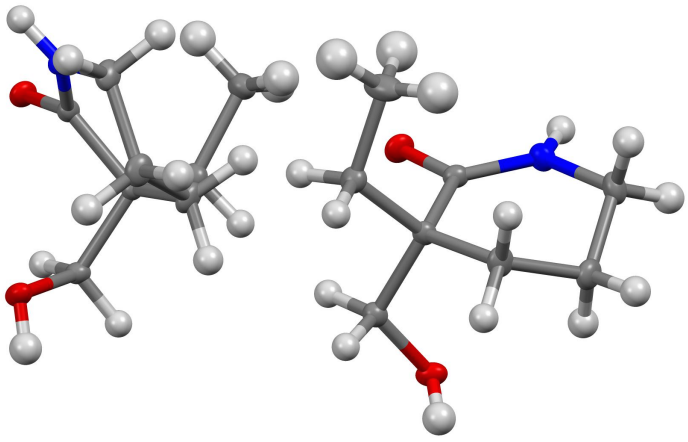
88 **(82% yield)** ***(–)-84***

Alcohol (–)-84. To a suspension of $NaBH_4$ (49.4 mg, 1.3 mmol, 5.0 equiv) and $CeCl_3 \bullet 7H_2O$ (146 mg, 0.39 mmol, 1.5 equiv) in EtOH (4.0 mL) was added at 0 °C solid **88** (40.5 mg, 0.26 mmol, 1.0 equiv) in one portion, after evolution of hydrogen gas had subsided. After stirring for 33 h at 23 °C, the heterogeneous reaction mixture was quenched with sat. NH_4Cl (15 mL) and diluted with CH_2Cl_2 (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (20 mL). Since phase separation was tedious due to the presence of boronic acid salts (emulsion), the aqueous layer was then basified with 6 M NaOH (2 mL) and was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was

removed under reduced pressure. The residue was purified by column chromatography (50% → 67% acetone in hexanes) to afford (–)-**84** (33.8 mg, 82%) as a colorless, viscous oil. R_f = 0.33 (67% acetone in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66 (brs, 1H), 3.85 (brs, 1H), 3.59–3.45 (m, 2H), 3.32–3.20 (m, 2H), 1.89–1.64 (m, 5H), 1.47 (ddd, J = 13.7 Hz, 10.0 Hz, 3.6 Hz, 1H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.3, 67.4, 45.3, 42.2, 26.9, 26.5, 19.4, 7.9. IR (Neat Film NaCl) 3289, 2939, 2875, 1643, 1492, 1355, 1324, 1208, 1055 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_8H_{15}NO_2$ $[M+H]^+$: 158.1176, found 158.1179. $[\alpha]_D^{24}$ –12.9° (*c* 1.69, $CHCl_3$) (Lit.[117] for (*R*)-**65**: $[\alpha]_D^{27}$ +13.5° (*c* 1.05, $CHCl_3$)).

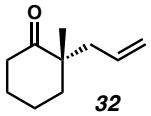
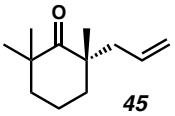
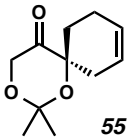
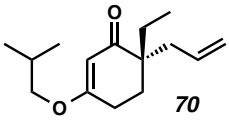
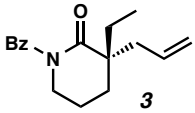
During the synthesis of the racemic compound, alcohol (±)-**84** solidified upon storage in the freezer to give a white crystalline solid: mp: 91–93 °C. X-ray quality crystals were obtained by slow diffusion of heptane (with a few drops of benzene) into a solution of the alcohol in EtOAc at 23 °C. X-ray structure has been deposited in the Cambridge Database (CCDC) under the deposition number 1002339.

*Figure 3.4 Crystal structure of (±)-**84** (ellipsoids, 50% probability level)*



3.10.9 Methods for the Determination of Enantiomeric Excess

Table 3.1 Analytical GC and HPLC assays and retention times

entry	product	assay conditions	retention time of major isomer (min)	retention time of minor isomer (min)	% ee
1	 **32**	Chiral GC Agilent GT-A 100 °C isotherm	11.1	12.7	88
2	 **45**	Chiral GC Agilent GT-A 80 °C isotherm	29.1	30.5	91
3	 **55**	HPLC Chiralpak AD Hexanes isocratic, 1.0 mL/min 220 nm	11.462	10.307	92
4	 **70**	HPLC Chiralcel OD 2% EtOH in hexanes isocratic, 1.0 mL/min 254 nm	7.4	8.2	86
5	 **3**	SFC Chiralcel OJ-H 3% MeOH in CO_2 isocratic, 5.0 mL/min 254 nm	3.85	2.49	99

3.11 Notes and References

(1) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369–396.

(2) Mohr, J. T.; Stoltz, B. M. *Chem. Asian J.* **2007**, *2*, 1476–1491.

(3) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A., Jr.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz. B. M. *Chem. — Eur. J.* **2011**, *17*, 14199–14223.

(4) McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738–7739.

(5) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810–811.

(6) Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231.

(7) Enquist, J. A., Jr.; Virgil, S. C.; Stoltz, B. M. *Chem. — Eur. J.* **2011**, *17*, 9957–9969.

(8) Enquist, J. A., Jr.; Stoltz, B. M. *Nat. Prod. Rep.* **2009**, *26*, 661–680.

(9) Levine, S. R.; Krout, M. R.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 289–292.

(10) Petrova, K. V.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 293–295.

(11) White, D. E.; Stewart, I. C.; Seashore-Ludlow, B. A.; Grubbs, R. H.; Stoltz, B. M. *Tetrahedron* **2010**, *66*, 4668–4686.

(12) Day, J. J.; McFadden, R. M.; Virgil, S. C.; Kolding, H.; Alleva, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6814–6818.

(13) Wei, Y.; Zhao, D.; Ma, D. *Angew. Chem., Int. Ed.* **2013**, *52,* 12988–12991.

(14) Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135,* 19127–19130.

(15) Hu, Q.-Y.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126,* 13708–13713.

(16) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III.; Sharpless, K. B.; Walker, F. J. *Science* **1983**, *220,* 949–951.

(17) Inamori, Y.; Morita, Y.; Sakagami, Y.; Okabe, T.; Ishida, N. *Biocontrol Science* **2006**, *11,* 49–54.

(18) Chetty, G. L.; Dev, S. *Tetrahedron Lett.* **1965**, *6,* 3773–3776.

(19) Ito, S.; Endo, K.; Honma, H.; Ota, K. *Tetrahedron Lett*. **1965**, *6,* 3777–3781.

(20) Oh, I.; Yang, W.- Y.; Park, J.; Lee, S.; Mar, W.; Oh, K.-B.; Shin, J. *Arch. Pharm. Res.* **2011**, *34,* 2141–2147.

(21) Yano, M. *J. Soc. Chem. Ind. Jpn.* **1913**, *16,* 443–463.

(22) Uchida, S. *J. Soc. Chem. Ind. Jpn.* **1928**, *31,* 501–503.

(23) Miyazaki, Y. *Mokuzai Gakkaishi* **1996**, *42,* 624–626.

(24) Hiramatsu, Y.; Miyazaki, Y. *J. Wood. Sci.* **2001**, *47,* 13–17.

(25) Dauben, W. G.; Ashcraft, A. C. *J. Am. Chem. Soc.* **1963**, *85,* 3673–3676.

(26) Büchi, G.; White, J. D. *J. Am. Chem. Soc.* **1964**, *86,* 2884–2887.

(27) Mori, K.; Ohki, M.; Kobayashi, A.; Matsui, M. *Tetrahedron* **1970**, *26,* 2815–2819.

(28) McMurry, J. E.; Blaszczak, L. C. *J. Org. Chem.* **1974**, *39,* 2217–2222.

(29) Branca, S. J.; Lock, R. L.; Smith, A. B., III. *J. Org. Chem.* **1977**, *42,* 3165–3168.

(30) Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1982**, *104,* 4290–4291.

(31) Lee, E.; Shin, I.-J.; Kim, T.-S. *J. Am. Chem. Soc.* **1990**, *112,* 260–264.

(32) Zhang, C. X.; Fang, L. J.; Bi, F. Q.; Li, Y. L. *Chinese Chem. Lett.* **2008**, *19,* 256–258.

(33) Srikrishna, A.; Anebouselvy, K. *J. Org. Chem.* **2001**, *66,* 7102–7106.

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

(35) Rapado, L. P.; Bulugahapitiya, V.; Renaud, P. *Helv. Chim. Acta* **2000**, *83,* 1625–1632.

(36) Wolinsky, J.; Novak, R.; Vasilev, R. *J. Org. Chem.* **1964**, *29,* 3596–3598.

(37) Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Tetrahedron: Asymmetry* **1997**, *8,* 3515–3545.

(38) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126,* 9552–9553.

(39) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127,* 5970–5978.

(40) Garg, N. K.; Stoltz, B. M. *Chem. Commun.* **2006**, 3769–3779.

(41) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *Synlett* **2006**, 3081–3087.

(42) Rohloff, J. C., Kent, K. M.; Postich, M. J.; Becker, M. W.; Chapman, H. H.; Kelly, D. E.; Lew, W.; Louie, M. S.; McGee, L. R.; Prisbe, E. J.; Schultze, L. M.; Yu, R. H.; Zhang, L. *J. Org. Chem.* **1998**, *63,* 4545–4550.

(43) Seto, M.; Roizen, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2008**, *47,* 6873–6876.

(44) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1,* 953–956.

(45) Gunasekera, S. P.; McCarthy, P. J.; Kelly-Borges, M. *J. Am. Chem. Soc.* **1996**, *118,* 8759–8760.

(46) Millar, J. B. A.; Russel, P. *Cell* **1992**, *68,* 407–410.

(47) Boukouvalas, J.; Cheng, Y.-X.; Robichaud, J. *J. Org. Chem.* **1998**, *63,* 228–229.

(48) Magnuson, S. R.; Sepp-Lorenzino, L.; Rosen, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120,* 1615–1616.

(49) Miyaoka, H.; Kajiwara, Y.; Yamada, Y. *Tetrahedron Lett*. **2000**, *41,* 911–914.

(50) Takahashi, M.; Dodo, K.; Hashimoto, Y.; Shirai, R. *Tetrahedron Lett.* **2000**, *41,* 2111–2114.

(51) Demeke, D.; Forsyth, C. *Org. Lett.* **2000**, *2,* 3967–3969.

(52) Miyaoka, H.; Yamada, Y. *Bull. Chem. Soc. Jpn.* **2002**, *75,* 203–222.

(53) Demeke, D.; Forsyth, C. J. *Tetrahedron* **2002**, *58,* 6531–6544.

(54) Corey, E. J.; Roberts, B. E. *J. Am. Chem. Soc.* **1997**, *119,* 12425–12431.

(55) Miyaoka, H.; Kajiwara, Y.; Hara, Y.; Yamada, Y. *J. Org. Chem.* **2001**, *66,* 1429–1435.

(56) Jung, M. E.; Nishimura, N. *Org. Lett.* **2001**, *3,* 2113–2115.

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

(58) Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Org. Synth.* **2009**, *86,* 194–211.

(59) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, Chapter 1.

(60) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85,* 2872–2873.

(61) Ban, Y.; Sato, Y.; Inoue, I.; Nagai, M.; Oishi, T.; Terashima, M.; Yonematsu, O.; Kanaoka, Y. *Tetrahedron Lett.* **1965**, *6,* 2261–2268.

(62) Lawton, G.; Saxton, J. E.; Smith, A. J. *Tetrahedron* **1997**, *33,* 1641–1653.

(63) Meyers, A. I.; Berney, D. *J. Org. Chem.* **1989**, *54,* 4673–4676.

(64) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85,* 2872–2873.

(65) Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4,* 1943–1946.

(66) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38,* 1775–1776.

(67) Bennett, N. B.; Hong, A. Y.; Harned, A. M.; Stoltz, B. M. *Org. Biomol. Chem.* **2012**, *10*, 56–59.

(68) Banerji, A.; Majumder, P. L.; Chatterjee, A. G. *Phytochemistry* **1970**, *9,* 1491–1493.

(69) Linde, H. H. A. *Helv. Chim. Acta* **1965**, *48,* 1822–1842.

(70) Thoison, O.; Guénard, D.; Sévenet, T.; Kan-Fan, C.; Quirion, J.-C.; Husson, H. P.; Deverre, J.-R.; Chan, K. C.; Potier, P. *C. R. Acad. Sci. Paris II* **1987**, *304,* 157–160.

(71) Abraham, D. J.; Rosenstein, R. D.; Lyon, R. L.; Fong, H. H. S. *Tetrahedron Lett.* **1972**, *13,* 909–912.

(72) Alazard, J.-P.; Millet-Paillusson, C.; Boyé, O.; Guénard, D.; Chiaroni, A.; Riche, C.; Thal, C. *Bioorg. Med. Chem. Lett.* **1991**, *1,* 725–728.

(73) Edler, M. C.; Yang, G.; Jung, M. K.; Bai, R.; Bornmann, W. G.; Hamel, E. *Arch. Biochem. Biophys.* **2009**, *487,* 98–104.

(74) For a review, see: Kholod, I.; Vallat, O.; Buciumas, A.-M.; Neier, R. *Heterocycles* **2011**, *82,* 917–948.

(75) Ratcliffe, A. H.; Smith, G. F.; Smith, G. N. *Tetrahedron Lett.* **1973**, *14,* 5179–5184. doi:

(76) Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2000**, *122,* 6321–6322.

(77) Bowie, A. L.; Hughes, C. C.; Trauner, D. *Org. Lett.* **2005**, *7,* 5207–5209.

(78) Johnson, J. A.; Ning, L.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124,* 6900–6903.

(79) Banwell, M. G.; Beck, D. A. S.; Willis, A. C. *ARKIVOC* **2006**, *3,* 163–174.

(80) Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128,* 10352–10353.

(81) Gu, Z.; Zakarian, A. *Org. Lett.* **2010**, *12,* 4224–4227.

(82) Sugimoto, K.; Toyoshima, K.; Nonaka, S.; Kotaki, K.; Ueda, H.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2013**, *52,* 7168–7171.

(83) Magnus, P.; Rainey, T. *Tetrahedron* **2001**, *57,* 8647–8651.

(84) Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nature Chem.* **2012**, *4,* 130–133.

(85) Saxton, J. E. In *The Alkaloids. Alkaloids of the Aspidospermine Group*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, Chapter 1.

(86) Deutsch, H. F.; Evenson, M. A.; Drescher, P.; Sparwasser, C.; Madsen, P. O. *J. Pharm. Biomed. Anal.* **1994**, *12,* 1283–1287.

(87) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. *Angew. Chem., Int. Ed.* **2007**, *46,* 6159–6162.

(88) Bajtos, B.; Pagenkopf, B. L. *Eur. J. Org. Chem.* **2009**, 1072–1077.

(89) Hsu, S.-W.; Cheng, H.-Y.; Huang, A.-C.; Ho, T.-L.; Hou, D.-R. *Eur. J. Org. Chem.* **2014**, 3109–3115.

(90) Temme, O.; Taj, S.-A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63,* 6007–6015.

(91) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124,* 4628–4641.

(92) Sattely, E. S.; Meek, S. J.; Malcolmson, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131,* 943–953.

(93) Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2007**, *72,* 4431–4439.

(94) Smith, G. F.; Wahid, M. A. *J. Chem. Soc.* **1963**, 4002–4004.

(95) Szántay, C. *Pure Appl. Chem.* **1990**, *62,* 1299–1302.

(96) Danieli, B.; Lesma, G.; Palmisano, G. *J. Chem. Soc., Chem. Commun.* **1981**, 908–909.

(97) Sápi, J.; Szabó, L.; Baitz-Gács, E.; Kalaus, G.; Szántay, C. *Tetrahedron* **1988**, *44,* 4619–4629.

(98) Calabi, L.; Danieli, B.; Lesma, G.; Palmisano, G. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1371–1379.

(99) Kutney, J. P.; Chan, K. K.; Failli, A.; Fromson, J. M.; Gletsos, C.; Nelson, V. R. *J. Am. Chem. Soc.* **1968**, *90,* 3891–3893.

(100) Laronze, P. J.-Y.; Laronze-Fontaine, J.; Lévy, J.; Le Men, J. *Tetrahedron Lett.* **1974**, *15,* 491–494.

(101) Kuehne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43,* 3705–3710.

(102) Barsi, M.-C.; Das, B. C.; Fourrey, J.-L.; Sundaramoorthi, R. *J. Chem. Soc., Chem. Commun.* **1985**, 88–89.

(103) Yoshida, K.; Nomura, S.; Ban, Y. *Tetrahedron* **1985**, *41,* 5495–5501.

(104) Kalaus, G.; Greiner, I.; Kajtár-Peredy, M.; Brlik, J.; Szabó, L.; Szántay, C. *J. Org. Chem.* **1993**, *58,* 1434–1442.

(105) Kobayashi, S.; Peng, G.; Fukuyama, T. *Tetrahedron Lett.* **1999**, *40,* 1519–1522.

(106) Kuehne, M. E.; Podhorez, D. E. *J. Org. Chem.* **1985**, *50,* 924–929.

(107) Pandey, G.; Kumara, P. C. *Org. Lett.* **2011**, *13,* 4672–4675.

(108) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475,* 183–188.

(109) Zhao, S.; Andrade, R. B. *J. Am. Chem. Soc.* **2013**, *135,* 13334–13337.

(110) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2002**, *41,* 4732–4734.

(111) (a) Peer, M.; de Jong, J. C.; Kiefer, M.; Langer, T.; Riech, H.; Schell, H.; Sennhenn, P.; Sprinz, J.; Steinhagen, H.; Wiese, B.; Helmchen, G. *Tetrahedron* **1996**, *52*, 7547–7583. (b) Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. *Org. Lett.* **2007**, *9*, 2529–2931.

(112) 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.

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

(114) Seto, M.; Roizen, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6873–6876.

(115) Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nature Chem.* **2012**, *4*, 130–133.

(116) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4732–4734.

(117) Pandey, G.; Kumara, P. C. *Org. Lett.* **2011**, *13*, 4672–4675.