Natural Product Synthesis

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The Total Synthesis of *Isodon* Diterpenes

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Isodon diterpenes · maoecrystal V · natural products · total synthesis

***F**amilies of structurally related molecules often provide stimulating targets for organic chemists that are engaged in the development of new methods and strategies for natural product synthesis. While typically focused on specific molecules, these synthetic investigations often lead to generalizable concepts and significant opportunities for learning in a greater sense. Historically well-investigated families of natural products, such as the prostanoids, indole alkaloids, and macrolide antibiotics, provide ample evidence for the enduring value of these collective activities. In this Minireview, we turn our attention to the polycyclic family of diterpenes isolated from the Isodon genus of plants and provide an account of the recent methods and strategies utilized for their total synthesis.*

1. Introduction

Plants of the *Isodon* genus (formerly known as *Rabdosia*) have been an abundant source of terpene natural products, prized both for the diversity and complexity of their chemical structures, and for their extensive profile of biological activity.[1] The medicinal attributes of the *Isodon* family (and their terpene constituents by extension) have been appreciated for centuries. Traditional Chinese folk medicine has relied on this family of shrubs and herbs to treat a wide spectrum of maladies, including, but not limited to, inflammation, malaria, bacterial infections of the lung or gut, and pneumonia. The curative properties of these plants are so respected that, in fact, some are known as *enmei-so* or "grass effective for the prolongation of human life."[1]

The initial examination of the chemical constituents within *Isodon* family members began with the isolation of enmein (**1**) in 1964 by Iitaka and Mitsutaka (Figure 1).[2] Isolated from *I. japonica*, one of the species alternatively known as *enmei-so*, the structure was unambiguously determined by X-ray crystallography. Isotope-labeling experiments indicated that enmein (**1**) is biosynthesized from *ent*-kaurene (**5**).[3] Subsequently, a remarkably diverse array of polycyclic natural products were isolated from various species within the *Isodon* genus. Much of the credit for these discoveries is due to Sun and his research group at the Kunming Institute of Botany, who reported a comprehensive review of the isolation and structures of the *Isodon* diterpenes in 2006.[4] A selection of representative structures is shown in Figure 1.

In comparison to enmein (**1**), longikaurin E (**2**)[5] is a closer biosynthetic link to the structure of *ent*-kaurene (**5**), as the C6–C7 bond of **2** remains intact, while sculponeatin N (**3**)[6] is less related because of the C6–C7 bond scission. Fragmentation or rearrangement within these diterpenes is incredibly common and leads to a variety of additional structures that are even further removed from the biogenetic prototype (i.e., **5**). The contraction of the A ring leads to the unusual cyclopropane-fused derivative neolaxiflorin A (**4**),[7] while cleavage of the centrally located C8–C9 bond affords rabdohakusin (**6**),[8]

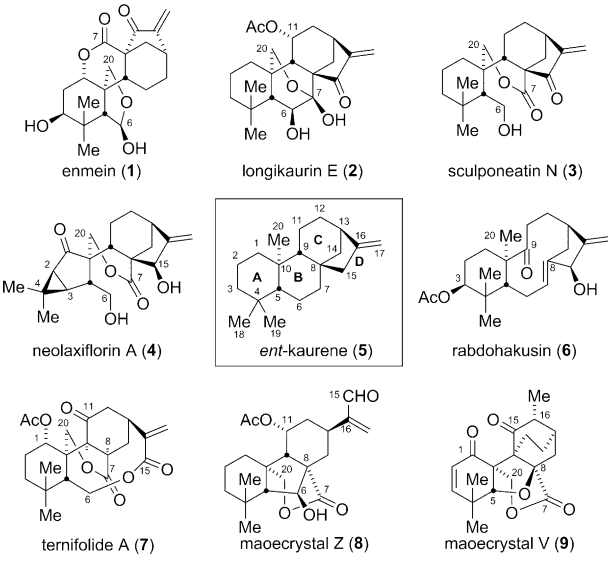

Figure 1. Selected *Isodon* diterpenes and their biogenic precursor.

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which features a ten-membered ring. Cleavage of the C8–C15 bond leads to species such as ternifolide A (**7**)[9] and maoecrystal Z (**8**),[10] both of which possess additional rings formed by lactonization and an aldol reaction, respectively. While these natural products display a significant deviation from the parent *ent*-kaurene carboskeleton (i.e., **5**), the structure of maoecrystal V (**9**)[11] is perhaps the least related from **5** in terms of a putative biosynthetic progression. The bicyclo[3.2.1]octane core of **5** has undergone rearrangement to a bicyclo[2.2.2]octane core, C6 has been completely deleted, and a highly strained ether ring has formed between C5 and C8. The presence of vicinal quaternary stereocenters within **9** provides another level of complexity not seen in other family members.

The structural diversity of the *Isodon* diterpenes, coupled with potent and often highly selective cytotoxic activity, has led a number of groups to initiate synthesis research programs aimed at exploring the chemistry of these compounds. In this Minireview, we will cover in detail only those studies that have led to the successful total synthesis of an *Isodon* diterpene since 2010. The reader who is interested in learning more about other synthetic studies towards *Isodon* diterpenes is directed toward the appropriate literature.[12]

2. Total Syntheses

In the following sections we detail the approaches taken by several research groups that are actively engaged in the total synthesis of one or more of the diterpenes in the *Isodon* family. Much of the recent activity in this field was initiated by the report of Sun and co-workers on maoecrystal V (**9**),[11] whose structure captured the imagination of many practitioners of total synthesis.[13] Before discussing these most recent efforts, we outline the synthetic efforts prior to 2010.

2.1. Total Syntheses Prior to 2010

2.1.1. Enmein (1974)

The first total synthesis of an *Isodon* diterpene was reported in 1974 by Fujita and his group at Kyoto University, when they showed that enmein (**1**) could be prepared from phenanthrene derivative **10** in 44 steps (Scheme 1).[14] The key inspiration for their approach was drawn from their previous research into the biosynthesis of enmein and relied heavily upon the use of the advanced kaurene derivative **11**, which could be prepared by degradation of natural enmein. Racemic **11** could be obtained in 19 steps from **10**, while the optically pure material was obtained by the aforementioned degradation. Using the degradation material, the synthesis was completed via diene **12**, and can thus be considered an enantioselective "relay" synthesis.

2.1.2. 15-Desoxy-effusin (1986)

In 1986, Mander and his group at The Australian National University reported the de novo synthesis of the *Isodon* diterpene derivative 15-desoxy-effusin (**16**) in 29 steps from

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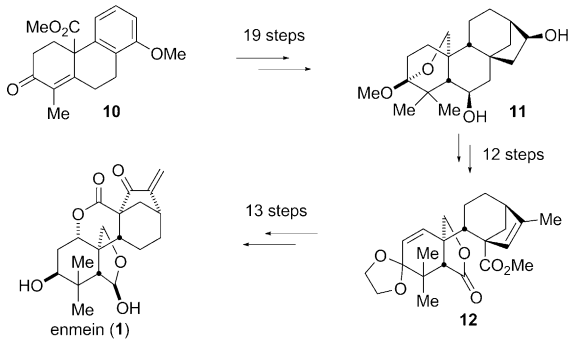
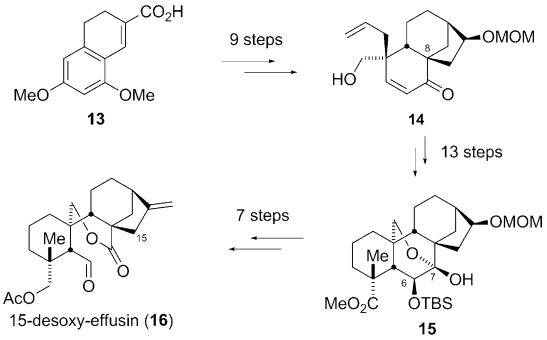
Prof. Regan J. Thomson was born in Balclutha, New Zealand. He received his Ph.D. in 2003 at The Research School of Chemistry at The Australian National University working with Prof. Lewis N. Mander. Following postdoctoral studies with Prof. David A. Evans at Harvard University, he began his independent career at Northwestern University in 2006, where he is currently an Associate Professor.



Scheme 1. Synthesis of enmein (**1**) by Fujita and co-workers.

dihydronaphthoic acid **13** (Scheme 2).[15] Their construction of the carbocyclic skeleton drew heavily from prior work in the group that had culminated in the successful synthesis of gibberellin natural products a few years earlier.[16] Thus, the key bicyclo[3.2.1]octane ring system within **14** was forged by a diazoketone-based electrophilic alkylation of the aryl ring within **13**, while the A ring of hemiacetal **15** was constructed by an intramolecular Michael addition and subsequent enolate alkylation. Oxidative cleavage of the C6–C7 bond

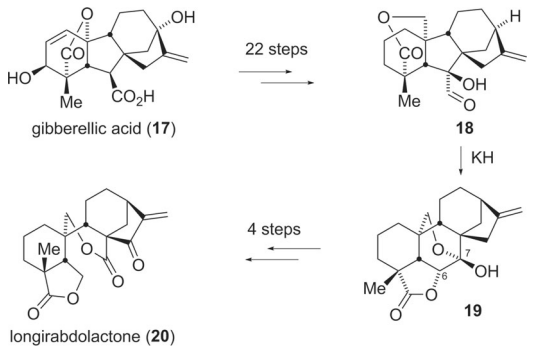


Scheme 2. Synthesis of 15-desoxy-effusin (**16**) by Mander and co-workers.

within **15** ultimately rendered the target compound 15-desoxy-effusin (**16**).

2.1.3. Longirabdolactone (2003)

Mander and his group spent significant efforts on the conversion of gibberellic acid (**17**) and related abundant gibberellins into rare high-value gibberellin derivatives.[17] In 2003, Mander and Adamson took advantage of this expertise to devise an interesting route to longirabdolactone (**20**) from **17** in 27 steps (Scheme 3).[18] Aldehyde **18** was accessed in



Scheme 3. Mander and Adamson's synthesis of longirabdolactone (**20**).

22 steps from **17**, setting the stage for an anionic acyloin ring-expansion to lactone **19**. This transformation of the gibberellane skeleton into the kaurene skeleton is of particular interest, as it is formally the reversal of the pathway involved in the biosynthesis of gibberellin. Oxidative scission of the C6–C7 bond within **19** then mimics the biosynthesis of longirabdolactone (**20**), affording the natural product in four more steps.

2.2. Maoecrystal V

Maoecrystal V (**9**) was first isolated by Sun and co-workers in the mid-1990s. Its structure was not published until ten years later, when a suitable crystal was grown for X-ray analysis to verify the unprecedented structure indicated by NMR and MS spectral data.[11] The structure of maoecrystal V

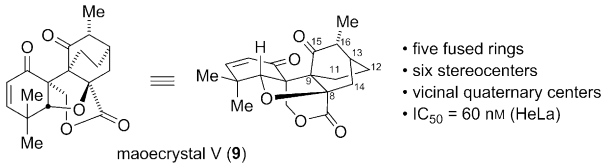


Figure 2. Representations of maoecrystal V (**9**).

is unique among isolated terpenes (Figure 2). In biological assays performed by the chemists who isolated the compound, **9** was screened against five different human tumor cell lines: K562, A549, BGC-823, CNE, and HeLa. Maoecrystal V demonstrated potent activity against HeLa cells and was inactive against all other lines. This impressive selectivity gives maoecrystal V a unique activity profile, which may indicate a novel mechanism of cellular action. In spite of this remarkable biological activity, it has been the fascinating structure of maoecrystal V that has garnered much interest from the scientific community. Its skeleton consists of five interwoven carbocyclic rings and six stereogenic centers, two of which are vicinal quaternary centers. This mixture of stereochemical complexity and challenging topology has driven organic chemists to use maoecrystal V as a testing ground for new chemical tactics and synthetic strategies.

To date, three total syntheses of maoecrystal V (**9**)[19–21] and numerous model studies have been published.[12,13] Each of the three total syntheses reported thus far have utilized intramolecular Diels–Alder (IMDA) reactions to form the congested bicyclo[2.2.2]octane ring system (Figure 3). Both

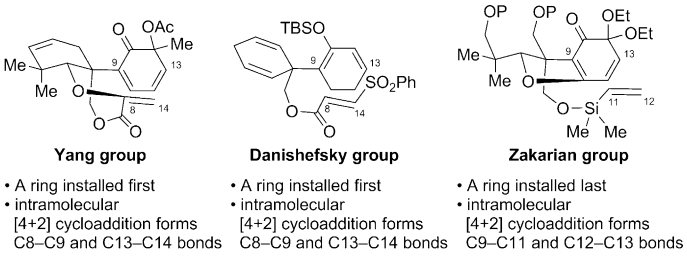


Figure 3. Synthetic intermediates of maoecrystal V (**9**).

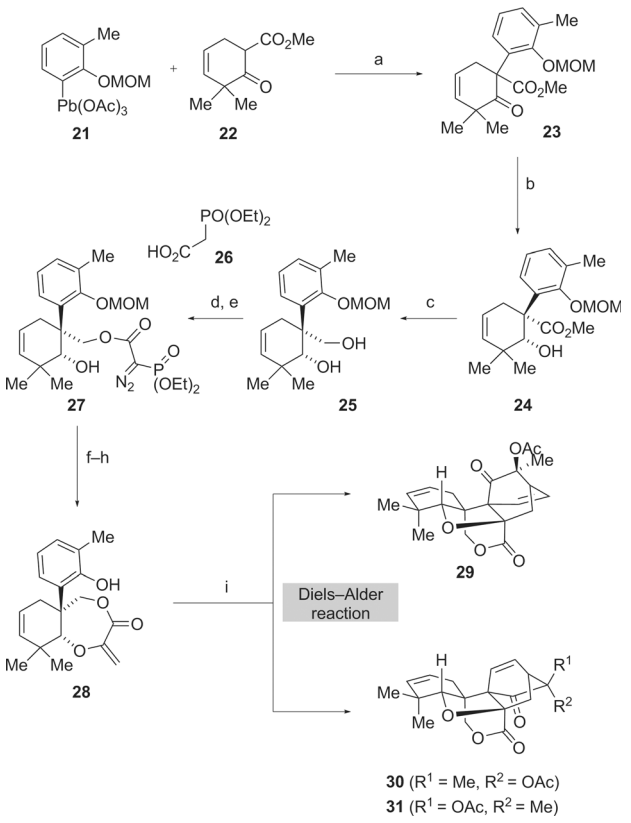
the groups of Yang and Danishefsky utilized an A ring synthon as starting material and built the maoecrystal V skeleton through an intramolecular cycloaddition that forged the C8–C9 and C13–C14 bonds. On the other hand, Zakarian and co-workers constructed the A ring last in their synthesis and made use of an alternative intramolecular cycloaddition that formed the C9–C11 and C12–C13 bonds. The successful total syntheses by these groups are summarized in chronological order within the next section, where both similarities and key differences in strategy can be discovered upon deeper inspection.

2.2.1. Approach of the Yang Group (2010)

In November of 2010, Yang and co-workers at Peking University reported the first total synthesis of maoecrystal V

(**9**).[19] Their approach was the successful culmination of a previously published model study, in which they demonstrated the feasibility of accessing the core of maoecrystal V by an intramolecular Diels–Alder reaction that simultaneously installed the tetrahydrofuran, lactone, and bicyclo-[2.2.2]octane rings.[12a]

The results of their synthetic efforts that led to the desired Diels–Alder adduct are detailed in Scheme 4. Aryl plumbane

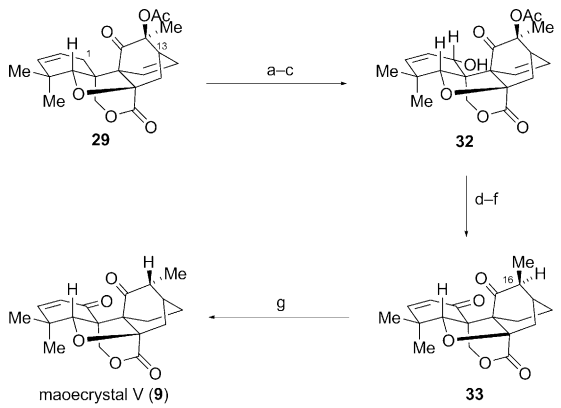


Scheme 4. Reaction conditions: a) pyridine, 60 °C, 88%; b) $(Bu_4N)BH_4$, 40 °C, 65% (89% brsm); c) $LiAlH_4$, 88%; d) EDCI, **26**; e) TsN_3, DBU, 66% over two steps from **25**; f) $[Rh_2(OAc)_4]$, 60%; g) *t*BuOK, CH_2O, 95%; h) TFA, 90%; i) $Pb(OAc)_4$, AcOH, 0 °C; then toluene, 145 °C, 36% (**29**), 28% (**30**), 12% (**31**). Brsm = based on recovered starting material; EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TFA = trifluoroacetic acid.

21 was coupled to β-keto ester **22** (prepared in three steps from 2,2-dimethylcyclohexa-1,3-dione)[22] to provide the linked bicyclic ring system **23**. Initial attempts to reduce the ketone and methyl ester in concert gave the undesired relative stereochemistry between the secondary alcohol and aryl ring. Instead, a two-step procedure was developed that reduced the ketone diastereoselectively using $(Bu_4N)BH_4$ as the reducing agent, giving secondary alcohol **24** as the sole product. The authors hypothesize that the selectivity may be the result of a directing effect caused by attractive cation–π interactions between the ammonium salt and the electron-rich aromatic ring. Reduction of the methyl ester by lithium aluminum hydride generated diol **25**. Subsequent chemoselective coupling of the primary alcohol within **25** with 2-(diethoxyphosphoryl)acetic acid (**26**), followed by treatment with tosyl azide furnished α-diazo phosphonate **27** in good overall yield. An O–H bond insertion reaction was then initiated by heating diazoester **27** at reflux in toluene in the presence of rhodium acetate dimer. This interesting bond connection elegantly established a Horner–Wadsworth–Emmons reagent that was fit to install the dienophile required for the planned intramolecular Diels–Alder reaction.

After methylenation with formaldehyde, the acidic liberation of the MOM-protected phenol completed the synthesis of the oxidative dearomatization precursor **28**. Exposure of phenol **28** to the Wessely oxidation conditions the Yang group had explored in their model studies ($Pb(OAc)_4$, AcOH, 0 °C) gave a mixture of oxidatively dearomatized products, which were taken up in toluene and heated at reflux to actuate the desired cycloaddition. The authors recovered three products: the desired Diels–Alder adduct **29** (36%), and two diastereomers that resulted from cycloadditions with the incorrect facial selectivity, namely **30** (28%) and **31** (12%). While both the chemical yield of the desired product and diastereoselectivity of this reaction are quite modest, the structural complexity achieved is impressive. In nine steps from **22**, the complete architecture of maoecrystal V was assembled using an innovative and efficient strategy.

The endgame of the Yang group's synthesis is shown in Scheme 5. Treatment of Diels–Alder adduct **29** with NBS and



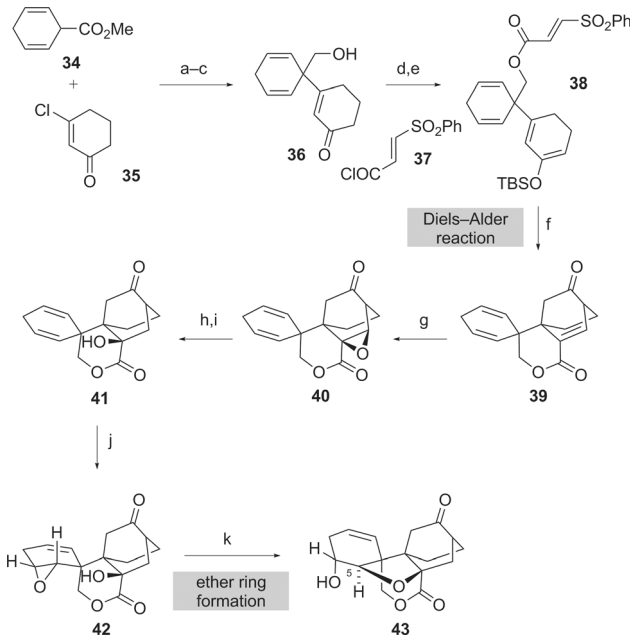
Scheme 5. Reaction conditions: a) NBS, $(PhCO_2)_2$, 90%; b) Bu_3SnH, TEMPO, 75%; c) Zn, AcOH, THF/H_2O, 70 °C, 85%; d) SmI_2, THF/MeOH, RT, 88%; e) Lindlar's catalyst, RT, 92%; f) DMP, RT, 88%; g) DBU, 100 °C, 48% (90% brsm). NBS = *N*-bromosuccinimide; TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy; DMP = Dess–Martin periodinane; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

benzoylperoxide enabled a regio- and chemoselective allylic bromination at C1. Dehalogenation using tributyltin hydride resulted in a carbon-centered radical that was trapped with TEMPO. Zinc-mediated reduction of the oxygen–nitrogen bond proceeded without hazard to liberate the free alcohol **32** and complete the three-step formal allylic hydroxylation of **29** in 57% overall yield. Next, SmI_2 was employed to reduce the acetoxy group, and while the reduction took place efficiently, protonation of the incipient samarium enolate delivered the incorrect stereochemistry of the methyl substituent. Hydrogenation of the now exposed olefin and subsequent DMP

oxidation gave access to *epi*-maoecrystal V (**33**) in good yield. Heating **33** in toluene at reflux in the presence of base allowed an equilibration of the labile C16 position to provide maoecrystal V (**9**) in 48% yield along with recovered starting material (45%). In this way, maoecrystal V (**9**) was synthesized by a 16-step sequence from **22**. The synthesis featured an interesting O-H insertion and a Horner–Wadsworth–Emmons reaction to install the dienophile, an oxidative dearomatization to install the diene, and an intramolecular Diels–Alder reaction to efficiently construct the skeletal framework of maoecrystal V.

2.2.2. Approach of the Danishefsky Group (2012)

In 2012, Danishefsky and Peng at Columbia University and the Sloan-Kettering Institute for Cancer Research reported the second total synthesis[20] of maoecrystal V by leveraging the information gathered in their previous studies.[12c,i] Their successful synthesis (Scheme 6) commenced

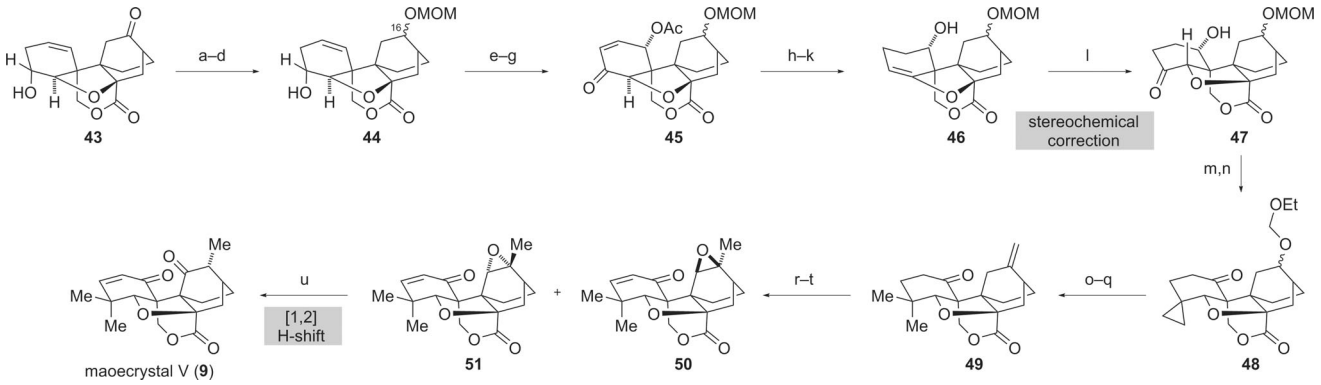


Scheme 6. Reaction conditions: a) LDA, −78 °C, 40%; b) DIBAL-H, −78 °C; c) MnO_2, 68% over two steps; d) pyridine, **37**, 0 °C, 86%; e) TBSOTf, NEt_3, −78 °C, 91%; f) toluene, sealed tube, 166 °C, 1 h; then TBAF, THF, 62%; g) H_2O_2, NaOH, MeOH, 0 °C, 95%; h) MgI_2, CH_2Cl_2, 45 °C; i) Bu_3SnH, AIBN, toluene, reflux, 50% over two steps; j) *m*-CPBA, CH_2Cl_2, 72%; k) *p*-TsOH·H_2O, 90%. LDA = lithium diisopropylamide; DIBAL-H = diisobutylaluminum hydride; TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate; TBAF = tetrabutylammonium fluoride; AIBN = azobis(isobutyronitrile); *m*-CPBA = *meta*-chloroperoxybenzoic acid.

with the union of ester **34** with 3-chlorocyclohexenone (**35**), followed by the adjustment of oxidation states to afford alcohol **36**. Acylation of the primary alcohol within **36** with vinyl sulfone **37**, and the subsequent generation of an enol silane gave **38**, which set the stage for the key intramolecular Diels–Alder reaction. In the event, heating of **38** in toluene at 166 °C for one hour induced a smooth cycloaddition to generate an intermediate that was subsequently treated with TBAF to reveal the ketone function with concomitant elimination of the phenyl sulfone through an $E1_{CB}$ mechanism. In this manner, cycloadduct **39** was generated in 62% yield. While similar to the Diels–Alder reaction employed by Yang and co-workers, there is one significant difference that sets it apart. That is, Danishefsky and Peng made superb use of the symmetry to avoid the stereochemical issues faced by Yang and co-workers (see Scheme 4), thus ensuring that cycloadduct **39** is the only product formed in the reaction.

With the core carboskeleton of maoecrystal V (**9**) accessed in a concise and controlled fashion from ester **34** in only six steps, the next task was the installation of the strained tetrahydrofuran ring. To this end, the authors envisioned an "east-to-west" strategy that first called for the α hydroxylation of the lactone. Initial attempts at hydroxylation through a conjugate reduction/enolate oxidation cascade from **39** resulted in a 1.5:1 mixture of diastereomers, slightly favoring the desired product (i.e., **41**). A more selective oxidation was achieved through the nucleophilic epoxidation of the unsaturated lactone to generate epoxide **40** in d.r. > 20:1. The authors speculated that the bicyclic ketone is spatially less demanding than an sp^3-hybridized carbon atom, thus making the nucleophilic approach across the β face of the olefin more favorable. Reductive opening of the epoxide within **40** was achieved by a two-step sequence via an intermediate iodohydrin species to afford alcohol **41** as a single stereoisomer. Attempts to activate the cyclohexene functionality to enable the construction of the cyclic ether directly from **41** were unsuccessful. Instead, an alkene-selective epoxidation directed by the α-hydroxy group within **41** delivered epoxide **42** and set the stage for an acid-catalyzed etherification to provide dihydrofuran **43** in 90% yield. Despite the efficiency of this transformation, the undesired diastereomer at C5 was obtained; a situation that complicated the endgame of the synthesis and required several steps to correct (Scheme 7).

Moving forward, acylation of alcohol **43** followed by reduction of the ketone with $NaBH_4$ resulted in a 1:1 mixture of alcohols at C16 (Scheme 7). However, the mixture of diastereomers was inconsequential, because the stereocenter at C16 would be destroyed later in the synthesis. The epimeric alcohols were masked as MOM ethers and the acetate hydrolyzed to afford **44**. γ-Acetoxy enone **45** was synthesized in three steps, beginning with the stereoselective epoxidation of the double bond within **44**. Dess–Martin oxidation of the secondary alcohol, followed by silica gel purification resulted in the formation of a γ-hydroxyenone, which was readily converted to the acetate **45**. A conjugate addition using thiophenol, followed by sodium borohydride reduction of the ketone and desulfurization reduced the enone within **45** to the secondary alcohol. After dehydration of the hydroxy group at C4, the acetate group was removed to afford the key enol ether **46**, which was now set to undergo stereochemical reconfiguration at the C5 position. Consistent with their previous studies, sequential treatment of the cyclic enol ether **46** with DMDO and $BF_3{\cdot}OEt_2$ successfully promoted a suprafacial hydride migration of the intermediate epoxide and properly established the stereocenter at C5 within **47**.



Scheme 7. Reaction conditions: a) Ac_2O, pyridine, CH_2Cl_2; b) $NaBH_4$, CH_2Cl_2/EtOH, d.r. = 1:1, 85% over two steps; c) MOMCl, iPr_2NEt; d) K_2CO_3, MeOH, 90% over two steps; e) *m*-CPBA, RT, 95%; f) DMP, $NaHCO_3$, CH_2Cl_2, 0°C, 85%; g) Ac_2O, pyridine, CH_2Cl_2, 90%; h) PhSH, Et_3N; then $NaBH_4$, EtOH/CH_2Cl_2, 78%; i) Raney-Ni; j) MsCl, DMAP, 65% over two steps; k) K_2CO_3, MeOH, RT, 95%; l) DMDO; then $BF_3{\cdot}OEt_2$, 82%; m) Lombardo reagent, CH_2Cl_2, RT, 85%; n) CH_2I_2, Zn/Ag, Et_2O, 36°C, 88%; o) PCC, CH_2Cl_2, RT, 76%; p) H_2, PtO_2, AcOH, 40%; q) Lombardo reagent, CH_2Cl_2, 0°C, 80%; r) *p*-TsOH·H_2O, benzene, 76°C, 85%, s) LDA, TMSCl, THF, −78°C, 90%; then $Pd(TFA)_2$, CH_3CN, 80%; t) TFDO, CH_2Cl_2, −78°C–0°C, 90%, d.r. = 1:1; u) $BF_3{\cdot}OEt_2$, CH_2Cl_2, RT, 85%. MOMCl = chloromethyl methyl ether; *m*-CPBA = *meta*-chloroperoxybenzoic acid; DMP = Dess–Martin periodinane; DMAP = 4-dimethylaminopyridine; DMDO = dimethyldioxirane; PCC = pyridinium chlorochromate; LDA = lithium diisopropylamide; TMSCl = chlorotrimethylsilane; TFDO = methyl(trifluoromethyl)dioxirane; Lombardo reagent = $Zn/CH_2Br_2/TiCl_4$.

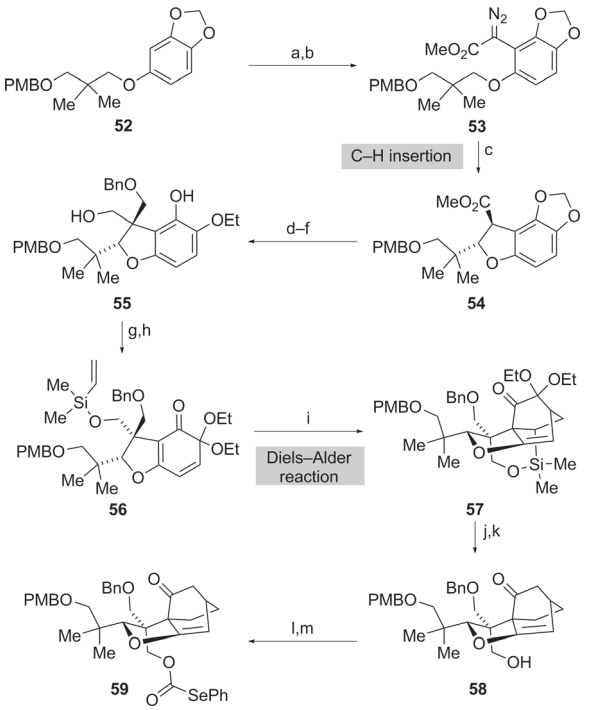
With the tetrahydrofuran ring appropriately installed, further functional-group manipulations were required to establish the γ-dimethyl enone. Ketone **47** was converted to the cyclopropane **48** through a two-step sequence that consisted of a Lombardo olefination followed by Simmons–Smith cyclopropanation. Interestingly, during the cyclopropanation step a methylene insertion into the MOM ether provided the methoxy ethyl ether. Homologation of the alkoxy ether was inconsequential, as the exposure of the intermediate to PCC conditions removed the MOE ether and then oxidized the epimeric alcohols. Next, reductive cleavage of the cyclopropane ring provided the geminal dimethyl groups. The diketone was again subjected to the Lombardo conditions and regioselective olefination occurred at the ketone at C16 to furnish exocyclic olefin **49**. Acid-mediated isomerization of the *exo*-methylene group resulted in a trisubstituted olefin, providing the methyl functionality present in the natural product. A Saegusa oxidation was then performed on the remaining ketone. Epoxidation of the trisubstituted olefin with TFDO gave a separable mixture of diastereomeric epoxides **50** and **51**. When epoxide **51** was treated with $BF_3{\cdot}OEt_2$, maoecrystal V (**9**) was delivered as a single isomer. Critical to the success of this endeavor were an intramolecular Diels–Alder cycloaddition to construct the carbon skeleton and a Lewis acid-mediated epoxide isomerization of a highly advanced intermediate to reconfigure the troublesome ether stereocenter.

2.2.3. Approach of the Zakarian Group (2013)

In September of 2013, Zakarian and co-workers at the University of California at Santa Barbara reported the completion of their synthetic efforts toward maoecrystal V (**9**),[21] which built upon their previously reported studies.[12h] Key aspects of their approach were an intramolecular Diels–Alder reaction and an acyl radical cyclization sequence that forged the bicyclo[2.2.2]octane ring system and central lactone in an efficient fashion. The Diels–Alder reaction is particularly distinctive in that, unlike both Yang and Danishefsky's approaches, which generated the C8–C9 and C13–C14 bonds, Zakarian formed the C9–C11 and C12–C13 bonds through the cycloaddition of a tethered ethylene equivalent.

The synthesis of the Zakarian group commenced from ether **52**, and entailed formation of the dihydrobenzofuran **54** through a rhodium-catalyzed C–H insertion of diazoester **53** (Scheme 8). A zinc-mediated alkylation installed the first quaternary center with d.r. = 9:1. Reduction of the ester, followed by an interesting regioselective nucleophilic opening of the acetal produced phenol **55** in good yield. The crucial intramolecular Diels–Alder reaction precursor **56** was then accessed after PIFA-mediated oxidation of the phenol and subsequent silylation of the primary alcohol within **55**. Heating ketal quinone **56** in toluene at reflux smoothly induced the desired cycloaddition to deliver polycyclic silacycle **57** as a single stereoisomer in 95% yield. The diethyl acetal was then reduced using samarium diiodide and the silicon functionality was removed by TBAF-induced protodesilylation. After the installation of the vicinal quaternary centers with excellent selectivity and the establishment of the bicyclo[2.2.2]octane ring system in a highly concise manner, alcohol **58** was converted to the selenocarbonate **59** in preparation of the planned radical lactonization.

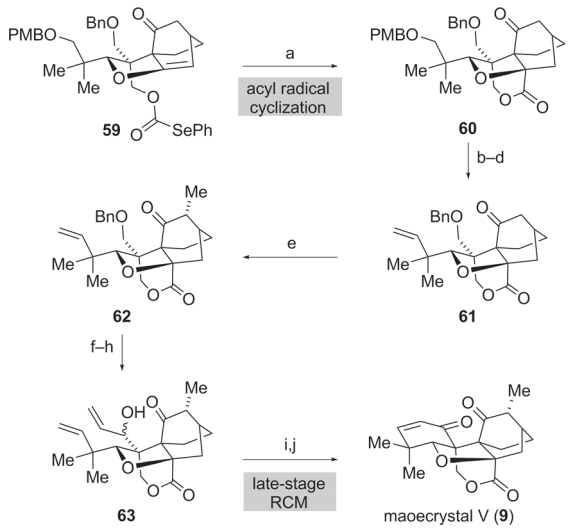
Initial efforts to induce the desired ring closure by treating selenocarbonate **59** with AIBN and tri-*n*-butyltin hydride failed. It was hoped that these conditions would induce a 6-*exo*-trig cyclization, thereby closing the central lactone ring (Scheme 9). Unfortunately, regardless of the initiator, the formation of the desired product (i.e., **60**) was not observed under these conditions. Instead, the selenocarbonate **59** underwent either deoxygentation to the corresponding methyl group or deselenation to the corresponding formate. The authors hypothesized that the acyl radical was reacting too quickly with the hydrogen atom donor (nBu_3SnH), which precluded the desired cyclization. They reasoned that a less



Scheme 8. Reaction conditions: a) *n*BuLi, THF; $ZnCl_2$, $ClCOCO_2Me$, 47% (96% brsm); b) $TsNHNH_2$, PhH; DBU, CH_2Cl_2, 82%; c) 1 mol% $[Rh_2(OAc)_4]$, CH_2Cl_2, 74%, d.r. = 10:1; d) LDA, THF; Et_2Zn, $BnOCH_2Cl$, 76%, d.r. = 9:1; e) $LiAlH_4$, THF, 88%; f) CH_3MgBr, PhH, 80°C, 95%; g) $PhI(O_2CCF_3)_2$, EtOH; h) CH_2=CHSi(Me)$_2$Cl, 85% over two steps; i) toluene, 110°C, 95%; j) SmI_2, MeOH-THF, 90%; k) TBAF, DMPU, 0°C, 50%; l) Im_2CO, THF; m) Ph_2Se_2, $NaBH_4$, 68% over two steps. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; LDA = lithium diisopropylamide; TBAF = tetra-*n*-butylammonium fluoride; DMPU = *N*,*N*′-dimethyl-*N*,*N*′-propylene urea.

efficient hydrogen atom donor might slow this reaction pathway down enough to allow a productive cyclization to occur. Zakarian and co-workers therefore investigated tris(trimethylsilyl)silane ($(TMS)_3SiH$) as the donor, because it possesses a considerably higher bond dissociation energy than tributyltin hydride (79 kcal mol^{-1} for $(TMS)_3Si$–H vs. 74 kcal mol^{-1} for $(n\text{Bu})_3Sn$–H).[23] Experimentation proved that their reasoning was sound, and in this way lactone **60** was synthesized in 55% yield from the selenocarbonate **59**.

Functional-group manipulations of lactone **60** converted the PMB ether into the terminal olefin present in **61**. The authors identified ketone **61** as the optimal substrate for achieving stereocontrol in the methylation of the bicyclooctanone, and to this end, the installation of the requisite methyl group was achieved with d.r. = 7:1 and in 90% yield. Next, deprotection and oxidation of the primary alcohol within **62** allowed the addition of a vinyl Grignard reagent, setting the stage for the introduction of the final ring by ring-closing metathesis. Thus, exposure of **63** to the Hoveyda–Grubbs second generation catalyst afforded a mixture of diastereomeric cyclohexenols, which were oxidized using Dess–Martin periodinane to produce the natural product (i.e., **9**) in high yield. The synthesis of maoecrystal V by Zakarian and co-workers is noteworthy for its use of non-obvious disconnections and for the high levels of stereocontrol that were achieved in all of the key bond-forming events.



Scheme 9. Reaction conditions: a) $(TMS)_3SiH$, AIBN, PhH, 80°C, 55%; b) DDQ, aq. CH_2Cl_2; c) DMP, CH_2Cl_2; d) Ph_3P=CH_2, 68% over three steps; e) $LiN(SiMe_3)_2$, MeI, THF, −40°C, 90%, d.r. = 7:1; f) DDQ, aq. CH_2Cl_2; g) DMP, CH_2Cl_2; h) CH_2=CHMgBr, $CeCl_3$, THF, 71% over three steps; i) 20 mol% Hoveyda-Grubbs II, $(CH_2Cl)_2$, 80°C; j) DMP, CH_2Cl_2, 86% over two steps. AIBN = azobis(isobutyronitrile); DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMP = Dess–Martin periodinane.

2.3. Maoecrystal Z

Maoecrystal Z (**8**) was isolated from *Isodon eriocalyx* by Sun and co-workers, who reported its structure in 2006 and showed it to exhibit cytotoxic activity at micromolar concentrations against breast cancer cells (Figure 4).[10]

As with maoecrystal V (**9**), maoecrystal Z (**8**) is a singularly unique member of the *Isodon* terpene family. While it possesses the common spirocyclic lactone and cleaved C6–C7 bond, **8** has undergone fragmentation of its biogenetic kaurene precursor at C8–C15 and formed a new C8–C6 bond by way of an intramolecular aldol reaction.

In 2011, Reisman and co-workers at the California Institute of Technology reported the first, and to date only, total synthesis of maoecrystal Z (**8**), through a concise route that features a number of innovative transformations (Scheme 10).[24] Drawing inspiration from the biosynthetic construction of the central cyclopentanol, their strategy forges the C6–C8 bond late in the synthesis through an aldol reaction. Their synthesis also represents the only enantioselective total synthesis of an *Isodon* terpene reported to date. Their synthesis commences from optically active (−)-γ-cyclogeraniol (**64**), a compound that is readily prepared in five steps, including a resolution, from commercially available precursors.[25] Protection of the alcohol with TBSCl followed by epoxidation with *m*-CPBA provided a 3:1 mixture of diastereomers of epoxide **65**. With the epoxide in hand, the group attempted an initial reductive coupling of the epoxide with methyl acrylate, in accordance to the protocol reported

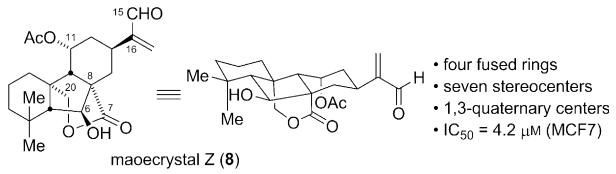
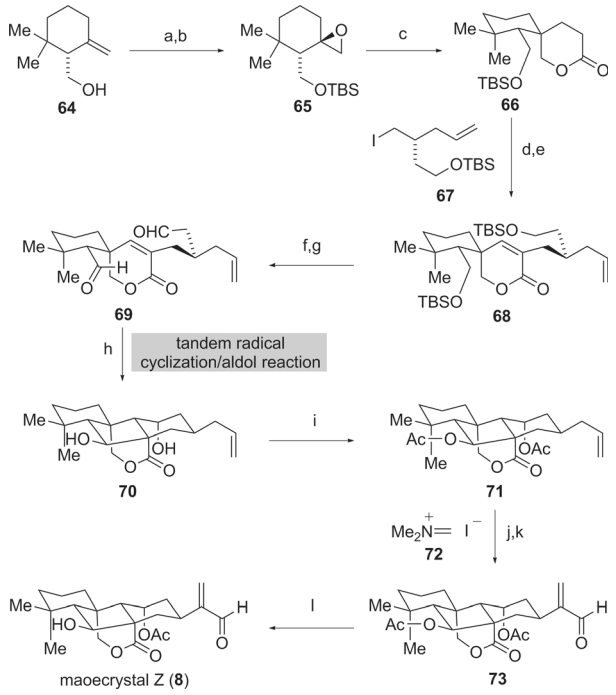


Figure 4. Representations of maoecrystal Z (**8**).



Scheme 10. Reaction conditions: a) TBSCl, Im, b) *m*-CPBA, $NaHCO_3$, 91% over two steps, d.r. = 3:1; c) $[Cp_2TiCl_2]$, Zn, 2,4,6-collidine·HCl, 2,2,2-trifluoroethylacrylate, 74%; d) **67**, LiHMDS, 0→23 °C, 74%; e) KHMDS, −78 °C, PhSeBr; H_2O_2, 81%; f) H_2SiF_6; g) DMP, 86% over two steps; h) SmI_2, LiBr, *t*BuOH, −78 °C, 54%; i) Ac_2O, TMSOTf, 74%; j) O_3, NEt_3; k) NEt_3, **72**, 80% over two steps; l) 1:1 MeOH:H_2O, 1.0 M NaOH, 38%. Im = imidazole; LDA = lithium diisopropylamide; LiHMDS = lithium hexamethyldisilazide; KHMDS = potassium hexamethyldisilazide; DMP = Dess–Martin periodinane.

by RajanBabu and Nugent.[26] While spirolactone **66** was indeed furnished, the low yield (28%) led them to explore the use of an alternative acrylate derivative. Ultimately, 2,2,2-trifluoroethylacrylate provided the desired spirolactone **66** in 74% yield as a single diastereomer.

This stereoconvergent coupling reaction takes the 3:1 mixture of epoxide starting material and generates the key quaternary center at C10 as a single isomer in high yield. Next, alkylation of **66** with enantiopure iodide **67** and subsequent desaturation via the selenide delivered lactone **68**. Dual cleavage of both TBS ethers and a double oxidation led to dialdehyde **69** and set the stage for a remarkable transformation. Treatment of **69** with SmI_2 in the presence of lithium bromide and *tert*-butanol induced a cascade process that most likely involves initial reduction of the aldehyde at C11 to the ketyl radical, which then undergoes a tandem conjugate addition/aldol reaction to furnish tricyclic diol **70** in 54% yield and as a single diastereomer. Thus, the remaining two rings are formed in a single step with the simultaneous setting of the hydroxy-functionalized stereocenters at C6 and C11.

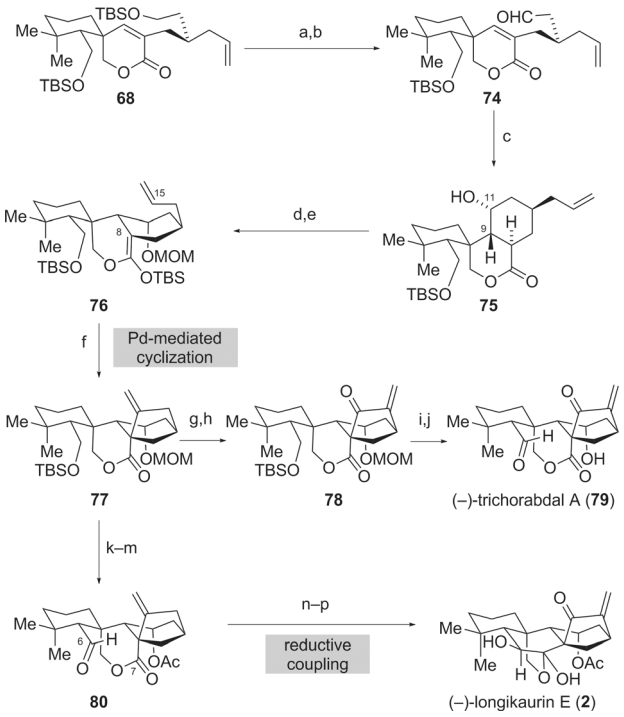
The somewhat diabolical placement of the functional groups in close proximity within **70** made what should have been a trivial task of acetylating the carbinol at C11 more monumental than anticipated. Attempts at regioselective acetylation of the hydroxy group at C11 with acetic anhydride were not successful, as the carbinol at C6 was first to be acetylated. Attempts to first protect the more reactive hydroxy group at C6 and then acetylate the hydroxy group at C11 were likewise unfruitful. Even attempts to introduce two acetate groups into **70** using an excess of acetic anhydride and 4-dimethylaminopyridine were thwarted because of undesired skeletal rearrangements. Ultimately, both alcohols could be acetylated under TMSOTf-catalyzed conditions to provide diacetate **71** in 74% yield. Ozonolytic cleavage of the terminal alkene and treatment of the resulting aldehyde with Eschenmoser's salt (**72**) provided enal **73**. Finally, hydrolysis of the acetate at C6 provided maoecrystal Z (**8**), along with varying amounts of monodeacetylation at C11 and diol **70**. This concise and elegant synthesis by Reisman and co-workers constitutes the first total synthesis of **8** in 12 steps from (−)-γ-cyclogeraniol (**64**), and is distinguished by a highly efficient and inventive reductive cascade process.

2.4. Trichorabdal A and Longikaurin E

Building upon their successful approach to maoecrystal Z (Scheme 10), Reisman and co-workers next reported the enantioselective synthesis[24b,27] of both trichorabdal A (**79**)[28] and longikaurin E (**2**).[5] Key to this enterprise was the realization that lactone **68**, a key intermediate in their total synthesis of **8**, could also serve as a common precursor to both **79** and **2** (Scheme 11).

Selective cleavage of the less-hindered of the two primary TBS ethers within **68** allowed the preparation of aldehyde **74** after an oxidation with Dess–Martin periodinane. Exposure of **74** to their previously devised conditions for reductive cyclization en route to maoecrystal Z (**8**) induced the formation of the C9–C11 bond along with the formation of the hydroxy group at C11. Attempts to trap the enolate formed during this cyclization, as a prelude to the construction of the bicyclo[3.2.1]octane core, were not successful. Likewise, the attempted bis(silylation) of the lactone and hydroxy group failed, necessitating the initial protection of the carbinol at C11 as its MOM ether. This then allowed the smooth generation of silyl ketene acetal **76** in 77% yield from **75**.

At this juncture, Reisman and co-workers were poised to investigate the possibility to form the key C8–C15 bond through a palladium-mediated oxidative cyclization. After an extensive exploration of reaction conditions, they were able to generate exocyclic alkene **77** in 56% yield by treating **76** with a stoichiometric amount of palladium(II) acetate in the presence of 0.5 equivalents of acetic acid. According to the authors, this reaction represents the first time a silyl ketene acetal was used as a substrate for a palladium-mediated oxidative cyclization of this nature.



Scheme 11. Reaction conditions: a) nBu$_4$NHSO$_4$, *p*-TsOH, MeOH, 0 °C; b) DMP, 77% over two steps; c) SmI_2, LiBr, tBuOH, −78 °C, 57%; d) MOMCl, nBuNI, DIPEA, 45 °C; e) KHMDS, TBSCl, DMPU, −78 °C, 77% over two steps; f) $Pd(OAc)_2$ (1.0 equiv), AcOH (0.5 equiv), DMSO, air, 45 °C, 56%; g) O_3, −94 °C; then PPh_3; h) $Me_2NCH_2NMe_2$, Ac_2O, 95 °C, 57% over two steps; i) 6.0 M aq. HCl, dioxane, 45 °C; j) TEMPO, $PhI(OAc)_2$, 73% over two steps; k) 6.0 M aq. HCl, dioxane, 45 °C; l) TEMPO, $PhI(OAc)_2$; m) Ac_2O, DMAP, 52% over three steps; n) SmI_2, 23 °C; o) O_3, −94 °C; then PPh_3; p) $Me_2NCH_2NMe_2$, Ac_2O, 95 °C, 24% over three steps. DMP = Dess–Martin periodinane; MOMCl = chloromethyl methyl ether; DIPEA = *N*,*N*-diisopropylethylamine; KHMDS = potassium hexamethyldisilazide; DMPU = *N*,*N*′-dimethylpropyleneurea; TEMPO = (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl; DMAP = 4-dimethylaminopyridine.

Advanced intermediate **77** represented a point of divergence in their synthesis plan. On one hand, the initial oxidative cleavage of the exocyclic alkene within **77** and subsequent methylenation at C16 provided enone **78** in 57% yield. Acidic removal of both the MOM and TBS ethers allowed selective oxidation at C6 using $PhI(OAc)_2$ and TEMPO to deliver trichorabdal A (**79**). Alternatively, manipulations of the hydroxy groups prior to cleaving the alkene within **77** led to acetate **80** in good yield. At this juncture, a rather unusual reductive ring closure to forge a bond between C6 and C7 was conducted using SmI_2, which ultimately enabled the synthesis of longikaurin E (**2**). In essence, the reductive formation of the C6–C7 bond within **2** from a *seco*-6,7 precursor (i.e., **80**) is the reverse of the biogenetic process leading to all of the *seco*-6,7 *Isodon* terpenes.

The Reisman group's syntheses of both trichorabdal A (**79**) and longikaurin E (**2**) made good use of their advanced intermediate **68** to access additional natural products, and nicely demonstrated the generality of their overall strategy. The development of conditions for a novel palladium-mediated oxidative alkene cyclization of silyl ketene acetals is likely to find additional utility in future complex total syntheses.

2.5. Sculponeatin N

Isolated from the aerial parts of the Chinese perennial herb *Isodon sculponeatus* by Sun and co-workers in 2010, sculponeatin N (**3**) was shown to exhibit cytotoxicities against K562 and HepG2 human tumor cell lines, with IC_{50} values of 0.21 and 0.29 μM, respectively (Figure 5).[6] The structure of **3**, established by NMR spectroscopic analysis, exhibits a compact tetracyclic skeleton containing a spirolactone and a bicyclo[3.2.1]octane ring system. Among the *Isodon* diterpenes, sculponeatin N (**3**) is perhaps the least oxidized, lacking oxidation in both the A and C rings.

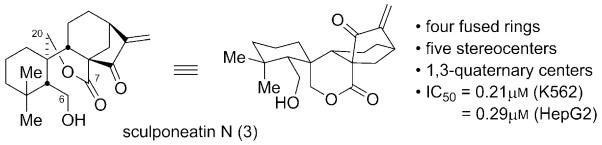
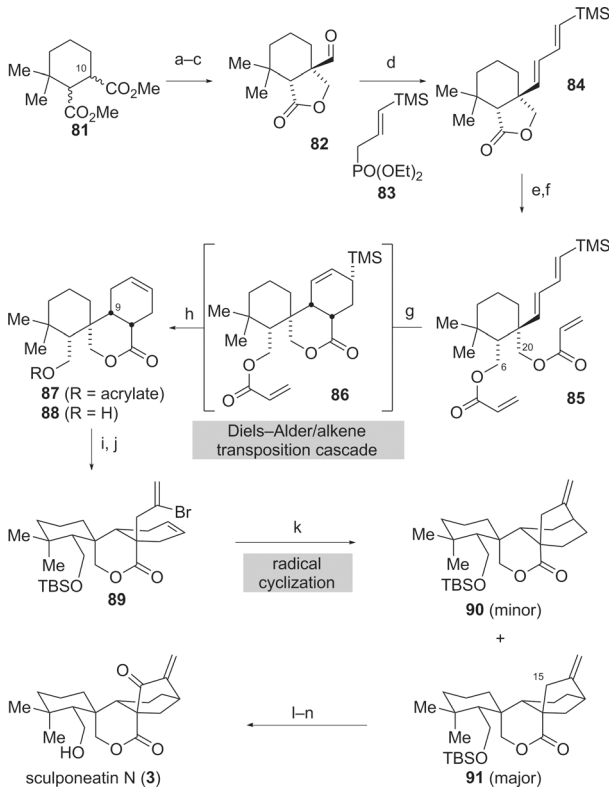


Figure 5. Representations of sculponeatin N (**3**).

2.5.1. Approach of the Zhai Group (2014)

Zhai and co-workers at Lanzhou University reported the first total synthesis of sculponeatin N (**3**) in early 2014 (published online in late 2013).[29] Their approach hinged upon a key intramolecular Diels–Alder reaction of a silyl-substituted diene that forged the C ring and set the stage for a radical cyclization to produce the bicyclo[3.2.1]octane nucleus.

The synthesis of Zhai and co-workers commenced from diester **81** (Scheme 12), which is readily prepared in four steps from *trans*-dimethyl succinate by following a reported procedure.[30] An aldol reaction with paraformaldehyde at C10 installed one of the two quaternary stereocenters required for the synthesis in 72% yield. Subsequent reduction and lactonization of the less-hindered ester led to aldehyde **82** after oxidation. Next, a Horner–Wadsworth–Emmons olefination with the known phosphate **83** generated diene **84**, which was reduced using $LiAlH_4$ and diacylated to afford the Diels–Alder precursor **85**. Heating diene **85** in toluene in a sealed tube at 190 °C for two days afforded a mixture of products in 80% yield as a 60:9:9:2 ratio of stereoisomers. Analysis of the mixture showed that the *endo* product **86** was the major constituent, as confirmed by NMR spectroscopy and X-ray crystallographic analysis. Treatment of **86** and its isomers with anhydrous TsOH afforded a single isomer of alkene **87**. The acid-mediated protodesilylation demonstrated that the epimers at C8 could undergo isomerization and afford the desired *cis*-fused ring system. Based on these results, the group attempted a one-pot IMDA/protodesilylation/methanolysis reaction starting with **85**, and were rewarded with the construction of the tricyclic intermediate **88** in



Scheme 12. Reaction conditions: a) LDA, $(CH_2O)_n$, −78→0 °C, 72%; b) $NaBH_4$; c) DMP, $NaHCO_3$, 84% over two steps; d) **83**, *n*BuLi, HMPA, −78→23 °C, 75%; e) $LiAlH_4$, 0 °C; f) acryloyl chloride, DIPEA, −78 °C, 84% over two steps; g) BHT, toluene, 190 °C, sealed tube, 2 days; h) TsOH, 120 °C, sealed tube, 5 h; then K_2CO_3, MeOH, 12 h, 80% from **84**; i) TBSCl, imidazole; j) LDA, HMPA, −78 °C, then 2,3-dibromoprop-2-ene, 84% over two steps; k) BEt_3, $(TMS)_3SiH$, 27% (**90**, 68%); l) SeO_2, *t*BuOOH; m) DMP, $NaHCO_3$; n) 1 M HCl, 80% over three steps. LDA = lithium diisopropylamide; DMP = Dess–Martin periodinane; HMPA = hexamethylphosphoramide; DIPEA = *N*,*N*-diisopropylethylamine; BHT = 2,6-di-*tert*-butyl-4-methylphenol.

80% overall yield. This impressive sequence nicely installed the stereocenter at C9, and the clever use of alkene transposition set the stage for the crucial radical cyclization that was explored next.

Protection of the free hydroxy group within **88** allowed a stereoselective enolate alkylation to deliver vinyl bromide **89** in good yield. Generation of the desired vinyl radical species was achieved using triethylborane and hexamethyldisilazane. Under these conditions, the desired bicyclo[3.2.1]octane species **91** was obtained in 68% yield, along with the undesired bicyclo[2.2.2]octane isomer (i.e., **90**) in 27% yield. Completion of the synthesis was achieved by an allylic hydroxylation at C15, followed by oxidation to the ketone and removal of the TBS protecting group to deliver sculponeatin N (**3**) in 80% yield over three steps. The synthesis of Zhai and co-workers is particularly noteworthy for its convergent assembly and elegant use of an alkene transposition to set the stage for a radical cyclization to form the desired sculponeatin N skeleton in only a few steps.

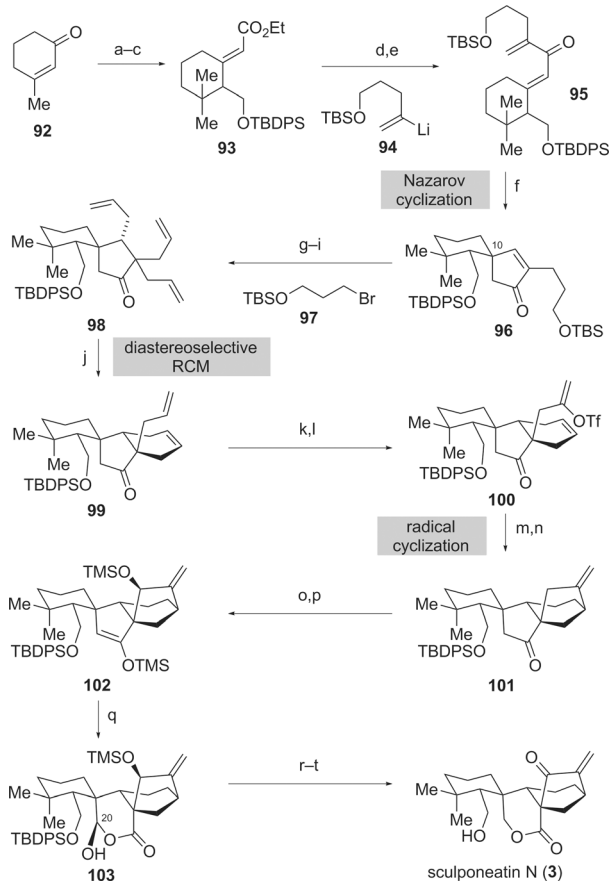
2.5.2. Approach of the Thomson Group (2014)

In early 2014, our own group at Northwestern University reported the total synthesis[31] of sculponeatin N (**3**) through a strategy that was influenced by earlier work we had conducted toward maoecrystal V (**9**).[12f,k] Key to the our approach was the use of a spirocyclic cyclopentanone as a masked equivalent of the central lactone within **3**, which allowed the quaternary center at C10 to be set by a Nazarov cyclization (Scheme 13).

Our synthesis commenced with the generation of dienone **95** in five steps from 3-methylcyclohexenone (**92**), which set the stage for the planned Nazarov spirocyclization. Exposure of **95** to $AlCl_3$ induced the smooth generation of the requisite carbon skeleton, but unfortunately led to varying levels of TBS group cleavage. Resilylation of the mixture, however, afforded cyclopentenone **96** as a single stereoisomer in 80% yield from **95**. Our initial plan called for a Diels–Alder reaction of **96** with butadiene, but we were unable to effect the desired transformation under a variety of conditions, including high pressure. The failure of this route led to the inception of an alternative approach that, while more stepwise, opened the possibility to explore a diastereoselective ring-closing metathesis. To this end, trisallyl species **98** was accessed from cyclopentenone **96** in a few simple steps. We had postulated that a ring-closing metathesis reaction of **98** would lead selectively to the desired *cis*-hydrindane (i.e., **99**) as a result of the increased strain present within the corresponding *trans*-hydrindane isomer (not shown). As it transpired, exposure of **98** to 5 mol% of Grubbs II catalyst led to the generation of the desired product (i.e., **99**) in 91% yield and as a single stereoisomer.

A selective Wacker oxidation of the remaining terminal alkene led to the clean formation of the corresponding methyl ketone, which was subsequently transformed into vinyl triflate **100** in preparation for a reductive Heck cyclization that we hoped would deliver bicyclo[3.2.1]octane **101**. The exploration of conditions to induce a reductive Heck cyclization was met with limited success. While in some cases, useful ratios of the desired product to the regular Heck product could be obtained, we observed significant decomposition of the vinyl triflate to the corresponding terminal alkyne. Ultimately, this elimination pathway was optimized in order to allow a reductive radical cyclization of the alkyne to deliver the desired polycyclic compound **101** in 77% yield from triflate **100**. Unlike Zhai and co-workers, we did not observe any formation of the undesired bicyclo[2.2.2]octane isomer.

At this juncture, we were poised to install the desired lactone by oxidative fragmentation of the central cyclopentanone ring. We failed to achieve this goal through direct methods, while a route via the corresponding α-hydroxy ketone suffered from uncontrollable ketol isomerization. We were initially suspicious of the possibility of cleaving the cyclopentanone by ozonolysis of an enol derivative because of concerns over competitive ozonolysis of the *exo*-methylene group. To attenuate the reactivity of this exocyclic alkene, we first conducted an allylic oxidation of **101** with SeO_2 to produce an allylic alcohol, which was then exposed to excess TMSOTf to cleanly provide enol silane **102**. Ozonolysis then



Scheme 13. Reaction conditions: a) MeMgBr, CuI (5 mol%), LiCl (10 mol%); then CH_2O, 88%; b) TBDPSCl, Im, 98%; c) $TMSCH_2CO_2Et$, LDA, 57% (87% brsm); d) Me(OMe)NH·HCl, *i*PrMgCl, 85%; e) **94**, 95%; f) 1. $AlCl_3$; 2. TBSCl, Im, 80%; g) **97**, *t*BuLi, (2-thiophene)Cu(CN)Li, $BF_3{\cdot}Et_2O$, 78%; h) 1. 10% HF, acetonitrile; 2. Grieco's reagent, Bu_3P; then H_2O_2, 71%; i) 1. TMSOTf, NEt_3; 2. MeLi, allyl iodide, 57%; j) Grubbs II (5 mol%), 91%; k) $PdCl_2$ (25 mol%), CuCl, O_2; l) KHMDS, Comins' reagent, 48% over two steps; m) TBAF, THF, RT; n) Bu_3SnH, AIBN, toluene, reflux; silica gel, 77%; o) SeO_2, *t*BuOOH; p) TMSOTf, NEt_3; q) O_3, Py, methanol, chloroform, 49% over 3 steps; r) $LiBH_4$, 50°C, 47%; s) TBAF, 38%; t) MnO_2, 95%. LDA = lithium diisopropylamide; Py = pyridine; HMPA = hexamethylphosphoric triamide; TMSOTf = trimethylsilyl triflate; TBAF = tetrabutylammonium fluoride; TBDPS = *tert*-butyldiphenylsilyl; Im = imidazole; TMS = trimethylsilyl; TBS = *tert*-butyldimethylsilyl; KHMDS = potassium hexamethyldisilazide; Grieco's reagent = 1-nitro-2-selenocyanatobenzene; Comins' reagent = *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide).

allowed the isolation of lactol **103** in good yield over three steps from **101**. Reduction of the relatively unreactive acetal at C20 to the lactone was achieved using $LiBH_4$ at 50°C. The synthesis of sculponeatin N (**3**) was then completed by removal of both silyl protecting groups and oxidation of the allylic alcohol.

3. Conclusions and Outlook

While all three syntheses of maoecrystal V (**9**) reported to date employed intramolecular Diels–Alder reactions, the diversity of transformations and divergence in strategies at key junctures shows the creative possibilities that natural product synthesis allows. In each of these syntheses, inventive ideas had to be utilized in order to overcome key challenges associated with the complex nature of the interwoven and sterically congested ring system of maoecrystal V. Similarly, the unified approach the Reisman group took to access maoecrystal Z (**8**), trichorabdal A (**79**), and longikaurin E (**2**) from a common intermediate entailed the development of several novel transformations. A comparison between the synthesis of sculponeatin N (**3**) by the Zhai group and our own shows similarities with which the bicyclo[3.2.1]octane core was furnished, but also highlights key elements of strategy design in the different means with which the radical cyclization precursors were generated.

Future research in this field will no doubt generate new and efficient approaches to the natural products highlighted herein, but should also be directed toward accessing the more recently isolated and highly unusual members of this family, such as neolaxiflorin A (**4**) and ternifolide A (**7**). Our hope is that these synthetic efforts will serve to continue our education in synthesis design and execution, but will culminate ultimately in a richer understanding of the biological activity and medicinal potential of these compounds.

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