

CHAPTER ONE

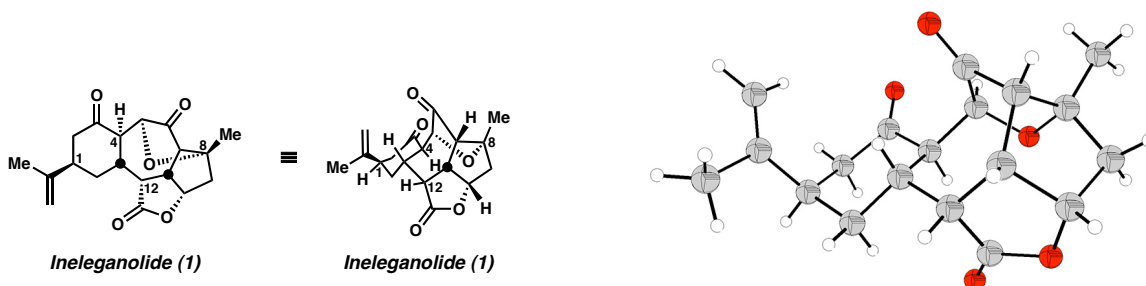
Ineleganolide and Related Natural Products

1.1 Background and Introduction

1.1.1 Isolation and Biological Activity

In 1999, Duh and co-workers isolated a norditerpene¹ from the soft coral *Sinularia*² *inelegans* and termed it ineleganolide (**1**, Figure 1.1.1).^{3a} The molecule (**1**) was subsequently identified by Sheu and co-workers in a variety of coral species, namely *S. scabra*, *S. leptoclados*, *S. parva*, and *S. lochmodes*.^{3b-d} The rigid structure of ineleganolide was elucidated by single crystal X-ray analysis,^{3a} revealing the relative configuration of nine stereocenters, six of which lined a central cycloheptanone core.

Figure 1.1.1 The structure of ineleganolide



The absolute stereochemistry of ineleganolide has not been proven. We propose that ineleganolide has an *R* configuration at C(1) because this is the absolute configuration of sinuleptolide (**9**, *vide infra*), a postulated biosynthetic precursor to ineleganolide. This proposal is in keeping with common lore about cembranoid stereochemistry. In 1978, Tursch and co-workers surveyed the absolute stereochemistry of cembranoids derived from alcyonacean corals, such as *Sinularia*,^{2b} and found this

small sample of cembranoids to have an *R* configuration at C(1).⁴ Since then, the absolute configuration of sinuleptolide (**9**, *vide infra*) has been unambiguously assigned through a modified Mosher ester analysis as *1R*.⁵

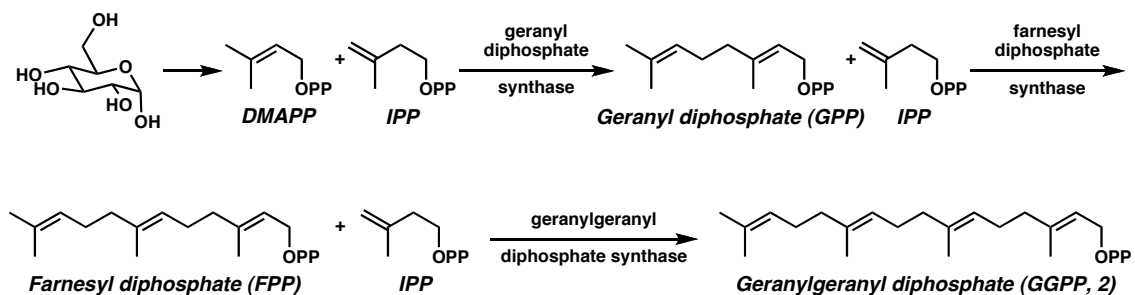
In addition to structural complexity, ineleganolide boasts biological activity: it demonstrates *in vitro* cytotoxicity against murine lymphocytic leukemia P388 cell lines ($ED_{50} = 3.82 \mu\text{g/mL}$).^{3a} Ineleganolide has also been tested for activity against human oral epidermoid (KB) and liver (Hepa59T/VGH) carcinoma cells, without demonstrating effect ($ED_{50} > 20 \mu\text{g/mL}$).^{3b-c}

1.2 Biosynthesis of Ineleganolide

1.2.1 Proposed Biosynthesis of Ineleganolide

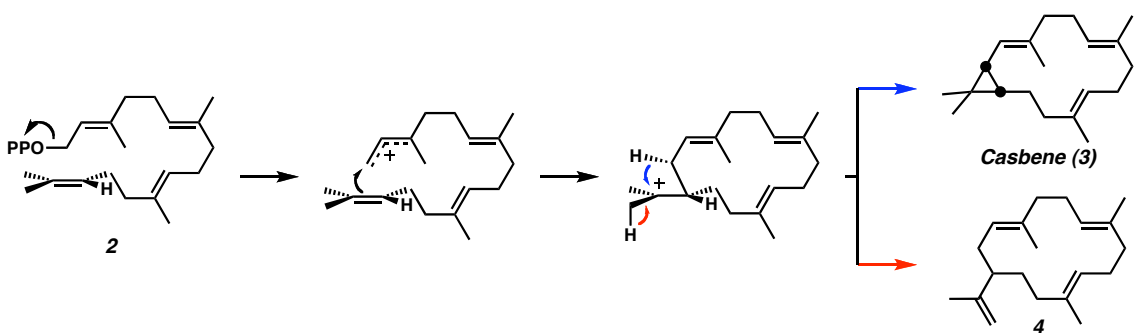
Biosynthetically, ineleganolide, and other diterpenes are derivatives of geranylgeranyl diphosphate (GGPP, **2**),⁶ an indirect product of glucose metabolism to isopentyl diphosphate (IPP) and dimethyl allyl diphosphate (DMAPP, Scheme 1.2.1). GGPP arises through sequential enzyme-catalyzed condensations of IPP (3 equiv) and DMAPP (1 equiv). Initially, IPP and DMAPP combine to generate geranyl diphosphate (GPP) in a reaction catalyzed by geranyl diphosphate synthase. With farnesyl diphosphate synthase as a catalyst, this chain is elongated through addition of IPP to furnish farnesyl diphosphate (FPP). A final IPP is appended to form GGPP, as catalyzed by geranylgeranyl diphosphate synthase.

Scheme 1.2.1 Biosynthesis of geranylgeranyl diphosphate



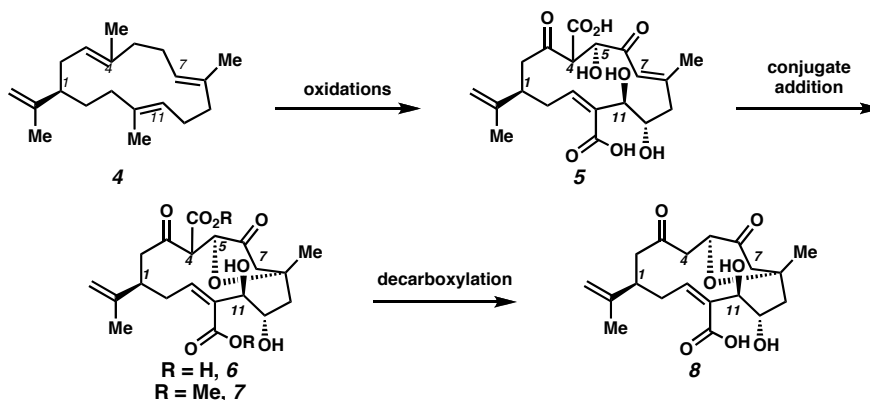
The cembrane skeleton arises through cyclization of GGPP (**2**)⁶ to generate a fourteen-member ring with an external isopropenyl cation (Scheme 1.2.2). En route to casbene (**3**), this cation is quenched through cyclopropane formation catalyzed by casbene synthase.⁷ By analogy, en route to ineleganolide, this cation would be quenched through deprotonation to form hypothetical cembranoid **4**.

Scheme 1.2.2 Initial steps in the proposed biosynthesis of ineleganolide



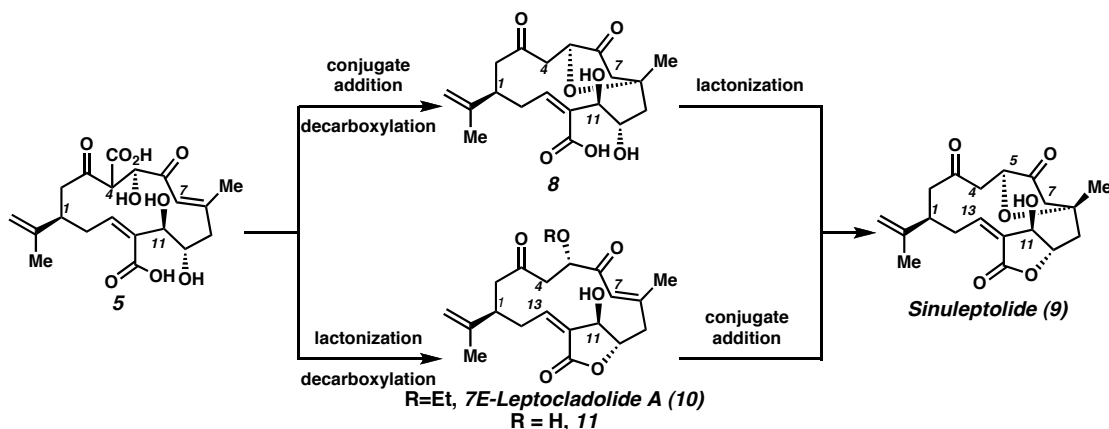
Based on analogous proposals by Anjaneyulu, we expect that a series of oxidations transform simple cembrane skeleton **4** to hypothetical diketone **5**. The C(5) alcohol in carboxylic acid **5** is poised for conjugate addition to the C(6)–C(8) enone to form proposed furanyl ether **6**.⁸ Subsequent decarboxylation would generate norcembranoid **8**, which Anjaneyulu has isolated from *Sinularia granosa*.⁸ Anjaneyulu's proposals for the biosyntheses of the mandapamates (**18–20**) and havellocate (**25**) diverge from the methyl ester analogue of carboxylic acid **6** (e.g., **7**, *vide infra*, Scheme 1.2.6).

Scheme 1.2.3 The proposed biosynthesis of sinuleptolide en route to ineleganolide



By extension, we propose norcembranoid **8** as a precursor to ineleganolide via a sequence of reductive condensation, and conjugate additions (Scheme 1.2.4). Lactonization may furnish sinuleptolide (**9**).⁵ It is also conceivable that lactonization occurs prior to conjugate addition. The intermediate on this pathway would be the hydroxy analogue (**11**) of 7*E*-leptocladolide A (**10**), an antihepatic agent that has been isolated from *S. parva*.^{3c}

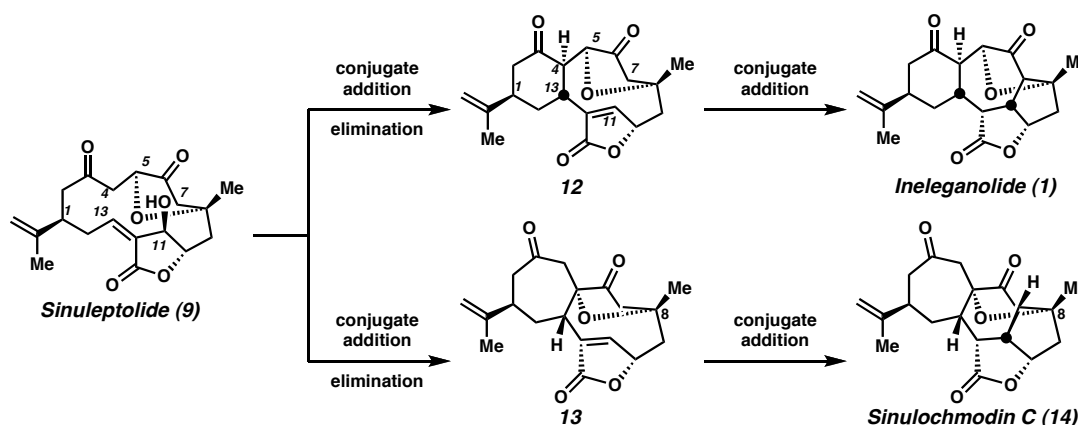
Scheme 1.2.4 The proposed biosynthesis of sinuleptolide en route to ineleganolide



The final bonds in ineleganolide are expected to form through a double Michael addition sequence (Scheme 1.2.5). Michael addition of a C(4) enolate into the $\Delta_{12,13}$ -unsaturated lactone would form the C(4)–C(13) bond, generating a hypothetical

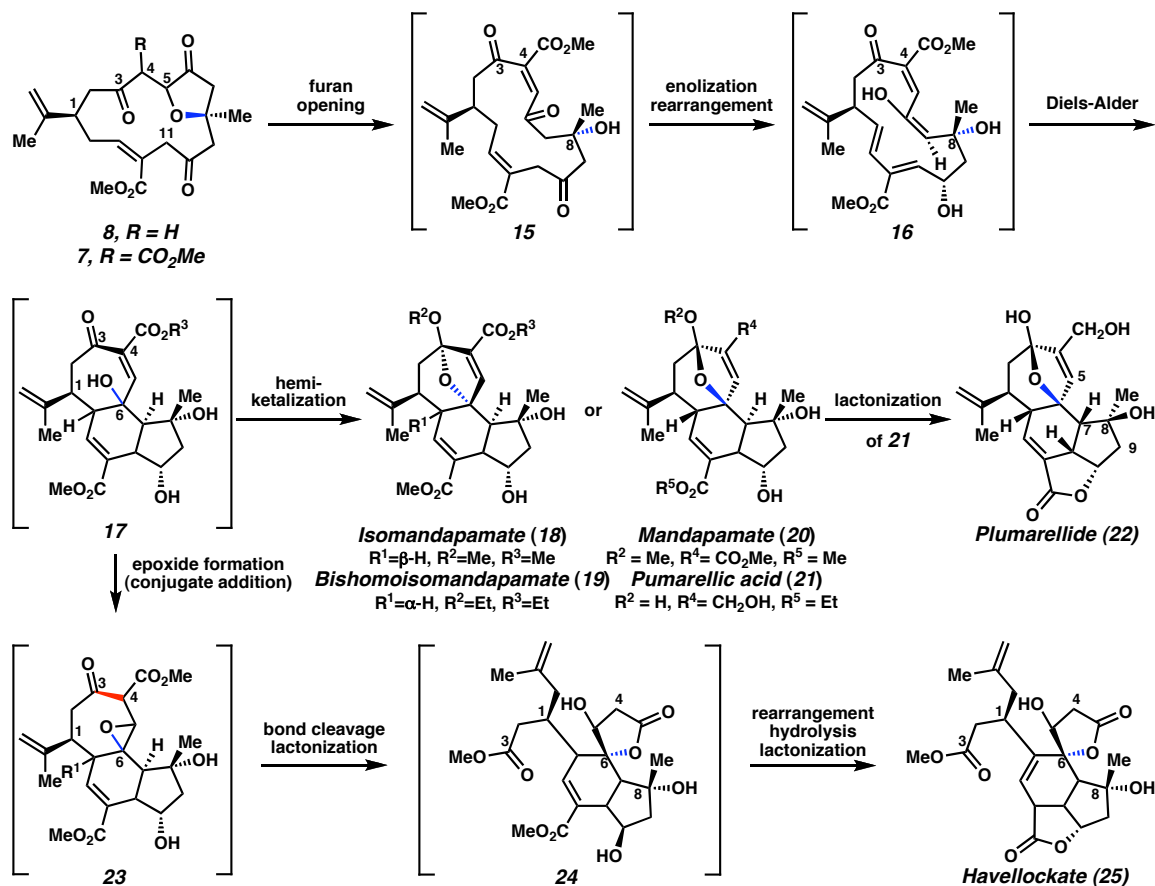
carbocycle (**12**) on elimination of the C(11) hydroxyl. Finally, Michael addition of a C(7) enolate to the butenolide system would generate ineleganolide (**1**). An analogous pathway would furnish sinulochmodin C (**14**)⁵ if the first of these Michael additions had instead involved a C(5) enolate.

Scheme 1.2.5 Continuation of the proposed biosynthesis of ineleganolide



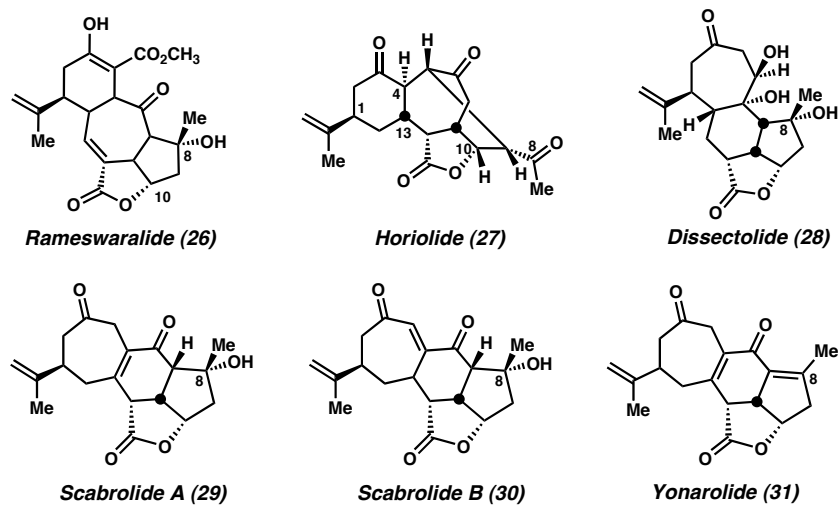
Anjaneyulu has proposed related biosyntheses for the mandapamates (**18–20**) and havellocate (**25**, Scheme 1.2.6).⁸ Anjaneyulu anticipates that the mandapamates arise from furanyl ether **7** via β -elimination of the C(5) furan linkage to form hypothetical bis-diene **15**. Hypothetical bis-diene **15** is poised for an inverse-demand Diels-Alder reaction and subsequent hemiketalization to generate the mandapamate scaffold. Anjaneyulu also proposes that furanyl ether **7** is the precursor to havellocate.

Scheme 1.2.6 Anjaneyulu's proposed biosyntheses of mandapamates



We postulate that norcembranoid **8** and its predicted furanyl ether progenitor (**6**) are also potential biosynthetic precursors for rameswaralide (**26**),⁹ horiolide (**27**),¹⁰ dissectolide (**28**),¹¹ scabrolides A (**29**)⁵ and B (**30**),⁵ and yonarolide (**31**, Figure 1.2.1).¹²

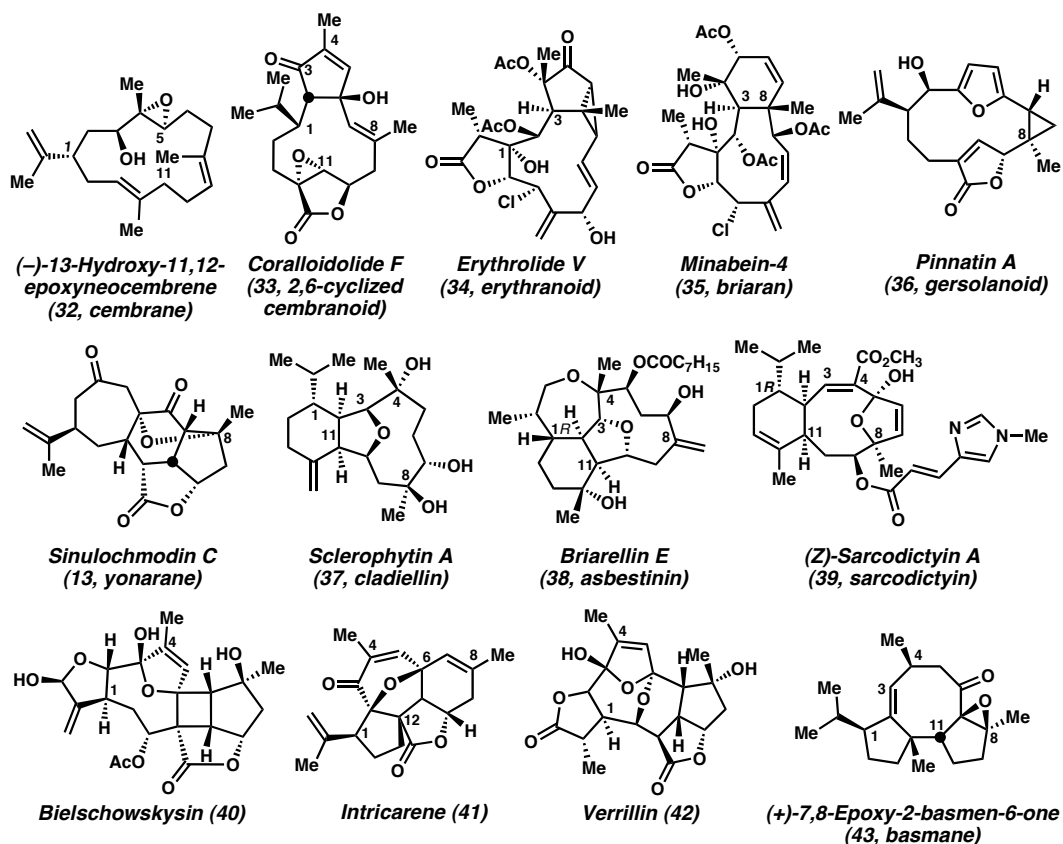
Figure 1.2.1 Proposed biosynthetic derivatives of furanyl ether **6**



1.2.2 Related Natural Products

As a cembranoid, ineleganolide is part of a broad class of structurally related natural products. Cembranoids have been isolated from insects, tobacco, and marine invertebrates, such as the soft corals from which ineleganolide has been isolated. Marine invertebrates produce many classes of cembranoids, including cembranes (e.g., **32**),¹³ 2,6-cyclized cembranoids (e.g., **33**),¹⁴ erythranoids (e.g., **34**),¹⁵ briarans (e.g., **35**),¹⁶ gersolanoids (e.g., **36**),¹⁷ yonaranes (e.g., **14**),⁵ cladiellins (e.g., **37**),¹⁸ asbestinins (e.g., **38**),¹⁹ sarcodictyins (e.g., **39**),²⁰ and other compounds that defy these classifications (e.g., **40**, **41**, **42**),²¹ Figure 1.2.2). Of cembranoids, tobacco produces only cembranes, capnosanes and basmanes (e.g., **43**).²² Insects provide cembranoids that fit into orthogonal skeletal classes,²³ as well as cembranes.

Figure 1.2.2 Members of each class of cembranoids isolated from marine invertebrates

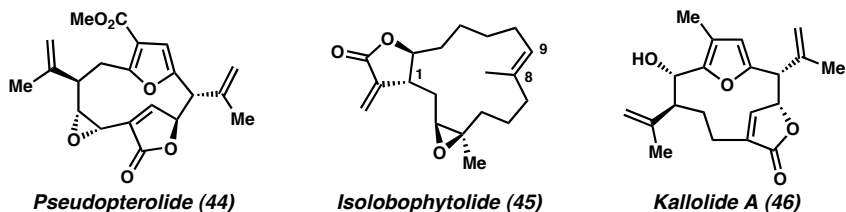


1.2.3 Biogenesis of Norcembranoids

Corals are simple animals with endo-symbiotic algae (zooxanthellae). It is unclear whether the zooxanthellae or corals are primarily responsible for the wealth of cembranoids in these symbiotic organisms. To address this question, natural products have been isolated from separately cultivated zooxanthellae and corals.

Cembranoids have been isolated from these corals in the absence of zooxanthellae, including pseudopterolide (44)²⁴ and isolobophytolide (45),²⁵ from *Pseudopterogorgia acerosa* and *Lobophytum compactum*, respectively (Figure 1.2.3). These studies argue in favor of assembly of these cembranoids by the corals themselves.

Figure 1.2.3 Cembranoids that form in corals in the absence of zooxanthellae (e.g., **44** and **45**) or in zooxanthellae in the absence of corals (e.g., **46**)

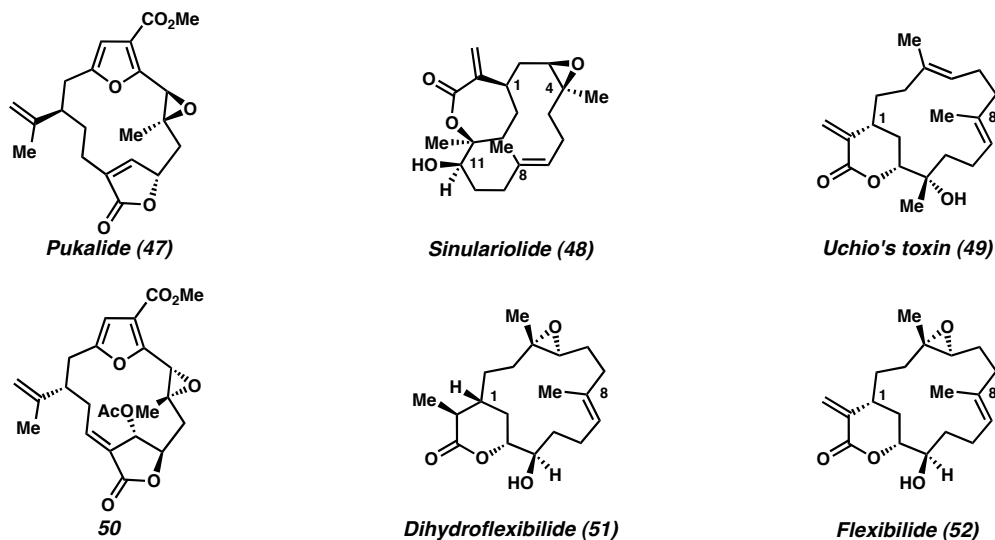


In analogous experiments, zooxanthellae produce cembranoids. Kerr cultivated *Symbiodinium*, a type of zooxanthellae, in the absence of host corals. When Kerr fed *Symbiodinium* ³H-labeled geranylgeranyl diphosphate (GGPP), the metabolic precursor to cembranes, the team isolated ³H-labeled kallolide A (**46**),²⁶ another cembranoid.

1.2.4 Importance of Cembranoids to Coral Colonies

In *Sinularia* colonies, cembranoids facilitate coral survival and reproduction (Figure 1.2.4).^{2b} Pukalide (**47**)²⁷ helps to expel an egg from the polyp in *Sinularia polydactyla*. Sinularolide (**48**)^{4, 28} controls the amount and type of symbiotic algae associated with *Sinularia flexibilis*. *Sinularia flexibilis* also contains Uchio's toxin (**49**),²⁹ which is toxic to mosquitofish. Similarly, *Sinularia maxima* possesses furanyl **50**,³⁰ which deters local fish from eating it. Finally, cembranoids participate in allelopathy — to eliminate competition by other corals. *Sinularia flexibilis* contain dihydroflexibilide (**51**)³¹ and flexibilide (**52**),³¹ which kills hard corals over 8 hours at 5–10 ppm.

Figure 1.2.4 Cembranoids with documented import to coral survival

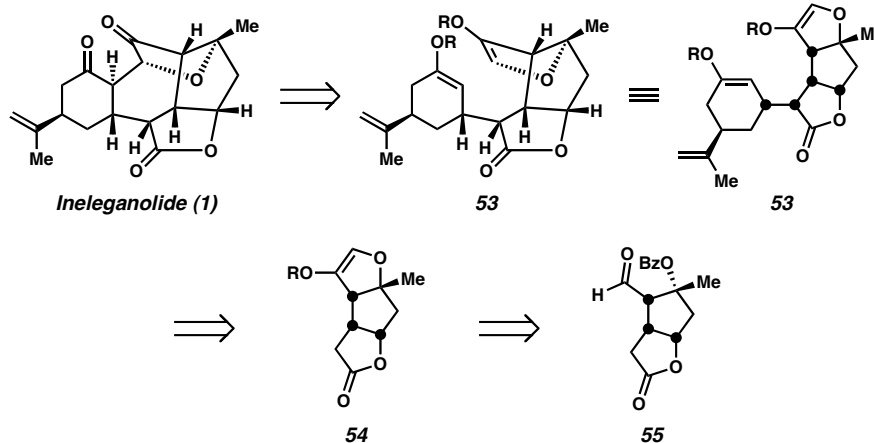


1.3 Synthetic Approaches to Ineleganolide and Related Natural Products

1.3.1 Synthetic Approaches to Ineleganolide

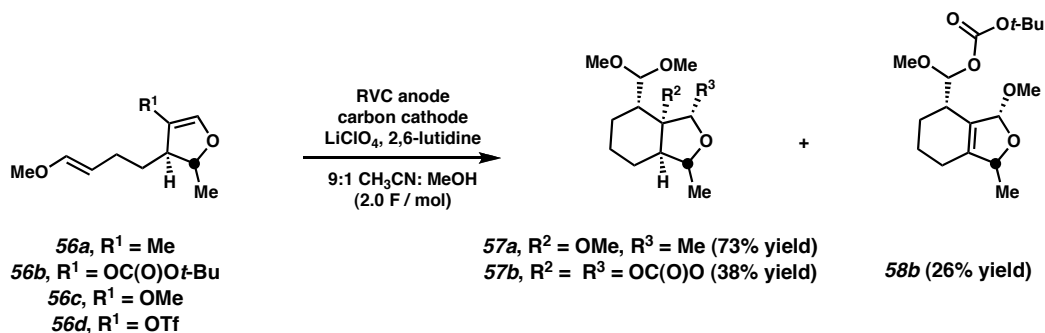
The total synthesis of ineleganolide has not been reported in the literature. Moller and Tang disclosed an approach to the total synthesis of ineleganolide, based upon a key intramolecular anodic olefin coupling.³² Aside from our work in this area, one approach to ineleganolide has been reported. Moller proposed that ineleganolide (**1**) could be retrosynthetically simplified to tetracyclic **53**, initially disconnecting the cycloheptane ring. This transformation would proceed by an anodic olefin coupling. The substrate for the cyclization would be accessed from [5,5,5]-fused **54**, which in turn would be available from lactone **55**.

Scheme 1.3.1 Moller and Tang's retrosynthetic analysis for ineleganolide



Moller modeled anodic couplings with initiating bisoxygenated olefins, and found that these reactions proceeded when substrates maintained the polarization necessary to form the intermediate radical cation. For example, enediol **56b** provided 38% yield of cyclized **57b** and an additional 26% yield of cyclized eliminated **58b** when the substrate incorporated an electronically neutral *tert*-butoxycarbonyl substituent on the initiating olefin. Cyclization did not proceed with the more donating methoxy substituent, which did not maintain bond polarization. Nor did cyclization occur when the more withdrawing triflated substituent was employed, as this substrate incorporated a double bond with a much higher oxidation potential in calculations.

Scheme 1.3.2 Moller modeled the anodic olefin coupling approach to ineleganolide



1.4 Notes and References

- (1) A norditerpene is missing one or more of the carbons from the C(20) skeleton that defines a diterpene. A diterpene is derived from four isoprene subunits.
- (2) For a review on the terpenoids that have been isolated from *Sinularia*, see (a) Kamel, H. N.; Slattery, M. Terpenoids of *Sinularia*: Chemistry and Biomedical Applications. *Pharmaceutical Biology*. **2005**, *43*, 253–269. The taxonomy of *Sinularia* has been well reviewed in (b) Coll, J. C. The Chemistry and Chemical Ecology of Octocorals. *Chem. Rev.* **1992**, *92*, 613–631.

Corals within the genus *Sinularia* are members of the animal kingdom within the cnidaria phylum, which means that they are radially symmetric with a single opening that functions as a mouth and anus. *Sinularia* are within the anthozoa subphylum (including sea anemias and corals) so they reproduce asexually because they lack a medusa stage in development. *Sinularia* are in the class of octocorallia, which are distinguished by 8 pinnate tentacles per polyp. They are in the alcyonacea order of soft corals (comprised of 0–75% CaCO₃), and alcyoniidae family.

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