

Chapter 3

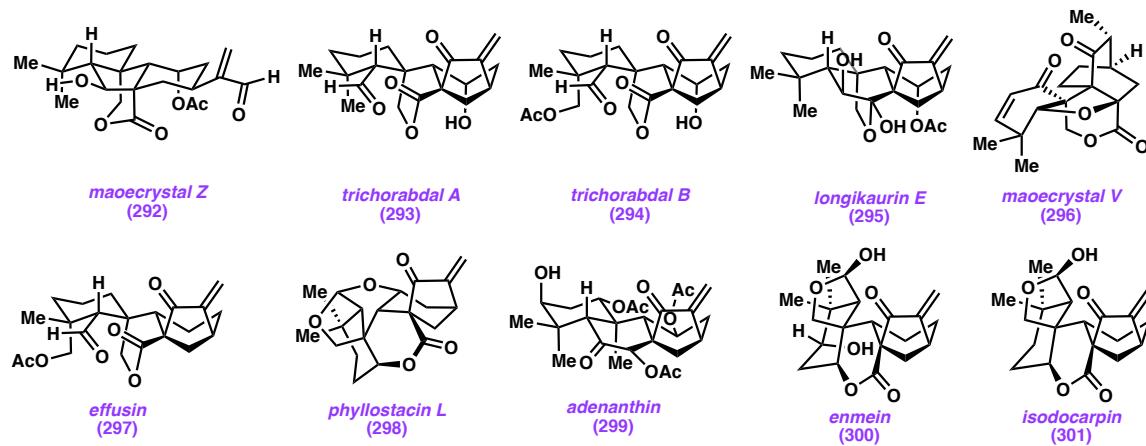
An Introduction to the Enmein-type Ent-Kauranoids

3.1 INTRODUCTION

Extracts from plants of the *Isodon* species have been used for centuries in traditional Chinese medicine.¹ In an effort to identify the bioactive chemical constituents, over 1,000 novel diterpenoids have been isolated from these plants and characterized to date.¹¹ Compounds such as trichorabdal A (293),² adenanthin (299),³ and isodocarpin (301)⁴ have demonstrated potent antibacterial, anti-inflammatory, and antitumor activities, and since their identification in the 1960s have become the focus of study for both chemists and biologists (Scheme 3.1). For example, 299 was shown to selectively inhibit two isoforms of peroxiredoxin enzymes and prolong survival in murine models of acute promyelocytic leukemia.³ *Ent*-kauranoids possessing the exocyclic enone moiety are thought to have enhanced biological activity through covalent modification of target proteins.⁵ It is hypothesized that molecules in this class arise biosynthetically from common progenitors

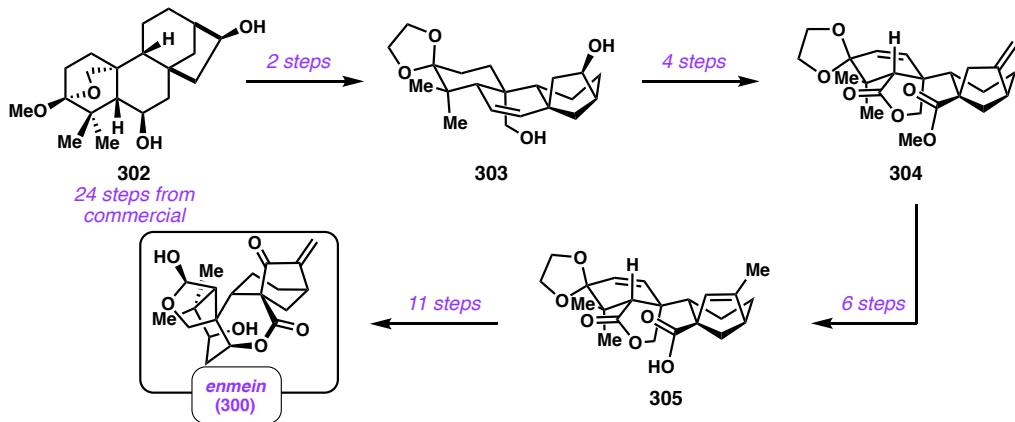
and all contain a caged polycyclic core bearing varying oxidation patterns (Figure 1).¹¹ However, the wide range of biological activity in this family of natural products suggests that the stereochemical and regiochemical oxidation patterns embedded within the core of these compounds impart significant changes to their bioactivity. Despite the intriguing biological properties of these highly oxygenated terpenes, there have been few successful total syntheses of this class of natural products.

Scheme 3.1 Representative examples of bioactive ent-kauranoids.

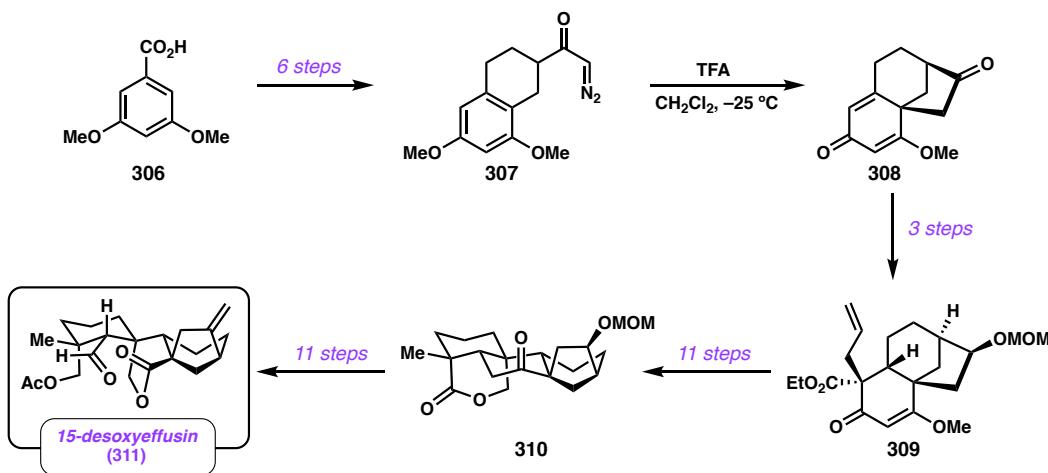


3.2 PREVIOUS SYNTHESES OF RELATED NATURAL PRODUCTS

Several research groups have made contributions to the total synthesis of Isodon diterpenoids. In 1974, Fujita and coworkers disclosed a biomimetic synthesis of enmein (**300**) (Scheme 3.2).^{5–7} Diol **302** can be accessed in 24 steps from commercial material as a racemate. From diol **302**, two additional steps provides **303**. Diol **303** can be elaborated to lactone **304**, which can be derivatized to access **305** in six additional steps. From **305**, it takes the Fujita lab an additional eleven steps to finally access **300**, in a largely linear synthesis.

Scheme 3.2 Fujita synthesis of enmein (300).

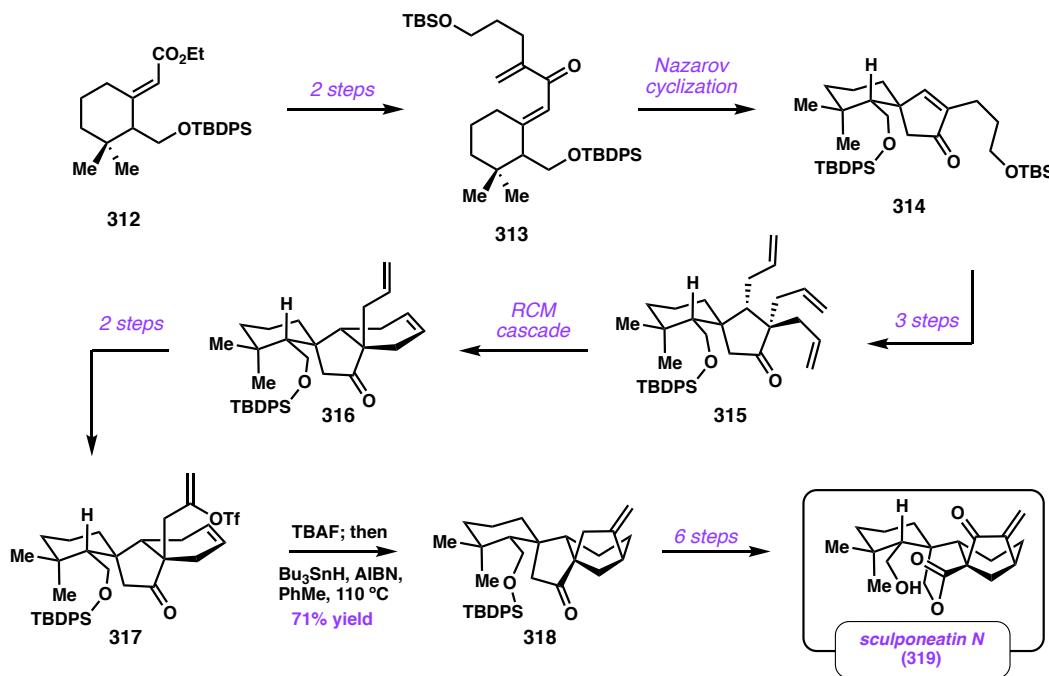
Notably, their synthesis could only be rendered asymmetric through a semi-synthetic route, in which they use plant materials to isolate a single enantiomer of **302**. With enantioenriched **302**, Fujita and coworkers could carry out their established route to access enmein (**300**) as a single enantiomer.

Scheme 3.3 Mander's synthesis of 15-desoxyeffusin (311).

In 1986, Mander reported a series of studies toward the total synthesis of effusin (**297**) (Scheme 3.3).^{8,9} A key intramolecular arene alkylation of α -diazoketone **307** was used to construct the bridging bicyclo[3.2.1]octane moiety present in **308**. Tricycle **308**

could be advanced three steps to build a second all-carbon quaternary center present in **309**. This vinylogous ester **309** could be elaborated to 15-desoxyeffusin (**311**) in an additional 22 steps; however, any attempts to oxidize the C15 methylene proved unsuccessful.

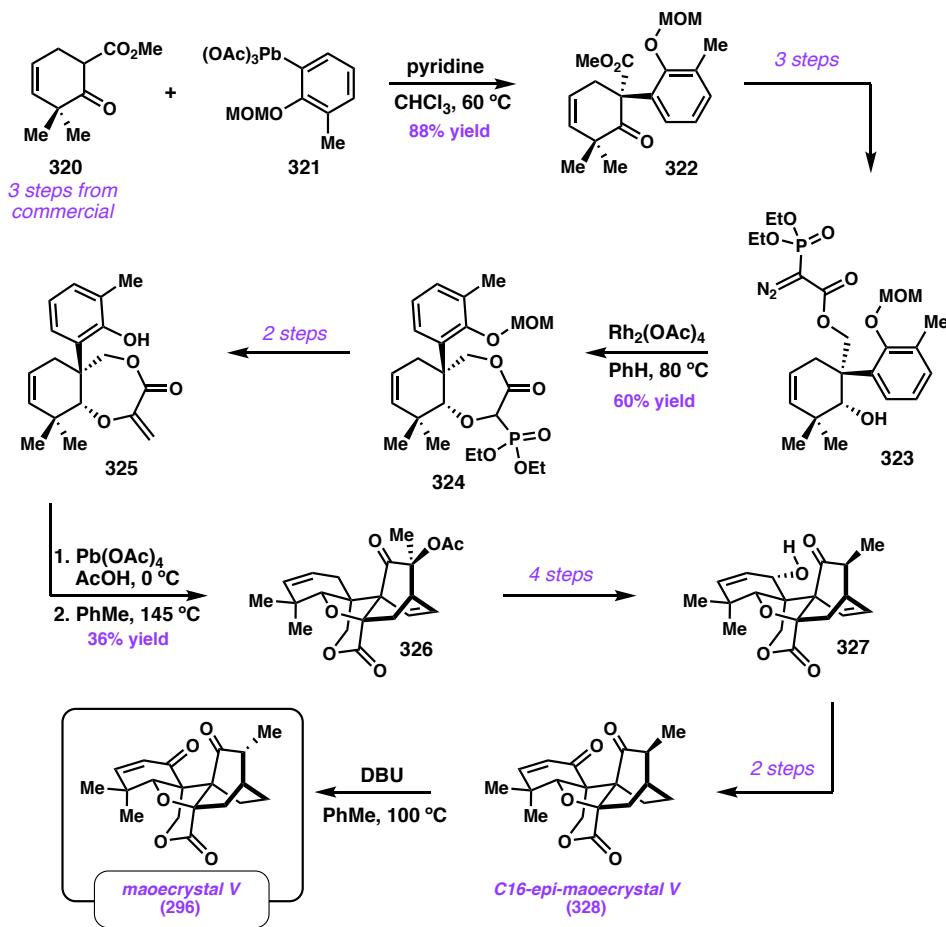
Scheme 3.4 Thomson's synthesis of sculponeatin N (**319**).



In 2014, the Thomson lab reported a total synthesis of sculponeatin N (**319**), starting from **312**, which can be prepared in three steps from commercial material (Scheme 3.4).¹⁰ Acrylate **312** can be advanced two additional steps to access diene **313**, which undergoes a key Nazarov cyclization to form the cyclopentenone moiety in **314**. Three additional steps enables the installation of three olefins present in **315**, which can be subjected to a ring closing metathesis cascade to prepare **316**. With **316** in hand, oxidation and triflation provides **317**, which is then poised to undergo elimination and a subsequent radical

cyclization to form the key [3.2.1]-bicycle of **318**. Sculponeatin N (**319**) can be accessed in six additional steps, forming **319** in 19 steps from commercial material.

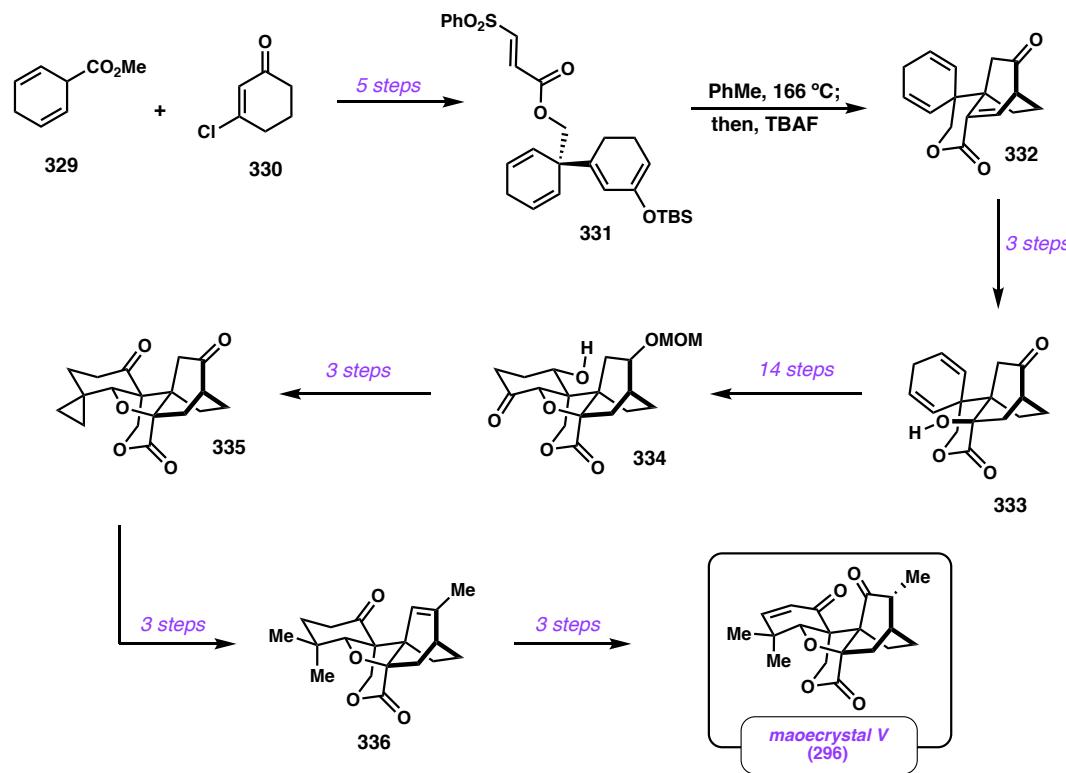
Scheme 3.5 Yang's synthesis of maoecrystal V (**296**).



Several research groups have targeted maoecrystal V (**296**) since its structural elucidation in 2004.¹¹ The first successful total synthesis of **296** was completed in 2010 by Yang and coworkers (Scheme 3.5).¹² Their synthesis commences with b-ketoester **320**. Treatment with aryl lead reagent **321** enables an a-arylation reaction. Ketone **322** can be elaborated to diazoester **323** in two additional steps. A key intramolecular O–H insertion reaction creates the C–O bond present in **324**, which can be elaborated in two additional

steps to provide enone **325**. A Wessely oxidative acetoxylation followed by an intramolecular thermal [4+2] cycloaddition provides **326**. With the key carbon skeleton intact, Yang and co-workers are tasked with oxidative manipulation of the framework. Four steps are required to install the allylic alcohol and to remove the acetoxy group at C16 to provide **327**. From **327**, an oxidation mediated by DMP and a catalytic reduction of the bicyclic produces epi-C16-maoecrystal V (**328**). A final epimerization delivers **296**.

Scheme 3.6 Danishefsky's synthesis of maoecrystal V (**296**).

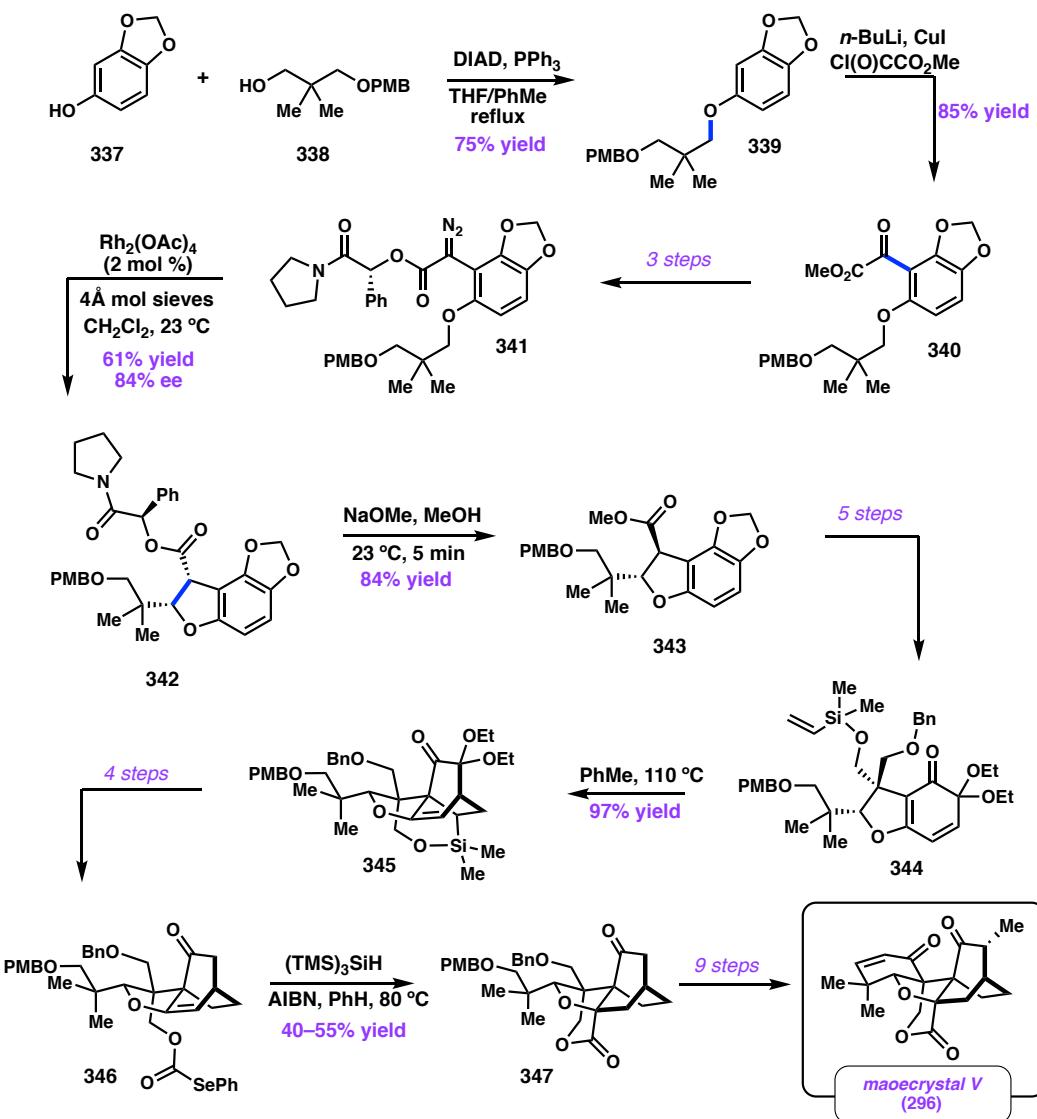


The Danishefsky lab also completed a synthesis of **296** in 2012 (Scheme 3.6).¹³ Key to their strategy was an intramolecular Diels-Alder between an unsaturated sulfone and a pendant silyl dienol ether **331**. Following elimination, they are able to establish the key carbo skeleton in **332**. From here, it takes them three steps to install the necessary

oxidation at the bridgehead and then 14 steps to deliver the central tetrahydrofuran **334**.

From here, modification of A and E rings can be carried out in nine additional steps, delivering **296**.

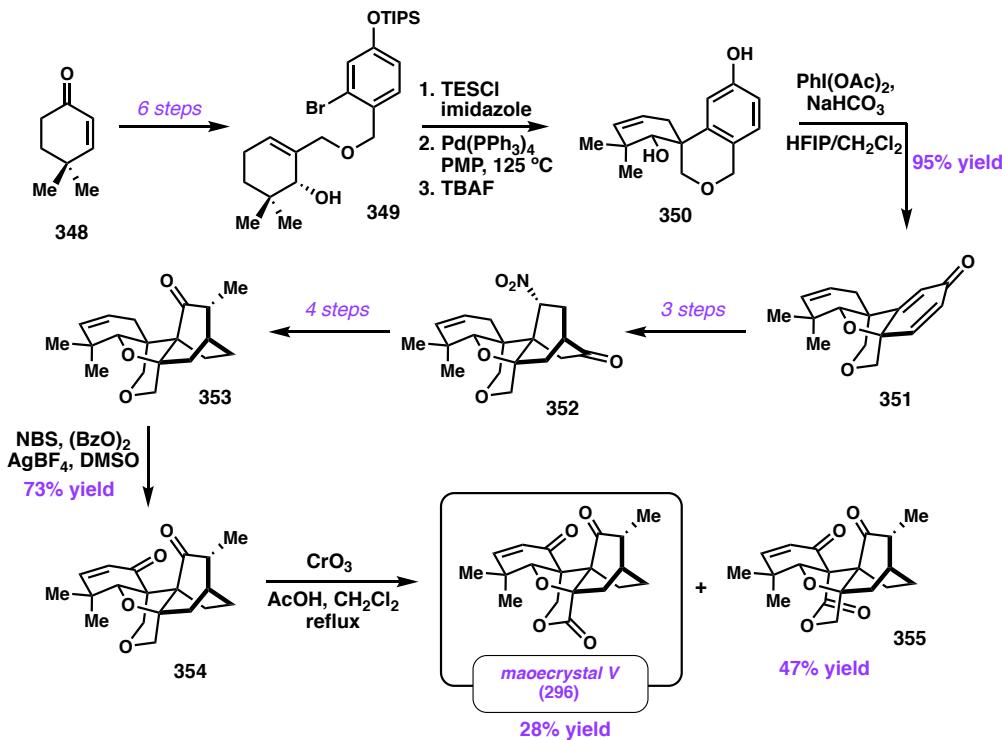
Scheme 3.7 Zakarian's synthesis of maoecrystal V (**296**).



The first asymmetric synthesis of **296** was reported in 2014 by Zakarian and coworkers (Scheme 3.7).¹⁴ Their synthesis commences with a Mitsunobu reaction between

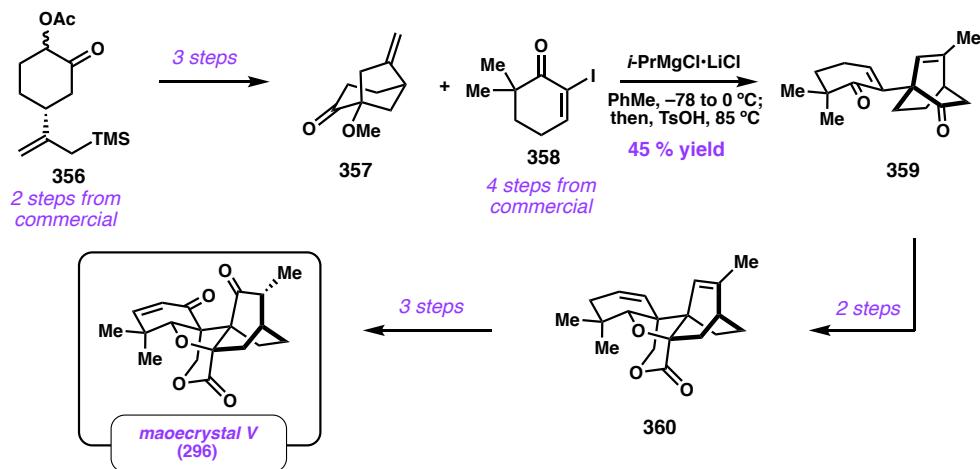
337 and **338**. They can then elaborate **339** in four additional steps, delivering key diazoester **341**. With **341** in hand, they are poised to examine their key C–H insertion reaction—they determined that using a chiral diazo mandelamide delivered their 2,3-dihydrobenzofuran in high yields with low levels of erosion of ee. Methanolysis with concomitant epimerization delivers **343**. Zakarian and coworkers are then able to elaborate **343** to vinyl silyl ether **344**, which can be subjected to a thermal, intramolecular [4+2] reaction to build the key [2.2.2]-bicycle. Cleavage of the C–Si bond along with reduction and installation of the acyl selenide delivers **346**. The key acyl selenide **346** can be subjected to a radical cyclization reaction to install the central lactone ring of **347**. Nine additional steps are required to forge the cyclohexenone A ring as well as the additional methyl group on the [2.2.2]-bicycle, furnishing **296** in 28 steps from commercial material.

Scheme 3.8 Thomson’s synthesis of maoecrystal V (**296**).



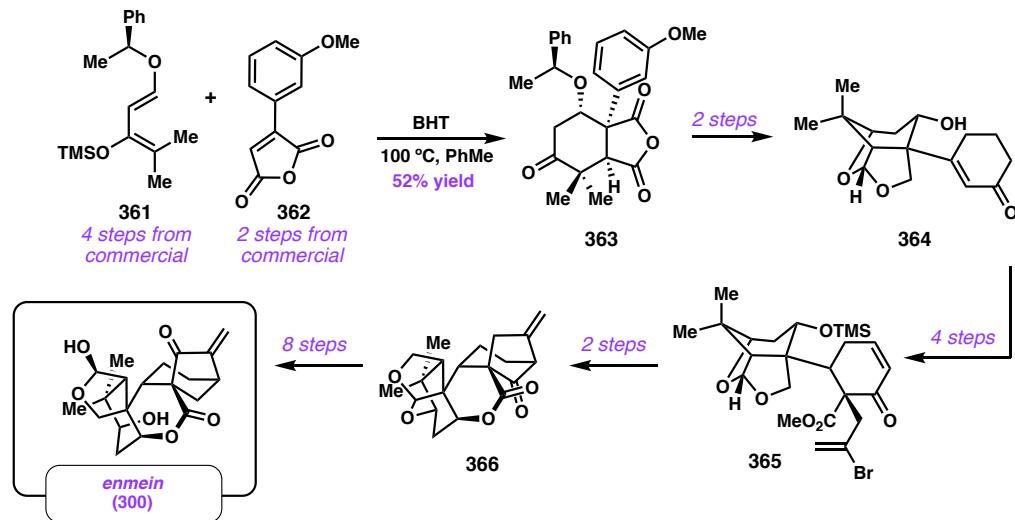
Thomson and coworkers also recently reported an asymmetric synthesis of **296** (Scheme 3.8).¹⁵ Their synthesis starts from 4,4-dimethylcyclohexenone (**348**). The first stereocenter is set through an asymmetric Sharpless epoxidation. The aryl bromide is subsequently installed through a TfOH promoted etherification reaction, providing **349**. At this point, a key intramolecular Heck cyclization delivers the all-carbon quaternary center of **350**. The resultant phenol is then subjected to an oxidative cyclodearomatization reaction to deliver **351**. With **351** in hand, Thomson and coworkers advance this intermediate three additional steps, including an intermolecular Diels-Alder with nitroethylene to provide **352**, building the central [2.2.2]-bicycle. With the skeletal framework assembled, they turn their attention toward oxidative manipulation of **352**. Four steps allows for reduction of the bicyclic, oxidation of the nitro group and installation of the alpha-disposed methyl group to provide **353**. Allylic oxidation of **353** delivers **354**, at which point a low-yielding and poorly selective remote C–H oxidation provides a mixture of **296** and **355**.

Scheme 3.9 Baran’s synthesis of maoecrystal V (**296**).



Baran's lab recently disclosed a convergent total synthesis of **296** (Scheme 3.9).¹⁶ Their route involves synthesis of a [3.2.1]-bicycle (**357**) through an intramolecular Sakurai allylation. Their key 1,2-addition is then carried out between a Grignard reagent prepared from **358** and **357**. Subsequent treatment of the 1,2-adduct with acid promotes a pinacol rearrangement to convert the [3.2.1]-bicycle to the requisite [2.2.2]-bicycle present in **359**. Two additional steps provides the key central lactone in **360**, with three additional steps required to convert **360** to **296**. Their strategy is highly convergent and vastly improved upon prior syntheses of **296**. With a robust synthetic route to access ample quantities of **296**, Baran and coworkers disappointingly observed limited biological activity against a number of cancer cell lines, despite compelling preliminary biological data reported in the literature.¹¹ This discovery highlights the value of total synthesis as a tool to access bioactive molecules for extensive biological study.

Scheme 3.10 Dong's synthesis of enmein (**300**).



During the course of our investigation, the Dong lab reported a total synthesis of enmein (**300**) (Scheme 3.10).¹⁷ Their synthesis commences with a convergent

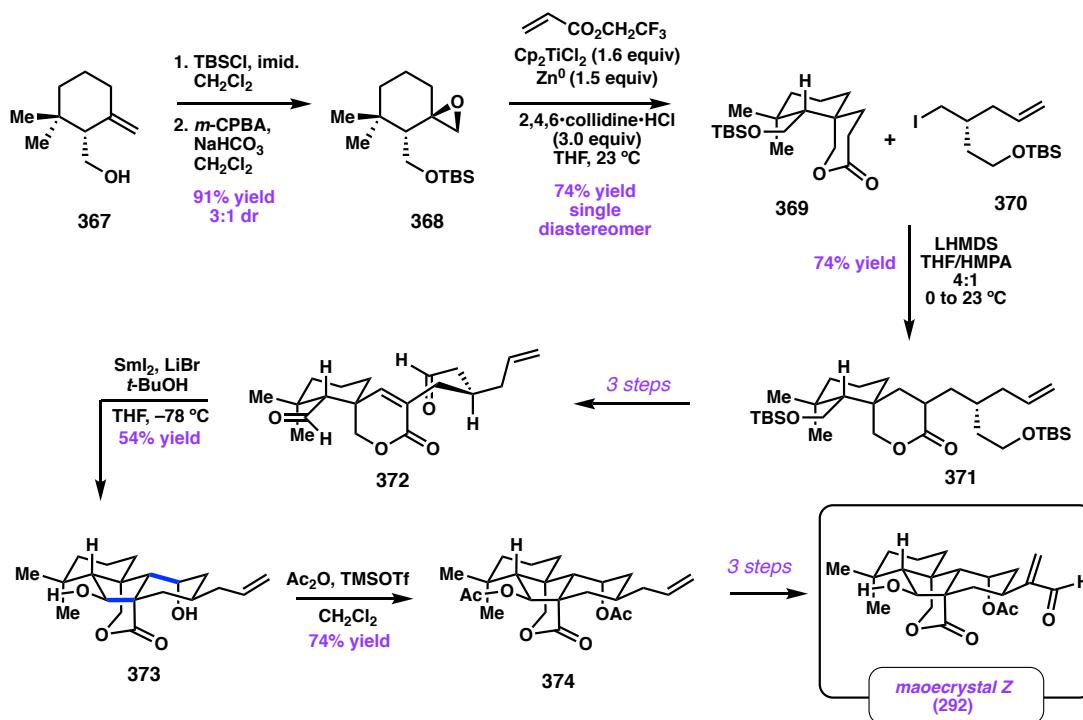
cycloaddition between **361** and **362**, delivering a single diastereomer of **363**. The stereochemistry is notably controlled by the chiral auxiliary present in **361**. Two additional steps including a Birch reduction delivers **364**, which is advanced through four steps to deliver **365**. The vinyl bromide **365** can be used as a radical precursor to close the final [3.2.1]-bicycle present in **366**. Unfortunately, manipulation of the stereochemistry and oxidation of the carboskeleton requires an additional eight steps before they can access **300**. While the end of their synthesis requires substantial functional group interconversions, this synthesis represents a vast improvement over the synthesis of **300** presented by Fujita.

3.3 THE REISMAN LAB'S APPROACH TO THE ENT-KAURANOIDS

Our lab has also worked extensively in the field of ent-kauranoid total synthesis. We felt that both the structural complexity as well as the biological activity of these natural products make them formidable targets for a total synthesis endeavor. In 2011, our lab reported a total synthesis of maoecrystal Z (**292**) commencing from γ -cyclogeraniol (**367**) (Scheme 3.11).¹⁸ A silylation followed by a selective epoxidation delivers **368**, a 3:1 mixture of diastereomers. Our lab determined that both diastereomers could be taken forward through an epoxide homolysis mediated by Cp_2TiCl with a Giese-type addition to trifluoroethylacrylate delivers lactone **369**. At this point, **369** could be alkylated with alkyl iodide **370**. Lactone **371** was then advanced three steps to deliver aldehyde **372**, which is poised to undergo a key reductive cyclization. Treatment with *in situ* generated SmBr_2 delivers a single diastereomer of tetracycle **373**, in which two key bonds have been formed. With the key carbocyclic core assembled, attention turned toward the installation of the

requisite acetates and installation of the enal moiety. Bis acylation of **373** followed by three additional steps delivers maoecrystal Z (**292**) in only 12 steps from **367**.

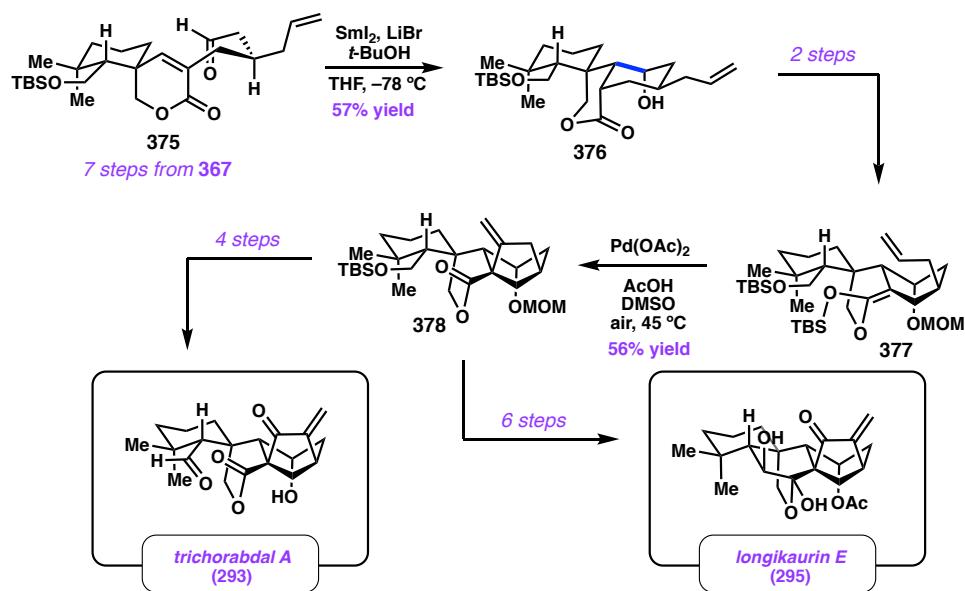
Scheme 3.11 Reisman's synthesis of maoecrystal Z (**292**).



Having developed a rapid and scalable approach to **292**, our lab became interested in using an analogous strategy to target other *ent*-kauranoids within this family of natural products. Again commencing from **367**, seven analogous steps delivered unsaturated lactone **375**, bearing a silyloxy group rather than an aldehyde on the cyclohexane ring (Scheme 3.12).^{19,20} From here, a reductive cyclization to forge one key bond provided **376**, again as a single diastereomer. With **376** in hand, attention turned toward the construction of the requisite [3.2.1]-bicycle present in **293** and **294**. Protection of the secondary alcohol and conversion to the corresponding silyl ketene acetal delivered **377**, which was then poised to undergo an oxidative cyclization. After substantial optimization, we found that

treatment of **377** with stoichiometric $\text{Pd}(\text{OAc})_2$ with AcOH as an additive in DMSO in the presence of O_2 provided good yields of **378**, a key intermediate. We found that **378** could be diverted to two different natural products. Ketone **378** could be converted to **293** in four steps from commercial and could be converted to **294** in six steps from commercial, completing the synthesis.

Scheme 3.12 Reisman's syntheses of trichorabdal A (**293**) and longikaurin E (**295**).



3.4 CONCLUDING REMARKS

A number of groups, including our own, have been interested in the synthesis of the structurally complex ent-Kauranoid natural products. Their complex skeletal structures, dense oxidation, and promising biological activities have attracted the attention of many synthetic chemists. Many of the approaches presented thus far are highly linear and rely upon cycloaddition chemistry to build the skeletal structure. While there have been several elegant syntheses of these molecules, we feel that the complexity of these natural products

demonstrate the difficulties and shortcomings inherent in natural product total synthesis, and as such, continued synthetic campaigns will continue to be instructive and informative.

3.5 NOTES AND REFERENCES

- (1) Fuji, K.; Node, M.; Sai, M.; Fujita, E.; Takeda, S.; Unemi, N. *Chem. Pharm. Bull. (Tokyo)* **1989**, *37*, 1472.
- (2) 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.; et al. *Nat. Chem. Biol.* **2012**, *8*, 486.
- (3) Yang, J.; Wang, W.-G.; Wu, H.-Y.; Du, X.; Li, X.-N.; Li, Y.; Pu, J.-X.; Sun, H.-D. *J. Nat. Prod.* **2016**, *79*, 132.
- (4) *Planta Med.* **2004**, *70*, 401.
- (5) Fujita, E.; Taoka, M.; Shibuya, M.; Fujita, T.; Shingu, T. *J. Chem. Soc. Perkin I* **1973**, 2277.
- (6) Fujita, E.; Shibuya, M.; Nakamura, S.; Okada, Y.; Fujita, T. *J. Chem. Soc. Chem. Commun.* **1972**, No. 19, 1107.
- (7) Fujita, E.; Shibuya, M.; Nakamura, S.; Okada, Y.; Fujita, T. *J. Chem. Soc. Perkin I* **1974**, 165.
- (8) Kenny, M. J.; Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1986**, *27*, 3923.
- (9) Kenny, M. J.; Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1986**, *27*, 3927.
- (10) Pan, Z.; Zheng, C.; Wang, H.; Chen, Y.; Li, Y.; Cheng, B.; Zhai, H. *Org. Lett.* **2014**, *16*, 216.
- (11) 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.; et al. *Org. Lett.* **2004**, *6*, 4327.
- (12) Gong, J.; Lin, G.; Sun, W.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 16745.
- (13) Peng, F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 18860.
- (14) Lu, P.; Mailyan, A.; Gu, Z.; Guptill, D. M.; Wang, H.; Davies, H. M. L.; Zakarian, A. *J. Am. Chem. Soc.* **2014**, *136*, 17738.
- (15) Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. *J. Am. Chem. Soc.* **2014**, *136*, 17750.
- (16) Cernijenko, A.; Risgaard, R.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 9425.
- (17) Pan, S.; Chen, S.; Dong, G. *Angew. Chem. Int. Ed.* **2018**, *57*, 6333.
- (18) Cha, J. Y.; Yeoman, J. T. S.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 14964.
- (19) Yeoman, J. T. S.; Mak, V. W.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 11764.
- (20) Yeoman, J. T. S.; Cha, J. Y.; Mak, V. W.; Reisman, S. E. *Tetrahedron* **2014**, *70*, 4070.