Chapter 1

An Introduction to the Isodon Diterpenoids

1.1 INTRODUCTION

The *Isodon* diterpenoids are a large family of natural products isolated from the *Isodon* genus of plants, comprising more than 600 members to date.[1,2] As these plants have long been used in the folk medicine traditions of China and Japan for treatment of inflammation, gastric and respiratory infections, cancer, and other maladies, it is no surprise that many of these natural products have been found to display potent and selective biological activity, including anticancer and antibacterial properties.[3] Though investigations of the *Isodon* plants began in 1910,[4] it was the isolation of enmein (**11**)[2h–j] and its structural elucidation in 1966[5] that opened the door for more thorough studies of these plants and their bioactive constituents. In the years hence, continued studies of this genus have revealed that the vast majority of diterpenoids isolated bear carbon frameworks derived from *ent*-kaurene (**1**), though many diverse oxidation patterns and

C–C bond scissions are exhibited. For instance, maoecrystals V (**9**)[2f] and Z (**10**)[2g] are two of the most highly modified diterpenoids isolated from *Isodon* species, each possessing a unique, rearranged 6,7-*seco*-*ent*-kauranoid framework.

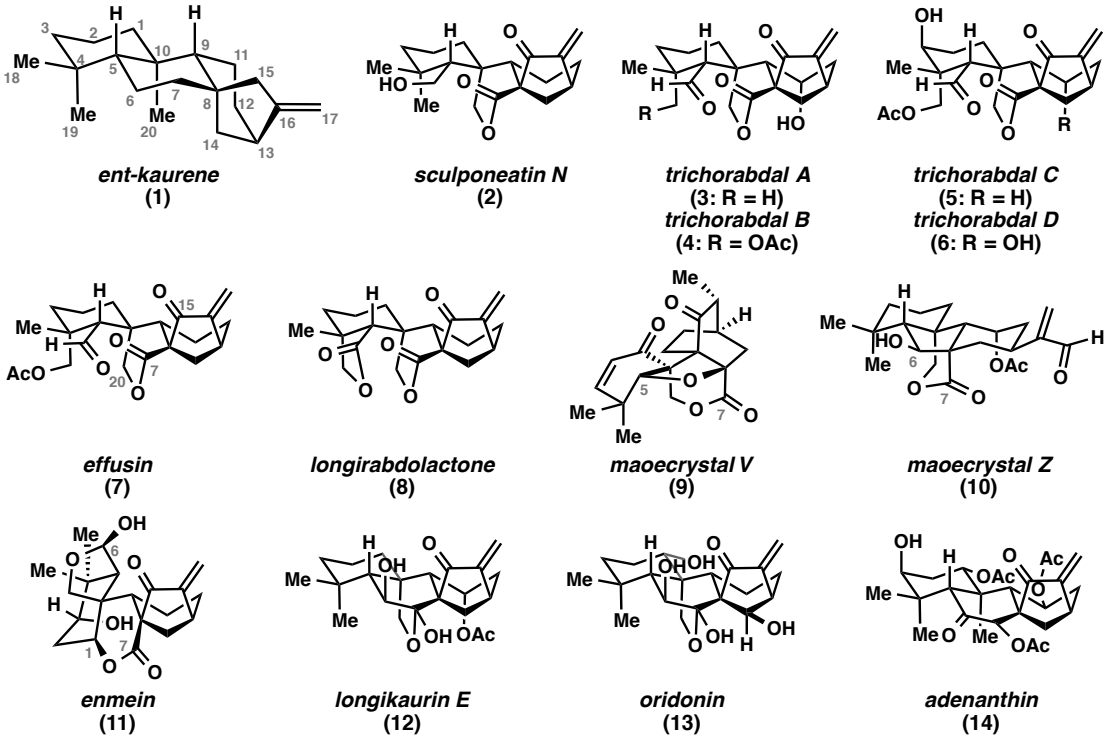


Figure 1.1. *Ent*-kaurene and selected *Isodon* diterpenoids.

Despite the multitude of *Isodon* diterpenoids isolated and characterized since the 1970s, reports of total synthesis efforts prior to 2009 are conspicuously sparse. Attention from synthetic laboratories has largely been focused on the 6,7-*seco*-*ent*-kauranoids (*e.g.*, **2**–**11**), and in the last five years, maoecrystal V (**9**) has been particularly well studied as a result of its unique structural composition and remarkable selectivity profile. Discussed herein are the strategies that have been employed to access the 6,7-*seco*-*ent*-kauranoid natural products. Additionally, a brief history detailing the isolation, structural characterization, and proposed biosynthetic pathway of this class of natural products is presented.

1.2 ISOLATION AND STRUCTURE

The earliest known studies of the *Isodon* diterpenoids are investigations by Yagi of the Japanese remedy "enmei-so," a mixture of the leaves of *I. japonicus* and *I. trichocarpa*. In a 1910 report, he detailed the isolation of a crystalline bitter principle from this remedy, termed plectranthin.[4] In 1958, independent investigations of *I. japonicus* by three Japanese research groups resulted in the isolation of enmein as the major bitter principle.[2h–j] X-ray crystallographic studies reported in 1966 confirmed the structure of enmein as a 6,7-*seco*-*ent*-kauranoid with the structure **11**.[5] Throughout the 1970s, additional *Isodon* diterpenoids bearing the "enmein-type" 1,7-lactone framework were isolated, as were other 6,7-*seco*-*ent*-kauranoids containing a spiro-fused 7,20-lactone (*e.g.*, **7**). In addition to the spirolactone, an *α,β*-unsaturated carbonyl was also found to be characteristic of many bioactive *ent*-kauranoids, frequently found as part of a bridging cyclopentanone (see **2**–**8** and **11**–**14**).

This motif has been found to be a pharmacophore important for the biological activity of the *ent*-kauranoids. For instance, Fujita reported the isolation of trichorabdals A–D[2b,c] (**3**–**6**) in 1981 and subsequently conducted limited studies on the structure-activity relationships (SAR) of various derivatives in an in vivo murine Ehrlich ascites carcinoma assay.[3b] This report and an earlier SAR study[3a] of *ent*-kauranoid derivatives for antitumor and antibacterial activity indicated that enone hydrogenation significantly weakened (**4** and **5**) or abolished (**11** and **13**) the observed bioactivity. As enones are known to react as conjugate acceptors, these findings suggest a mode of action by covalent modification.[6] Corroborating this hypothesis, adenanthin (**14**) was recently shown to exhibit anticancer activity through selective inhibition of the peroxiredoxin enzymes by covalent

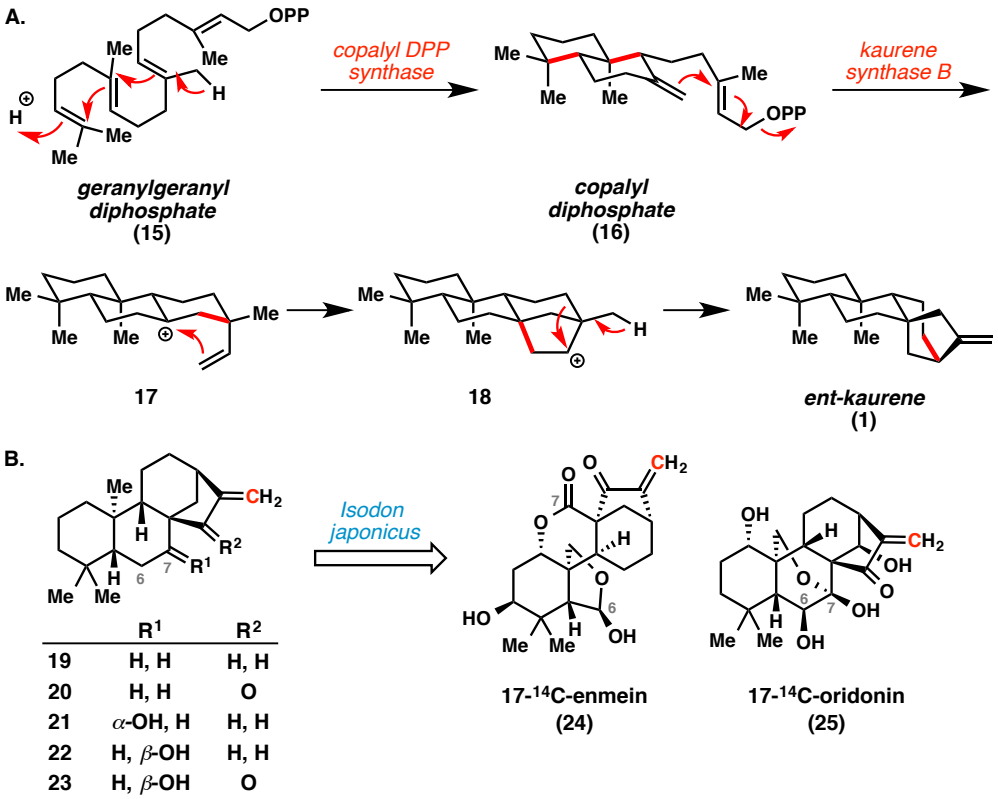
modification of a key cysteine residue; its saturated analog was likewise found to be inactive.[7] Further detailed investigations will be required in order to evaluate the biological target selectivity and elucidate the mechanism of action for other *ent*-kauranoids.

In recent years, the number of known *Isodon* diterpenoids has climbed in excess of 600, and members with novel bond cleavages and rearrangements have emerged.[1] Maoecrystals V (**9**)[2f] and Z (**10**),[2g] reported in 2004 and 2006, respectively, represent two of the most highly modified members of this family. The pentacyclic C_{19} skeleton of **9** has been excised of C6 and comprises a unique bicyclo[2.2.2]octane, three vicinal fully substituted carbons, and an ether linkage. The compact tetracyclic framework of **10**, also unprecedented among naturally occurring *ent*-kauranoids, exhibits a congested and densely functionalized central five-membered ring. The rearranged nature of **9** and **10** raises interesting questions about their biosynthetic origins.

1.3 BIOSYNTHESIS

Plant diterpenoid biosynthesis is widely established to proceed via the enzymatic cyclization of geranylgeranyl diphosphate (**15**).[8] The initial step toward *ent*-kaurene (**1**) is the cyclization of **15** by copalyl diphosphate synthase (see Figure 1.2a), giving the bicyclic copalyl diphosphate (**16**). A separate enzyme, kaurene synthase B, then transforms **16** to **1**, believed to be the ultimate progenitor of the *ent*-kauranoids. Fujita and coworkers have investigated the biosynthesis of enmein (**11**) and oridonin (**13**) by preparing a variety of oxygenated derivatives (see Figure 1.2b, **20**–**23**) of *ent*-[17-^{14}C]-kaurene (**19**) for feeding experiments with *I. japonicus*.[9] Analysis of the enmein and

oridonin isolated demonstrated some level of radiolabeling (**24** and **25**), confirmed to be localized to C17 through ozonolysis and analysis of the recovered formaldehyde. While these findings were inconclusive with respect to the probable order of oxygenations, they did support the conclusion that 6,7-*seco*-*ent*-kauranoids such as enmein (**11**) and others (Figure 1.1, **2**–**10**) arise via cleavage of oxidized *ent*-kaurene derivatives.



	R^1	R^2
19	H, H	H, H
20	H, H	O
21	α-OH, H	H, H
22	H, β-OH	H, H
23	H, β-OH	O

Figure 1.2. (a) *Ent*-kaurene biosynthesis. (b) Feeding studies. (**C** = ^{14}C isotopic label)

The biosynthetic relationships among the majority of *ent*-kauranoids can be generally summarized in terms of three transformations: oxygenation of the carbon skeleton, oxidative cleavage of the C6–C7 bond, and various skeletal rearrangements (Figure 1.3). In particular, the spiro-fused 7,20-lactone framework (*e.g.*, **27**) can be viewed as the direct product of the oxidative cleavage of the C6–C7 bond of a 7,20-epoxy-*ent*-kaurene precursor (**26**), a transformation which has been replicated in chemical synthesis.[2c,10]

However, if an α-oriented hydroxyl is present at C1 (see **30**), translactonization often occurs to afford the enmein-type 1,7-lactone (**32**). Rearrangements through retro-aldol pathways are also hypothesized: the maoecrystal Z ring system likely arises via a rearrangement paralleling that of **27** to **29**.[2g]

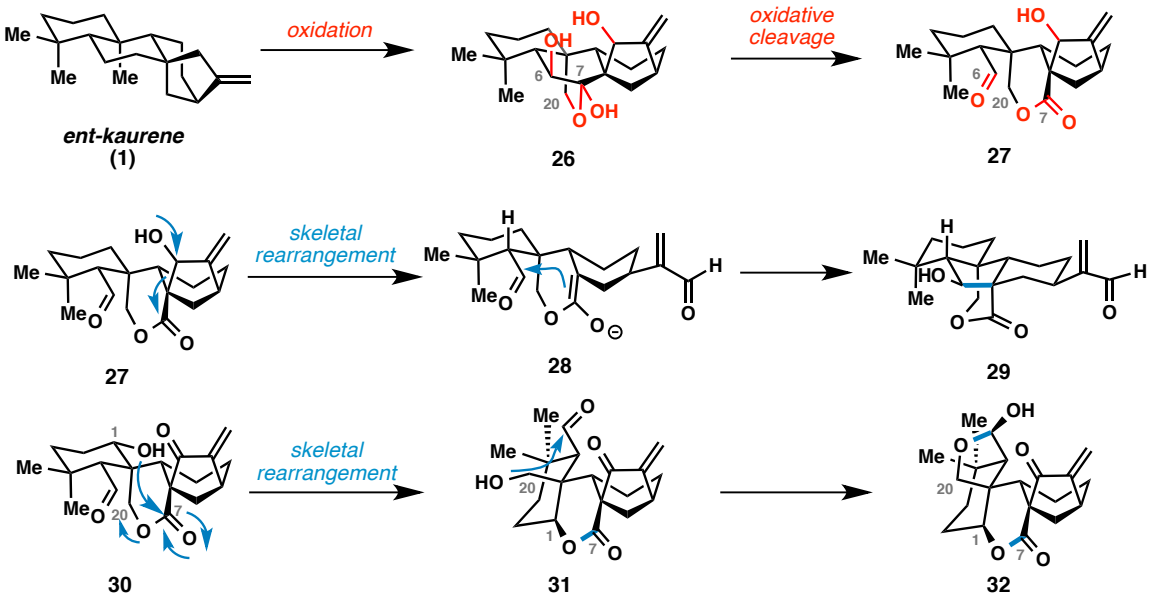


Figure 1.3. Biosynthetic oxidations, cleavages, and rearrangements of *ent*-kaurene.

1.4 PREVIOUS AND CONCURRENT SYNTHETIC EFFORTS

Prior to the elucidation of maoecrystal V (**9**) in 2004,[2f] efforts in *seco*-*ent*-kauranoid total synthesis were few and far between. Moreover, many of the racemic total syntheses reported do not provide clear entry to an enantioselective synthesis, either by asymmetric catalysis or from chiral pool starting materials. More thorough investigation of the novel biological activity displayed by members of this class requires that synthetic chemists take up this charge. The endeavors presented below are intended to highlight the history and current state of the art through the discussion of the principal transformations and strategies employed for the construction of these complex frameworks.

1.4.1 Fujita's Relay Synthesis of Enmein

As part of a larger program focused on the isolation and characterization of *Isodon* diterpenoids, Fujita and colleagues disclosed the synthetic preparation of enmein (**11**) in 1972.[11] A strategy passing through relay compound **38**, available from **11** in 14 steps, was used. Beginning with phenanthrene derivative **33**, ketone **35** is accessed in 9 steps. Formylation and thioether formation blocks C13, allowing for selective enolization and allylation of C8 to afford **36**. Following cleavage of the blocking group and ozonolysis, exposure to NaOMe affords the *ent*-kaurane framework via aldol cycliation. Moving forward, **37** is advanced through relay compound **38** to olefin **39**. The C6–C7 bond is

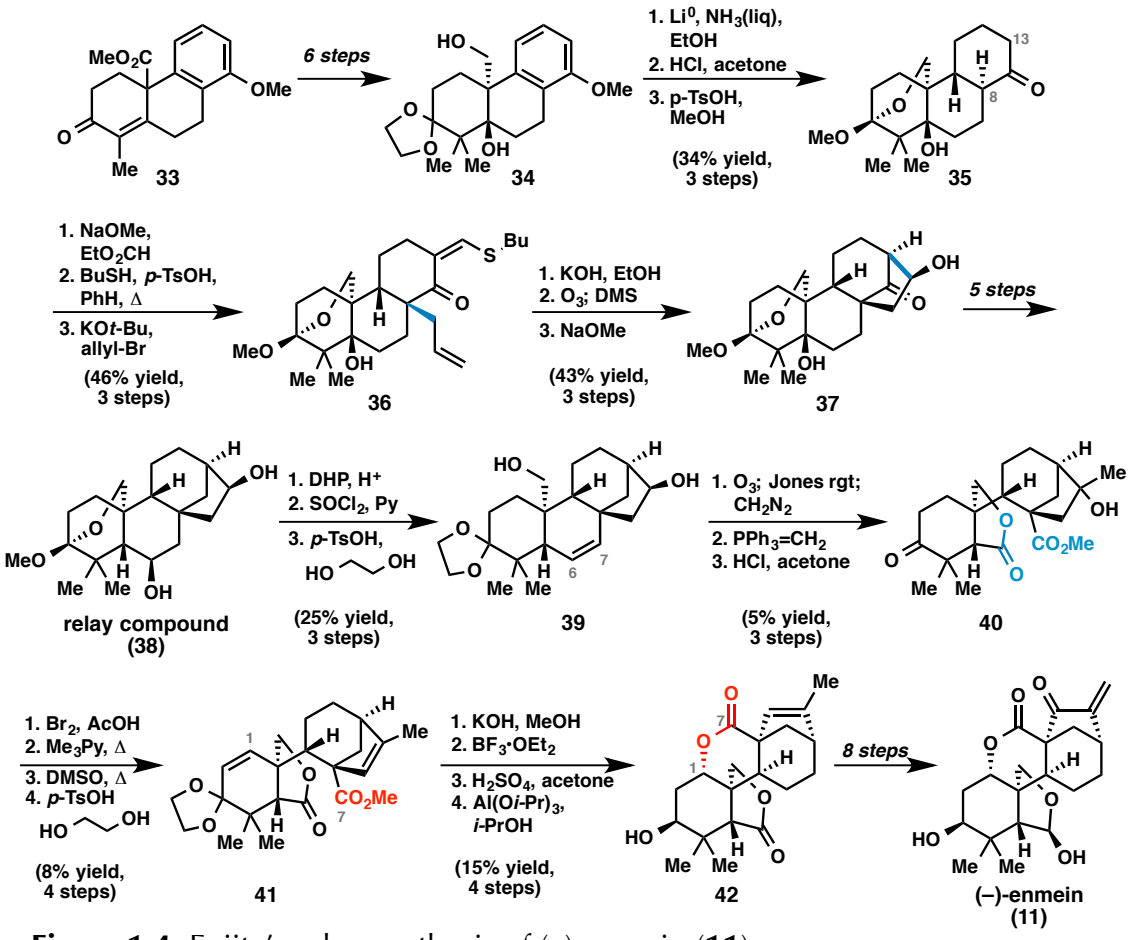


Figure 1.4. Fujita's relay synthesis of (–)-enmein (**11**).

cleaved via ozonolysis and oxidative workup to yield lactone **40**. The enmein 1,7-lactone (see **42**) is later accessed by BF_3•OEt_2-promoted intramolecular conjugate addition of the acid derived from **41**.

1.4.2 Mander's Synthesis of 15-Desoxyeffusin

Mander and colleagues disclosed the first effort toward a spirolactone-type 6,7-*seco*-*ent*-kauranoid in 1986.[12] In similar fashion to Fujita's strategy, C6–C7 oxidative cleavage of a suitably functionalized lactol precursor was envisioned to provide access to the *seco*-*ent*-kauranoid architecture of effusin (**7**).[2d]

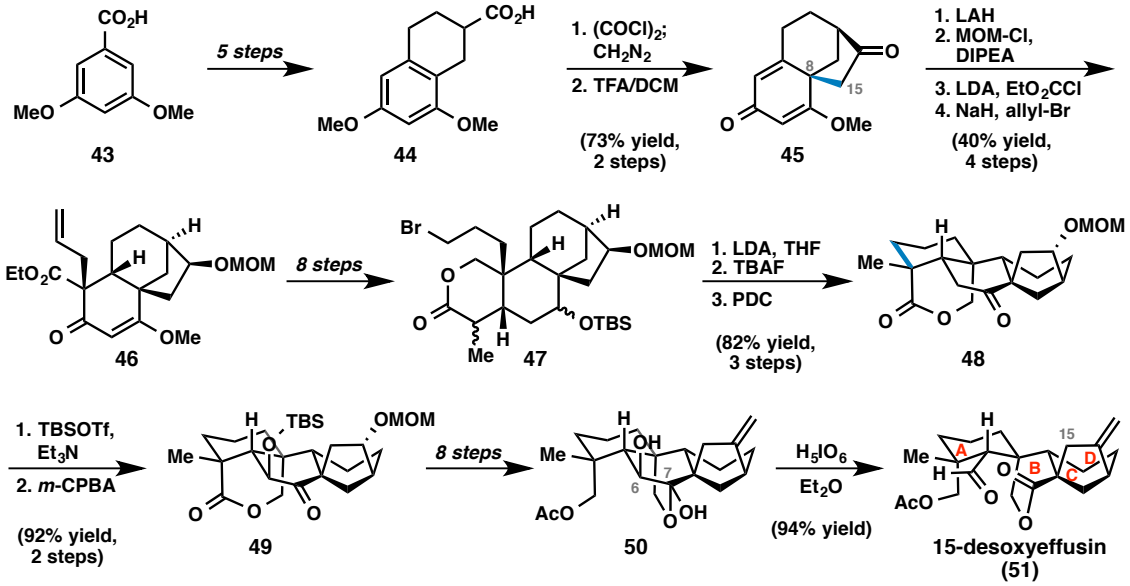


Figure 1.5. Mander's total synthesis of (±)-15-desoxyeffusin (**51**).

Beginning from 3,5-dimethoxybenzoic acid (**43**), bicyclic acid **44** is prepared in 5 steps. Acid **44** is converted to the α-diazomethylketone, which undergoes intramolecular alkylation of the aromatic ring upon treatment with trifluoroacetic acid to form the C8–C15 bond and afford bridged tricycle **45**. Exposure to LAH reduces the cyclopentanone

and delivers hydride to the *β*-face of the more electron-deficient enone to give the desired *cis*-fused 6,6-bicyclic system. Enolate alkylation and acylation install functional handles for appending the A ring in *β*-ketoester **46**, which was further advanced to lactone **47** in 8 steps.

Deprotonation of **47** with LDA resulted in cyclization to form the *ent*-kaurane framework. A sequence of protecting group and redox manipulations advanced **48** to lactol **50**, with the requisite C6 hydroxyl group for oxidative cleavage arising by Rubottom oxidation.[13] Lactol **50** was then treated with periodic acid to afford 15-desoxyeffusin (**51**) in 94% yield. The authors note that they were unable to introduce the C15 ketone by oxidation of **50** or **51** with selenium dioxide, a transformation which was successfully applied to similar gibberellin frameworks. Mander's 33-step route to **51** and a strategically similar 29-step semisynthesis of longirabdolactone (**8**)[14] would remain as the state of the art until recent efforts toward maoecrystal V (**9**).

1.4.3 Yang's Total Synthesis of Maoecrystal V

Since its structure was disclosed in 2004, **9** has quickly become the most highly targeted 6,7-*seco*-*ent*-kauranoid natural product, due to its remarkably selective cyctoxicity toward HeLa cells and complex pentacyclic architecture.[2f] To date, fifteen reports detailing efforts from nine laboratories have been published.[15,16] A 2010 communication from Yang and coworkers represents the first of three completed total syntheses of **9**.[16a]

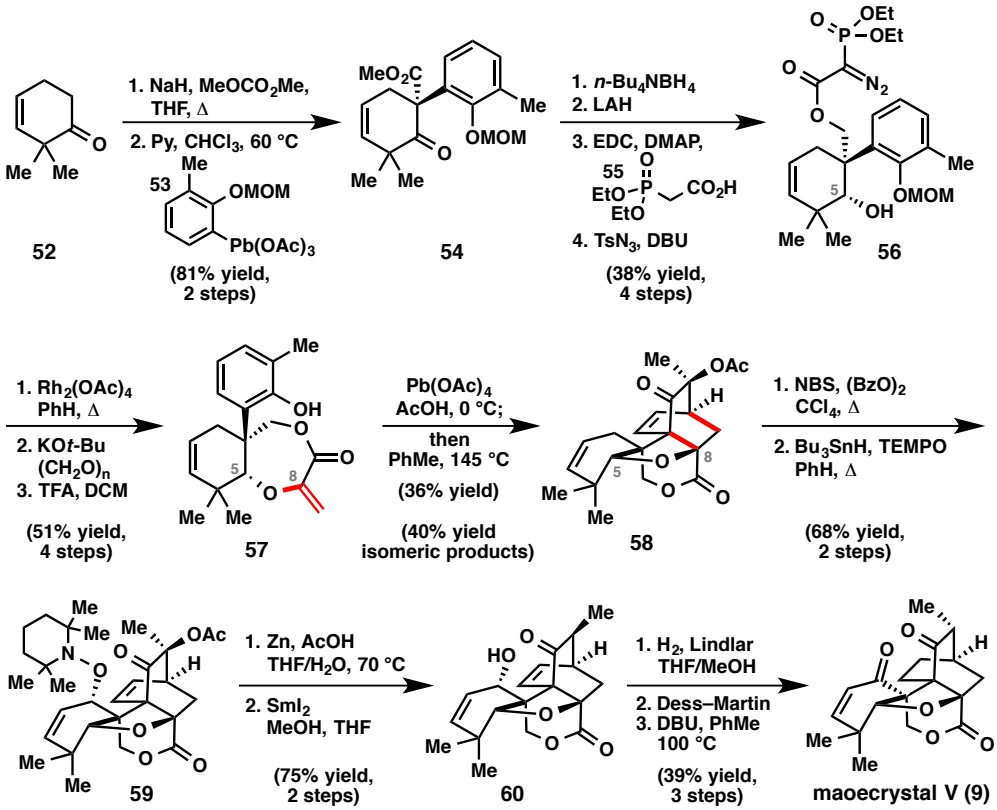


Figure 1.6. Yang's total synthesis of (±)-maoecrystal V (**9**).

Yang's strategy centers on an oxidative dearomatization/intramolecular Diels–Alder sequence used to prepare the bicyclo[2.2.2]octane and access the complete pentacyclic core. Oxidative arylation of the *β*-ketoester derived from cyclohexenone **52** by arylplumbane **53** delivers arylketone **54** in good yield. A two-step reduction sequence employing *n*-Bu_4NBH_4 followed by LAH provides the correct secondary alcohol relative stereochemistry for what will become the C5 to C8 ether bridge; the authors note that direct reduction of **54** with LAH or DIBAL provides the incorrect *β*-disposed alcohol. Following an EDC coupling of acid **55** and diazo transfer, a rhodium-catalyzed O–H bond insertion forms the second ether C–O bond. Horner–Wadsworth–Emmons olefination and cleavage of the MOM group with TFA reveals key Diels–Alder precursor **57**.

Indeed, treatment with lead tetraacetate results in oxidative dearomatization to provide an *ortho*-quinol acetate, which when heated in toluene undergoes Diels–Alder cycloaddition to deliver 36% yield of pentacycle **58**, as part of a mixture of three isomeric cycloaddition products. Pentacycle **58**, prepared in just ten steps, constitutes the framework of **9** and contains all the necessary carbons, but still requires a number of redox manipulations for conversion to the natural product. Allylic bromination and radical trapping with TEMPO are used to install necessary A ring oxygenation; N–O bond cleavage and reductive acetate removal are facilitated by zinc in AcOH and SmI_2, respectively, to yield allylic alcohol **60**. Lindlar hydrogenation, Dess–Martin oxidation, and epimerization with DBU completed the synthesis of **9**.

Though no clear entry point for asymmetry is present, the dearomatization/Diels–Alder strategy employed by Yang delivers a concise, 17-step preparation of maoecrystal V (**9**).

1.4.4 Danishefsky's Total Synthesis of Maoecrystal V

The Danishefsky laboratory has investigated multiple intramolecular Diels–Alder approaches for the synthesis of **9**.[15c,j,16b] Early attempts with functionalized model compound **61** provided undesired cycloadduct **62**, arising from improper diene facial selectivity. As the oxidation about the resulting bicyclo[2.2.2]octane of **62** was therefore incorrect for advancement to **9**, this route was abandoned.

The authors hypothesized that an achiral Diels–Alder precursor might provide a solution to the observed regioselectivity problem. Toward this end, the enolate of **63** was coupled with chloroenone **64**. Exhaustive reduction with DIBAL followed by reoxidation

of the allylic alcohol furnished enone **65**. Condensation with acyl chloride **66** and conversion to the silyl enol ether afforded Diels–Alder precursor **67**. Heating **67** in toluene effected cycloaddition as well as β-elimination of the phenyl sulfinate to reveal tetracycle **68** upon exposure to TBAF. The use of a vinyl phenyl sulfinate dienophile as a propiolate equivalent precludes the formation of isomeric products, as they converge to enantiomers upon elimination to form the olefin.

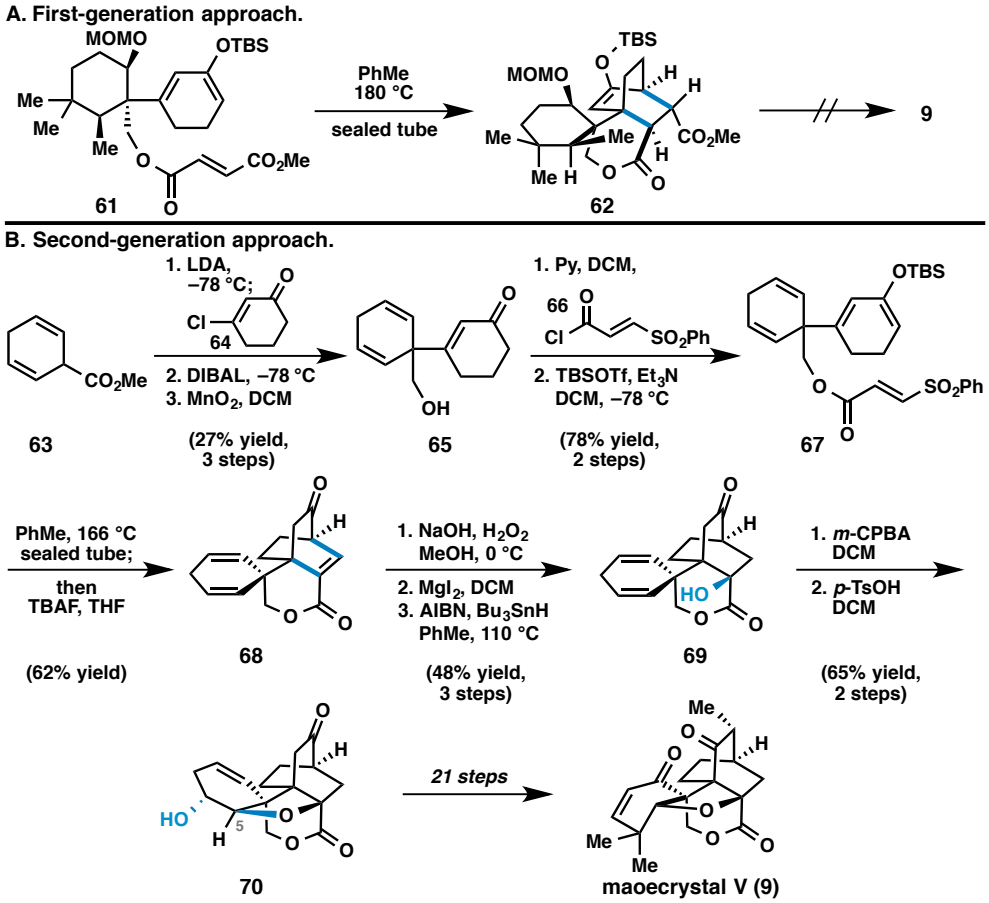


Figure 1.7. Danishefsky's total synthesis of (±)-maoecrystal V.

The authors note that the challenge in advancing **68** to **9** now lies in the differentiation of three olefins with similar levels of steric hindrance. One double bond, however, is contained within an α,β-unsaturated ester and is therefore electronically differentiated. Thus, exposure of **68** to NaOH and H_2O_2 effects chemoselective

epoxidation of the electron-deficient olefin. This epoxide can be readily converted to the iodohydrin by MgI_2, which is hydrodehalogenated under radical conditions to give tertiary alcohol **69**. The placement of the resulting alcohol now serves to activate the proximal olefin toward epoxidation by *m*-CPBA; subsequent treatment with *p*-TsOH promotes cyclization to form pentacyclic ether **70**.

With **70** in hand, Danishefsky has prepared the core of maoecrystal V (**9**), albeit epimeric at C5. The achiral precursor employed facilitates rapid preparation of the majority of the structural complexity of **9** via a single isomer of cycloadduct **68** in just six steps, further functionalized through deft use of substrate control to arrive at pentacycle **70** in eleven steps. However, due to the relative absence of substitution in **70**, a further 21 steps are required to install the enone and *gem*-dimethyl group and to properly functionalize the bicyclo[2.2.2]octane. Although **9** was prepared as a racemate, this strategy allows for the possibility of asymmetric induction during the Diels–Alder cycloaddition through the use of a chiral catalyst.

1.4.5 Zakarian's Total Synthesis of Maoecrystal V

In 2013, Zakarian and colleagues also disclosed a total synthesis of **9**.[16c] A different Diels–Alder disconnection from those employed by Yang and Danishefsky is used, employing a silyl-tethered precursor. Additionally, the lactone is constructed by a novel late-stage radical cyclization. The authors hypothesized, quite correctly, that early introduction of the tetrahydrofuran ring would likely improve stereocontrol later in the synthesis and avoid the risks of attempting ether formation on a strained polycyclic system.

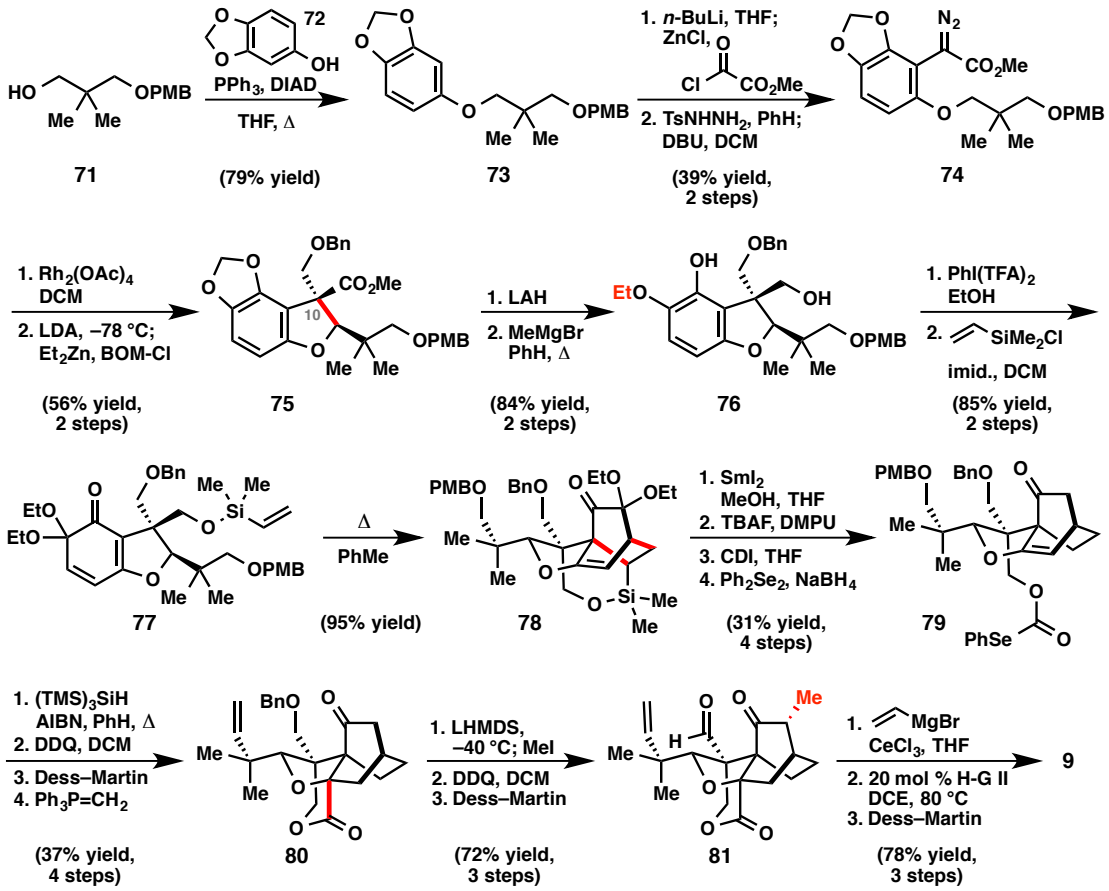


Figure 1.8. Zakarian's total synthesis of (±)-maoecrystal V (**9**).

The synthesis commenced with coupling of PMB ether **71** and sesamol (**72**) under Mitsunobu conditions.[17] Directed lithiation and acylation with methyl chlorooxoacetate followed by conversion to the *α*-diazoester using tosyl hydrazide afforded **74**. Catalytic $Rh_2(OAc)_2$ effected C–H insertion to form the furan ring, and alkylation with LDA and benzyloxymethyl chloride delivered dihydrobenzofuran **75** and the C10 all-carbon quaternary stereocenter. Moving forward, cycloaddition of *ortho*-quinone ketal **77** proceeded in refluxing toluene to form the bicyclooctane in 95% yield. Following removal of the *gem*-diethoxy substituents with SmI_2 and desilylation with TBAF, selenocarbonate **79** was accessed through successive treatment with carbonyl diimidazole (CDI) and sodium phenyl selenide.

The authors observed that only tris(trimethylsilyl)silane acted as an effective hydrogen atom donor for the desired radical cyclization, which proceeded upon exposure to AIBN. A series of functional group manipulations furnished tetracycle **80**, which was alkylated on the ketone bridge using LHMDS and iodomethane and advanced to aldehyde **81**. Vinyl Grignard addition, ring closing methathesis using Hoveyda-Grubbs II catalyst, and Dess–Martin oxidation completed the synthesis of **9**.

Zakarian's route proceeds to **9** in 24 steps, while avoiding the majority of selectivity pitfalls prevalent in Danishefsky's and Yang's strategies. Early-stage formation of the tetrahydrofuran ring proved advantageous in this regard; the authors also note that its construction via C–H insertion of diazoester **74** could potentially be rendered asymmetric through the use of chiral rhodium catalysts.

1.4.6 Zhai's Total Synthesis of Sculponeatin N

In contrast to Mander's 33-step preparation of 15-desoxyeffusin, Zhai and colleagues have recently disclosed a concise total synthesis of a quite similar 6,7-*seco*-*ent*-kauranoid, sculponeatin N (**1**).[18] Rather than employ a biomimetic oxidative cleavage, Zhai elected to pursue an intramolecular Diels–Alder for the simultaneous preparation of the B and C rings, followed by alkylation and radical cyclization to install the bridging *exo*-enone.

Beginning with known diester **82**, treatment with LDA and paraformaldehyde effects a regio- and stereoselective aldol reaction and lactonization to give bicyclic lactone **83**, which is advanced quickly to cycloaddition precursor **85**. Heating to 190 °C in a sealed tube effects the intramolecular Diels–Alder, and the authors were able to devise a one-pot

cycloaddition/protodesilation/methanolysis sequence to furnish a single *cis*-fused bicyclic product. Following TBS protection, alkylation of **86** with 2,3-dibromopropene (**87**) proceeds in good yield using LDA and HMPA to form the second quaternary center. Exposure to triethylborane and tris(trimethylsilyl)silane at room temperature results in radical cyclization to give a 68% yield of **89** along with 27% yield of the isomeric bicyclo[2.2.2]octane. Use of AIBN and tributyltin hydride on the other hand favors the undesired isomer in a 3:1 ratio. Allylic oxidation and TBS ether cleavage furnishes **2**.

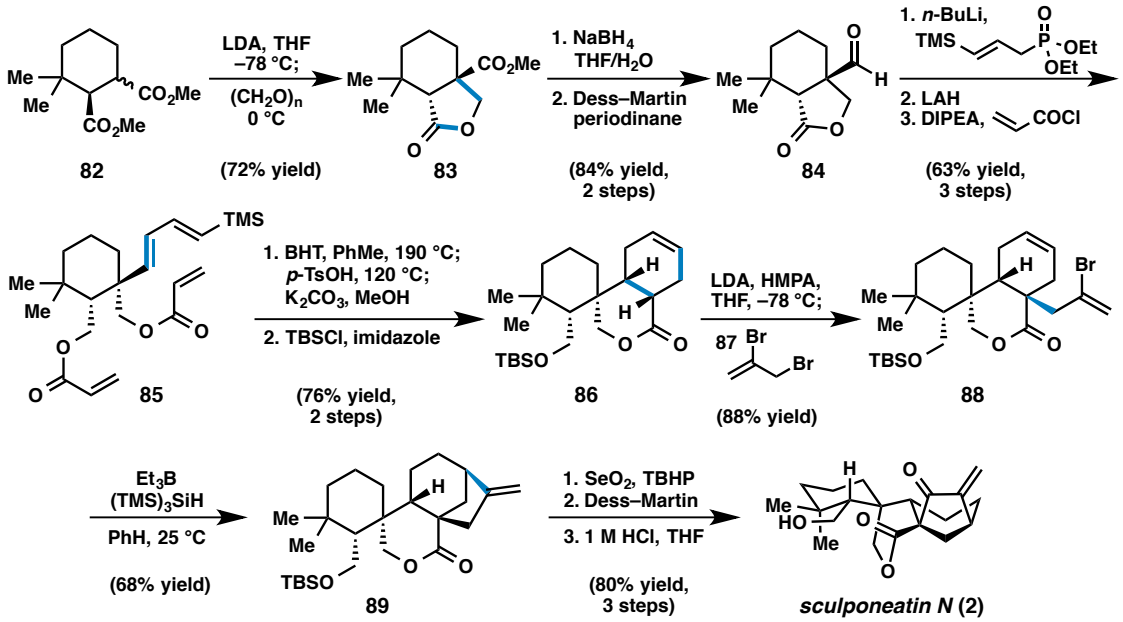


Figure 1.9. Zhai's total synthesis of (±)-sculponeatin N.

1.5 CONCLUDING REMARKS

Though the *Isodon* diterpenoids have been scantly studied by synthetic chemists for much of the last fifty years, there is renewed interest in this family of natural products brought about by the isolation of new members possessing complex and novel architectures. Improvements in synthetic methodology have enabled shorter syntheses of these targets, though asymmetric preparations and more general strategies remain out of reach. The investigation of enantioselective approaches to this class, as well as the development of new methods for the synthesis of these complex targets, will encourage and facilitate new inquiries into their biological activity.

1.6 NOTES AND REFERENCES

(1) Sun, H.-D.; Huang, S.-X.; Han, Q.-B. *Nat. Prod. Rep.* **2006**, *23*, 673.

(2) For isolation reports, see the following references. Sculponeatin N: (a) Li, X.; Pu, J.-X.; Weng, Z.-Y.; Zhao, Y.; Zhao, Y.; Xiao, W.-L.; Sun, H.-D. *Chem. Biodiversity* **2010**, *7*, 2888. Trichorabdals A, C and D: (b) Node, M.; Sai, M.; Fuji, K.; Fujita, E.; Shingu, T.; Watson, W. H.; Grossie, D. *Chem. Lett.* **1982**, 2023. Trichorabdal B: (c) Fujita, E.; Fuji, K.; Sai, M.; Node, M.; Watson, W. H.; Zabel, V. *J. Chem. Soc., Chem. Commun.* **1981**, 899. Effusin: (d) Kubo, I.; Kamikawa, T.; Isobe, T.; Kubota, T. *J. Chem. Soc., Chem. Commun.* **1980**, 1206. Longirabdolactone: (e) Takeda, Y.; Ichihara, T.; Otsuka, H.; Kido, M. *Phytochemistry* **1993**, *33*, 643. Maoecrystal V: (f) Li, S.-H.; Wang, J.; Niu, X.-M.; Shen, Y.-H.; Zhang, H.-J.; Sun, H.-D.; Li, M.-L.; Tian, Q.-E.; Lu, Y.; Cao, P.; Zheng, Q.-T. *Org. Lett.* **2004**, *6*, 4327. Maoecrystal Z: (g) Han, Q.-B.; Cheung, S.; Tai, J.; Qiao, C.-F.; Song, J.-Z.; Tso, T.-F.; Sun, H.-D.; Xu, H.-X. *Org. Lett.* **2006**, *8*, 4727. Enmein: (h) Takahashi, M.; Fujita, T.; Koyama, Y. *Yakugaku Zasshi*, **1985**, *78*, 699. (i) Ikeda, T.; Kanatomo, S. *Yakugaku Zasshi* **1958**, *78*, 1128. (j) Naya, K. *Nippon Kagaku Zasshi*, **1958**, *79*, 885. Longikaurin E: (k) Fujita, T.; Takeda, Y.; Shingu, T. *Heterocycles*, **1981**, *16*, 227. Oridonin: (l) Fujita, E.; Fujita, T.; Katayama, H.; Shibuya, M. *J. Chem. Soc., Chem. Commun.* **1967**, 252. Adenanthin: (m) Xu, Y.-L.; Sun, H.-D.; Wang, D.-Z.; Iwashita, T.; Komura, H.; Kozuka, M.; Naya, K.; Kubo, I. *Tetrahedron Lett.* **1987**, *28*, 499.

(3) (a) Fujita, E.; Nagao, Y.; Kaneko, K.; Nakazawa, S.; Kuroda, H. *Chem. Pharm. Bull.* **1976**, *24*, 2118. (b) Fuji, K.; Node, M.; Sai, M.; Fujita, E.; Takeda, S.; Unemi, N. *Chem. Pharm. Bull.* **1989**, *37*, 1472.

(4) Yagi, S. *J. Kyoto Med. Soc.* **1910**, *7*, 30.

(5) (a) Iitaka, Y.; Natsume, M. *Tetrahedron Lett.* **1964**, *5*, 1257. (b) Natsume, M.; Iitaka, Y. *Acta Cryst.* **1966**, *20*, 197.

(6) (a) Serafimova, I. M.; Pufall, M. A.; Krishnan, S.; Duda, K.; Cohen, M. S.; Maglathlin, R. L.; McFarland, J. M.; Miller, R. M.; Frödin, M.; Taunton, J. *Nat. Chem. Biol.* **2012**, *8*, 471. (b) Gersch, M.; Kreuzer, J.; Sieber, S. A. *Nat. Prod. Rep.* **2012**, *29*, 659.

(7) Liu, C.-X.; Yin, Q.-Q.; Zhou, H.-C.; Wu, Y.-L.; Pu, J.-X.; Xia, L.; Liu, W.; Huang, X.; Jiang, T.; Wu, M.-X.; He, L.-C.; Zhao, Y.-X.; Wang, X.-L.; Xiao, W.-L.; Chen, H.-Z.; Zhao, Q.; Zhou, A.-W.; Wang, L.-S.; Sun, H.-D.; Chen, G.-Q. *Nat. Chem. Biol.* **2012**, *8*, 486.

(8) Bohlmann, J.; Meyer-Gauen, G.; Croteau, R. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 4126.

(9) (a) Fujita, T.; Takao, S.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1973**, 434. (b) Fujita, T.; Masuda, I.; Takao, S.; Fujita, E. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2098. (c) Fujita, T.; Takao, S.; Fujita, E. *J. Chem. Soc., Perkin Trans. 1* **1979**, 910. (d) Fujita, T.; Masuda, I.; Takao, S.; Fujita, E. *J. Chem. Soc., Perkin Trans. 1* **1979**, 915. (e) Fujita, T.; Takao, S.; Fujita, E. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2468.

(10) Fuji, K.; Node, M.; Sai, M.; Fujita, E.; Shingu, T.; Watson, W. H.; Grossie, D. A.; Zabel, V. *Chem. Pharm. Bull.* **1989**, *37*, 1465.

(11) (a) Fujita, E.; Shibuya, M.; Nakamura, S.; Okada, Y.; Fujita, T. *J. Chem. Soc., Chem. Commun.* **1972**, 1107. (b) Fujita, E.; Shibuya, M.; Nakamura, S.; Okada, Y.; Fujita, T. *J. Chem. Soc., Perkin Trans. 1* **1974**, 165. (c) Shibuya, M.; Fujita, E. *J. Chem. Soc., Perkin Trans. 1* **1974**, 178.

(12) (a) Kenny, M. J.; Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1986**, *27*, 3923. (b) Kenny, M. J.; Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1986**, *27*, 3927.

(13) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, *15*, 4319.

(14) Adamson, G.; Mander, L. N. *Aust. J. Chem.* **2003**, *56*, 805.

(15) For efforts toward maoecrystal V, see: (a) Gong, J.; Lin, G.; Li, C.-C.; Yang, Z. *Org. Lett.* **2009**, *11*, 4770. (b) Krawczuk, P. J.; Schöne, N.; Baran, P. S. *Org. Lett.* **2009**, *11*, 4774. (c) Peng, F.; Yu, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2009**, *50*, 6586. (d) Nicolaou, K. C.; Dong, L.; Deng, L.; Talbot, A. C.; Chen, D. Y. K. *Chem. Commun.* **2010**, *46*, 70. (e) Singh, V.; Bhalerao, P.; Mobin, S. M. *Tetrahedron Lett.* **2010**, *51*. (f) Lazarski, K. E.; Hu, D. X.; Stern, C. L.; Thomson, R. J. *Org. Lett.* **2010**, *12*, 3010. (g) Baitinger, I.; Mayer, P.; Trauner, D. *Org. Lett.* **2010**, *12*, 5656. (h) Gu, Z.; Zakarian, A. *Org. Lett.* **2011**, *13*, 1080. (i) Dong, L.; Deng, L.; Lim, Y. H.; Leung, G. Y. C.; Chen, D. Y. K. *Chem.–Eur. J.* **2011**, *17*, 5778. (j) Peng, F.; Danishefsky, S. J. *Tetrahedron Lett.* **2011**, *52*, 2104. (k) Lazarski, K. E.; Akpinar, B.; Thomson, R. J. *Tetrahedron Lett.* **2013**, *54*, 635. (l) Carberry, P.; Viernes, D. R.; Choi, L. B.; Fegley, M. W.; Chisholm, J. D. *Tetrahedron Lett.* **2013**, *54*, 1734.

(16) For completed total syntheses of maoecrystal V, see: (a) Gong, J.; Lin, G.; Sun, W.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 16745. (b) Peng, F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 18860. (c) Lu, P.; Gu, Z.; Zakarian, A. *J. Am. Chem. Soc.* **2013**, *135*, 14552.

(17) Mitsunobu, O. *Synthesis* **1981**, *1981*, 1.

(18) Pan, Z.; Zheng, C.; Wang, H.; Chen, Y.; Li, Y.; Cheng, B.; Zhai, H. *Org. Lett.* **2014**, *16*, 216.