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Topics in Heterocyclic Chemistry

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Topics in Heterocyclic Chemistry

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The series *Topics in Heterocyclic Chemistry* presents critical reviews on "Heterocyclic Compounds" within topic-related volumes dealing with all aspects such as synthesis, reaction mechanisms, structure complexity, properties, reactivity, stability, fundamental and theoretical studies, biology, biomedical studies, pharmacological aspects, applications in material sciences, etc. Metabolism will be also included which will provide information useful in designing pharmacologically active agents. Pathways involving destruction of heterocyclic rings will also be dealt with so that synthesis of specifically functionalized non-heterocyclic molecules can be designed.
The overall scope is to cover topics dealing with most of the areas of current trends in heterocyclic chemistry which will suit to a larger heterocyclic community.
As a rule contributions are specially commissioned. The editors and publishers will, however, always be pleased to receive suggestions and supplementary information. Papers are accepted for *Topics in Heterocyclic Chemistry* in English.
In references *Topics in Heterocyclic Chemistry* is abbreviated *Top Heterocycl Chem* and is cited as a journal.

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Preface to the Series

Topics in Heterocyclic Chemistry presents critical accounts of heterocyclic compounds (cyclic compounds containing at least one heteroatom other than carbon in the ring) ranging from three members to supramolecules. More than 50% of billions of compounds listed in *Chemical Abstracts* are heterocyclic compounds. The branch of chemistry dealing with these heterocyclic compounds is called heterocyclic chemistry, which is the largest branch of chemistry and as such the chemical literature appearing every year as research papers and review articles is vast and can not be covered in a single volume.

This series in heterocyclic chemistry is being introduced to collectively make available critically and comprehensively reviewed literature scattered in various journals as papers and review articles. All sorts of heterocyclic compounds originating from synthesis, natural products, marine products, insects, etc. will be covered. Several heterocyclic compounds play a significant role in maintaining life. Blood constituent hemoglobin and purines as well as pyrimidines, the constituents of nucleic acid (DNA and RNA) are also heterocyclic compounds. Several amino acids, carbohydrates, vitamins, alkaloids, antibiotics, etc. are also heterocyclic compounds that are essential for life. Heterocyclic compounds are widely used in clinical practice as drugs, but all applications of heterocyclic medicines can not be discussed in detail. In addition to such applications, heterocyclic compounds also find several applications in the plastics industry, in photography as sensitizers and developers, and in dye industry as dyes, etc.

Each volume will be thematic, dealing with a specific and related subject that will cover fundamental, basic aspects including synthesis, isolation, purification, physical and chemical properties, stability and reactivity, reactions involving mechanisms, intra- and intermolecular transformations, intra- and intermolecular rearrangements, applications as medicinal agents, biological and biomedical studies, pharmacological aspects, applications in material science, and industrial and structural applications.

The synthesis of heterocyclic compounds using transition metals and using heterocyclic compounds as intermediates in the synthesis of other organic compounds will be an additional feature of each volume. Pathways involving the destruction of heterocyclic rings will also be dealt with so that the synthesis of specifically functionalized non-heterocyclic molecules can be designed. Each

volume in this series will provide an overall picture of heterocyclic compounds critically and comprehensively evaluated based on five to ten years of literature. Graduates, research students and scientists in the fields of chemistry, pharmaceutical chemistry, medicinal chemistry, dyestuff chemistry, agrochemistry, etc. in universities, industry, and research organizations will find this series useful.

I express my sincere thanks to the Springer staff, especially to Dr. Marion Hertel, executive editor, chemistry, and Birgit Kollmar-Thoni, desk editor, chemistry, for their excellent collaboration during the establishment of this series and preparation of the volumes. I also thank my colleague Dr. Mahendra Kumar for providing valuable suggestions. I am also thankful to my wife Mrs. Vimla Gupta for her multifaceted cooperation.

Jaipur, 31 January 2006 R.R. Gupta

Preface

A variety of marine natural products have been isolated to date, some of which are unique to marine organisms. Many of these compounds exhibit potent biological activity, and thus constitute an important source of medicinal and agrochemical leads. Progress in this branch of chemistry is achieved thus: a) observation of biological phenomena; b) isolation and structure elucidation of the key compounds; c) synthesis of the natural products and their derivatives; and d) bioassays. In exemplifying these studies, this book mainly refers to non-aromatic heterocyclic compounds such as (poly)ethers, macrolides, peptides and amines. The first three chapters cover the origins, structures and biological activities of marine-specific compounds, and the subsequent five report the progress made in their synthetic study. The first chapter is a review of bioactive, heterocyclic compounds including cyclic peptides and macrolides isolated from cyanobacteria, written by Prof. Tatsufumi Okino. The second chapter, by Prof. Masayuki Satake, reviews the isolation and bioactivities of marine polyethers and related compounds. The third chapter, by Prof. Mari Yotsu-Yamashita, gives a pictorial structural analysis of zetekitoxin AB, a strong sodium channel blocker. In the fourth chapter, I review recent synthetic studies of marine natural products with bicyclic and/or spirocyclic ring systems, such as the didemniserilolipids, attenols, bistramides, and pinnatoxins. Prof. Kenshu Fujiwara, in the fifth chapter, explains how to construct difficult 7–9-membered ether ring compounds. The sixth chapter, by Prof. Makoto Sasaki, describes the challenging and artistic syntheses of various polyethers, brevetoxins, ciguatoxins, gambierol and gymnocins, accomplished by competing research groups. The seventh chapter, by Prof. Mitsuru Shindo, details various methodologies towards and total syntheses of the marine macrolides lasonolide, dactynolide and leucascandrolide A. In the final chapter, Prof. Atsushi Nishida reports the strategies used to synthesize the large-ring, amine-bearing manzamine alkaloids. Despite more than half a century of tremendous effort relatively little is known about marine chemistry and a plethora of phenomena and compounds remain undiscovered. I hope this book serves to advance progress in this field. I wish to thank Prof. R. R. Gupta for giving me a chance to organize this volume of important and interesting area.

Sendai, March 2006 Hiromasa Kiyota

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Microwave-Assisted Synthesis of Heterocycles

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Heterocycles from Cyanobacteria

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Abstract Targets of cyanobacterial heterocyclic cytotoxins classify into tubulin, actin, and the sodium channel. In addition, cyanobacteria produce a number of enzyme inhibitors. Polyketide synthase and the nonribosomal peptide synthase complex of cyanobacteria supply a variety of heterocycles. The relationships between bioactive compounds in cyanobacteria and invertebrate are also highlighted.

Keywords Sodium channel · Tubulin · Actin · Peptide · Nonribosomal peptide synthase · Thiazole · Protease inhibitor

1 Introduction

Cyanobacteria are attractive as continuing sources of new bioactive natural products. Cyanobacteria produce not only unique compounds but also compounds in common with marine invertebrates. Although marine invertebrates are sources of drug candidates, there is a hurdle in that we cannot obtain enough material for market use, sometimes not even for clinical trials. Obtaining bioactive compounds from a culturable source is one solution to the issue of supply of marine natural products for practical use. However, a number of marine natural products have been isolated from unculturable sources, which are even not their producers. In contrast, cyanobacteria are the real producers of some of products derived from sponges, mollusks, and tunicates. Culture of cyanobacteria could supply bioactive compounds. Unfortunately, to date, cyanobacterial products that have gone to clinical trial were produced by synthesis. However, some commercially available biochemical reagents derived from cyanobacteria are produced by culture. Recently a search for new compounds from marine microorganism such as actinomycetes is emerging as a possible solution to the supply issue. Fermentation technology of microorganisms is more established than for cyanobacteria. Still, cyanobacteria have an advantage in that they have more common metabolites with sponges, tunicates, and mollusks. In other words, cyanobacteria have already been proved to produce possible clinical targets.

The characteristics of cyanobacterial products is richness of peptides, especially modified peptides. Most modified peptides from marine cyanobacteria contains thiazole and thiazoline rings derived from cysteine. These peptides are generally produced by poleketide synthase and nonribosomal peptide synthase complexes (PKS/NRPS), which are exciting topics in antibiotics research. A number of researchers are exploring these genes from cyanobacteria as well.

In this manuscript, some neurotoxins are reviewed. The beginning era of marine natural products focused on toxins. As a result, cyanobacteria are known to produce saxitoxin, which is a well known shellfish and dinoflagellate neurotoxin. Anatoxin a(s) is another cyanobacterial neurotoxin. Harmful algal bloom is still an important issue in terms of public health and marine environment. In fact, several new toxins have been discovered from dinoflagellates. Neurotoxins, which are reviewed in this manuscript, might be a public health problem in the future.

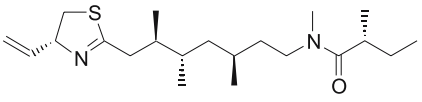
Since several good reviews covering cyanobacterial bioactive compounds have been published [1, 2], this review focuses on the specific recent topic of heterocycles from cyanobacteria, including some freshwater species because marine and freshwater cyanobacteria often produce common metabolites.

2
Sodium Channel Toxins

2.1
Kalkitoxin

Kalkitoxin (**1**) was originally isolated from a Caribbean sample of *Lyngbya majuscula* [3], which is the most productive cyanobacterium of bioactive compounds. The first isolation was conducted during brine shrimp and fish toxicity assays. Kalkitoxin was a strong ichthyotoxin to the common gold fish (LC_{50} 700 nM) as well as a potent brine shrimp toxin (LC_{50} 170 nM). Thereafter, this compound appeared to be active for a variety of assays. It inhibited IL-1β-induced sPLA2 secretion from HepG2 cells (IC_{50} 27 nM) and cell division in a fertilized sea urchin embryo assay (IC_{50} 25 nM). More importantly, kalkitoxin showed toxicity to primary cell cultures of rat neurons (LC_{50} 3.86 nM) and its neurotoxicity was inhibitable with NMDA receptor antagonists [4]. As mentioned later, antillatoxin showed neurotoxicity as well. At this point, two different types of compounds from *Lyngbya* appeared to be neurotoxins. To explore details of their neurotoxicity, the sodium channel was selected as a possible target because a number of marine neurotoxins such as tetrodotoxin, saxitoxin, ciguatoxin, and brevetoxin are known to target the voltage-sensitive sodium channel. A cell culture based assay for the sodium channel was used to screen cyanobacterial metabolites and extracts [5]. As a result, kalkitoxin was suggested to be a potent blocker of the voltage-sensitive sodium channel in mouse neuro-2a cells (EC_{50} 1 nM) [3]. In addition, kalkitoxin was evaluated by using cerebellar granule neuron cultures. Kalkitoxin antagonized veratridine-induced cytotoxicity and Ca^{2+} influx in cerebellar granule neuron and inhibited deltamethrin-enhanced [^{3}H] batrachotoxin binding in intact cerebellar granule neuron. More pharmacological experiments provided direct evidence for an interaction of kalkitoxin with the neuronal tetrodotoxin-sensitive, voltage-sensitive sodium channel [6]. The results also suggested that kalkitoxin interacts at a novel high affinity site on the voltage-sensitive sodium channel. Not only the neurotoxicity of kalkitoxin but also its solid tumor-selective cytotoxicity should be mentioned.

Kalkitoxin showed potent cytotoxicity against the human colon cell line HCT-116 (IC_{50} 1.0 ng/mL) [7]. In a zone differential cytotoxicity assay, kalkitoxin showed differential cytotoxicity for a solid tumor cell (Colon 38) versus



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both L1210 leukemia and normal CFU-GM cells. Furthermore, it showed differential cytotoxicity Colon HCT-116 versus human leukemia CEM. Finally, a clonogenic assay provided interesting results. Kalkitoxin was not cytotoxic against HCT-116 cells for exposures up to 24 h at 10 μg/mL. However, when kalkitoxin was exposed for 168 h, significant cytotoxicity appeared even at 2 ng/mL. The cytotoxic effect of kalkitoxin could be maintained by daily administration of the drug in vivo. Most preliminary assays of kalkitoxin were conducted using the natural compound. However, detailed experiments on the sodium channel assay and solid tumor selective cytotoxicity assay were done by Shioiri's group and White's group using synthesized compounds [7, 8]. The power of synthesis should be emphasized. Stereostructure elucidation was also achieved by extensive collaboration on the analyses of natural compounds by Gerwick's group and synthesis by Shioiri's group [3, 8].

Structure elucidation of kalkitoxin is a good standard example of recent techniques. Although the presence of two conformers in the *N*-methyl amide portion of kalkitoxin hampered straightforward structure elucidation, 2D NMR techniques gave the full planar structural assignment of kalkitoxin. Kalkitoxin has five stereocenters. The stereochemistries of the middle portion were especially difficult to determine, but applicable to *J*-based configuration analysis (JBCA method) [9]. In fact, this is an early example of JBCA method application. In this analysis, HSQMBC pulse sequence [10] was used for measurement of the $^{3}J_{CH}$ values, and the $^{3}J_{HH}$ values were determined utilizing the E.COSY pulse sequence. Due to the chemical instability of kalkitoxin, only 300 μg was available for this experiment. Cryoprobe technology solved the problem of the limited sample size. As a few years have passed since then, recent development of LC/NMR and capillary NMR has reduced the sample requirement to μg and lower. Finally, relative stereochemistry of the middle portion was proposed by JBCA analysis. Stereochemistry of a thiazoline ring was determined by Marfey's analysis after ozonolysis and hydrolysis. These stereochemical analyses reduced the total number of stereochemical possibilities from 32 to four. Synthesis of all possible configurations of kalkitoxin enabled deduction of the stereostructure to be 3*R*, 7*R*, 8*S*, 10*S*, 2′*R*. Notably the most difference of four diastereoisomers and natural kalkitoxin in ^{13}C NMR is less than 0.2 ppm. Only one isomer showed maximal ^{13}C NMR differences of 0.026 ppm.

Thanks to recent developments in synthesis methodology, synthetic chemists sometimes try synthesizing complex natural compounds whose structure has not been determined. In fact, Shioiri's group synthesized seven diastereoisomers of kalkitoxin. The CD spectrum of the synthesized 3*R*, 7*R*, 8*S*, 10*S*, 2′*R*-isomer matched the natural compound. Where there is only a small amount of natural product, CD analysis is more reliable than optical rotation for absolute stereochemical analysis.

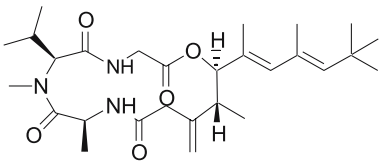
Kalkitoxin must be derived from a mixed polyketide/nonribosomal peptide synthase pathway. In spite of intensive research on cyanobacterial PKS/NRPS, the kalkitoxin biosynthesis gene was not disclosed.

In research on kalkitoxin, collaboration with synthetic chemists provided remarkable results in structural assignment as well as in pharmacological studies. Still more extensive pharmacological study will be needed to identify of the site of kalkitoxin binding to the voltage-sensitive sodium channel, as well as clonological and solid tumor selective cytotoxicity. Kalkitoxin is a possible lead for analgesic and neuroprotection drugs, if chemical stability is improved.

2.2 Antillatoxin

Antillatoxin (**2**) was originally isolated as ichthyotoxin from curacin A-producing *Lyngbya* strain [11]. This cyclic lipodepsipeptide was demonstrated to be neurotoxic in primary cultures of rat cerebellar granule neurons [4]. The neurotoxic response of antillatoxin was prevented by co-exposure with noncompetitive antagonists of the *N*-methyl-D-aspartate (NMDA) receptor such as MK-801 and dextrorphan. Neuro-2a assay using ouabain and veratridin, which was also used to investigate kalkitoxin, showed that antillatoxin was an activator of voltage-sensitive sodium channels. Furthermore, the antillatoxin-induced Ca^{2+} influx in cerebellar granule cells was antagonized in a concentration-dependent manner by tetrodotoxin. Antillatoxin stimulated $^{22}Na^{+}$ influx in cerebellar granule cells and its stimulation was inhibited by tetrodotoxin as well. Additionally, antillatoxin induced allosteric enhancement of [^{3}H] batrachotoxin binding to site 2 of the sodium channel. Antillatoxin also showed a synergistic stimulation of [^{3}H]batrachotoxin binding with brevetoxin, which is a ligand of site 5. To date, more pharmacological studies excluded antillatoxin interaction with sites 1, 2, 3, 5, and 7 of the sodium channel. Site 4 is an extracellular recognition domain of large peptide toxins. Therefore, antillatoxin was suggested to be a new type of sodium channel activator [12]. More experiments will be required to clarify the recognition site of antillatoxin on the sodium channel.

Stereochemistry of antillatoxin was revised from its proposed structure by total synthesis of four diastereoisomers of C-4 and C-5 [13]. This total



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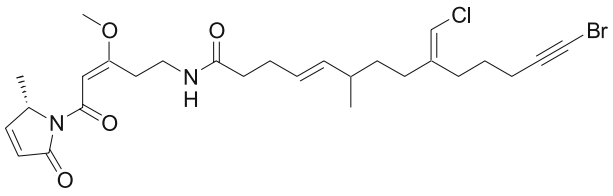
synthesis project of antillatoxin isomers led us to explore the preferred stereochemistry for the neuropharmacologic actions of antillatoxin [14]. Four stereoisomers, (4*R*,5*R*)-, (4*S*,5*R*)-, (4*S*,5*S*)-, and (4*R*,5*S*)-antillatoxin were estimated for ichthyotoxicity, microphysiometry assay, LDH efflux, and intracellular Ca^{2+} concentration using cerebellar granule cells, and cytotoxicity to neuro-2a cells. The natural antillatoxin (the 4*R*, 5*R*-isomer) showed the most potent activities in all the assays. Molecular modeling studies of antillatoxin isomers showed that change of overall molecular topologies of unnatural antillatoxin decreased the potency of bioactivities. Natural antillatoxin presents an overall "L-shaped" topology and its cluster of hydrophilic groups exist on the exterior of the macrocycle. The solution structure of antillatoxin will facilitate recognition of a binding site on the sodium channel.

2.3 Jamaicamide A

Jamaicamide A (**3**) is one of recently discovered neurotoxins from laboratory culture of the marine cyanobacterium *Lyngbya majuscula* [15]. A cell-based assay using neuro-2a cell line was applied for bioassay-guided fractionation of jamaicamide A. Although detailed analysis of neurotoxins requires electrophysiological experiments and primary cell culture assay, neuro-2a assay was easily conducted and convenient for natural product chemists [5]. In fact, isolation of jamaicamide A showed the usefulness of neuro-2a assay in detecting neurotoxin in natural products. A striking feature of the structure of jamaicamide A is the presence of alkynyl bromide as well as vinyl chloride and a pyrrolinone ring. Jamaicamide A exhibited sodium channel blocking activity at 5 μM. At 0.15 μM, it showed half the response of the well-known sodium channel blocker, saxitoxin. Interestingly, jamaicamide A showed very weak ichthyotoxicity to gold fish, used to detect the other sodium channel toxins, kalkitoxin and antillatoxin. It did not show brine shrimp toxicity either. A strong paper [15] on jamaicamides contained not only structure elucidation by NMR and biological activities, but also stable isotope feeding experiments and cloning studies of biosynthetic gene cluster. This unique mixed PKS/NRPS pathway indicates the diversity of cyanobacterial metabolites.



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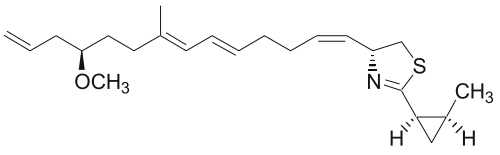
3
Cytotoxins

3.1
Curacin A

Curacin A (**4**) is one of the most well-known metabolites of *Lyngbya majuscula* [16, 17]. The structure of curacin A, consisting of a 2,4-disubstituted thiazoline and a lipophilic chain, is similar to kalkitoxin. The potent cytotoxicity of curacin A is due to tubulin polymerization inhibition. The instability of curacin A (e.g., the presence of the readily oxidized thiazoline heterocycle) and low water solubility hampered its development for therapeutic use, unlike taxol. However, a recent study of synthetic analogs improved bioavailability toward anticancer agents. Wipf et al. reported the combinatorial synthesis of six-compound mixture libraries of analogs of curacin A. Replacement of the heterocyclic and the homoallylic ether termini of curacin A was achieved by synthesis of two second generation curacin A analogs (e.g., **5**) [18]. These compounds inhibited tubulin polymerization (IC_{50} 1 μM) and inhibited [^{3}H] colchicines binding to tubulin at nanomolar concentrations. They aimed further to replace the (*Z*)-alkene moiety of the second generation library. Chemical modification of this double bond, such as by unsaturation, had resulted in inactive derivatives. Recently, a novel oxime analog of curacin A (**6**) demonstrated superior bioactivity and an increase in chemical stability [19]. The oxime-based analog of curacin A inhibited the GTP/glutamate-induced polymerization of tubulin remarkably (IC_{50} 0.17 μM), and was clearly superior to natural curacin A (IC_{50} 0.52 μM). The details of SAR studies of curacins as well as its total synthesis by several groups were well reviewed by Wipf et al. [17].



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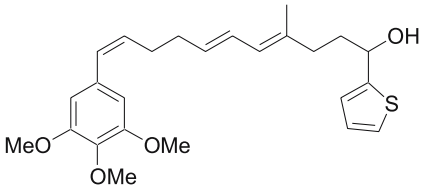

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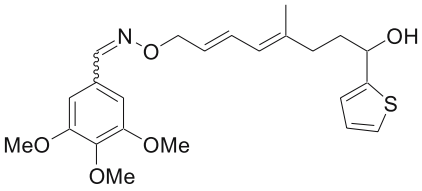

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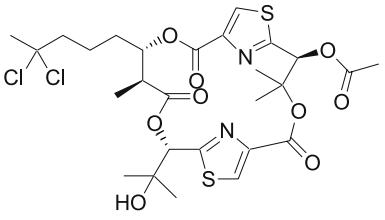
Despite a strong trend in natural products research towards molecular studies on biosynthetic genes, few biosynthetic studies have been reported from cyanobacteria due to problems with their culture. However, a curacin A-producing strain has been maintained for over a decade for biosynthetic studies. Molecular genetics together with precursor incorporation studies, biosynthetic pathway, and gene cluster analysis of curacin A was reported in 2004 [20]. In particular, cyclopropyl ring formation was shown to be mediated by a HMG-CoA synthase. A final decarboxylative dehydration was proposed to terminate the biosynthetic sequence to form the terminal double bond. Another characteristic is the largely monomodular nature of the biosynthetic gene cluster.

Although development of anticancer agents from curacin A is still in an early stage, improvement of chemical stability and water solubility of curacin A will lead to practical development. In addition, insight gained from curacin A derivatization will facilitate the investigation of other heterocycles, such as kalkitoxin, which have the same problem of chemical instability.

3.2
Hectochlorin and Dolastatin 10

Hectochlorin (**7**) is a cyclic lipopeptide containing two thiazole rings and a *gem*-dichloro substituted carbon [21]. This lipopeptide was isolated from a culture of *Lyngbya majuscula* collected in Hector Bay, Jamaica and from field collections made in Panama. Total synthesis was reported at the same time [22]. Hectochlorin is a potent promoter of actin polymerization. In addition, it is a fungicide which demonstrated activity on pathogens in crop



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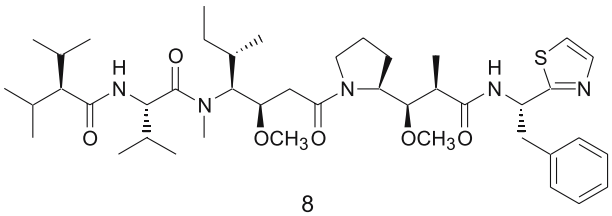

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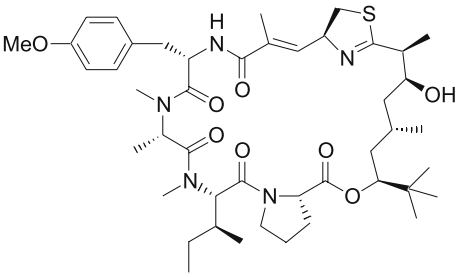
disease screens. An original paper on hectochlorin [21] pointed out the similarity of structure to cyanobacterial metabolites lyngbyabellins and dolabellin, isolated from the sea hare *Dolabella auricularia*. Recently, hectochlorin itself was isolated from Thai sea hare, *Bursatella leachii* with deacetylhectochlorin [23]. These lipopeptides from sea hare are believed to originate from dietary cyanobacteria. Several co-occurrences of natural products in sea hare and dietary cyanobacteria have been reported [24]. The most well-known example is dolastatin 10, which is under clinical trial as an anticancer agent. Fourteen years after the first isolation of dolastatin 10 from the sea hare *Dolabella auricularia* [25], dolastatin 10 was isolated from the marine cyanobacterium *Symploca* sp. [26] A significant difference between the two isolations is the yield (10^{-6} to 10^{-7}% from the sea hare vs. 10^{-2}% dry wt. from the cyanobacterium). In contrast to the fact that nudibranch concentrate isocyano compounds from sponges [27] (which is general in the food web), the sea hare does not have the ability to concentrate dolastatins. The low yield from the sea hare threatens sustainable use of the animal. Culturable cyanobacteria, which are the real producers, are preferred sources of dolastatins. However, culture of cyanobacteria needs a special facility, which has not yet been established industrially, and is expensive. At least, cyanobacteria will be maintained in the position of possible industrial producers of natural products. More examples of co-occurrence of related compounds in sea hare and cyanobacteria (including malyngamides, aplysiatoxin, dolabelides, scytophycins) are reviewed by Luesch et al. [24].

3.3
Apratoxin A

Apratoxin A (**9**) was isolated from *Lyngbya majuscula* as a potent cytotoxin [28]. The cyclodepsipeptide was reported to be the most potent cytotoxin produced by a variety of the cyanobacterium *Lyngbya* by Moore, who is the pioneer and the most productive chemist of cyanobacterial metabolites. It showed remarkable in vitro cytotoxicity (IC_{50} 0.52 nM to KB cell line, 0.35 nM to LoVo cell line). However, it was only marginally active in vivo against a colon tumor and ineffective against a mammary tumor. The structure of apratoxin A contains a thiazole moiety. Apparently it originates from a mixed biogenesis of polyketide and nonribosomal peptide synthase. Re-



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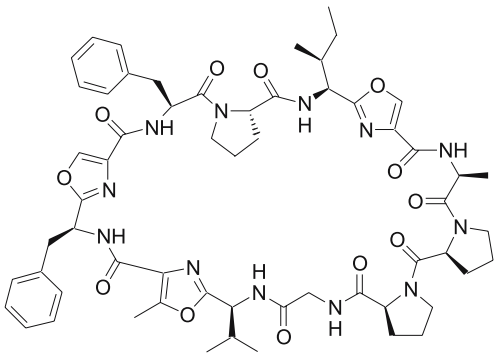
cently apratoxin A was reported to mediate antiproliferative activity through the induction of cell cycle arrest and of apoptosis, which is at least partially initiated through antagonism of FGF signalling [29].

3.4 Wewakazole

Wewakazole (**10**) was isolated from a Papua New Guinea *Lyngbya majuscula* [30]. Although no biological activity was reported for this cyclic dodecapeptide, its structure is intriguing. Most of *Lyngbya* peptides are classified into lipopeptides, which are products of a complex of polyketide synthase and nonribosomal polypetide synthase. However, wewakazole is comprised of only amino acid derivatives. We do not know whether this compound is biosynthesized PKS/NRPS or ribosomally like patellamide A (**11**). Thiazole and a thiazoline ring formed from cysteine residues, like in kalkitoxin (**1**) and curacin A (**2**), are often found in *Lyngbya*. On the other hand, the oxazole and methyloxazole residues contained in wewakazole are formed from serine and threonine. Although they are found in marine invertebrates, their occurrence in marine cyanobacteria is very rare. Considering the close relationship



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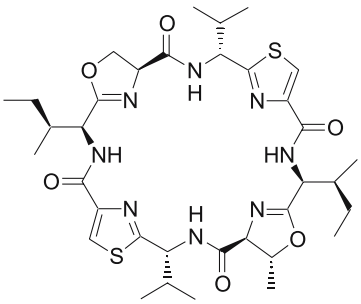

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between cyanobacterial products and invertebrate metabolites, this is very surprising. The author of the paper on wewakazole pointed out that the presence of six heterocyclic rings in wewakazole is without precedent in marine-derived cyclic peptides. Nature continues to produce novel structures. In addition, structure elucidation of wewakazole required multiple NMR experiments because of overlapping of chemical shifts and lack of HMBC correlation.

3.5 Patellamide A

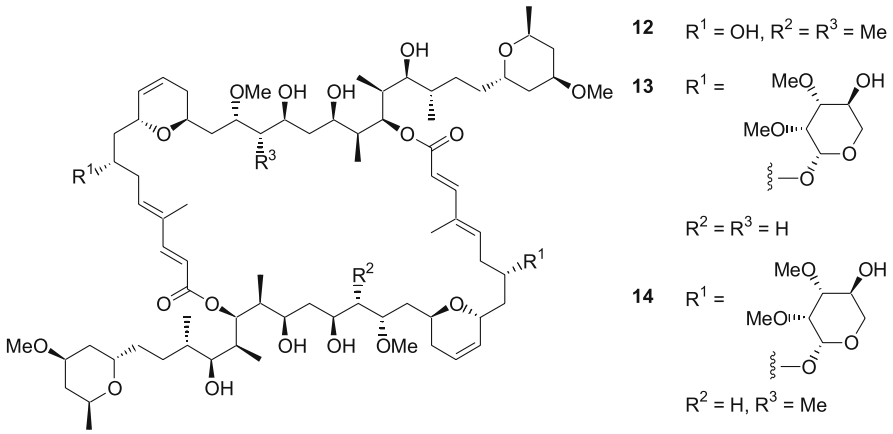
Patellamide A (**11**) is a cytotoxic peptide isolated from the tunicate *Lissoclinum patella* [31]. Its similar structure to cyanobacterial peptides suggested that the symbiotic cyanobacteria *Prochloron* spp. in the tunicate is the real producer of this peptide [32, 33]. A recent cell-separation study reported that the peptide was located in the ascidian tunic [34], but the author did not deny the possibility of cyanobacterial production of the peptide. In 2005, biosynthetic genes of patellamide A were identified in the *Prochloron didemni* genome [35]. This modified peptide is not biosynthesized by nonribosomal peptide synthase, but its precursor is encoded on a single ORF. Posttranslation (heterocyclization and cyclization) by surrounding gene clusters results in patellamide biosynthesis. The heterologous expression in *Escherichia coli* confirmed the biosynthetic function of the gene clusters identified. This paper clearly proved patellamide A is produced by the cyanobacterium *Prochloron didemni*. Interestingly, a related cluster was identified in the draft genome sequence of *Trichodesmium erythraeum* IMS101. *T. erythraeum* has not been intensively studied by natural chemists, but is common and important in tropical open-ocean as a nitrogen-fixing cyanobacterium. From an ecological and biological point of view, relationships between symbiosis and bioactive compounds have been discussed. However, we should consider the existence of symbiotic *Prochloron*, which do not produce patellamides, and the presence of biosynthetic genes of the peptide in a free-living cyanobacterium. The ecological importance of these peptides remains a big issue.

4
Macrolides

4.1
Swinholide A

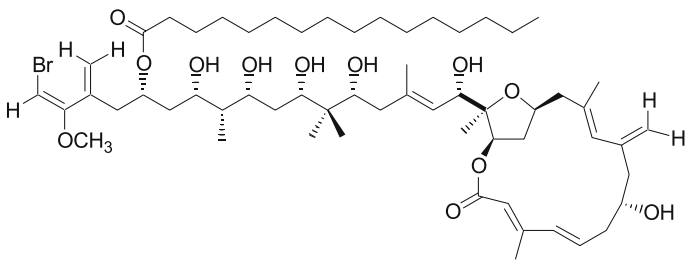
Swinholide A (**12**) is a well-known macrolide originally isolated from the marine sponge *Theonella swinhoei* [36, 37]. It was suggested to be a product of symbiotic microorganisms. Since the structure of swinholide A is similar to scytophycins isolated from the cyanobacterium *Scytonema* [38], symbiotic cyanobacteria were long thought to be its real producer. In 1996, swinholide A was reported to be located in a heterotrophic eubacterial fraction of the sponge *Theonella swinhoei*, which suggested it was a bacterial metabolite [39]. However, in 2005, swinholide A was isolated from the field collection of Fijian *Symploca* cf. sp. [40]. At least, cyanobacterium is a producer of swinholide A. The patellamide case demonstrated that cell-separation studies did not give conclusive results: both cyanobacteria and heterotrophic eubacteria could be its producers. More detailed analysis will be required to deduce which organism produces swinholide A in sponges.

Further, two glycosylated swinholides, ankaraholides A (**13**) and B (**14**), were isolated from a Madagascar field collection of *Geitlerinema* sp. [40]. Swinholide-type compounds are potently cytotoxic (IC_{50} 0.37 nM–1.0 μM against several cancer cell lines) by disruption of the actin cytoskeleton. Ankaraholide A inhibited proliferation (IC_{50} 119 nM to NCI-H460, 262 nM to neuro-2a, and 8.9 nM to MDA-MB-435). Ankaraholide A caused complete loss of the filamentous (F)-actin. This suggested additional sugar moieties do not affect its activity compared to swinholide A.



4.2
Phormidolide

Phormidolide (**15**) is a rare macrolide-type natural product from cyanobacteria [41]. A previous example of this class is oscillariolide, which was isolated from cultures of *Oscillatoria* sp. [42] Oscillariolide inhibited development of fertilized echinoderm eggs at a concentration of 0.5 μg/mL. However, its stereochemistry remains to be solved. Phormidolide was isolated in 15–20% yield from the lipophilic extract of aged cultures of *Phormidium* sp., originally from Indonesia. It was a potent brine shrimp toxin (LC_{50} 1.5 μM), but was not active in the NCI's in vitro 60-cell line toxicity assay. A ^{13}C-enriched sample of phormidolide was helpful in determining planar structure by the INADEQUATE NMR experiment. The relative stereochemistry at its 11 chiral centers was established by *J*-based configuration analysis. Absolute stereochemistry was determined on a bis-acetonide derivative using the variable temperature Mosher ester method. Even though the JBCA method is available, structure determination of phormidolide was achieved only by excellent application of new NMR experiments. Most of phormidolide is derived from polyketide metabolism. However, biosynthesis of a unique portion, the vinyl bromide functionality, is unknown. Some of the pendant carbon atoms, such as methyl or exomethylene groups, are derived from C-1 of acetate units. The metabolic origins of these pendant atoms is also interesting.



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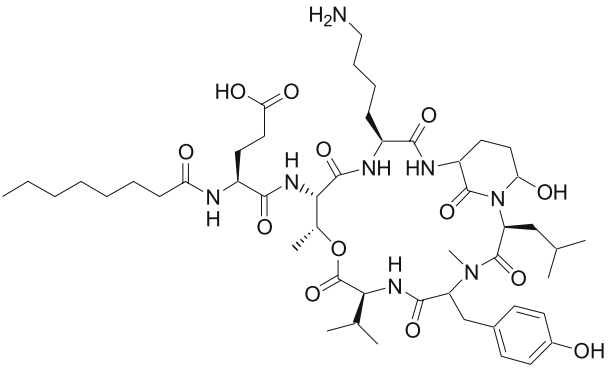
5
Enzyme Inhibitors

5.1
Micropeptins and Aeruginosins

Freshwater cyanobacteria produce a variety of peptides and similar peptides were also reported from marine cyanobacteria. Hepatotoxic microcystins are the most extensively studied peptides because of environmental con-

cern [43]. In addition, a great number of peptides are reported as protease inhibitors [44]. This class of peptides has begun to attract attention from the research of micropeptins isolated from the freshwater cyanobacterium *Microcystis aeruginosa* [45]. This type of peptide is characterized by the existence of Ahp (3-amino-6-hydroxy-2-piperidone). The peptide containing a basic amino acid inhibits trypsin, thrombin, or plasmin (Micropeptin A (**16**) [45]; IC_{50} 0.071 μg/mL to trypsin, 0.026 μg/mL to plasmin). The other peptides, which do not contain a basic amino acid, inhibit chymotrypsin and elastase (nostopeptin A [46]; IC_{50} 1.3 μg/mL to elastase, 1.4 μg/mL to chymotrypsin). Examples of Ahp-containing peptides from marine cyanobacteria are somamides [47] and tasipeptins [48].

Other intriguing protease inhibitory peptides are the aeruginosins. Aeruginosin 298-A (**17**) was isolated from *Microcystis aeruginosa* [49]. This peptide was characterized by the existence of Choi (2-hydroxy-6-hydroxyoctahydroindole) and the serine protease inhibition (IC_{50} 1.0 μg/mL to trypsin, 0.3 μg/mL to thrombin). Several synthetic chemists accomplished the total synthesis of aeruginosin-type peptides. For example, enantioselective syntheses of aeruginosin 298-A and its analogs was also reported by applying catalytic asymmetric phase-transfer reaction [50]. Furthermore Radau et al. improved selectivity of thrombin inhibition by synthesis of its



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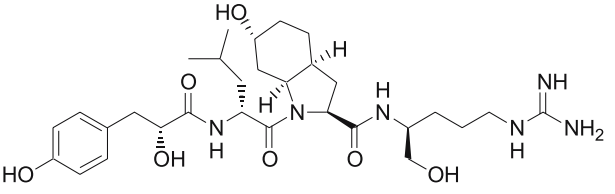

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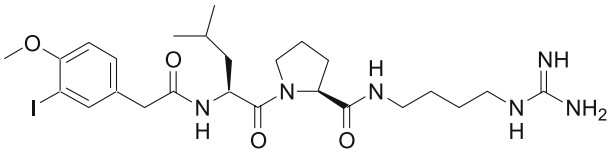

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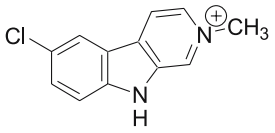
derivatives [44]. Their derivative, RA-1013 (**18**) showed moderate inhibition of thrombin, but did not show any inhibition against trypsin.

5.2 Nostocarboline

This review is focused on peptide-like compounds, however, some alkaloids have been reported from cyanobacteria. The most recent example is nostocarboline (**19**), which was isolated from cultured cells of the freshwater cyanobacterium *Nostoc* sp. [51]. This compound is a new quaternary β-carboline alkaloid. The structure was confirmed by its total synthesis. Strikingly, the alkaloid inhibited butyrylcholinesterase (IC_{50} 13.2 μM). The activity is comparable to an approved drug for the treatment of Alzheimer's disease. Cyanobacteria are thus possible sources of pharmaceuticals for neurological disorders.



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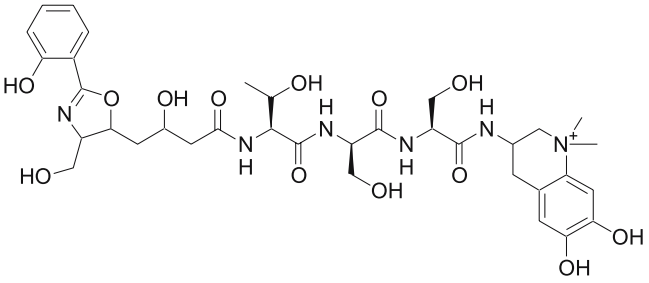
6 Siderophore

Siderophores are high-affinity Fe(III)-coordinating ligands secreted by microorganisms to facilitate iron uptake. Iron is the most important limiting nutrient for many microorganisms and cyanobacteria. Under iron-deficient conditions, many terrestrial microorganisms secrete siderophores. In the ocean, low levels of iron limit marine bacteria and phytoplankton. Recently new siderophores from marine bacteria have been investigated. In the case of cyanobacteria, anachelins (**20**) were reported by two groups as the second siderophores [52, 53]. Anachelins were isolated from the supernatant of an iron-starved culture of the freshwater cyanobacterium *An-*



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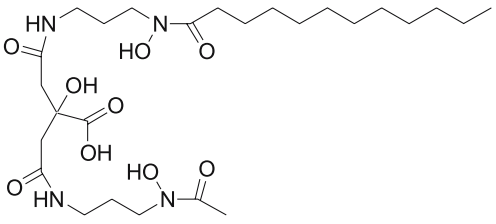
abaena cylindrica. Anachelins are peptidic alkaloids containing a 1,1-dimethyl-3-amino-1,2,3,4-tetrahydro-7,8-dihydroxyquinolin unit (Dmaq) and a 2-hydroxyphenyl-oxazoline system formed from the amino group and hydroxy group of the 6-amino-3,5,7-trihydroxyheptanoic acid moiety and salicylic acid moiety. Stereochemistries in the peptidic portion were determined, but four stereogenic centers in the polyketide portion have not been clarified. FABMS analysis showed that anachelins gave a 1 : 1 complex with iron. The functional groups for binding Fe^{3+} were the catecholate in Dmaq and the 2-hydroxyphenyl–oxazoline system. In contrast with *A. cylindrica*, the major bloom-forming species such as *Microcystis* spp. did not grow well in iron-deficient conditions. Axenic strains of *Microcystis* species were proposed not to have an effective system like siderophore biosynthesis for acquisition of traces of iron from an iron-starved environment. Recently total synthesis of anachelin H has been reported [54]. A stereodivergent synthesis of the polyketide fragment resulted in all possible diastereoisomers. Absolute stereochemistry of anachelin H was confirmed by total synthesis.

Structure of marine cyanobacterial siderophores has not been reported until recently. Synechobactins (**21**) are the first structurally elucidated siderophores from marine cyanobacteria [55] and are related to schizokinen isolated from freshwater cyanobacteria [56]. Synechobactins were isolated from the supernatant of the coastal marine cyanobacterium *Synechococcus* sp. Although they are not heterocycles, they are included in this review because



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it is intriguing that marine cyanobacteria produce a suite of photoreactive amphiphilic siderophores. Two hydroxamate groups and the α-hydroxy carboxylate of the citrate moiety seem to coordinate Fe(III).

7 Conclusion

This review has pointed out the continued finding of new structures from cyanobacteria. Some of the work was accomplished by recent NMR technology as well as through collaboration with synthetic chemistry.

A cryptophycin derivative not described here underwent clinical trial and was abandoned. Curacin A derivative is possibly going to clinical trial. These compounds prove that cyanobacterial products are potential sources of anticancer agents. Recent discovery of the neurochemicals described in this review could lead to development of drugs for neurological disorders as well. Until now, no enzyme inhibitor from cyanobacteria has gone to clinical trial, but apparently these studies are going to the next stage.

The relationship between cyanobacteria and invertebrates is deep. Cyanobacteria and mollusks contains not only similar compounds but also the same compounds. Symbiotic cyanobacteria in the tunicates have proved to produce modified peptides in genetic studies. The sponge–cyanobacteria relationship needs more detailed experiments.

Although cyanobacteria are culturable sources of bioactive compounds, no practical production of cyanobacteria by either culture or genetical expression has yet been conducted. Solution of this issue will open the next stage of cyanobacterial research.

References

1. Gerwick WH, Tan LT, Sitachitta N (2001) In: Cordell GA (ed) The alkaloids, vol 57. Academic, San Diego, p 75
2. Burja AM, Banaigs B, Abou-Mansour E, Burgess JG, Wright PC (2001) Tetrahedron 57:9347
3. Wu M, Okino T, Nogle LM, Marquez BL, Williamson RT, Sitachitta N, Berman FW, Murray TF, McGough K, Jacobs R, Colsen K, Asano T, Yokokawa F, Shioiri T, Gerwick WH (2000) J Am Chem Soc 122:12041
4. Berman FW, Gerwick WH, Murray TF (1999) Toxicon 37:1645
5. Manger RL, Leja LS, Lee SY, Hungerford JM, Hokama Y, Dickey RW, Granade HR, Lewis R, Yasumoto T, Wekell MM (1995) J AOAC Int 78:521
6. LePage KT, Goeger D, Yokokawa F, Asano T, Shioiri T, Gerwick WH, Murray TF (2005) Toxicol Lett 158:133
7. White JD, Xu Q, Lee CS, Valeriote FA (2004) Org Biomol Chem 2:2092
8. Yokokawa F, Asano T, Okino T, Gerwick WH, Shioiri T (2004) Tetrahedron 60:6859–6880

9. Matsumori N, Kaneno D, Murata M, Nakamura H, Tachibana K (1999) J Org Chem 64:866
10. Williamson RT, Márquez BL, Gerwick WH, Kövér KE (2000) Magn Reson Chem 38:265
11. Orjala J, Nagle DG, Hsu VL, Gerwick WH (1995) J Am Chem Soc 117:8281
12. Li WI, Berman FW, Okino T, Yokokawa F, Shioiri T, Gerwick WH, Murray TF (2001) Proc Natl Acad Sci USA 98:7599
13. Yokokawa F, Fujiwara H, Shioiri T (2000) Tetrahedron 56:1759
14. Li WI, Marquez BL, Okino T, Yokokawa F, Shioiri T, Gerwick WH, Murray TF (2004) J Nat Prod 67:559
15. Edwards DJ, Marquez BL, Nogle LM, McPhail K, Goeger DE, Roberts MA, Gerwick WH (2004) Chem Biol 11:817
16. Gerwick WH, Proteau PJ, Nagle DG, Hamel E, Blokhin A, Slate D (1994) J Org Chem 59:1243
17. Wipf P, Reeves JT, Day BW (2004) Curr Pharm Design 10:1417
18. Wipf P, Reeves JT, Balachandran R, Giuliano KA, Hamel E, Day BW (2000) J Am Chem Soc 122:9391
19. Wipf P, Reeves JT, Balachandran R, Day BW (2002) J Am Chem Soc 45:1901
20. Chang Z, Sitachitta N, Rossi JV, Roberts MA, Flatt PM, Jia J, Sherman DH, Gerwick WH (2004) J Nat Prod 67:1356
21. Marquez BL, Watts KS, Yokochi A, Roberts MA, Verdier-Pinard P, Jimenez JI, Hamel E, Scheuer PJ, Gerwick WH (2002) J Nat Prod 65:866
22. Cetusic JRP, Creen FR III, Graupner PR, Oliver MP (2002) Org Lett 4:1307
23. Suntornchashwej S, Chaichit N, Isobe M, Suwanborirux K (2005) J Nat Prod 68:951
24. Luesch H, Harrigan GG, Goetz G, Horgen FD (2002) Curr Med Chem 9:1791
25. Pettit GR, Kamano Y, Herald CL, Tuinman AA, Boettner FE, Kizu H, Schmidt JM, Baczynskyj L, Tomer KB, Bontems RJ (1987) J Am Chem Soc 109:6883
26. Luesch H, Moore RE, Paul VJ, Mooberry SL, Corvett TH (2001) J Nat Prod 64:907
27. Garson MJ, Simpson JS (2004) Nat Prod Rep 21:164
28. Luesch H, Yoshida WY, Moore RE, Paul VJ, Corbett TH (2001) J Am Chem Soc 123:5418
29. Luesch H, Chanda SK, Raya RM, DeJesus PD, Orth AP, Walker JR, Carlos J, Belmonte I, Schultz PG (2006) Nat Chem Biol 2:158
30. Nogle LM, Marquez BL, Gerwick WH (2003) Org Lett 5:3
31. Ireland CM, Durso AR, Newman RA, Hacker MP (1982) J Org Chem 47:1807
32. Prinsep MR, Moore RE, Levine IA, Patterson GML (1992) J Nat Prod 55:140
33. Hambley TW, Hawkins CJ, Lavin MF, Brenk AVD, Watters DJ (1992) Tetrahedron 48:341
34. Salomon CE, Faulkner DJ (2002) J Nat Prod 65:689
35. Schmidt EW, Nelson JT, Rasko DA, Sudek S, Eisen JA, Haygood MG, Ravel J (2005) Proc Natl Acad Sci USA 102:7315
36. Kashman Y, Carmely S (1985) Tetrahedron Lett 26:511
37. Kobayashi M, Tanaka J, Katori T, Matsuura M, Kitagawa I (1989) Tetrahedron Lett 22:2963
38. Ishibashi M, Moore RE, Patterson GML, Xu C, Clardy J (1986) J Org Chem 51:5300
39. Bewley CA, Holland ND, Faulkner DJ (1996) Experientia 52:716
40. Andrianasolo E, Gross H, Goeger D, Musafija-Girt M, McPhail K, Leal RM, Mooberry SL, Gerwick WH (2005) Org Lett 7:1375
41. Williamson RT, Boulanger A, Vulpanovici A, Roberts MA, Gerwick WH (2002) J Org Chem 67:7927

42. Murakami M, Matsuda H, Makabe K, Yamaguchi K (1991) Tetrahedron Lett 32:2391
43. Dittmann E, Wiegand C (2006) Mol Nutr Food Res 50:7
44. Radau G (2005) Curr Enzyme Inhibition 1:295
45. Okino T, Murakami M, Haraguchi R, Munekata H, Matsuda H, Yamaguchi K (1993) Tetrahedron Lett 34:8131
46. Okino T, Qi S, Matsuda H, Murakami M, Yamaguchi K (1997) J Nat Prod 60:158
47. Nogle LM, Williamson RT, Gerwick WH (2001) J Nat Prod 64:716
48. Williams PG, Yoshida WY, Moore RE, Paul VJ (2003) J Nat Prod 66:620
49. Murakami M, Okita Y, Matsuda H, Okino T, Yamaguchi K (1994) Tetrahedron Lett 35:3129
50. Fukuta Y, Ohshima T, Gnanadesiken V, Shibuguchi T, Nemoto T, Kisugi T, Okino T, Shibasaki M (2004) Proc Natl Acad Sci USA 101:5433
51. Becher PG, Beuchat J, Gademann K, Jüttner F (2005) J Nat Prod 68:1793
52. Beiderbeck H, Taraz K, Budzikiewicz H, Walsby AE (2000) Z Naturforsch 55c:681
53. Itou Y, Okada S, Murakami M (2001) Tetrahedron 57:9093
54. Gademann K, Bethuel Y (2004) Org Lett 6:4707
55. Ito Y, Butler A (2005) Limnol Oceanogr 50:1918
56. Simpson FE, Neilands JB (1976) J Phycol 12:44

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Marine Polyether Compounds

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Abstract Due to their chemical complexity and potent biological activity, marine polyether compounds produced by marine unicellular algae are of interest to many researchers in the life sciences including synthetic chemists, biochemists, and pharmacologists. These compounds, especially cyclic polyether compounds such as brevetoxins, ciguatoxins, maitotoxin and gymnocins, have been seen as characteristic of the dinoflagellates. Many of them are associated with seafood poisoning or massive fish fatalities. This review covers the structure, origin, and biological activity of marine polyether compounds.

Keywords Polyether · Marine toxin · Bioactivity · Phytoplankton

Abbreviations

BTX	Brevetoxin
VSSC	Voltage-sensitive sodium channel
NSP	Neurotoxic shellfish poisoning
ip	Intraperitoneal injection
po	Oral administration
CTX	Ciguatoxin

MTX	Maitotoxin
GA	Gambieric acid
DSP	Diarrhetic shellfish poisoning
OA	Okadaic acid
PTX	Pectenotoxin
YTX	Yessotoxin
TPPcinnamate	*p*-(meso-triphenylporphyrin)-cinnamate group

1 Introduction

Marine polyether compounds attract considerable attention among not only natural product chemists but also synthetic chemists, biochemists, and pharmacological scientists because of their complicated structures and very powerful biological actions. Many of them have been found through their association with seafood poisoning or massive fish fatalities. The producers of marine polyether compounds are unicellular eukaryotic algae, mostly dinoflagellates, which are primary producers in the marine food web. Consequently, fish and shellfish accumulate dinoflagellate toxins through the food chain. Dinoflagellates have few or no basic nuclear proteins, and due to their phylogenetic position between the prokaryotes and eukaryotes, they are also called mesocaryotes. Dinoflagellates produce a variety of metabolites including heterocycles, macrolides, and highly oxygenated alkyl compounds. Of these metabolites, the polycyclic ether compounds are the most characteristic products found in dinoflagellates. In this chapter, the structure and activities of marine polyether compounds isolated from phytoplankton are described.

2 Brevetoxin and its Related Compounds

Along the Florida coast and in the Gulf of Mexico, the dinoflagellate *Karenia brevis* often forms blooms known as "red tides" that lead to massive fish kills. The causative toxins, the brevetoxins, possess an unprecedented highly oxygenated structure. The brevetoxins were the first cyclic polyether compounds to be chemically identified, and were shown to possess a characteristic structural feature of a ladder-like skeleton consisting of *trans*-fused polyether rings.

Brevetoxin B (BTXB, **1**; also known as PbTx-2) was isolated from the dinoflagellate, *K. brevis* collected at the Gulf of Mexico. Its structure was determined by X-ray crystallography [1]. The structure of BTXB includes ten consecutive ether rings, a δ-lactone, and an $\alpha\beta$ unsaturated aldehyde side

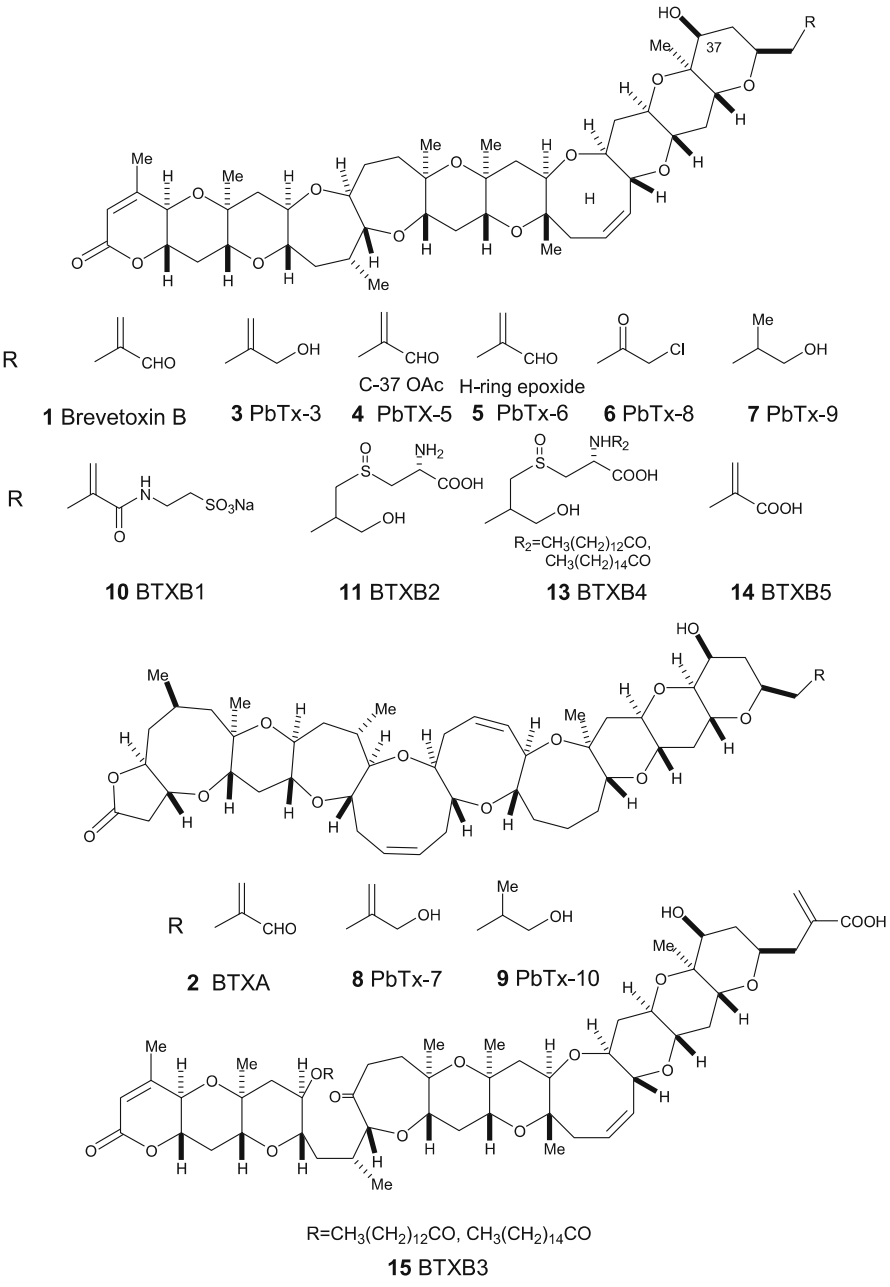
chain. Total synthesis of BTXB has been accomplished by three groups [2–4]. Brevetoxin A (BTXA, **2**; also known as PbTx-1) possesses a different structural backbone but is also produced by *K. brevis*. The structure of BTXA was elucidated by X-ray crystallography [5]. Interestingly, BTXA has five-, six-, seven-, eight-, and nine-membered rings in the molecule. Currently, seven brevetoxin analogs (**3–9**) have been isolated from the dinoflagellate and the structures were determined by comparison of spectra with those of BTXB and BTXA. Structural differences are confined to alteration of the side chain, epoxidation across the double bond in the H-ring of BTXB, or derivatization at the C-37 hydroxyl in BTXB [6].

Brevetoxins bind with high affinity to site 5 of the voltage-sensitive sodium channel (VSSC) in neurons, causing the channel to remain in the open state and inhibit channel inactivation, thus prolonging the duration of sodium currents across the membrane [7].

There have been catastrophic mortalities of threatened marine species, including manatees, bottlenose dolphins, and sea turtles. The bloom can also cause irritation of the eyes and throat in humans in the coastal areas. Neurotoxic shellfish poisoning (NSP) is a term referring to an illness resulting from ingestion of shellfish exposed to blooms of *K. brevis* [8, 9]. In early 1993, an NSP incidence occurred in New Zealand. Studies in response to this outbreak identified five new BTXB analogs, BTXB1–BTXB5 (**10–14**), from shellfish [10–14]. Toxins produced by *K. brevis* were metabolized in shellfish to new BTX analogs. BTXB2, BTXB3, and BTXB4, isolated from greenshell mussels retain the potency to activate Na channels but lost ichthyotoxicity, unlike BTXB. The Na channel activating potency of BTXB4 is three times higher than that of BTXB2 and comparable with that of PbTx-3. These results indicate that introducing a lipophilic acyl moiety into the side-chain of BTXB2 markedly enhances its potency.

Hemibrevetoxin-B (**15**) is the smallest cyclic polyether compound produced by *K. brevis* [15]. Hemibrevetoxin-B has a polyether backbone and a terminal unsaturated aldehyde, similar to brevetoxin, but contains only four fused cyclic ether rings. Cytotoxicity of hemibrevetoxin-B against mouse neuroblastoma cells was reported.

Brevenal (**16**) is a shorter cyclic polyether compound, which is the major constituent derived from *K. brevis* cultures and the environment [16]. Brevenal contains five fused ether rings (6/7/6/7/7), a terminal conjugated aldehyde, and a conjugated diene. The side chain and the 7-7-6 rings are similar to hemibrevetoxin-B. Brevenal and brevenal acetal (**17**) inhibited [^{3}H]-PbTx-3 binding to VSSC with 1.85 μM and 0.68 μM, respectively. The brevenals bind to site 5 of the VSSC on rat synaptosomes, however, their activities are 1000 times less potent than that of BTXB. Brevenals inhibit or delay brevetoxin-induced mortality in fish. Thus, they act as BTX antagonists with in vivo bioassays.


R
CHO
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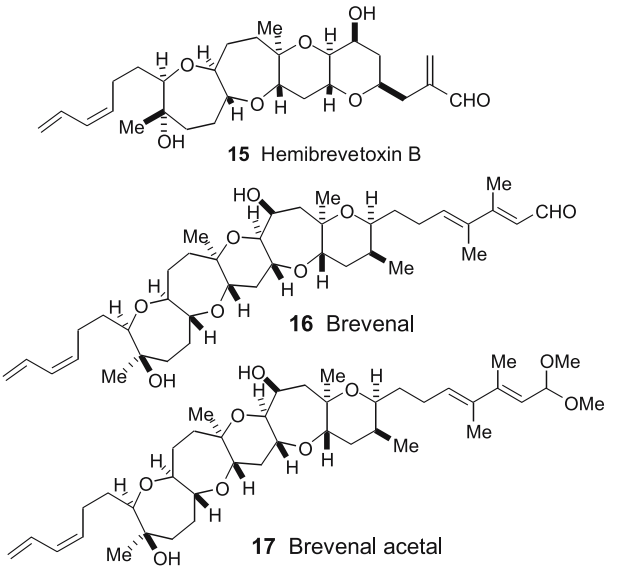
CHO
CHO
O
Cl
Me
OH
C-37 OAc
H-ring epoxide
1 Brevetoxin B
3 PbTx-3
4 PbTX-5
5 PbTx-6
6 PbTx-8
7 PbTx-9
R
SO3Na
NH2
COOH
OH
NHR2
R2=CH3(CH2)12CO,
CH3(CH2)14CO
COOH
10 BTXB1
11 BTXB2
13 BTXB4
14 BTXB5
R
CHO
OH
Me
OH
2 BTXA
8 PbTx-7
9 PbTx-10
COOH
OR
R=CH3(CH2)12CO, CH3(CH2)14CO
15 BTXB3

Scheme 1



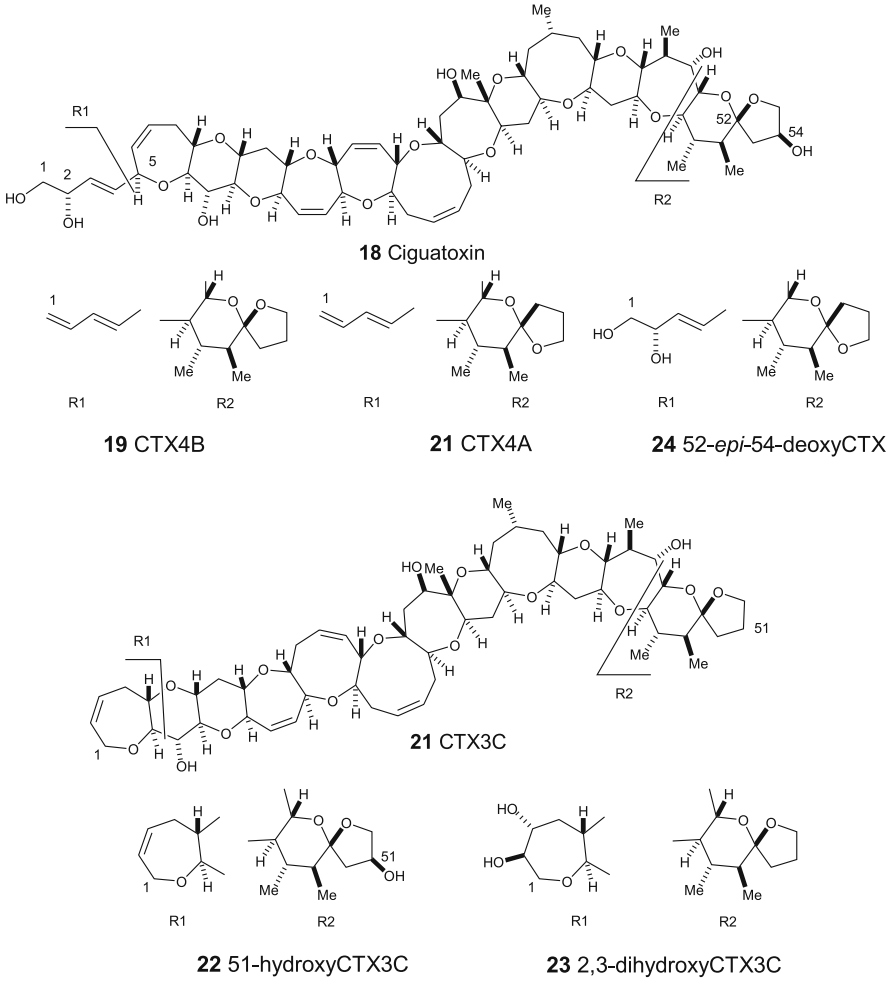
Scheme 2

3 Ciguatera Toxins

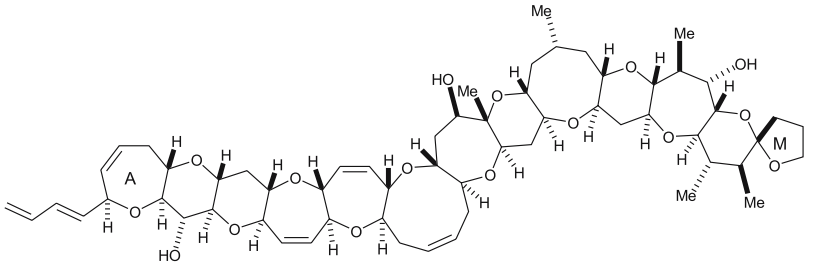
Ciguatera is the most famous seafood poisoning prevalent in circumtropical areas [17]. Its effects on human health and its economic impact are serious problems in those areas. The poisoning is caused by ingestion of coral reef fish that have become toxic through their diet. Ciguatera toxins are composed of two principal groups defined by ciguatoxin and its congeners, and by maitotoxin. Both groups are produced by the epiphytic dinoflagellate *Gambierdiscus toxicus* and transferred to herbivorous fish and subsequently to carnivores through the food chain. The clinical symptoms are diverse. Neurologic disturbances are prominent; reversal of thermal sensation, called "dry-ice sensation", is one of the most characteristic symptoms of ciguatera. Other illnesses includes joint pain, miosis, erethism, cyanosis, and prostration. Gastrointestinal disorders are nausea, vomiting, and diarrhea. Cardiovascular disturbances include low blood pressure and bradycardia. Maitotoxin was first detected in the gut of herbivorous fish. In French Polynesia, the poisoning caused by ingestion of herbivorous fish poses a more serious threat to public health than ingestion of carnivorous fishes.

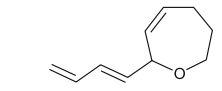
Ciguatoxin (CTX, **18**) was first isolated in 1980 and its structure was finally elucidated in 1989 [18, 19]. For that study, 4000 kg of moray eels (*Gymnothrax javanicus*) were collected in French Polynesian water and 124 kg of viscera were extracted to obtain 0.35 mg of pure CTX. The *G. toxicus* collected in the Gambier Islands yielded 0.75 mg of a precursor toxin that was coded

CTX4B (**19**). Although the amount of material was too small for ^{13}C-related NMR experiments, the structures were successfully solved to be the polycyclic ethers mainly on the basis of ^{1}H NMR data. Five congeners, CTX3C (**20**), CTX4A (**21**), 51-hydroxyCTX3C (**22**), 2,3-dihydroxyCTX3C (**23**), and 52-*epi*-54-deoxyCTX (**24**), have been isolated from the cultured *G. toxicus* and from fish [20–22]. Their structures, including relative stereostructure were elucidated by NMR analysis. Structures of 16 ciguatoxin congeners (**25–40**) were determined by CID FAB MS/MS experiments using samples of 5 μg or less [23]. From Caribbean toxic fish, C-CTX1 (**41**) and its 56 epimer, C-CTX-2 (**42**) were isolated [24]. The skeletal structure of those toxins is slightly modified and possesses 14 ether rings.

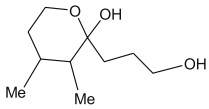


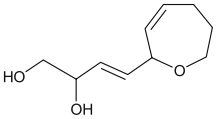
Scheme 3



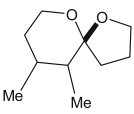


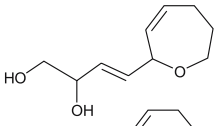
25 M-seco-CTX4A or 4B



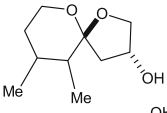


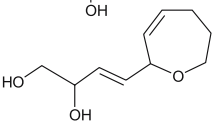
26 54-deoxyCTX



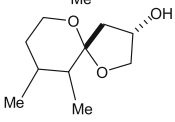


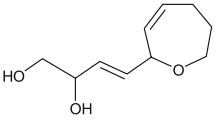
27 54-*epi*-CTX



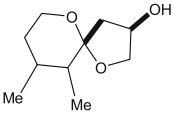


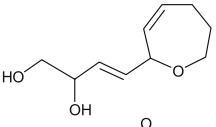
28 52-*epi*-CTX



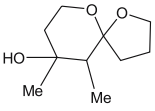


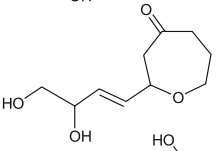
29 52,54-*epi*-CTX



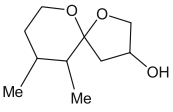


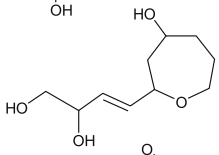
30 54-deoxy-50-hydroxyCTX



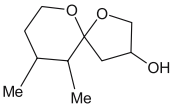


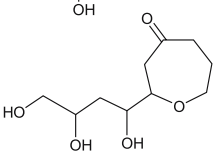
31 7-oxoCTX



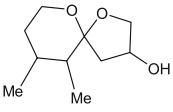


32 7-hydroxyCTX

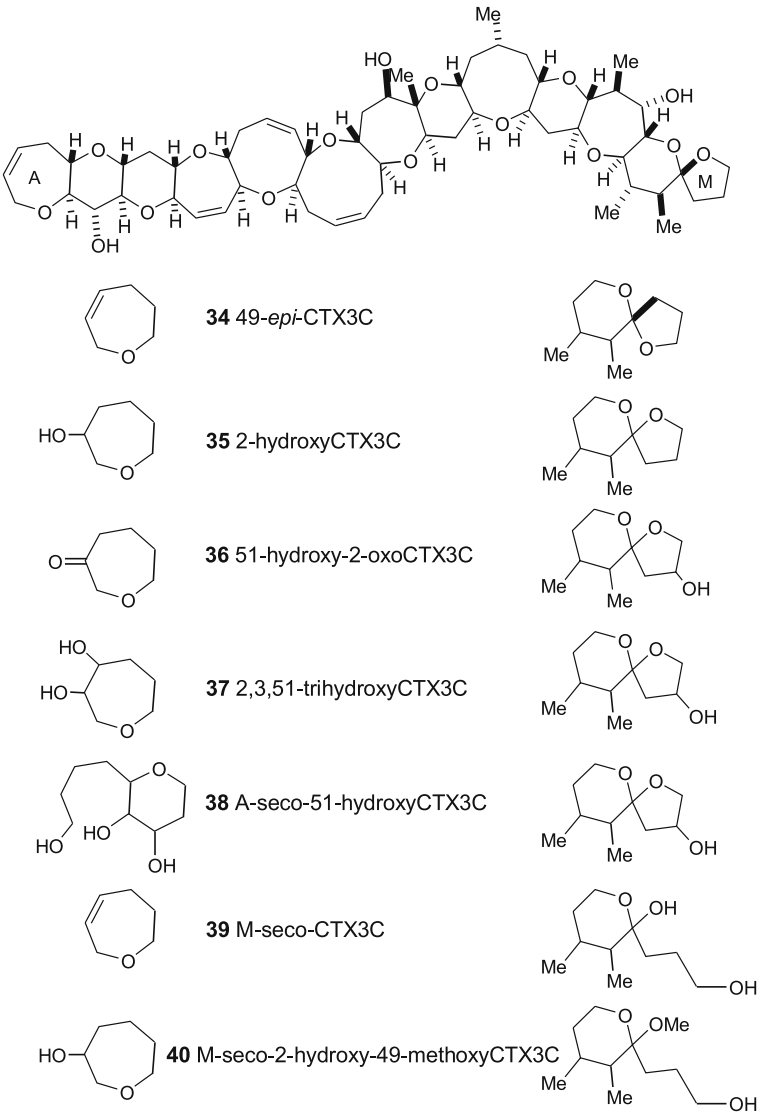




33 4-hydroxy-7-oxoCTX

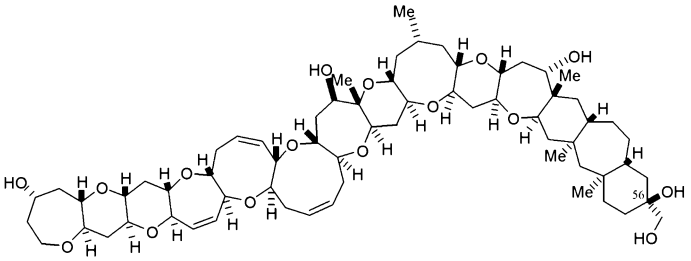


Scheme 4



Scheme 5

Since 1989 chemical studies on ciguatera toxins have made rapid strides. Nonetheless, the absolute configuration and stereochemistry at C2 was not determined until 1997 [25], when Yasumoto and co-workers determined the C2 stereochemistry of CTX by chemical degradation and chiral HPLC analysis. The absolute configuration of C5 in CTX4A was determined by comparing CD spectra of 11,32,46-*tris*(*p*-benzoyl)-CTX4A and the synthetic AB ring fragment. Only 5 μg of CTX and 100 μg of CTX4A were used for determin-



41 C-CTX1
42 C-CTX2 (epimer at C56)

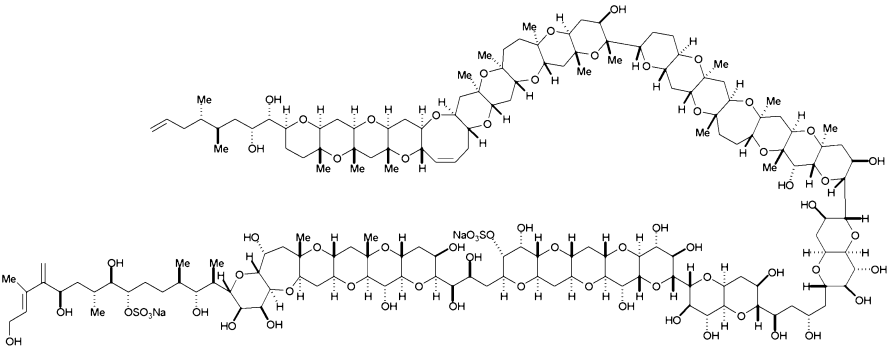
Scheme 6

ation of the absolute configuration of the CTXs. CTXs are attractive targets for synthetic chemists, and a number of synthetic strategies have been reported. The first total synthesis of this complicated and intriguing compound was accomplished by Hirama and co-workers in 2001 [26].

The lethality of CTX (0.35 μg/kg) by intraperitoneal injection into mice is 280 times greater than that of tetrodotoxin (10 μg/kg), which is a well-known non-polyether toxin from puffer fish. Orally, an amount as small as 70 ng of CTX can cause intoxication in humans.

The more highly developed organisms in the coral ecosystem tend to contain more oxygenated congeners while the dinoflagellates produce less oxygenated ones. These data suggest that less oxygenated congeners produced by *G. toxicus* are precursors to the more oxygenated toxins in fish, the latter formed by oxidative enzyme systems in the fish. The toxicity of the oxidized metabolites is often increased, as is the case with ciguatoxin which is 11 times more toxic than its precursor CTX4B. The pharmacological properties of the CTXs are similar to brevetoxins. Competitive binding assays indicate that they bind to the same site of a channel protein and inhibit depolarization to allow inward Na^+ influx to continue.

Maitotoxin (**43**) is the largest non-biopolymer natural product ($C_{164}H_{256}O_{68}S_2Na_2$, Mw 3422 Da) and is constructed from a 142 carbon chain containing 32 ether rings, 28 hydroxyl groups, and two sulfate esters [27, 28]. Elucidation of the structure of MTX was accomplished by isolation of three fragments following periodate oxidation, through extensive NMR experiments of the whole molecule of MTX and three fragments, and by charge-remote FAB/MS/MS studies to support the validity of the structures deduced by NMR experiments. Further structural confirmation and complete ^{13}C NMR assignments were accomplished by 3D PFG NOESY-HMQC experiments using a ^{13}C-enriched sample [29]. By combining the above results, the relative stereochemistry in MTX was determined, except for 11 chiral centers in the side-chain. The *J*-based configuration analysis was used to assign the stereochemistry in the terminal chains of MTX, which greatly reduced



43 Maitotoxin

Scheme 7

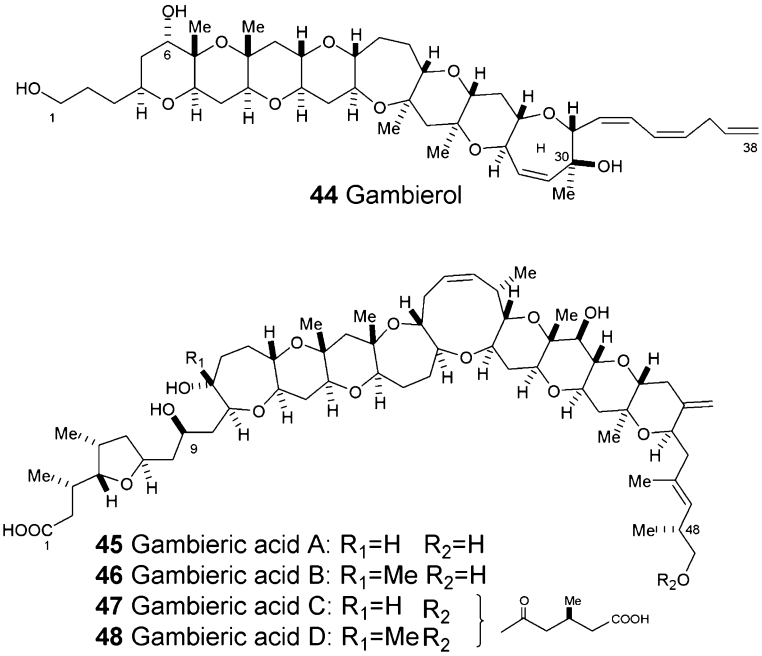
the number of diastereomers to be synthesized [30]. Finally, the absolute configurations of the acyclic segments and the whole molecule were determined by synthesis of the partial structures by two independent research groups [31–33].

Mouse lethality of MTX by intraperitoneal injection is 50 ng/kg and is exceeded only by that for a few bacterial toxins. MTX also exhibits extremely potent hemolytic, ichthyotoxic, and cytotoxic activities. MTX enhances the inward influx of Ca^{2+} ion across cell membranes. Existence of a ubiquitous Ca-channel sensitive to MTX was hypothesized but has not yet been proven. The true mechanism underlying the potent activity of MTX still remains to be clarified.

Gambierol (**44**) was also isolated as a toxic constituent of cultured cells of *G. toxicus* collected from the Rangiroa atoll in French Polynesia. Its structure, including relative stereochemistry was determined by extensive NMR studies [34]. The absolute configuration was established by derivatization and application of a modified Mosher method [35]. The structure of gambierol is characterized by a *trans*-fused octacyclic polyether core containing 18 stereogenic centers and a triene side chain including a conjugated (*Z*,*Z*)-diene system. The total synthesis of gambierol has been achieved by three groups [36–38].

Gambierol exhibits potent toxicity against mice by ip injection and its symptoms caused in mice resemble those shown for ciguatoxins. This finding implies that gambierol may also be responsible for ciguatera fish poisoning. Structure-activity relationship studies using synthetic intermediates indicated that the C28 = C29 double bond within the H ring and the unsaturated side chain are critical structural elements while the C1 and C6 hydroxyl groups, the C30 methyl group, and the C37 = C38 double bond have little effect on the mouse toxicities [39].

The lethal doses of synthesized gambierol in mice are about 50–80 μg/kg ip, and 150 μg/kg po. The toxin leads primarily to injury in the lung, with



Scheme 8

secondary effects on the heart, resulting in systemic congestion. Another toxic effect was seen in the stomach, inducing hypersecretion and ulceration [40].

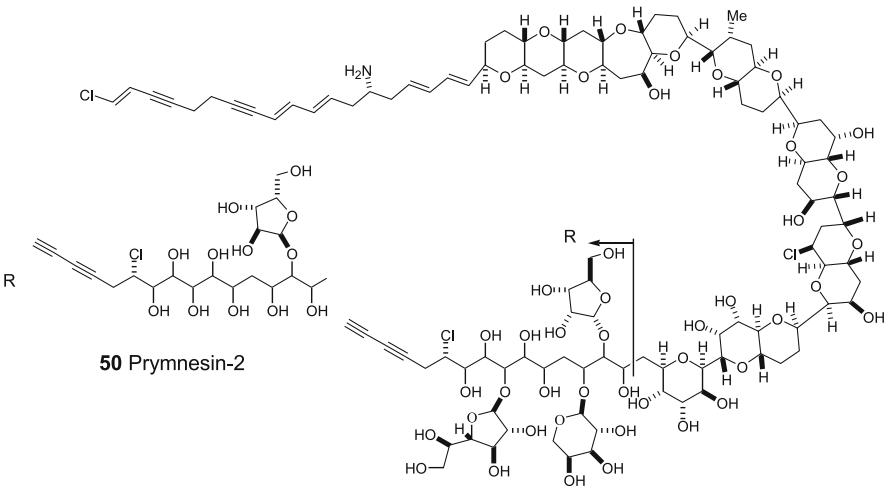
Gambierol inhibits voltage-gated potassium currents in mouse taste cells [41]. By applying the patch-clamp technique to single cells in isolated taste buds obtained from the mouse vallate papilla, gambierol markedly inhibited K^+ current in the nanomolar range (IC_{50} of 1.8 nM), whereas it showed no significant effect on Na^+ and Cl^- currents even at high concentration. The blockage of K^+ current was irreversible, even after a 50-min wash. In addition to affecting the current amplitude, gambierol significantly altered both the activation and inactivation processes of K^+ current.

Gambieric acids A–D (GA A–D, **45–48**) are potent antifungal compounds isolated from the culture medium of *G. toxicus* that produces maitotoxin [42, 43]. Their antifungal activities against *Aspergillus niger* by the paper disk method were 2000 times greater than that of amphotericin B. Adding to their remarkable range of biological activities, the acids **45–48** are also endogenous growth enhancers of the dinoflagellate [44]. The absolute configuration from C1 to C11 was determined by NMR analysis after introducing anisotropic reagents to the carboxyl group at C1 or 9-OH in GAB. Chiral fluorescent reagents for HPLC were used to determine the stereochemistry of C48 and 3-methylglutaric acid in GAC and GAD [45].

4
Cyclic Polyether Compounds from Red Tide Organisms

Prymnesium parvum CARTER (Haptophyceae) is a unicellular alga that blooms in brackish water and causes massive fish kills giving extensive damage to fish aquaculture facilities around the world. There are many reports in the literature, going back over 40 years, describing the hemolytic and ichthyotoxicity of various *Prymnesium* species including *P. parvum* and *P. patelliformis*. However, it was not until the late 1990s that the structure of two causative toxins, prymnesin-1 (**49**) and prymnesin-2 (**50**) obtained from a strain *P. parvum*, were reported [46, 47]. The prymnesins are the first cyclic polyether toxins to be isolated from a phytoflagellate other than a dinoflagellate (Dinophyceae). The highly oxygenated molecules are reminiscent of dinoflagellate polyether compounds such as ciguatoxin, brevetoxin, maitotoxin and palytoxin, yet the prymnesins possess distinct structural features of their own. The C_{90} carbon skeleton has no branching except for one methyl. Five contiguous ether rings resemble those in the dinoflagellate polyether compounds. However, the four repeats of a 1,6-dioxadecalin unit were previously unknown in natural products. Prymnesins contain multiple functional groups such as conjugated double and triple bonds, chlorine atoms, an amino group, and glycosidic residues including uncommon L-xylose. The lopsided distribution of hydroxyl groups endows the molecule amphiphilic properties.

Apart from these unique structural features, the extremely potent bioactivities are also worthy of mention. Both prymnesins posses hemolytic activity



50 Prymnesin-2

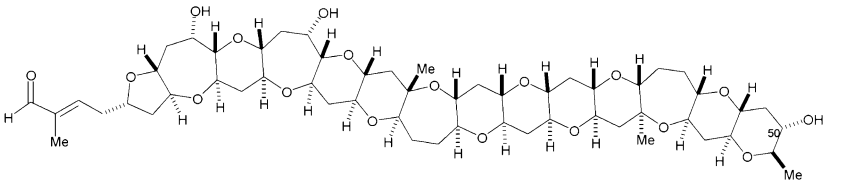
49 Prymnesin-1

Scheme 9

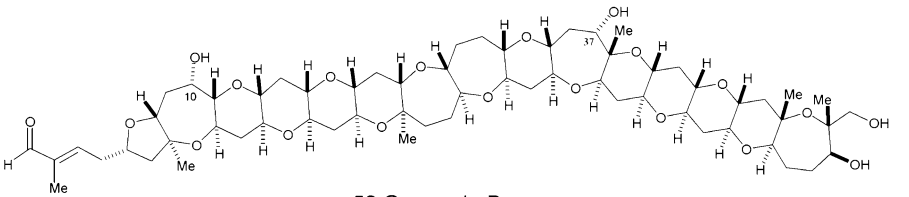
that is about 50 000-fold greater than that of a commercially available plant saponin. Prymnesins kill freshwater fish at 9 nM concentration and induce Ca^{2+} influx into rat glioma C6 cells at 70 nM concentration [48]. Such high potency of prymnesins raises an intriguing question about their mechanism of action.

The gymnocins are a series of cytotoxic polyether compounds isolated from the notorious red tide dinoflagellate *Karenia* (formerly *Gymnodinium*) *mikimotoi*. Blooms of *K. mikimotoi* have caused devastating damage to aquaculture and marine ecosystems worldwide and the mechanism of the toxic effect to fish yet remains unknown. Gymnocin-A [**51**] and gymnocin-B [**52**] were isolated from cultured cells of *K. mikimotoi*. Their structures were elucidated by 2D-NMR analysis and CID FAB MS/MS experiments. The structure of gymnocin-A was characterized by 14 contiguous saturated ether rings (5/7/6/7/6/6/7/6/6/6/6/7/6/6) and a 2-methyl-2-butenal side chain [49]. The absolute configuration of gymnocin-A was elucidated by applying the modified Mosher method at the 50-OH group. The total synthesis of gymnocin-A has been accomplished by Sasaki and co-workers [50].

Similar to gymnocin-A, gymnocin-B has fused contiguous saturated ether rings and a 2-methyl-2-butenal side chain. However, the manner of ring fusion (5/7/6/6/6/6/7/76/7/6/6/6/6/7) and the number of rings are quite different from gymnocin-A [51]. The system of 15 contiguous ether rings in gymnocin-B is the largest among the polyether compounds hitherto known. Steric hinderance of the hydroxyl groups in gymnocin-B hampered the use of Mosher reagents but determination of the absolute configuration of gymnocin-B was achieved by introduction of *p*-(meso-triphenylporphyrin)-cinnamate group (TPPcinnamate) on sterically hindered 10-, 37-hydroxyls. Conformational analysis at C-10 and C-37 positions and determination of



51 Gymnocin-A



52 Gymnocin-B

Scheme 10

the chirality at C-10 and C-37 on the basis of porphyrin/porphyrin circular dichroism exciton-coupled interaction over a large distance allowed determination of the absolute stereochemistry of gymnocin-B [52].

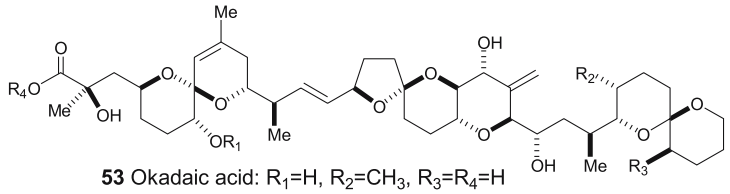
Gymnocin-A and gymnocin-B showed cytotoxicity against mouse lymphoid P388 cells at 1.3 μg/ml and 1.7 μg/ml, respectively.

5
Diarrhetic Shellfish Toxins and Related Compounds

The polyether carboxylic acid okadaic acid (OA, **53**) was first isolated from the sponge *Halichondlia okadai* and was subsequently found in the dinoflagellates *Prorocentrum* spp. and *Dinophysis* spp. [53–55]. OA and its analogs, dinophysistoxins 1–3 (DTX1–3, **54–56**) are the toxins responsible for diarrhetic shellfish poisoning (DSP) occurrences worldwide. DSP was discovered in 1976 when a mussel poisoning case occurred in northeastern Japan. DSP is a syndrome named after its predominant human symptom following the ingestion of shellfish such as mussels, scallops, or clams. The most prominent pharmacological property of okadaic acid is its potent and specific inhibition of protein phosphatases type 2A, 1 and 2B [56, 57]. Because many biological events, including tumor promotion, are regulated by phosphorylation and dephosphorylation of signal proteins, the acids are extensively used in biochemical studies.

DTX4–6 and OA diol esters (**57–62**) were isolated from cultured *Prorocentrum* spp. [58–60]. The rapid hydrolysis of the esters by esterases suggests that these less toxic ester analogs are probably the form of toxin stored within, and excreted from, the dinoflagellate cell.

Pectenotoxins (PTXs) are a family of polyether macrolide compounds isolated from scallops involved in diarrhetic shellfish poisoning events [61–63]. PTX1 (**63**) was first characterized as a unique polyether macrolide using X-ray crystallography. The absolute configuration of PTX6 and its analogs were determined based on the ^{1}H NMR data of the PGME-amide [64]. Structural alterations among them reside at C43, where all stages of oxidation from methyl to carboxylic acid are found (PTX2 (**64**), CH_3; PTX1, CH_2OH; PTX3 (**65**), CHO; and PTX6 (**66**), COOH), and stereostructure at C7, where PTX1, PTX2, PTX3, and PTX6 have *R* configuration, while PTX4 (**67**) and PTX7 (**68**) have *S* configuration. PTX2 was found in the genus *Dinophysis* that produces OA and dinophysistoxins. The oxidation at C43 occurs in the hepatopancreas of shellfish. PTX2 was first reported as a hepatotoxin, but drew renewed attention because of its selective as well as very potent cytotoxicity against human lung, colon, and breast cancer cell lines [65]. The lactone ring-opened analogs, PTX2 seco acid (**69**) and 7-*epi*-PTX2 seco acid (**70**) were isolated from dinoflagellates and shellfish [66]. Neither PTX2 seco acid nor 7-*epi*-PTX2 seco acid showed cytotoxicity against KB cells at a dose



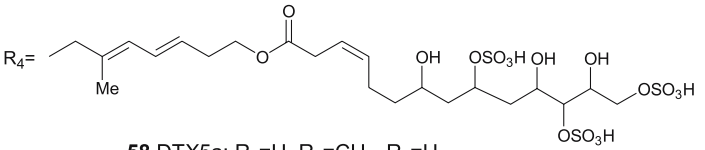
53 Okadaic acid: R_1=H, R_2=CH_3, R_3=R_4=H

54 Dinophysistoxin-1: R_1=H, R_2=R_3=CH_3, R_4=H

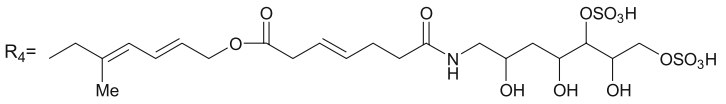
55 Dinophysistoxin-2: R_1=R_2=H, R_3=CH_3, R_4=H

56 Dinophysistoxin-3: R_1=acyl, R_2=R_3=CH_3, R_4=H

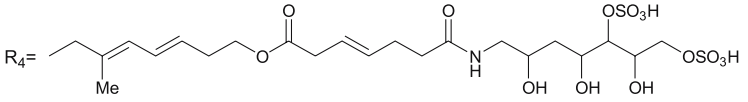
57 DTX4: R_1=H, R_2=CH_3, R_3=H



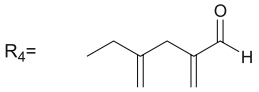
58 DTX5a: R_1=H, R_2=CH_3, R_3=H



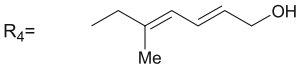
59 DTX5b: R_1=H, R_2=CH_3, R_3=H



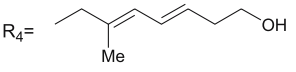
60 DTX6: R_1=H, R_2=CH_3, R_3=H



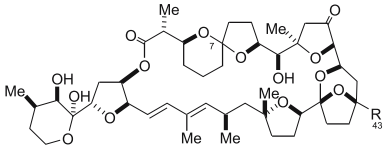
61 OA diol ester: R_1=H, R_2=CH_3, R_3=H



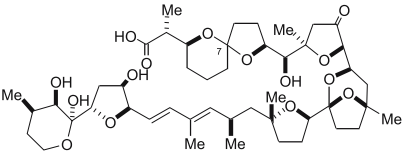
62 OA diol ester: R_1=H, R_2=CH_3, R_3=H



Scheme 11

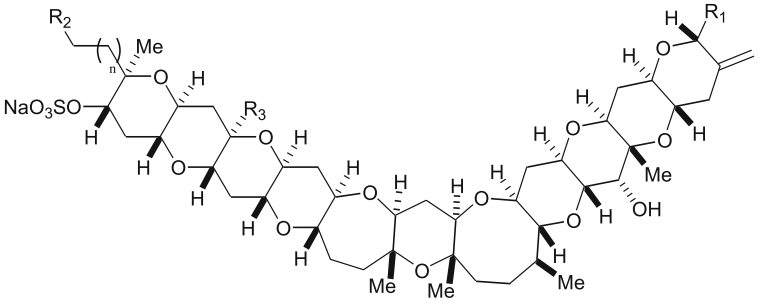


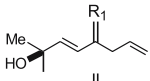
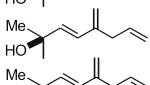
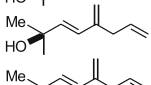
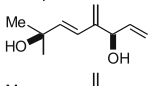
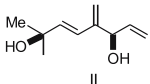
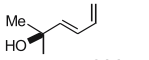
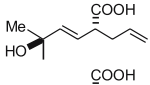
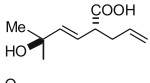
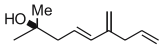
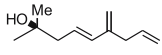
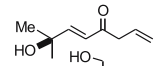
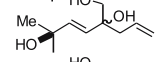
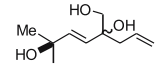
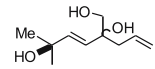
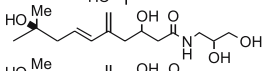
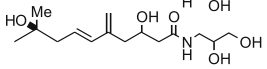
	R	C-7
63 Pectenotoxin-1:	CH_2OH	*R*
64 Pectenotoxin-2:	CH_3	*R*
65 Pectenotoxin-3:	CHO	*R*
66 Pectenotoxin-6:	COOH	*R*
67 Pectenotoxin-4:	CH_2OH	*S*
68 Pectenotoxin-7:	COOH	*S*



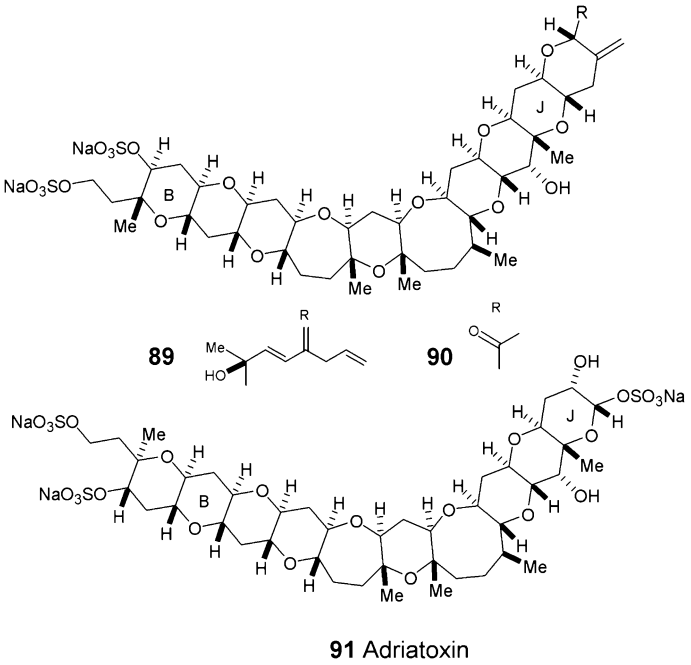
	C-7
69 PTX2 seco acid	*R*
70 7-*epi*-PTX2 seco acid	*S*

Scheme 12



	R_1	R_2	R_3	n
71 Yessotoxin (YTX)		OSO_3Na	H	1
72 homoYTX		OSO_3Na	H	2
73 1-desulfoYTX		OH	H	1
74 45-hydroxyYTX		OSO_3Na	H	1
75 45-hydroxyhomoYTX		OSO_3Na	H	2
76 45,46,47-trinorYTX		OSO_3Na	H	1
77 carboxyYTX		OSO_3Na	H	1
78 carboxyhomoYTX		OSO_3Na	H	2
79 heptanor-41-oxoYTX		OSO_3Na	H	1
80 heptanor-41-oxohomoYTX		OSO_3Na	H	2
81 41a-homoYTX		OSO_3Na	H	1
82 9-methyl-41a-homoYTX		OSO_3Na	Me	1
83 55-nor-43-oxoYTX		OSO_3Na	H	1
84 44,55-dihydroxyYTX		OSO_3Na	H	1
85 44,55-dihydroxy-41a-homoYTX		OSO_3Na	H	1
86 44,55-dihydroxy-9-methyl-41a-homoYTX		OSO_3Na	Me	1
87		OSO_3Na	H	1
88		OSO_3Na	Me	1

Scheme 13



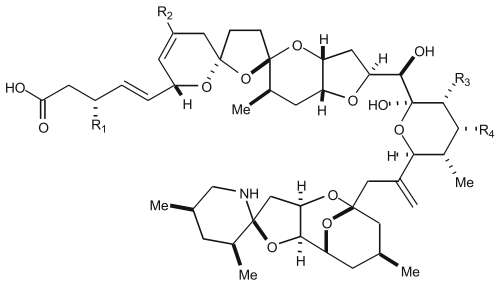
Scheme 14

1.8 μg/ml, while PTX2 did at 0.05 μg/ml, indicating the importance of the cyclic structure of **64** to exert the potency.

Yessotoxin (YTX, **71**) was first isolated from the scallop, *Patinopecten yessoensis*, cultured at Mutsu Bay, Japan, and its structure, including the absolute configuration, has been elucidated by extensive NMR analysis [67–69]. The biogenetic origin of YTX has been questioned over a long period. The dinoflagellates, *Protoceratium reticulatum* and *Linglodinium polyedrum*, were identified as the biogenetic origin of YTX [70–73]. So far more than 20 analogs (**71–88**) have been isolated from shellfish and dinoflagellates [74–84]. Ring truncated analogs (**89–91**) have been also found in shellfish and dinoflagellates [81, 85]. Although YTX shows high toxicity (100 μg/kg) to mice via ip injection, it is almost nontoxic via oral administration.

6
Azaspiracid Poisoning Toxins

Azaspiracid poisoning (AZP) was first reported in 1995 as a new toxic syndrome for a series of human intoxications in Europe, following the consumption of bivalves. The implicated toxins, azaspiracids (**92–96**), are polyethers with unprecedented structural features. Their structures are characterized



	R_1	R_2	R_3	R_4
92 Azaspiracid-1:	H	H	Me	H
93 Azaspiracid-2:	H	Me	Me	H
94 Azaspiracid-3:	H	H	H	H
95 Azaspiracid-4:	OH	H	H	H
96 Azaspiracid-5:	H	H	H	OH

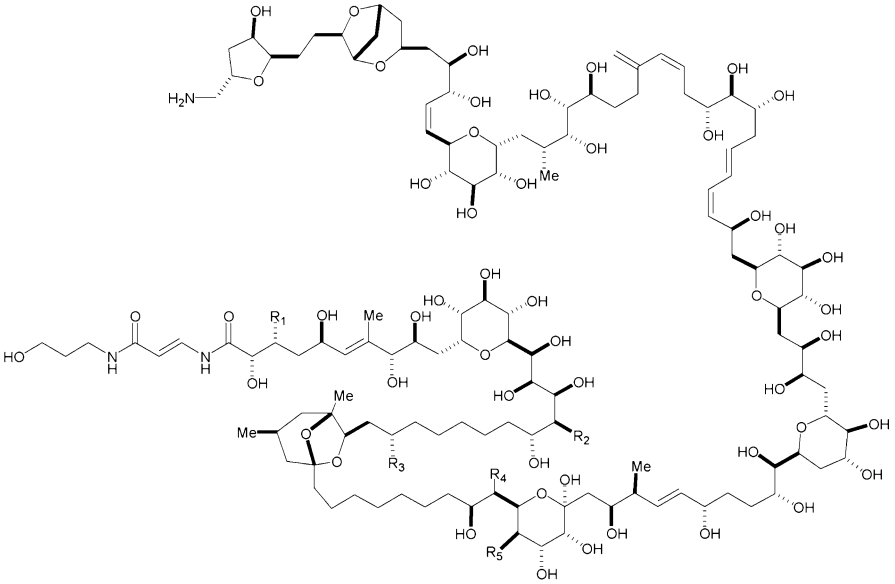
Scheme 15

by a trispiro ring assembly, an unusual azaspiro ring structure fused with a 2, 9-dioxabicyclo[3.3.1] nonane ring and a carboxylic acid [86–88]. Studies toward total synthesis by Nicolaou and co-workers revealed that the initial published structures were incorrect and they have since been revised [89, 90]. Toxicological studies have indicated that azaspiracids can induce multiple organ damage in mice with the several effects in the small intestine and liver and necrosis of T and B lymphocytes in the spleen, thymus, and Peyer's patches. Most importantly, repeated injection of azaspiracid caused lung tumor in some mice. Therefore, they are probably more dangerous than previously known classes of shellfish toxins [91].

Azaspiracid-1 increases cytosolic calcium and cAMP levels dependent on both the release of calcium from intracellular Ca^{2+} pools and the influx from extracellular media through Ni^{2+}-blockable channels.

7
Palytoxin and Zooxanthellatoxin

Palytoxin (**97**, $C_{129}H_{223}N_3O_{54}$) is one of the best-known natural products first isolated from the zoanthid *Palythoa toxica* [92, 93]. Its biogenetic origin has been questioned for a long time because palytoxin has been found in algae, crabs, herbivorous fish, and a surgeon fish, and the toxin content markedly fluctuates both seasonally and regionally. Ostreocins were isolated from the marine dinoflagellate *Ostreopsis siamensis*. Their NMR spectra resembled those of palytoxin [94]. Thus, this dinoflagellate was presumed to be one of the biogenetic origins of palytoxin. The structure of ostreocin D (**98**, $C_{127}H_{219}N_3O_{53}$), a major component in this strain, was determined to be 42-hydroxy-3,26-didemethyl-19,44-dideoxypalytoxin by detailed 2D NMR analyses of intact ostreocin D and its ozonolysis products [95]. The structure of ostreocin D deduced from the NMR study was successfully verified by FAB MS/MS experiments after introducing 2-sulfobenzoic anhydride into the terminal amine or hydroxyl groups [96]. Palytoxin has been proposed to convert Na^+/K^+ ATPase into a cation-selective ion channel.



	R_1	R_2	R_3	R_4	R_5
97 Palytoxin	Me	OH	Me	H	OH
98 Ostreocin D	H	H	H	OH	H

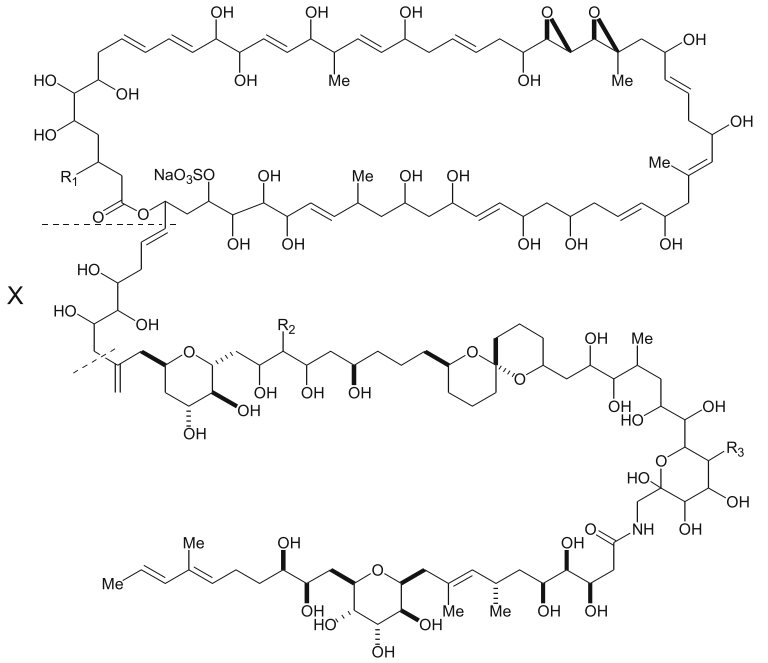
Scheme 16

Zooxanthellatoxins-A (**99**) and -B (**100**) were isolated as vasoconstrictive substances from a symbiotic marine dinoflagellate *Symbiodinium* sp. belonging to zooxanthella [97, 98]. The structure of zooxanthellatoxin-A is characterized by the presence of 15 double bonds, 42 hydroxyl groups, one sulfate, five ether rings, and a huge lactone ring. The 62-member lactone ring is the largest reported to date.

8
Polyether Imine Compounds

Prorocentrolide (**101**) has been isolated from the toxic dinoflagellate *Prorocentrum lima*, the producer of okadaic acid [99]. The structure was determined to be a macrocycle formed a C49 fatty acid that also containing a C27 macrolide and a hexahydroisoquinoline. An analog, prorocentrolide B (**102**), was isolated as a fast-acting toxin from *P. maculosum* [100].

Spiro-prorocentrimine (**103**) was also isolated from *P. lima* collected in Taiwan [101]. Spiro-prorocentrimine is characterized by a macrocyclic lactone possessing a spiro-linked cyclic imine with an *ortho*, *para*-disubstituted 3′-cyclohexene. Its mouse lethality (2.5 mg/kg) is less toxic than that of pro-



99 Zooxanthellatoxin-A: R_1=H, R_2=OH, R_3=OH

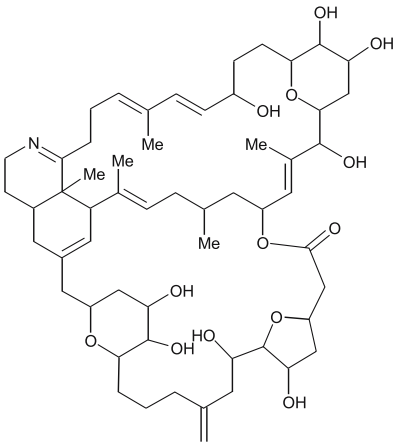
100 Zooxanthellatoxin-B: R_1=OH, R_2=H, R_3=H X=

Scheme 17

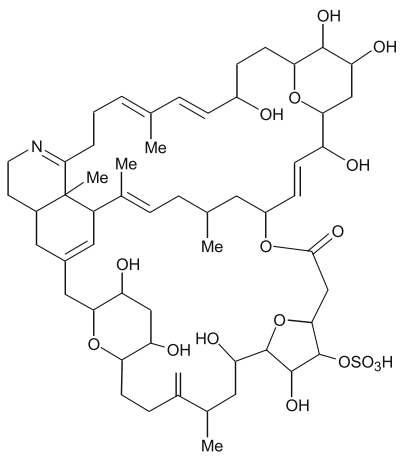
rocentrolide (0.4 mg/kg). Prorocentrolide and spiro-prorocentroimine may have some aspects of biosynthesis in common.

The adductor muscle of the shellfish *Pinna* sp. is eaten in Japan and China. Food poisoning resulting from its ingestion occurs frequently. Pinnatoxin A (**104**) was isolated from the Okinawan bivalve *P. muricata* as a major cause of food poisoning. The pinnatoxins are unique polyether carbocyclic imine compounds composed of a 6,7-spiroring, a 5,6-bicyclo ring, and a 6,5,6-trispiroketal ring [102]. Its analogs, pinnatoxins B (**105**) and C (**106**) were isolated from *P. muricata*, and pteriatoxins A (**107**), B (**108**) and C were isolated from the Okinawan bivalve *Pteria penguin* [103, 104]. The structure of pteriatoxin A was determined using only 20 μg of sample by NMR experiments. Acute toxicity of these compounds in mouse was found to be 180, 22, 100, and 8 μg/kg, respectively. Biological activity of pinnatoxin A has been suggested to possess novel Ca^{2+} channel-activating properties [105].

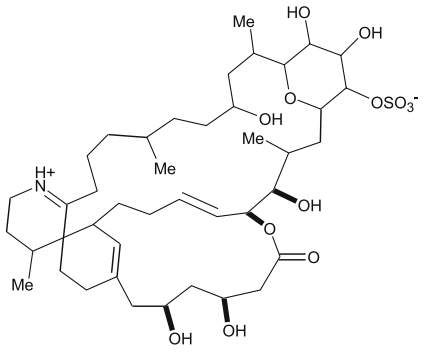
Spirolides A–D (**109–113**) are polyether imine macrolides produced by the dinoflagellate *Alexandrium ostenfeldii* [106–108]. They were first isolated



101 Prorocentrolide



102 Prorocentrolide B

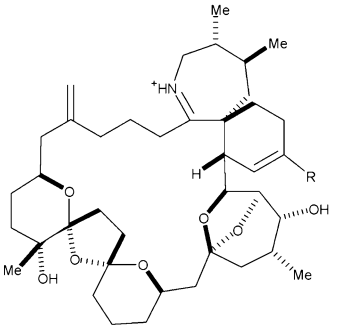


103 Spiro-prorocentrimine

Scheme 18

as toxic substances in extracts of shellfish collected in Canada, and possess structures similar to the pinnatoxins.

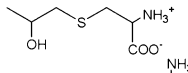
Gymnodimine (**114**) was isolated as a toxic substance from oysters and is unique in containing butenolide, a 16-membered carbocycle, and cyclic imine moieties. The structure of gymnodimine was determined by extensive 2D NMR experiments and its absolute configuration was elucidated by X-ray crystallography [109, 110]. Gymnodimine is a complex pentacyclic derivative incorporating a C24 carboxylic acid and a fused azine. The biogenetic origin of gymnodimine was determined to be the dinoflagellate *Karenia selliformis*. Two analogs, gymnodimine-B (**115**) and gymnodimine-C (**116**), were also isolated from the dinoflagellate [111, 112].

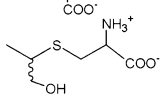


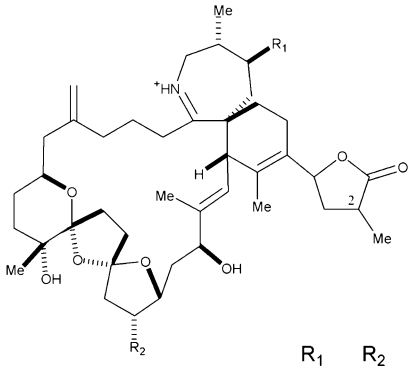
104 Pinnatoxin A: R=COO^-

105 Pinnatoxin B: R= 

106 Pinnatoxin C: R= 

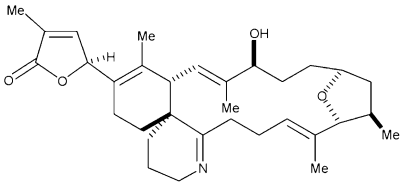
107 Pteriatoxin A :R= 

108 Pteriatoxins B and C: R= 

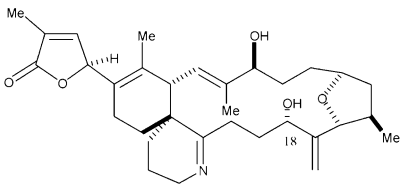


			R_1	R_2
109	Spirolide A	$\Delta^{2,3}$	H	Me
110	Spirolide B		H	Me
111	Spirolide C	$\Delta^{2,3}$	Me	Me
112	Spirolide D		Me	Me
113	13-deMethyl-C	$\Delta^{2,3}$	Me	H

Scheme 19



114 Gymnodimine

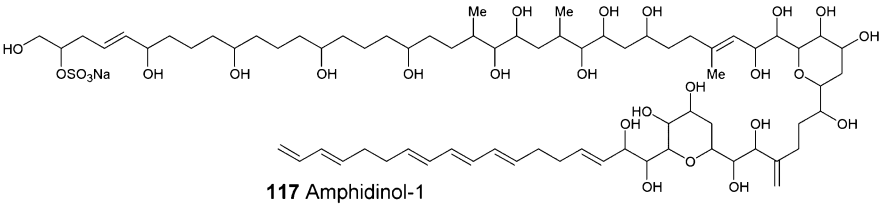


115 Gymnodimine B
116 Gymnodimine C (C-18 isomer)

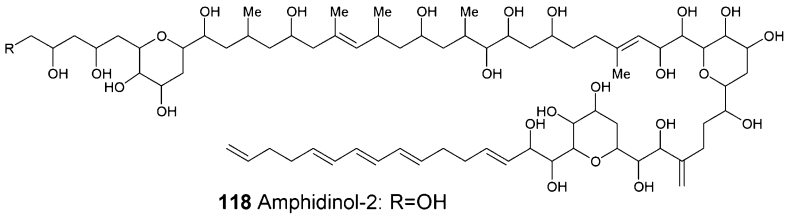
Scheme 20

9
Other Marine Polyether Compounds

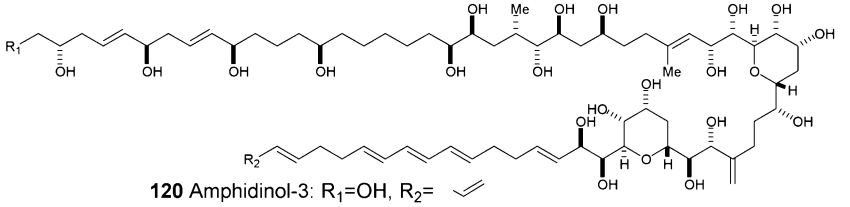
The genus *Amphidinium* is also a rich source of bioactive compounds, producing antifungal and hemolytic compounds such as amphidinols (**117–128**) [113–118], and the closely related compounds luteophanols A–C (**129–131**) [119, 120], and lingshuiols A–B (**132, 133**) [121], and cytotoxic macrolide, amphidinolides [122]. The amphidinols have common structural features characterized by two ether rings, polyolefins including a conjugated



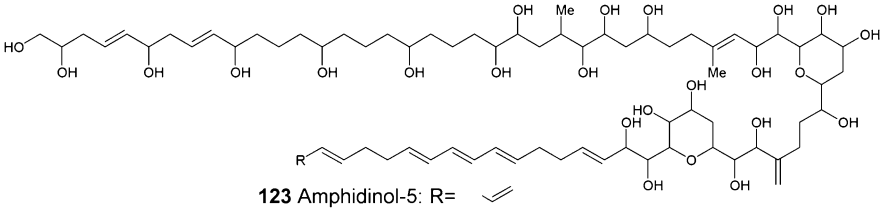
117 Amphidinol-1



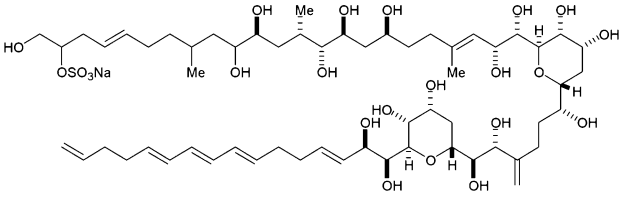
118 Amphidinol-2: R=OH
119 Amphidinol-11: R=OSO_3Na



120 Amphidinol-3: R_1=OH, R_2=
121 Amphidinol-4: R_1=OH, R_2=H
122 Amphidinol-12: R_1=OSO_3Na, R_2=H

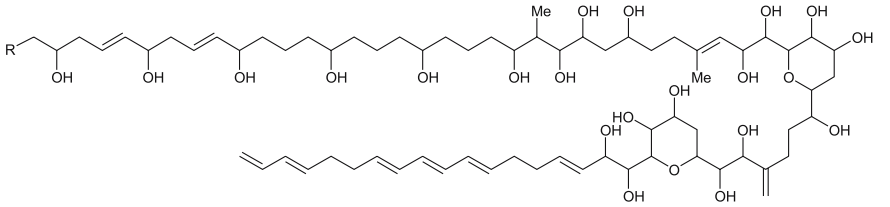


123 Amphidinol-5: R=
124 Amphidinol-6: R=H

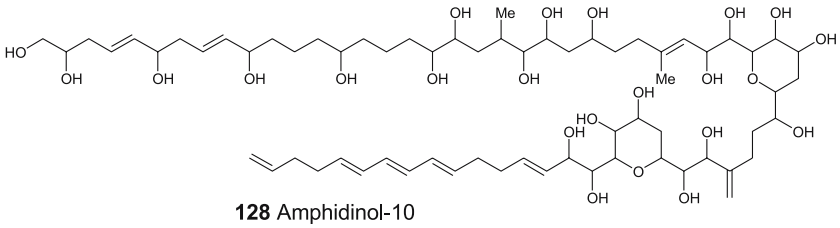


125 Amphidinol-7

Scheme 21



126 Amphidinol-9: R=OH
127 Amphidinol-13: R=OSO_3Na



128 Amphidinol-10

Scheme 22

triene and an exomethylene, a branching methyl, an olefinic methyl, and polyhydroxy groups.

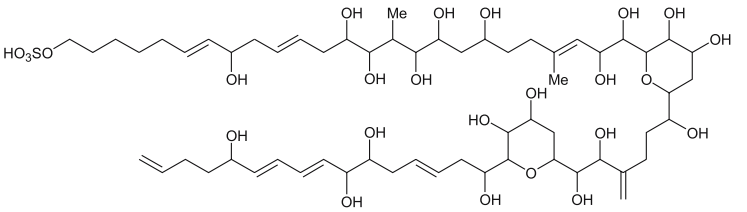
The mode of action of amphidinols can be accounted for by their membrane permeabilizing actions. The polyene and polyhydroxy moieties play important roles in binding lipid bilayer membrane and in forming ion-permeable pore/lesion across membrane. The central part involving two tetrahydropyran rings comprises a large hydrophilic part with a hairpin conformation and the polyolefin moiety penetrates deep into membrane. The size of the pore formed in the membrane is influenced by the polyhydroxy region [123].

Polycavernoside A (**134**) was isolated from the seaweed *Gracilaria* sp. that caused fatal intoxication in Guam [124, 125]. The macrocycle trioxatridecane aglycone, is similar to the trioxadodecane moiety found in the aplysiatoxins. The methylated fucose of polycavernoside suggests an algal origin. The total synthesis of polycavernoside A has been accomplished by three groups [126–128].

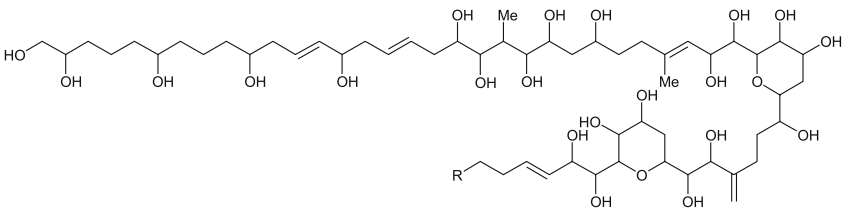
Goniodomin A (**135**), a polyether macrolide isolated from *Goniodoma psuedogoniaulax*, inhibited growth of *Mortierella ramannianus* and *Candida albicans* at 0.5 μg/ml [129].

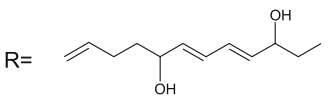
Wright et al. isolated a sulfated macrolide, hoffmanniolide (**136**), from *Prorocentrum hoffmannianum*. Although the structure of hoffmanniolide is similar to those of the cytotoxic macrolide amphidinolides, hoffmanniolide does not show any biological activities [130].

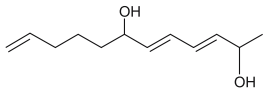
Prorocentin (**137**) was isolated from *Prorocentrum lima* collected in Taiwan [131]. Prorocentin is characterized by a C35 polyeketide chain with a 6/6/6-trans-fused/spiro-linked tricyclic ether rings, a furan ring, and an



129 Luteophanol A

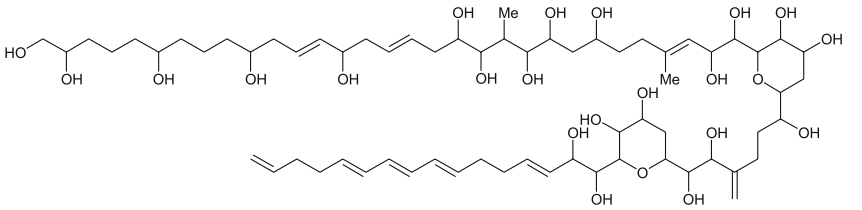




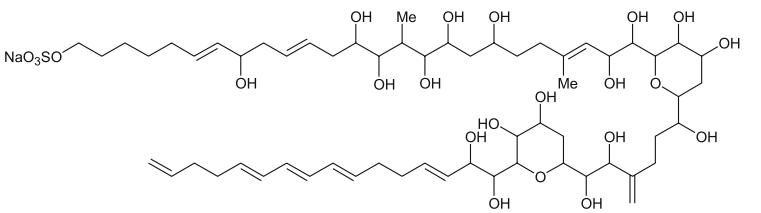


130 Luteophanol B

131 Luteophanol C



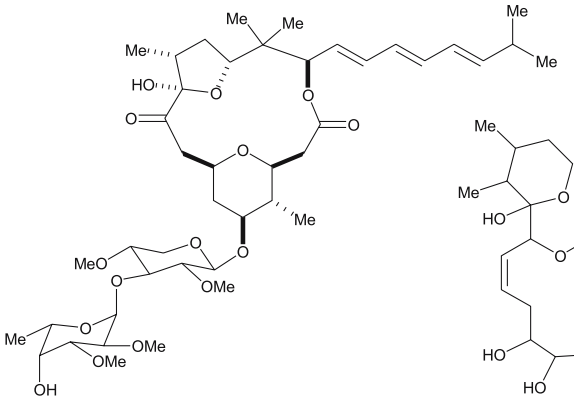
132 Lingshuiol A



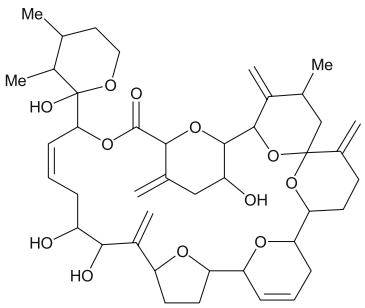
133 Lingshuiol B

Scheme 23

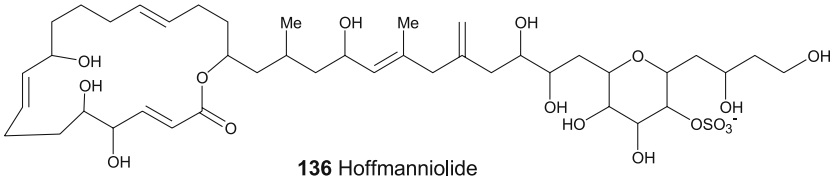
all-trans triene moiety. Prorocentin shows inhibitory activity against human colon adenocarcinoma DLD-1 and human malignant melanoma RPMI7951 at 16.7 and 83.6 μg/ml, respectively.



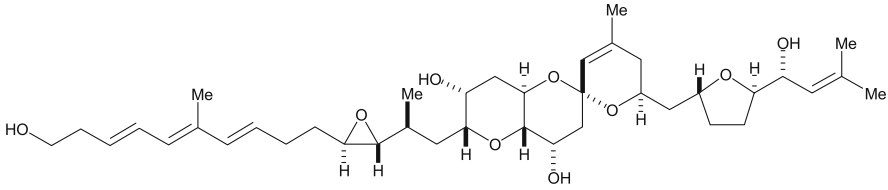
134 Polycavernoside-A



135 Goniodomin-A



136 Hoffmanniolide



137 Prorocentin

Scheme 24

10 Conclusion

A remarkable variety of polyether compounds with potent and specific activity have been found in phytoplankton and marine animals. Although the number of polyether compounds is increasing, the extremely limited availability of these compounds from natural sources has hampered detailed biological studies, including the precise biochemical mode of action. Recent progress in the total synthesis of these intriguing compounds will help to elucidate the molecular mode of action.

References

1. Lin Y-Y, Risk M, Ray MS, Van Engen D, Clardy J, Golik J, James JC, Nakanishi K (1981) J Am Chem Soc 103:6773
2. Nicolaou KC, Rutjes FPJT, Theodorakis EA, Tiebes J, Sato M, Untersteller E (1995) J Am Chem Soc 117:1173
3. Matsuo G, Kawamura K, Hori N, Matsukura H, Nakara T (2004) J Am Chem Soc 126:14374
4. Kadota I, Takamura H, Nishi H, Yamamoto Y (2005) J Am Chem Soc 127:9246
5. Shimizu Y, Chou H-N, Bando H, Van Duyne G, Clardy J (1986) J Am Chem Soc 108:514
6. Baden DG, Bourdelais JB, Jacocks H, Michelliza S, Narr J (2005) Environ Health Perspect 113:621
7. Catteral WA (1992) Physiol Rev 72:15
8. McFarren EF, Tanabe H, Silva EJ, Wilson WB, Campbell JE, Lewis KH (1965) Toxicon 3:111
9. Morris PD, Campbell DS, Taylor TJ, Freeman JI (1991) Am J Pub Health 81:471
10. Ishida H, Nozawa A, Totoribe K, Muramatsu N, Nukaya H, Tsuji K, Yamaguchi K, Yasumoto T, Kaspar H, Berkett N, Kosuge T (1995) Tetrahedron Lett 36:725
11. Morohashi A, Satake M, Murata K, Naoki H, Kaspar HF, Yasumoto T (1995) Tetrahedron Lett 36:8995
12. Murata K, Satake M, Naoki H, Kaspar HF, Yasumoto T (1998) Tetrahedron 54:735
13. Morohashi A, Satake M, Naoki H, Kaspar HF, Oshima Y, Yasumoto T (1999) Nat Toxins 7:45
14. Ishida H, Nozawa A, Hamano H, Naoki H, Fujita T, Kaspar HF, Tsuji K (2004) Tetrahedron Lett 45:29
15. Prasad AVK, Shimizu Y (1989) J Am Chem Soc 111:6476
16. Bourdelais AJ, Jacocks HM, Wright JLC, Bigwarfe PM, Baden DG (2005) J Nat Prod 68:2
17. Scheuer PJ (1994) Tetrahedron 50:3
18. Murata M, Legrand AM, Ishibashi Y, Yasumoto T (1989) J Am Chem Soc 111:8929
19. Murata M, Legrand AM, Ishibashi Y, Fukui M, Yasumoto T (1990) J Am Chem Soc 112:4380
20. Satake M, Murata M, Yasumoto T (1993) Tetrahedron Lett 34:1975
21. Satake M, Ishibashi Y, Legrand AM, Yasumoto T (1996) Biosci Biochem Biotech 60:2103
22. Satake M, Fukui M, Legrand AM, Cruchet P, Yasumoto T (1998) Tetrahedron Lett 39:1197
23. Yasumoto T, Igarashi T, Legrand AM, Cruchet P, Chinain M, Fujita T, Naoki H (2000) J Am Chem Soc 122:4988
24. Lewis RJ, Vernoux JP, Brereton IM (1998) J Am Chem Soc 120:5914
25. Satake M, Morohashi A, Oguri H, Oishi T, Hirama M, Harada N, Yasumoto T (1997) J Am Chem Soc 119:11325
26. Hirama M, Oishi T, Uehara H, Inoue M, Maruyama M, Oguri H, Satake M (2001) Science 1904: Nov 30
27. Murata M, Naoki H, Iwashita T, Matsunaga S, Sasaki M, Yokoyama A, Yasumoto T (1993) J Am Chem Soc 115:2060
28. Murata M, Naoki H, Matsunaga S, Satake M, Yasumoto T (1994) J Am Chem Soc 116:7098

29. Satake M, Ishida S, Murata M, Utsumi H, Hinomoto T, Yasumoto T (1995) J Am Chem Soc 117:7019
30. Matsumori N, Nonomura M, Sasaki M, Murata M, Tachibana K, Satake M, Yasumoto T (1996) Tetrahedron Lett 37:1269
31. Sasaki M, Matsumori N, Maruyama T, Nonomura M, Murata M, Tachibana K, Yasumoto T (1996) Angew Chem Int Ed Engl 35:1672
32. Nonomura M, Sasaki M, Matsumori N, Murata M, Tachibana K, Yasumoto T (1996) Angew Chem Int Ed Engl 35:1675
33. Zheng W, DeMattei JA, Wu J-P, Duan JJ-W, Cook LR, Oinuma H, Kishi Y (1998) J Am Chem Soc 118:7946
34. Satake M, Murata M, Yasumoto T (1993) J Am Chem Soc 115:361
35. Morohashi A, Satake M, Yasumoto T (1999) Tetrahedron Lett 40:97
36. Fuwa H, Kainuma N, Tachibana K, Sasaki M (2002) J Am Chem Soc 124:14983
37. Kadota I, Takamura H, Sato K, Ohno A, Matsuda K, Satake M, Yamamoto Y (2003) J Am Chem Soc 125:11893
38. Johnson HW, Majumder U, Rainier JD (2005) J Am Chem Soc 127:848
39. Fuwa H, Kainuma N, Tachibana K, Tsukano C, Satake M, Sasaki M (2004) Chem Eur J 10:4894
40. Ito E, Suzuki-Toyota F, Toshimori K, Fuwa H, Tachibana K, Satake M, Sasaki M (2003) Toxicon 42:733
41. Ghiaroni V, Sasaki M, Fuwa H, Rossini GP, Scalera G, Yasumoto T, Pietra P, Bigiani A (2005) Toxicol Sci 85:657
42. Nagai H, Murata M, Torigoe K, Satake M, Hirota H, Yasumoto T (1992) J Am Chem Soc 114:1102
43. Nagai H, Murata M, Torigoe K, Satake M, Yasumoto T (1992) J Org Chem 57:5448
44. Sakamoto B, Nagai H, Hokama Y (1996) Phycologia 35:350
45. Morohashi A, Satake M, Nagai H, Oshima Y, Yasumoto T (2000) Tetrahedron 56:8995
46. Igarashi T, Satake M, Yasumoto T (1996) J Am Chem Soc 118:479
47. Igarashi T, Satake M, Yasumoto T (1999) J Am Chem Soc 121:8499
48. Igarashi T, Aritake S, Yasumoto T (1998) Nat Toxins 6:35
49. Satake M, Shoji M, Oshima Y, Naoki H, Fujita T, Yasumoto T (2002) Tetrahedron Lett 43:5829
50. Tsukano C, Ebine M, Sasaki M (2005) J Am Chem Soc 127:4326
51. Satake M, Tanaka Y, Ishikura Y, Oshima Y, Naoki H, Yasumoto T (2005) Tetrahedron Lett 46:3537
52. Tanaka K, Itagaki Y, Satake M, Naoki H, Yasumoto T, Nakanishi K, Berova N (2005) J Am Chem Soc 127:9561
53. Tachibana K, Scheuer PJ, Tsukitani Y, Kikuchi H, Engen DV, Clardy J, Gopichand Y, Schmitz FJ (1981) J Am Chem Soc 103:2469
54. Yasumoto T, Oshima Y, Yamaguchi M (1978) Nippon Suisan Gakkaishi 44:1249
55. Yasumoto T, Murata M, Oshima Y, Sano M, Matsumoto GK, Clardy J (1985) Tetrahedron 41:1019
56. Takai A, Murata M, Torigoe K, Isobe M, Miwskes G, Yasumoto T (1992) Biochem J 284:539
57. Sueoka E, Fujiki H (1998) In: Reguera B, Blanco J, Fernandes ML, Wyatt T (eds) Harmful Algae. Xunta de Galicia and Intergovernmental Oceanographic Commission of UNESCO; Spain, p 573
58. Hu T, Curtis JM, Walter JA, Wright JLC (1995) J Chem Soc Chem Commun 5:597
59. Hu T, Curtis JM, Walter JA, McLachlan JL, Wright JLC (1995) Tetrahedron Lett 36:9273

60. Suárez-Gomez B, Souto ML, Norte M, Fernández JJ (2001) J Nat Prod 64:1363
61. Yasumoto T, Murata M, Oshima Y, Sano M, Matsumoto GK, Clardy J (1985) Tetrahedron 41:1019
62. Murata M, Sano M, Iwashita T, Naoki H, Yasumoto T (1986) Agric Biol Chem 50:2693
63. Sasaki K, Wright JLC, Yasumoto T (1998) J Org Chem 63:2475
64. Sasaki K, Satake M, Yasumoto T (1997) Biosci Biotech Biochem 61:1783
65. Zhou ZH, Komiyama MK, Terao T, Shimada Y (1994) Nat Toxins 2:132
66. Daiguji M, Satake M, James KJ, Bishop A, MacKenzie L, Naoki H, Yasumoto T (1998) Chem Lett 7:653
67. Murata M, Kumagai M, Lee JS, Yasumoto T (1979) Tetrahedron Lett 28:5869
68. Takahashi H, Kusumi T, Kan Y, Satake M, Yasumoto T (1996) Tetrahedron Lett 37:7087
69. Morohashi A, Satake M, Oshima Y, Yasumoto T (2000) Biosci Biotechnol Biochem 64:1761
70. Satake M, MacKenzie L, Yasumoto T (1997) Nat Toxins 5:164
71. Ciminiello P, Dell'Aversano C, Fattorusso E, Forino M, Magno S, Guerrini F, Pistocchi R, Boni L (2003) Toxicon 42:7
72. Samdal IA, Naustvoll LJ, Olseng CD, Briggs LR, Miles CO (2004) Toxicon 44:75
73. Eiki K, Satake M, Koike K, Ogata T, Mitsuya T, Oshima Y (2005) Fisheries Sci 71:633
74. Satake M, Terasawa K, Kadowaki Y, Yasumoto T (1996) Tetrahedron Lett 37:5955
75. Satake M, Tubaro A, Lee JS, Yasumoto T (1997) Nat Toxins 5:107
76. Daiguji M, Satake M, Ramstad H, Aune T, Naoki H, Yasumoto T (1998) Nat Toxins 6:235
77. Ciminiello P, Fattorusso E, Forino M, Poletti R, Viviani R (2000) Eur J Org Chem 291
78. Ciminiello P, Fattorusso E, Forino M, Poletti R, Viviani R (2000) Chem Res Toxicol 13:770–774
79. Ciminiello P, Fattorusso E, Forino M, Poletti R (2001) Chem Res Toxicol 14:596
80. Ciminiello P, Dell'Aversano C, Fattorusso E, Forino M, Magno S, Poletti R (2002) Chem Res Toxicol 15:979
81. Miles CO, Wilkins AL, Jensen DJ, Cooney JM, Quilliam MA, Aasen J, MacKenzie L (2004) Chem Res Toxicol 17:1414
82. Miles CO, Wilkins AL, Hawkes AD, Selwood AI, Jensen DJ, Aasen J, Munday R, Samdal IA, Briggs LR, Beuzenberg V, MacKenzie L (2004) Toxicon 44:325
83. Miles CO, Wilkins AL, Hawkes AD, Selwood A, Jensen DJ, Munday R, Cooney JM, Beuzenberg V (2005) Toxicon 45:61
84. Finch AC, Wilkins AL, Hawkes AD, Jensen DJ, MacKenzie L, Beuzenberg V, Quilliam MA, Olseng CD, Samdal IA, Aasen J, Selwood AI, Cooney JM, Sandvik M, Miles CO (2005) Toxicon 46:160
85. Ciminiello P, Fattorusso E, Forino M, Magno S, Poletti R, Viviani R (1998) Tetrahedron Lett 39:8897
86. Satake M, Ofuji K, Naoki H, James KJ, Furey A, McMahon T, Silke J, Yasumoto T (1998) J Am Chem Soc 120:9967
87. Ofuji K, Satake M, McMahon T, Silke J, James KJ, Naoki H, Oshima Y, Yasumoto T (1999) Nat Toxins 7:99
88. Ofuji K, Satake M, James KJ, Naoki H, Oshima Y, Yasumoto T (2001) Biosci Biotechnol Biochem 65:740
89. Nicolaou KC, Vyskocil S, Koftis TV, Yamada Y, Ling T, Chen DY, Tang W, Petrovic G, Frederick MO, Li Y, Satake M (2004) Angew Chem Int Ed 43:4312
90. Nicolaou KC, Koftis TV, Vyskocil S, Koftis TV, Ling T, Yamada Y, Tang W, Frederick MO (2004) Angew Chem Int Ed 43:4318

91. Ito E, Satake M, Ofuji K, Higashi M, Harigaya K, McMahon T, Yasumoto T (2002) Toxicon 40:193
92. Uemura D, Ueda K, Hirata Y (1981) Tetrahedron Lett 22:2781
93. Moore RE, Bartolini GJ (1981) J Am Chem Soc 103:2491
94. Usami M, Satake M, Ishida S, Inoue A, Kan Y, Yasumoto T (1995) J Am Chem Soc 117:5389
95. Ukena T, Satake M, Usami M, Oshima Y, Fujita T, Naoki H, Kan Y, Yasumoto T (2001) Biosci Biotechnol Biochem 65:2585
96. Ukena T, Satake M, Usami M, Oshima Y, Fujita T, Naoki H, Yasumoto T (2002) Rapid Mass Commun Spectro 16:2387
97. Nakamura H, Asari T, Murai A, Kan Y, Kondo T, Yoshida K, Ohizumi Y (1995) J Am Chem Soc 117:550
98. Nakamura H, Asari T, Fujimaki K, Maruyama K, Murai A, Ohizumi Y, Kan Y (1995) Tetrahedron Lett 36:7255
99. Torigoe K, Murata M, Yasumoto T (1988) J Am Chem Soc 110:7876
100. Hu T, deFreitas ASW, Curtis JM, Oshima Y, Walter JA, Wright JLC (1996) J Nat Prod 59:1010
101. Lu CK, Lee G-H, Huang R, Chou H-N (2001) Tetrahedron Lett 42:1713
102. Uemura D, Chou T, Haino T, Nagatsu A, Fukuzawa S, Zheng S, Chen H (1995) J Am Chem Soc 117:1155
103. Takada N, Umemura N, Suenaga K, Chou T, Nagatsu A, Haino T, Yamada K, Uemura D (2001) Tetrahedron Lett 42:3491
104. Takada N, Umemura N, Suenaga K, Uemura D (2001) Tetrahedron Lett 42:3495
105. Zheng SZ, Huang FL, Chen SC, Tan XF, Zuo JB, Peng J, Xie RW (1990) Chin J Mar Drugs 33:33
106. Hu T, Curtis JM, Walter JA, Wright JLC (1995) J Chem Soc Chem Commun: 2159
107. Hu T, Burton IW, Cembella A, Curtis JM, Quilliam MA, Walter JA, Wright JLC (2001) J Nat Prod 64:308
108. Falk M, Burton IW, Hu T, Walter JA, Wright JLC (2001) Tetrahedron 57:8659
109. Seki T, Satake M, Mackenzie L, Kaspar HF, Ysumoto T (1995) Tetrahedron Lett 36:7093
110. Stewart M, Blunt JW, Munro MHG, Robinson WT, Hannah DJ (1997) Tetrahedron Lett 38:4889
111. Miles CO, Wilkins AL, Stirling DJ, MacKenzie AL (2000) J Agri Food Chem 48:1373
112. Miles CO, Wilkins AL, Stirling DJ, MacKenzie AL (2003) J Agri Food Chem 51:4838
113. Satake M, Murata M, Fujita T, Naoki H, Yasumoto T (1991) J Am Chem Soc 113:9859
114. Paul GK, Matsumori N, Murata M, Tachibana K (1995) Tetrahedron Lett 36:6279
115. Paul GK, Matsumori N, Konoki K, Murata M, Tachibana K (1997) J Mar Biotechnol 5:124
116. Murata M, Matsuoka S, Matsumori N, Paul GK, Tachibana K (1999) J Am Chem Soc 121:870
117. Echigoya R, Rhodes L, Oshima Y, Satake M (2005) Harmful Algae 4:383
118. Morsy N, Matsuoka S, Houdai T, Matsumori N, Adachi S, Murata M, Iwashita T, Fujita T (2005) Tetrahedron 61:8606
119. Doi Y, Ishibashi M, Nakamichi H, Kosaka T, Ishikawa T, Kobayashi J (1997) J Org Chem 62:3820
120. Kubota T, Tsuda M, Doi Y, Takahashi A, Nakamichi H, Ishibashi M, Fukushi E, Kawabata J, Kobayashi J (1998) Tetrahedron 54:14455
121. Haung X-C, Zhao D, Guo Y-W, Wu H-M, Trivellone E, Cimino G (2004) Tetrahedron Lett 45:5501

122. Kobayashi J, Tsuda M (2004) Nat Prod Rep 21:77
123. Houdai T, Matsuoka S, Morsy N, Matsumori N, Satake M, Murata M (2005) Tetrahedron 61:2795
124. Yotsu-Yamashita M, Haddock RL, Yasumoto T (1993) J Am Chem Soc 115:1147
125. Yotsu-Yamashita M, Seki T, Paul VJ, Naoki H, Yasumoto T (1995) Tetrahedron Lett 36:5563
126. Fujiwara K, Murai A, Yotsu-Yamashita M, Yasumoto T (1998) J Am Chem Soc 120:10770
127. Paquette LA, Barriault L, Pissarnitski D, Johnston JN (2000) J Am Chem Soc 122:619
128. Blakemore PR, Browder CC, Hong J, Lincoln CM, Nagornyy PA, Robarge LA, Wardrop DJ, White JD (2005) J Org Chem 70:5449
129. Murakami M, Makabe K, Yamaguchi K, Konosu S (1988) Tetrahedron Lett 29:1149
130. Hu T, Curtis JM, Walter JA, Wright JLC (1999) Tetrahedron Lett 40:3977
131. Lu C-K, Chou H-N, Lee C-K, Lee T-H (2005) Org Lett 7:3893

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Spectroscopic Study of the Structure of Zetekitoxin AB

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Abstract Zetekitoxin (former name: atelopidtoxin) was reported by Mosher and colleagues in 1969 as a potent, water-soluble, guanidinium toxin found in extracts of skin from the brightly colored Panamanian golden frog *Atelopus zeteki*. We reported the possible structure of zetekitoxin AB in 2004 as a novel saxitoxin analog. We also reported that zetekitoxin AB was an extremely potent sodium channel blocker. In this review, the supplemental spectral data of zetekitoxin AB, with those of saxitoxin for comparison, are presented to support the proposed structure of zetekitoxin AB.

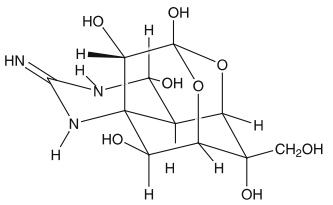
Keywords Frog · Mass spectrometry · NMR spectroscopy · Saxitoxin · Zetekitoxin

Abbreviations

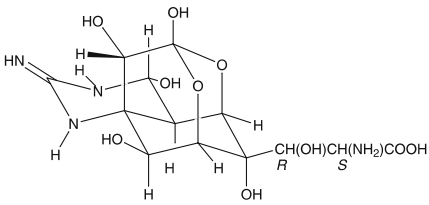
TTX	tetrodotoxin
ZTX AB	zetekitoxin AB
STX	saxitoxin
GTX	gonyautoxin
ESI/TOF	electrospray ionization/time of flight
CID	collision-induced dissociation
MS	mass spectrometry
IR	infra red

1 Introduction

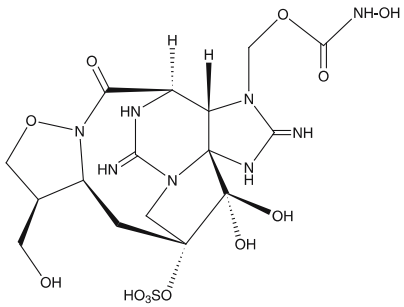
Since 1964 it has been thought that tetrodotoxin (TTX, **1**, Fig. 1) [1–3] occurred only in puffer fish and in newts of the family Salamandridae, and *Taricha trosa, Taricha rivularis*, and *Tarich granulosa* were found to be the most toxic species [4, 5]. However, in 1969, Mosher and colleagues reported the presence of a potent, water-soluble, guanidinium toxin in extracts of skin



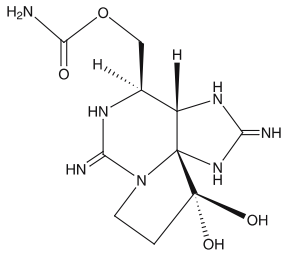
tetrodotoxin (TTX, **1**)



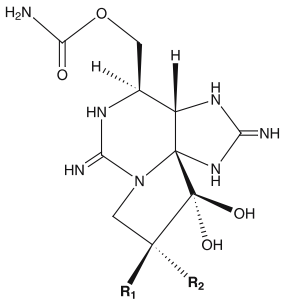
chiriquitoxin (**2**)



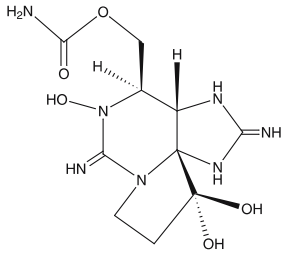
zetekitoxin AB (ZTX AB, **3**)



saxitoxin (STX, **4**)



gonyautoxin-2 (GTX-2, **5**) R_1=H, R_2=OSO_3H
gonyautoxin-3 (GTX-3, **6**) R_1=OSO_3H, R_2=H



neosaxitoxin (neoSTX, **7**)

Fig. 1 The structures of tetrodotoxin, saxitoxin, and their analogs

from the brightly colored Panamanian golden frog *Atelopus zeteki* [6]. This toxin was named atelopidtoxin at this time, and renamed zetekitoxin (ZTX) later. ZTX was indicated to occur in only *A. zeteki*. In 1975, they identified TTX as the major alkaloid of the frog *Atelopus varius* from Costa Rica, and they also found another guanidinium toxin, chiriquitoxin (**2**) as the major alkaloid of *Atelopus chiriquiensis* [7]. The structure of chiriquitoxin (Fig. 1) was determined by us as a TTX analog in 1990 [8]. In 1977, Mosher et al. reported purification of two components of zetekitoxins [9]. One was the minor, less toxic component (ZTX C) which had an LD_{50} of 80 μg/kg (i.p., mouse), and the other was the major, more toxic component (ZTX AB) (**3**) which had an LD_{50} of 11 μg/kg (i.p., mouse). In their studies, ZTXs were chemically and pharmacologically distinguished from TTX and saxitoxin (STX, **4**). STX is the toxic principle of paralytic shellfish poisoning [10]. The structure of ZTXs remained unknown for more than 30 years, partly because of the designation of the frog as an endangered species. In 2004, we reported the possible structure of ZTX AB possessing the carbon skeleton of STX deduced from spectroscopic data [11]. Further, Dudley et al. clarified that ZTX AB was an extremely potent sodium channel blocker [11]. This was the first finding of an STX analog in Amphibia. In this review, the supplemental spectral data of ZTX AB, with those of STX for comparison, are presented to support the proposed structure of ZTX AB (see also [12, 13]).

2 Purification

In 1986, ZTX AB was purified by Daly and Kim from the skin of *A. zeteki* guided by mouse bioassay. The toxin was extracted from the skin of *A. zeteki* with H_2O, and then with AcOH – H_2O (2 : 98, v/v). The homogenate was dialyzed (30 000 MW, cutoff) against H_2O, and the toxin was purified by gel filtration columns, Bio-Gel P-2, and then, TSK-gel G2000PW. The purified ZTX AB was applied to 270 MHz ^{1}H NMR spectroscopic analysis (Fig. 2B) in 1986 by Daly and Kim and was then lyophilized and stored at – 80 °C until 1999. In 1999, the ^{1}H NMR spectrum of this ZTX AB was measured with a 600 MHz spectrometer (Inova 600, Varian) (Fig. 2A). The rough consistency of this spectrum (Fig. 2A) compared with that measured in 1986 (Fig. 2B) and the unchanged LD_{50} to mice after storage suggested that ZTX AB survived during its long storage. This ZTX AB (approximately 0.3 mg) was used for the structural study [11]. Toxicity and chemical properties of STX, ZTX AB, and TTX are summarized in Table 1.

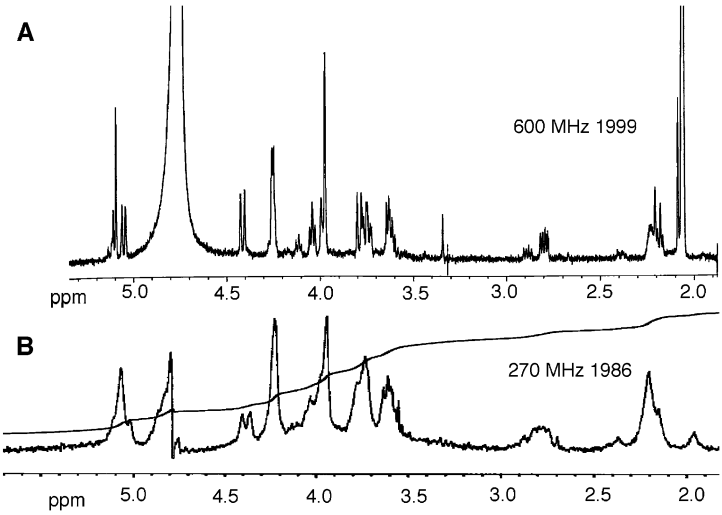


Fig. 2 ^{1}H NMR spectra of zetekitoxin AB. **A** 600 MHz spectrum in CD_3COOD/D_2O, 4 : 96, v/v, measured in 1999. **B** 270 MHz spectrum in D_2O, measured in 1986 by Daly and Kim. The spectrum was provided by Kim

Table 1 Toxicities and chemical properties of STX, ZTX AB, and TTX

	STX	ZTX AB	TTX
Toxicity μg/kg (mice, LD_{50} i.p.)	10	11 (ZTX C: 80) (by Mosher et al. [9])	10
Rf on TLC (Silica gel 60) py – EtOAc – AcOH – H_2O (15 : 7 : 3 : 6)	0.36	0.57	0.50
Detection on TLC (UV 365 nm, approximately 1 μg)			
1% H_2O_2, Heat	Fluorescence	Fluorescence	Not detected
10% KOH/MeOH, Heat	Not detected	Not detected	Fluorescence
10% $FeCl_3$/EtOH	Not detected	Orange color	Not detected

3 ESI-MS Spectra

The molecular weight of ZTX AB was determined to be 552 by the molecular ions that appeared at m/z 553 $[M + H]^+$ in the positive ion mode (Fig. 3A) of the electrospray ionization/time of flight (ESI/TOF) MS spectrum (Mariner, Applied Biosystems), and at m/z 551 $[M - H]^-$ in the negative

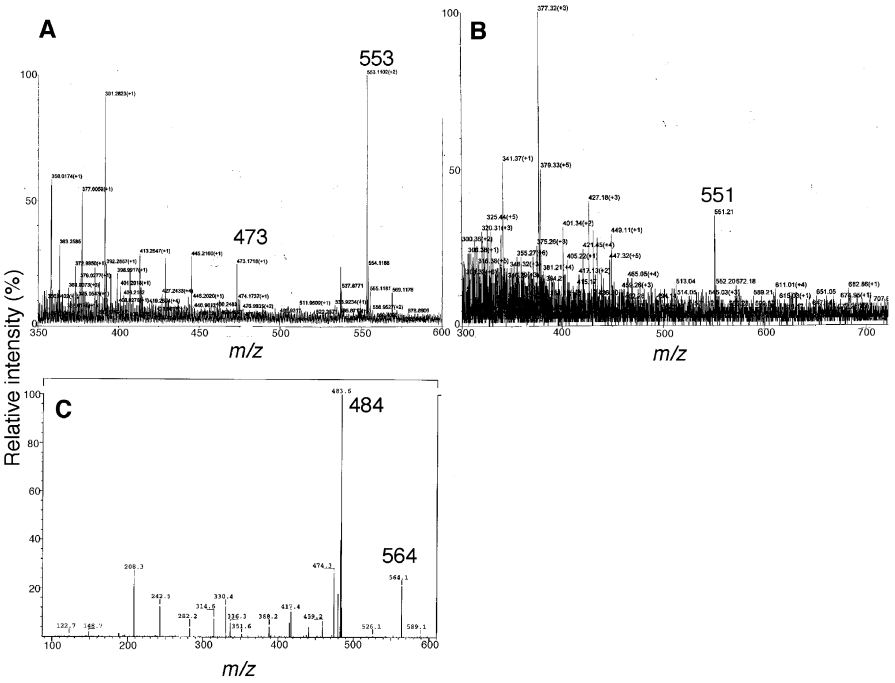


Fig. 3 ESI-MS spectra of zetekitoxin AB. **A** ESI-TOF MS spectrum (Mariner, positive, AcOH – MeOH – H_2O 1 : 50 : 50, v/v). **B** ESI-TOF MS spectrum (Mariner, negative, AcOH – MeOH – H_2O 1 : 50 : 50, v/v), **C** ESI-MS/MS spectrum (TSQ700, positive, precursor ion m/z 564, CD_3OD – D_2O 50 : 50, v/v)

ion mode (Fig. 3B). In the positive ion mode spectrum, an ion at m/z 473 corresponding to $[M - SO_3 + H]^+$ was also seen suggesting the presence of a sulfate ester. High resolution ESI/TOF-MS analysis of the m/z 553 $[M + H]^+$ peak showed that the exact mass was m/z 553.1326, corresponding to a formula of $C_{16}H_{25}N_8O_{12}S$ (calculated mass, m/z 553.1313). The number of the exchangeable protons was determined by the ESI-MS measurement with CD_3OD – D_2O (1 : 1) in the positive ion mode with the TSQ700 instrument (Finnigan-MAT, San Jose, CA). An ion at m/z 564 corresponding to $[M - 11H + 11D]^+$ was detected, suggesting the existence of ten exchangeable protons. Further, the presence of a sulfate ester was supported by the fragment ion at m/z 484, corresponding to $[M - SO_3 - 11H + 11D]^+$, shown on a collision-induced dissociation (CID) ESI-MS/MS spectrum measured with CD_3OD – D_2O (1 : 1) by choosing the ion at m/z 564 as the precursor ion (Fig. 3C).

4 IR Spectrum

The Fourier transform IR spectra were measured with an Impact 410 spectrometer (Nicolet) on a Zn/Se plate. The partial IR spectra (800–1800 cm^{-1}) of ZTX AB (Fig. 4A), STX (Fig. 4B), and the equilibrium mixture of gonyautoxin-2 (GTX-2) (**5**) and gonyautoxin-3 (GTX-3; **6**; epimers at C11 position) (Fig. 4C) were compared. The spectra of STX (Fig. 4B) and GTX-2,3 (Fig. 4C) looked similar, except for the presence of the band at 1224 cm^{-1} in the spectrum of GTX-2,3 (Fig. 4C), corresponding to the sulfate ester at C11. A similar band at 1268 cm^{-1} was seen in the spectrum of ZTX AB, supporting the presence of a sulfate ester, which was suggested by the fragmentation patterns of ESI-MS (Fig. 3A,C) [11]. The bands at approximately 1700 cm^{-1} commonly shown in all these spectra (Fig. 4A–C) were assignable to the carbonyl groups in carbamates and the ketones at C12, which are in equilibrium with the hydrate forms. The bands at approximately 1590 cm^{-1} in the spectra of STX and GTX-2,3 probably corresponded to the guanidinium groups. In the spectrum of ZTX AB (Fig. 3A), the bonds at 1561 cm^{-1} and 1420 cm^{-1} appeared to be significantly stronger than those in the spectra of STX (Fig. 3B) and GTX-2,3 (Fig. 3C). Although clear evidence has not been obtained, these bands might correspond to the *N*-substituted guanidinium group and the alkyl carbon chain around C14–C18 in ZTX AB, respectively.

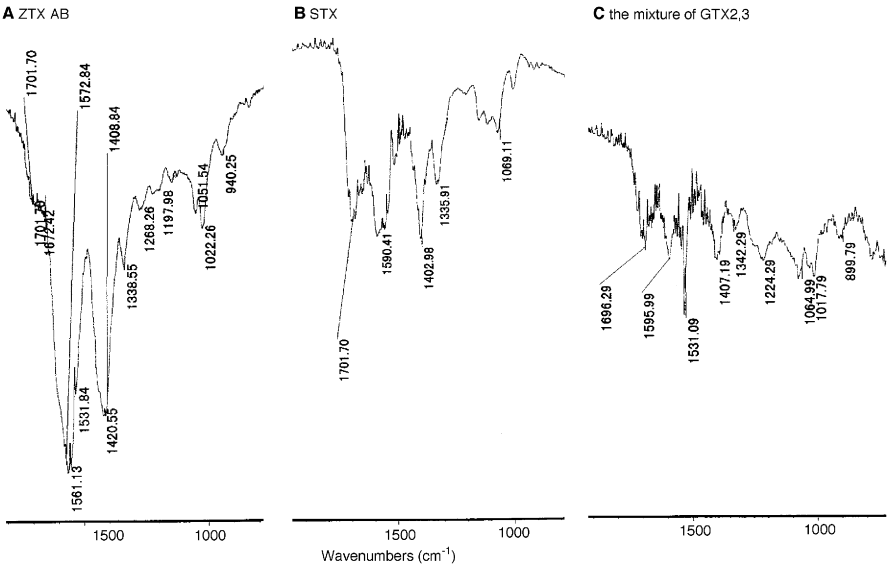


Fig. 4 The partial Fourier transform IR spectra of zetekitoxin AB, saxitoxin, and the mixture of gonyautoxin-2 and 3 measured on a Zn/Se plate

5 ^{13}C–^{1}H and ^{15}N–^{1}H HMBC Spectra

^{13}C–^{1}H and ^{15}N–^{1}H HMBC spectra of ZTX AB and STX were measured in CD_3COOD/D_2O (4 : 96) (J_{CH}, J_{NH} = 8 Hz) and reported in [11]. As shown in Figures 5 and 6, ^{13}C–^{1}H HMBC of C2/H6, C4/H5, C4/H6, C4/H10β C8/H5, C12/H10, and C12/H5, and ^{15}N–^{1}H HMBC of N1/H5 and N7/H6 were commonly seen in both spectra of ZTX AB and STX. The ^{15}N chemical shift at N7 of ZTX AB (an alkyl-substituted guanidinium nitrogen) was consistent with that of the methylated guanidinium nitrogen in creatinine (Fig. 6). These data supported that ZTX AB has the STX carbon skeleton, and alkyl substitutions at N7, C6, and C11.

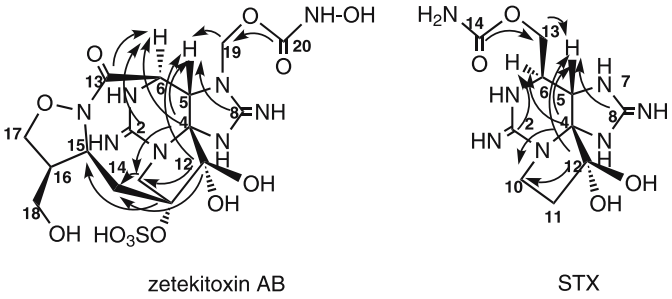


Fig. 5 ^{13}C–^{1}H HMBC of zetekitoxin AB and saxitoxin. Correlations only around the quaternary carbons are shown by the *arrows*

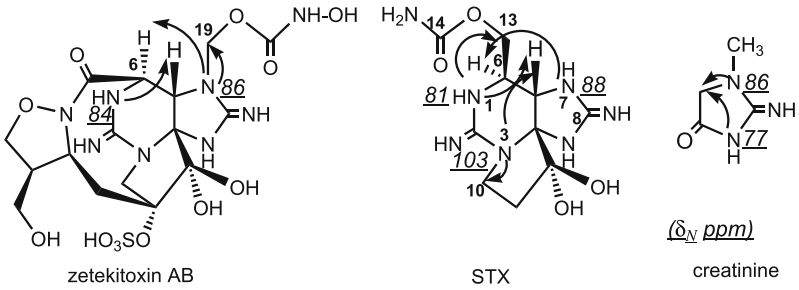


Fig. 6 ^{15}N–^{1}H HMBC of zetekitoxin AB, saxitoxin, and creatinine. The observed correlations are shown by the *arrows*, and the ^{15}N chemical shifts were roughly determined by ^{15}N–^{1}H HMBC and shown in *underlined italics*. The ^{15}N signal of benzamide (at 106 ppm) was used as the external reference

6
^{13}C NMR Spectrum

The assignment of the ^{13}C NMR signals of ZTX AB, STX, and neosaxitoxin (neoSTX) (**7**) [14] are shown in Fig. 7. The absence of hydroxyl groups both at N1 and N9 was implied by the relatively smaller downfield shifts of C6 (2.6 ppm) and C4 (4.3 ppm) of ZTX AB compared to those of STX, as a much larger downfield shift of C6 (11.2 ppm) was found for neoSTX. The signals at 155.8 or 156.5 ppm were interchangeably assigned to C2 or C13 based on the HMBC of both of these ^{13}C signals and H6 (see Fig. 5). A similar high-field resonance for an *N*-hydroxy amide carbon (156.7 ppm in deuterated dimethyl sulfoxide-d_6) had been reported for a cyclic hydroxamic acid, 2,4-dihydroxy-7-methoxy-1,4-bezoxazin-3-one [15]. The final structure of ZTX AB was deduced by the isotope shifts in ^{13}C NMR signals observed by the chemical shift difference between CD_3COOD/D_2O (4 : 96) and $CD_3COOD/D_2O/H_2O$ (4 : 6 : 90) solutions (Table 2). The isotope shifts (> 0.1 ppm) were observed for C5 (0.127 ppm), C6 (0.151 ppm), and C18 (0.130 ppm).

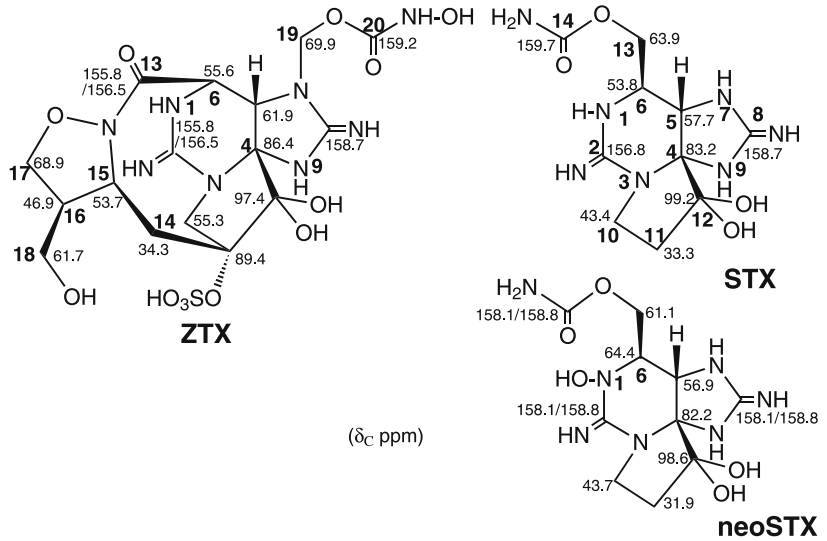


Fig. 7 Comparison of the ^{13}C NMR chemical shifts among zetekitoxin AB, saxitoxin, and neosaxitoxin [14]. The interchangeable assignments are shown by two chemical shifts

7
ESI-MS/MS Spectra

The structure of the side chain at N7 ($CH_2OCONHOH$) was supported by the ESI-MS/MS fragmentation patterns by comparison with those of the model

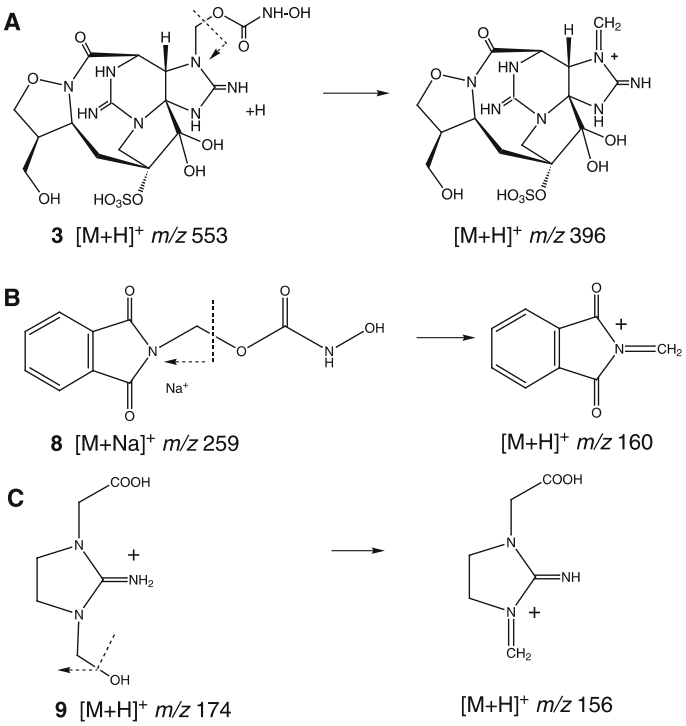


Fig. 8 The proposed fragmentation patterns detected by ESI-MS/MS in the positive ion mode for zetekitoxin AB (**A**) and model compounds **8** (**B**) and **9** (**C**) possessing $N-CH_2-O$ moieties

compounds that have similar partial structures, $N-CH_2OCONHOH$ (compound **8**) and $N-CH_2OH$ (compound **9**) (Fig. 8) [11]. The combination of CID ESI-MS/MS in the positive ion mode with $[M+H]^+$ or $[M+Na]^+$ of ZTX AB, and compounds **8** and **9**, commonly produced fragment ions that were interpreted as iminium ions probably produced by the cleavage of HOCONHOH for ZTX AB and compound **8**, and H_2O for compound **9**.

8 The Summary of NMR Data

NMR data of ZTX AB and STX are summarized in Table 2.

Table 2 NMR data of zetekitoxin AB (**3**) and saxitoxin (**4**)

	3				**4**		
	$^{13}C^a$	$^{13}C^b$	$^{15}N^c$	$^{1}H^d$	$^{13}C^a$	$^{15}N^c$	$^{1}H^{d,i}$
no.	δ	$\Delta\delta$	δ	δ (mul. J in Hz)	δ	δ	δ (mul. J in Hz)
1			84[e]			81[e]	
2	155.849[f]	ND[g]			159.704		
3			ND[g]			103[e]	
4	86.4[e]	ND[g]			83.184		
5	61.902	0.127		5.05 (s)	57.705		4.73 (d, 1.2)
6	55.568	0.151		3.98 (s)	53.785		3.82 (ddd, 1.2, 5.1, 9.3)
7			86[e]			88[e]	
8	158.708	ND[g]			158.674		
9			ND[g]			ND[g]	
10	55.295	0.000		α 3.78 (d, 12.6) β 4.41 (d, 12.6)	43.444		α 3.79 (ddd, 1.8, 9.6, 9.9) β 3.57 (ddd, 8.4, 9.9, 10.2)
11	89.433	0.018			33.3[h]		β 2.33 (ddd, 9.6, 10.2, 14.4) β 2.42 (ddd, 1.8, 8.4, 14.4)
12	97.4[e]	ND[g]			99.214		
13	156.459[f]	ND[g]			63.927		a 4.00 (dd, 5.1, 11.7) b 4.28 (dd, 9.3, 11.7)
14	34.255	0.000		β 2.19 (d, 16.2) β 2.80 (dd, 16.2, 7.8)	156.459		
15	53.732	0.006		4.04 (t, 7.8)			
16	46.943	0.011		2.23 (m)			
17	68.946	0.008		a 4.25 (br s) b 4.26 (br s)			
18	61.723	0.130		a 3.64 (dd, 12.0, 4.2) b 3.75 (dd, 12.0, 7.2)			
19	69.854	0.046		a 3.98 (d, 10.8) b 5.06 (d, 10.8)			
20	159.231	ND[g]					

solvent $CD_3COOD - D_2O$ (4 : 96), δ in ppm, 293 K;
[a] 150 MHz $^{13}CD_3COOD$ taken as 22.4 ppm;
[b] ^{13}C isotope shift (see text for details);
[c] 60.8 MHz, ^{15}N of benzamide (106 ppm) was used as the external reference;
[d] 600 MHz, CHD_2COOD taken as 2.06 ppm;
[e] roughly determined by HMBC spectrum;
[f] interchangeable assignments;
[g] ND, not determined;
[h] determined after deuterium exchanged;
[i] determined by Oshima et al. [16]

Acknowledgements The authentic saxitoxin and gonyautoxin-2,3 were provided by Prof. Yasukatsu Oshima, Tohoku University Japan. The structural study of zetekitoxin AB was a collaborative work with Dr. John W. Daly (NIH) and Prof. Yong H. Kim (KAIST, Korea). This work was supported by the Yamada Foundation, and by Grants-in-Aid for Scientific Research on Priority Areas (17035011 and 14560080) from The Ministry of Education, Culture, Sports, Science and Technology, and from JSPS (17580091).

References

1. Tsuda KS, Ikuma M, Kawamura R, Tachikawa R, Sakai K, Tamura C, Amakasu O (1964) Chem Pharm Bull Jpn 12:1357
2. Goto T, Kishi Y, Takahashi S, Hirata Y (1965) Tetrahedron 21:2059
3. Woodward RB (1964) Pure Appl Chem 9:49
4. Mosher HS, Fuhrman HD, Buchwald HD, Fischer HG (1964) Science 144:1100
5. Fuhrman FA (1986) Ann NY Acad Sci 479:44
6. Fuhrman FA, Fuhrman GJ, Mosher HS (1969) Science 165:1376
7. Kim YH, Brown GB, Mosher HS, Fuhrman FA (1975) Science 189:151
8. Yotsu M, Yasumoto T, Kim YH, Naoki H, Kao CY (1990) Tetrahedron Lett 31:3187
9. Brown GB, Kim YH, Kuntzel H, Mosher HS, Fuhrman GJ, Fuhrman FA (1977) Toxicon 15:115
10. Schantz EJ, Ghazarossian VE, Schnoes HK, Strong FM, Springer JP, Pezzanite JO, Clardy J (1975) J Am Chem Soc 97:1238
11. Yotsu-Yamashita M, Kim YH, Dudley SC Jr, Choudhary G, Pfahnl A, Oshima Y, Daly JW (2004) Ann N Y Acad Sci 101:4346
12. Kim YH, Kim YB, Yotsu-Yamashita M (2003) J Toxicol Toxin Reviews 22:521
13. Daly JW (2004) J Nat Prod 67:1211
14. Shimizu Y, Hsu CF, Fallon WE, Oshima Y, Murai I, Nakanishi K (1978) J Am Chem Soc 100:6791
15. Atkinson J, Mornad P, Arnason JT (1991) J Org Chem 56:1788
16. Onodera H, Satake M, Oshima Y, Yasumoto T, Camichiael WW (1997) Nat Toxins 5:146

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Synthesis of Marine Natural Products with Bicyclic and/or Spirocyclic Acetals

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Abstract A large number of marine natural products with bicyclic and/or spirocyclic acetals have been found to date. These compounds are usually biologically active, however, synthetic studies are essential for the structure elucidation and biological application. For spirocyclic acetals in particular, it is necessary to design precursors and to control the process of dehydrative ring-closing acetal formation. Synthetic studies of four types of acetal compounds that represent recent examples are described; didemniserinolipid B (6,8-dioxabicyclo[3.2.1]octane), attenols (6,8-dioxabicyclo[3.2.1]octane or 1,6-dioxaspiro[4.5]decane), bistramides (1,7-dioxaspiro[5.5]undecane), and pinnatoxins (6,8-dioxabicyclo[3.2.1]octane and 1,7,9-trioxadispiro[5.1.5.2]pentadecane)

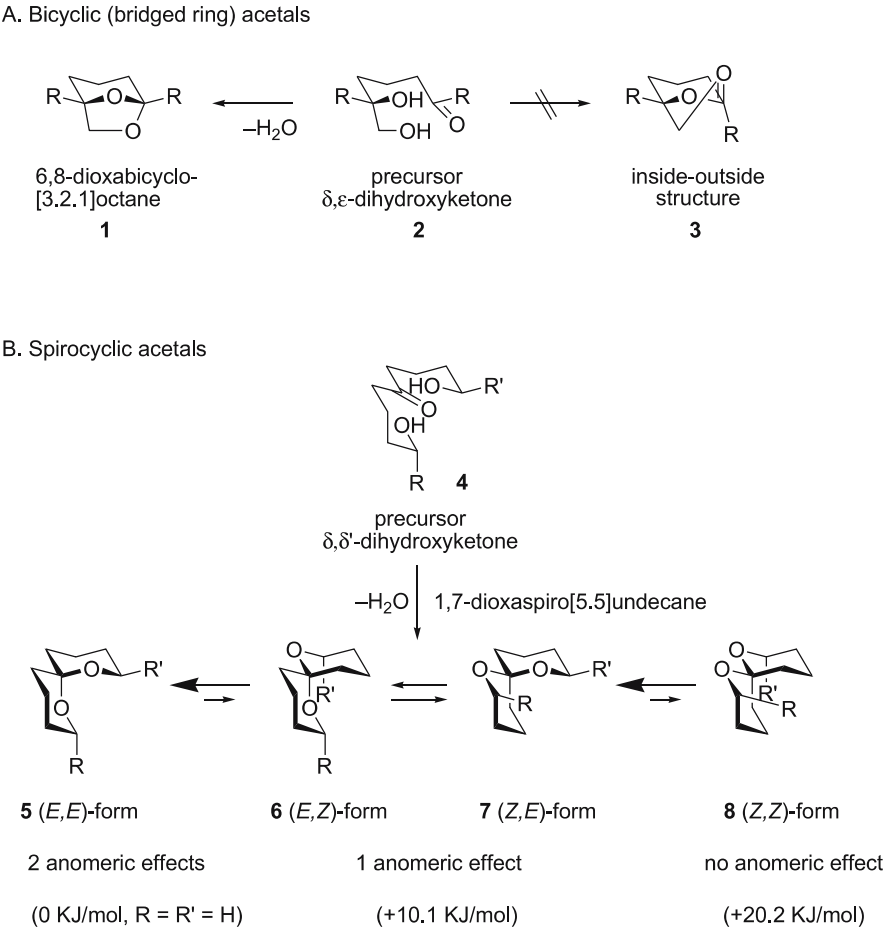
Keywords Marine natural products · Spiroacetals · Bicyclic acetals · Total synthesis

Abbreviations

Alloc	allyloxycarbonyl
DCM	dichloromethane
AD	asymmetric dihydroxylation
AE	asymmetric epoxidation
cat.	catalyst
Ipc	isopinocamphenyl
MAO	methylaluminoxane
MMTr	4,4′-dimethoxytrityl
MPM	*p*-methoxyphenylmethyl (PMB)
MTPA	α-methoxy-α-phenyl-α-(trifluoromethyl)acetyl
NaHMDS	sodium hexamethyldisilazide
NIS	*N*-iodosuccinimide
NMO	*N*-morphorine *N*-oxide
NOE	nuclear Overhauser effect
oxi.	oxidation
PyBOP	benzotriazol-1-yl-oxytripyrrolidino-phosphonium hexafluorophosphate
quant.	quantitative
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
SAMP	(*S*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine
TBAI	tetrabutylammonium iodide
TBS	*t*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidinyloxy radical
TES	triethylsilyl
TPAP	tetrapropylammonium perruthenate

1 Introduction

Most marine natural products, especially polyketides, possess polyhydroxy and polyoxy substituents in their structures. A number of bicyclic (bridged ring) and/or spirocyclic acetals have been isolated from marine organisms [1, 2], these motifs being the result of intramolecular dehydration of their hydroxy ketone precursors (Fig. 1). The stereochemistry of the newly constructed acetal carbon of the bicyclic acetal **1** is restricted by the configuration of hydroxyl groups of the precursor **2.** Formation of another diastereomer **3**, which has an inside–outside structure, was prohibited due to the ring strain. On the other hand, the stereochemistry of spiroacetal carbon depends on its thermodynamic stability. Dehydration of the precursor δ,δ'-dihydroxy ketone **4** afforded at most four diastereomers **5–8.** The most prevalent isomer **5**, which is called the (*E*,*E*)-form, was estimated to be ca. 10.1 KJ/mol more stable than **6** when R = R′ = H [3]. This was due to the double anomeric stability of **5**. Thermodynamic stability is affected by substituent patterns, i.e., in the case where the R substituent is a hydroxyl, hydrogen bonding with the ring oxygen atom would make isomer **7** more stable.



Scheme 1 Aspects of bicyclic and spirocyclic acetals

In planning the syntheses of these types of acetal natural product, chemists typically devise routes to their hydroxy ketone precursors, which can undergo acid-catalyzed dehydration–cyclization to give the target. Sometimes they set things up so only one product can be formed, and other times they hope thermodynamics will yield the product they desire [4].

In this work, synthetic studies of biologically active natural products isolated from marine sources and possessing bicyclic and/or spirocyclic acetals are reviewed.

2
Didemniserinolipids

Marine tunicates belonging to the genus *Didemnum* have proven to be a particularly rich source of structurally diverse and biologically potent marine metabolites. Recently, González et al. reported the isolation of didemniserinolipids A, B, and C (**9–11**) from a methanol extract of *Didemnum* sp., collected along the coast of Sulawesi Island (Indonesia) [5]. More recently, a related cyclodidemniserinol trisulfate (**12**) was isolated from the Palauan ascidian *Didemnum guttatum* as an HIV-1 integrase inhibitor [6] (Fig. 1). All these serinolipids possess an unprecedented serinol component and a 6,8-dioxabicyclo[3.2.1]octane core structure, thus these are attractive targets for synthesis.

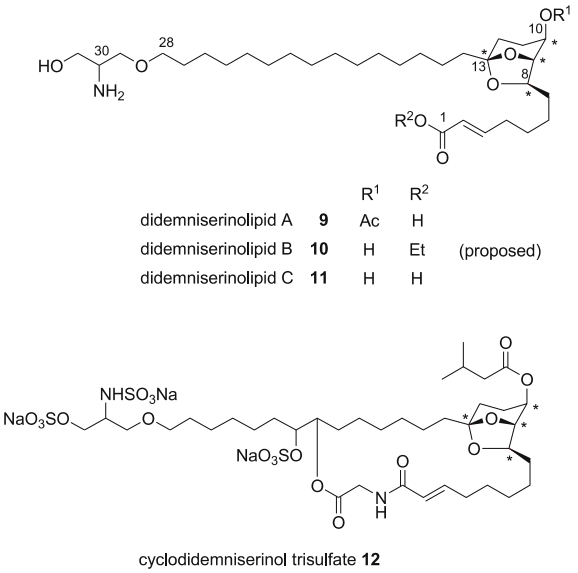
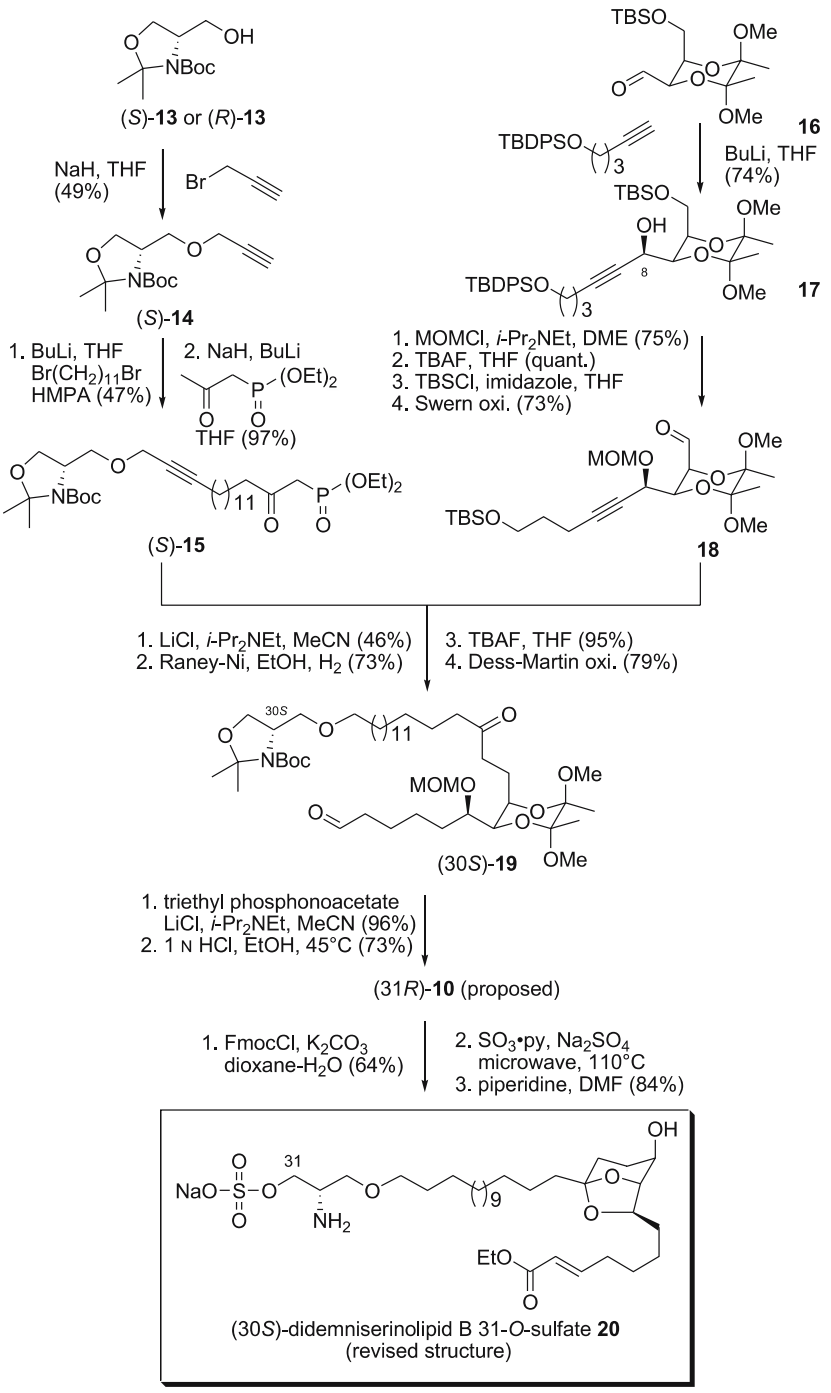


Fig. 1 Didemniserinolipids and related compounds

2.1
Synthesis and Structure Revision of Didemniserinolipid B

Kiyota and Ley et al. reported the synthesis and revision of the proposed structure of (+)-didemniserinolipid B (**10**) [7].

The key of the synthesis was preparation of the δ,ε-dihydroxy ketone intermediate, precursor of the 6,8-dioxabicyclo[3.2.1]octane skeleton. The serinol fragment (*S*)-**15** was prepared from the known D-serinol derivative (*S*)-**13** [8] in a series of straightforward steps. The hydroxyl group was first propargy-



Scheme 2 Synthesis and structure revision of (+)-didemniserinolipid B

lated to give ether (*S*)-**14** and the terminal alkyne was further elongated with 1,11-dibromoundecane and the resulting bromide was coupled with the dianion of β-ketophosphonate to give (*S*)-**15**. Following a similar procedure, (*R*)-**15** was prepared from L-serinol derivative (*R*)-**13**. On the other hand, the bicyclic core fragment was synthesized from the known butanediacetal (BDA) protected aldehyde **16** [9]. This compound was coupled with *O*-TBDPS protected pentynol using BuLi as a base with a diastereomeric ratio of 2.5 : 1. The stereochemistry of the 8-position in **17** was determined by the modified Mosher method [10]. The alcohol **17** was converted to aldehyde **18** in four steps. Wittig–Horner reaction of (*S*)-**15** with **18** gave the enone (30*S*)-**19** and the two triple and one double bonds were removed by hydrogenation over a Raney-nickel catalyst. Elongation of the side chain was done by the Wittig–Horner reaction and removal of all the protecting groups (acetonide, Boc, BDA and MOM) was achieved in one step using 1 N HCl in EtOH at 45 °C to obtain the target compound (30*R*)-**10** in 73% yield. The diastereomer (30*S*)-**10** was also prepared similarly. However, the ^{1}H NMR signals associated with the serinol unit were shifted significantly upfield. They prepared the corresponding 30-sulfates (30*S*)- and (30*R*)-**20** in view of the fact that related natural products were sulfated on the serinol unit. During this modification, they found an effective method of sulfation using microwave (SO_3·py at 110 °C) [11]. As a result, the true structure of the natural product was determined to be 31-*O*-sulfate **20** with 8*R*,9*R*,10*R*,13*S*,30*S* absolute configuration by the spectral comparison. The overall yield was 1.1% in over 15 steps.

3 Attenols

Attenols A (**21**) and B (**22**), isolated from the EtOH extract of the Chinese bivalve *Pinna attenuata* by Uemura et al. [12], exhibited cytotoxicity against P388 cells (IC_{50} values of 24 and 12 μg/mL, respectively) (Fig. 2). These com-

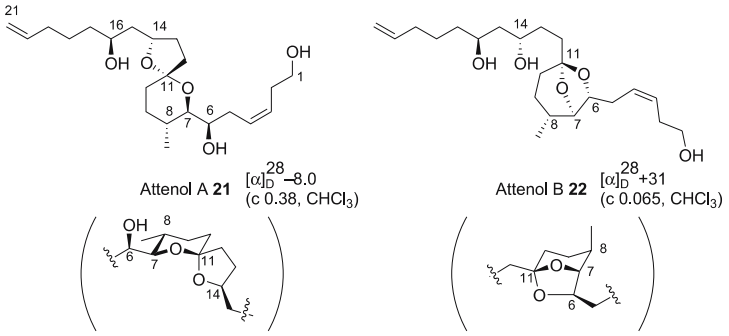


Fig. 2 Attenols A and B

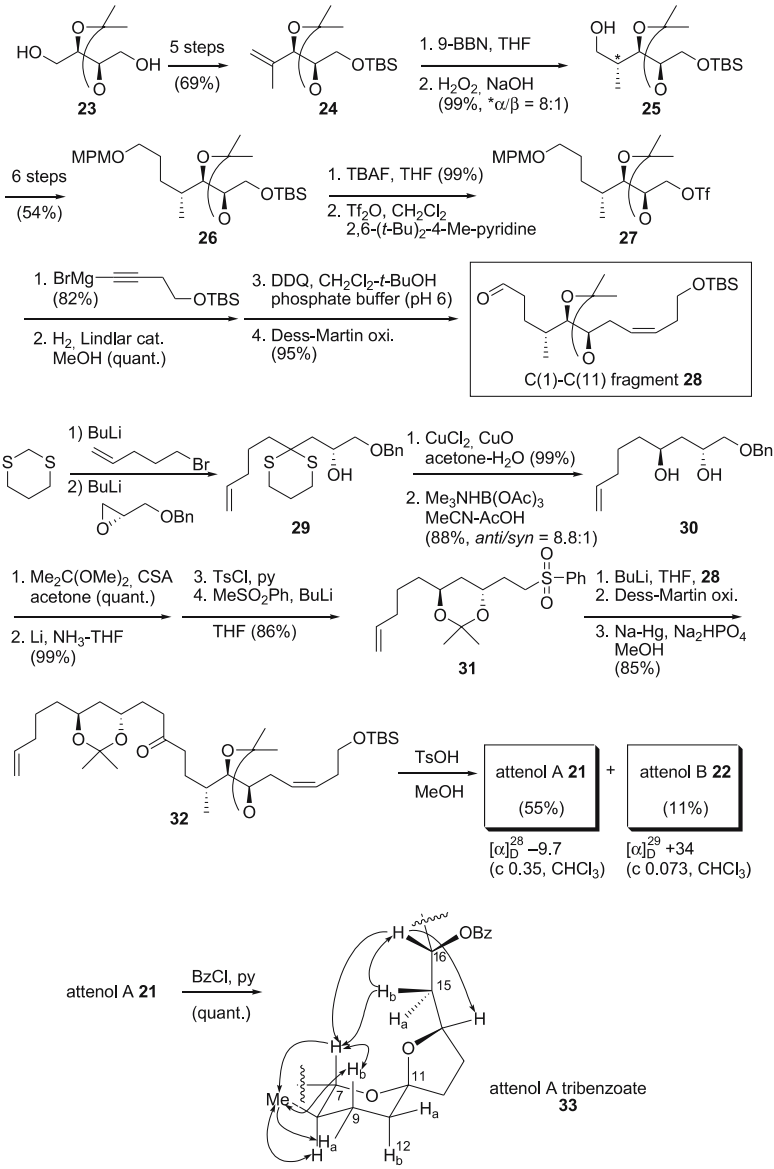
pounds are unique isomeric triols: attenol A has a 1,5-dioxaspiro[4.5]decane core and attenol B has a 6,8-dioxabicyclo[3.2.1]octane framework, and equilibrium under acidic conditions is **21/22** = 3 : 1. They determined their relative structures by 2D NMR and absolute configurations by the modified Mosher method [10], however, those of the spiroacetal carbon of **21** were assumed by considering the anomeric effect.

3.1
Uemura's Synthesis of Attenols A and B

Uemura's group also synthesized these compounds to confirm the stereochemistry [13, 14]. The southern fragment was prepared from 2,3-*O*-isopropylidene-D-threitol (**23**) (Scheme 3). After the protection of one hydroxyl group as TBS ether, another was subjected to chain elongation in several steps to give **24**. The *exo* olefin of **24** was oxidized by hydroboration (**25**) and a further two carbon elongation steps lead to **26.** Then the TBS group was removed and the hydroxyl group was converted to its triflate **27**, which was substituted by acetylide anion followed by partial reduction of the triple bond to afford the northern fragment **28**. 1,3-Dithiane was used for the southern fragment, i.e., double alkylation with 5-bromo-1-pentene and benzyl (*R*)-glycidyl ether afforded **29**. Removal of the dithiane group gave ketone, which was selectively reduced to give 1,3-*anti*-diol **30** using Evans' $Me_4NHB(OAc)_3$ [15]. After the diol part being protected as an acetonide, the compound was converted to sulfone **31**. Julia coupling reaction of **28** and **31** gave ketone **32,** which was treated with TsOH in MeOH to afford attenols A **21** and B **22** in 55% and 11% yield, respectively. They converted the synthetic attenol A **21** into its tribenzoate **33** and confirmed the stereochemistry around the spiroacetal ring by NOE experiments.

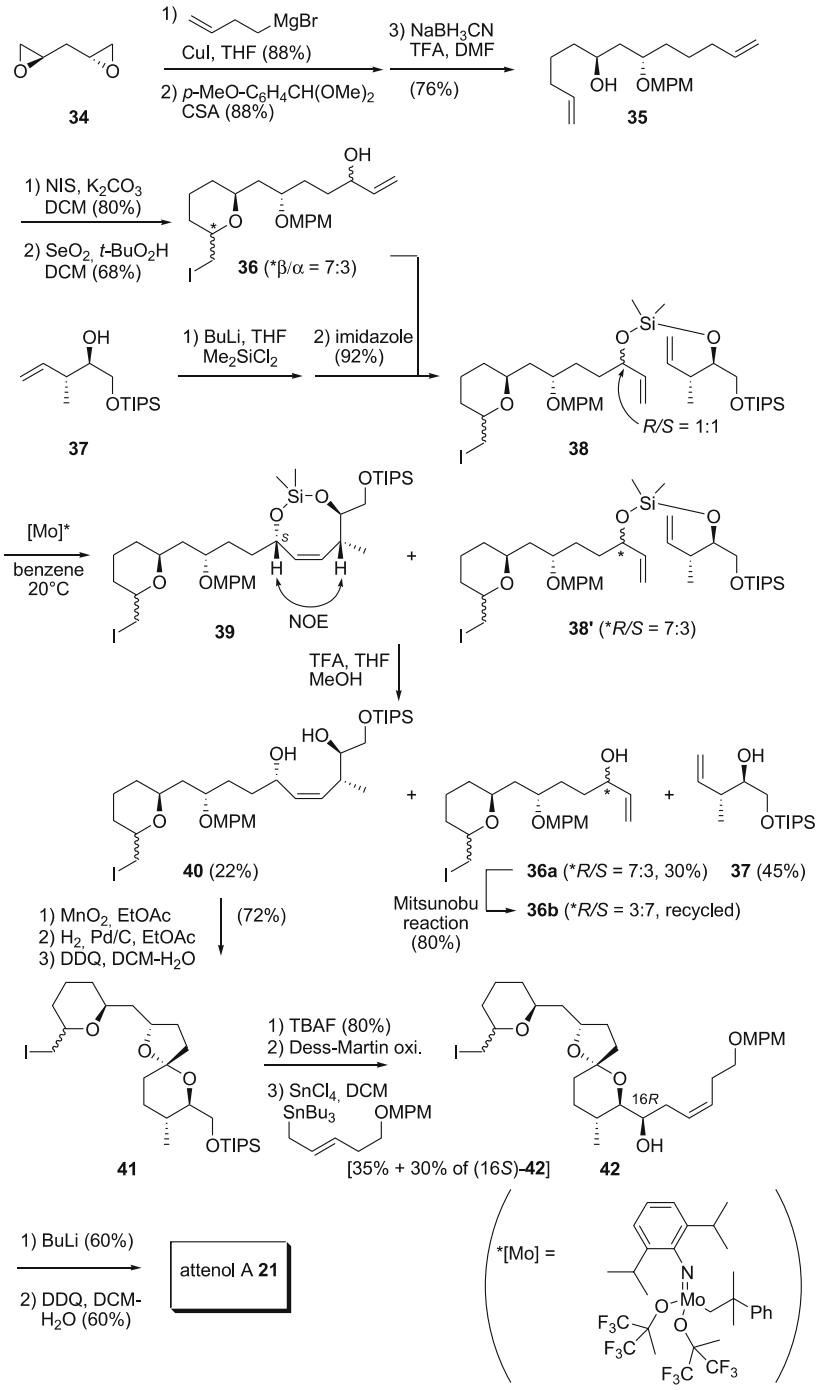
3.2
Van de Weghe's Synthesis of Attenol A

The second synthesis of attenol A was reported by Van de Weghe et al. in 2002 (Scheme 4) [16]. They used silicon tether-aided coupling metathesis [17]. Preparation of one fragment started from double alkylation of 1,2;4,5-diepoxypentane (**34**) [18] with 3-butenylmagnesium bromide to give *anti*-diol, one hydroxyl group of which was protected as MPM ether (**35**). Kinetic iodoetherification using NIS/K_2CO_3 gave a 7 : 3 mixture of *cis*- and *trans*-fused dihydropyrans and the allylic position was oxidized to give alcohol **36**. Silicon tether **38** was constructed by coupling of **36** and the known fragment **37** [19] using Me_2SiCl_2. Only 11*S*-isomer reacted in the key metathesis reaction [20] giving cyclic siladioxane **39**, which was treated with TFA to afford diol **40** at 22% in two steps, together with **36a** (R/S = 7 : 3) and **37**. The recovered **36a** (R/S = 7 : 3) was converted to **36a** (R/S = 3 : 7) by the



Scheme 3 Uemura's synthesis of attenols A and B

Mitsunobu reaction and re-used. The allylic hydroxyl group was selectively oxidized and the deprotection of the MPM group gave bicyclic acetal **41**. The TIPS group was then removed and the side chain elongation sequence using $SnCl_4$-catalyzed allylation [22] afforded **42**. Finally, attenol A **21** was prepared by reductive deiodination and deprotection of the MPM group.



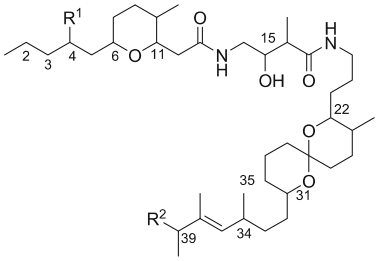
Scheme 4 Van de Weghe's synthesis of attenol A

3.3
Ender's Synthesis of Attenols A and B

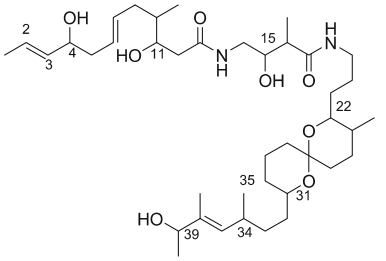
Enders and Lenzen used asymmetric alkylations of SAMP-hydrazones and Sharpless asymmetric dihydroxylation as the key steps (Scheme 5) [22]. Diastereoselective successive alkylations of **43** were directed by the SAMP group [23, 24] to give **44** and the removal of the SAMP hydrazone moiety afforded ketone **45**. A radical deoxygenation sequence (**46**), followed by deprotection of the TBS group and iodination gave **47**. SAMP-directed alkylation was again used for the introduction of the 8-methyl group into **48**. Methylated SAMP hydrazone **49** was converted to **50**, which was subjected to Sharpless asymmetric dihydroxylation to construct three successive asymmetric centers as in **51**. Chain elongation was achieved with alkynyllithium via the corresponding triflate in 89% yield to give **52**. This was converted to iodide **53** in three steps. The two fragments were joined by 1,3-dithiane alkylation to give **54** then **55**, whose protective groups were removed to give attenols A (**21**) and B (**22**) in 57% and 9% yield, respectively. These compounds were > 96% ee and de.

4
Bistramides

Bistramides A (bistratene A, BST-A, **56**), B, C, D and K (**57–60**) are a family of bioactive spiroacetals isolated from the marine ascidian *Lissoclinum bis-*

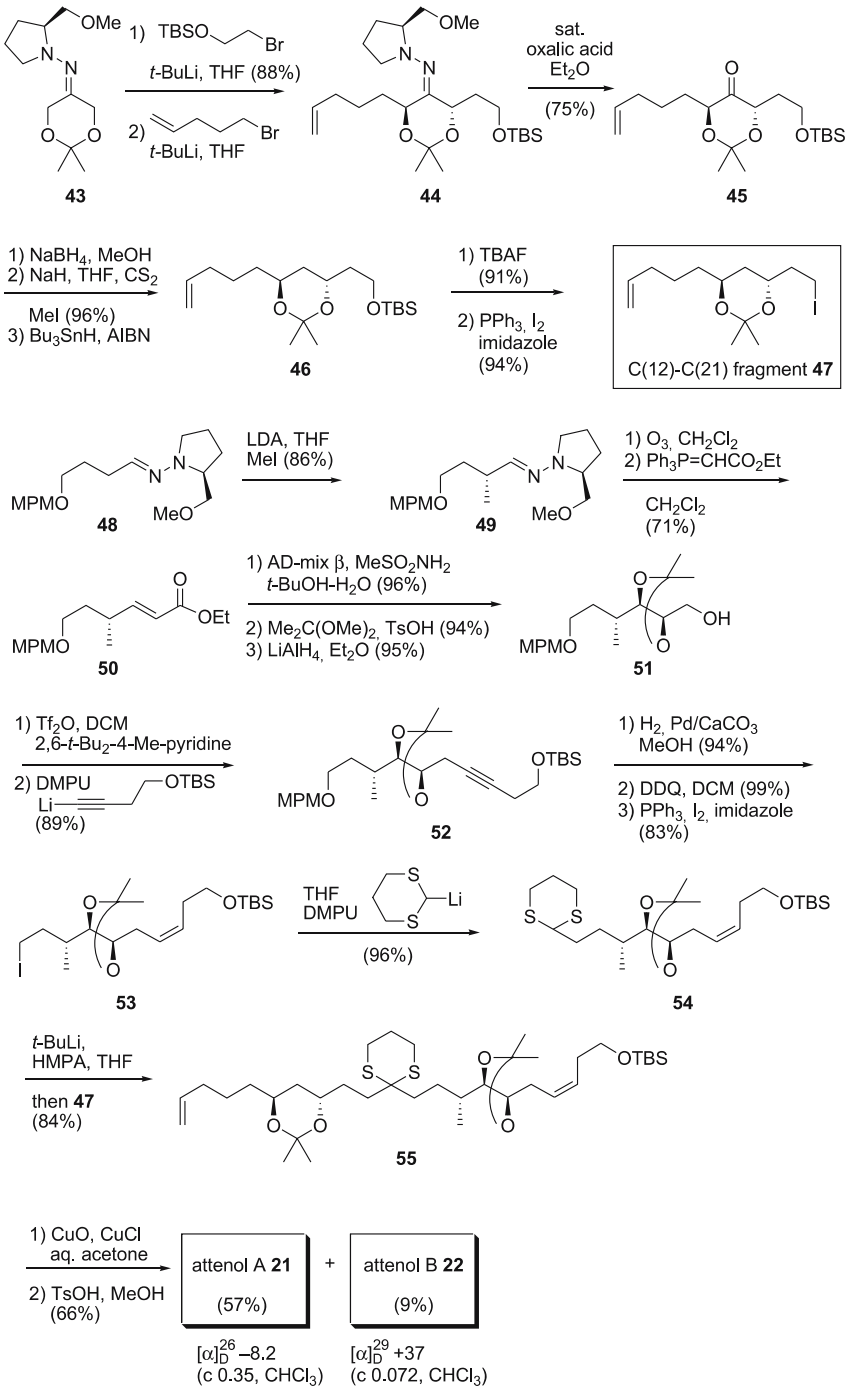


		R^1	R^2
bistramide A (BST-A) **56**	$\Delta^{2,3}$	=O	OH
bistramide B (BST-B) **57**		=O	OH
bistramide C (BST-C) **58**	$\Delta^{2,3}$	=O	=O
bistramide D (BST-D) **59**	$\Delta^{2,3}$	OH	OH



bistramide K (BST-K) **60**

Fig. 3 Bistramides

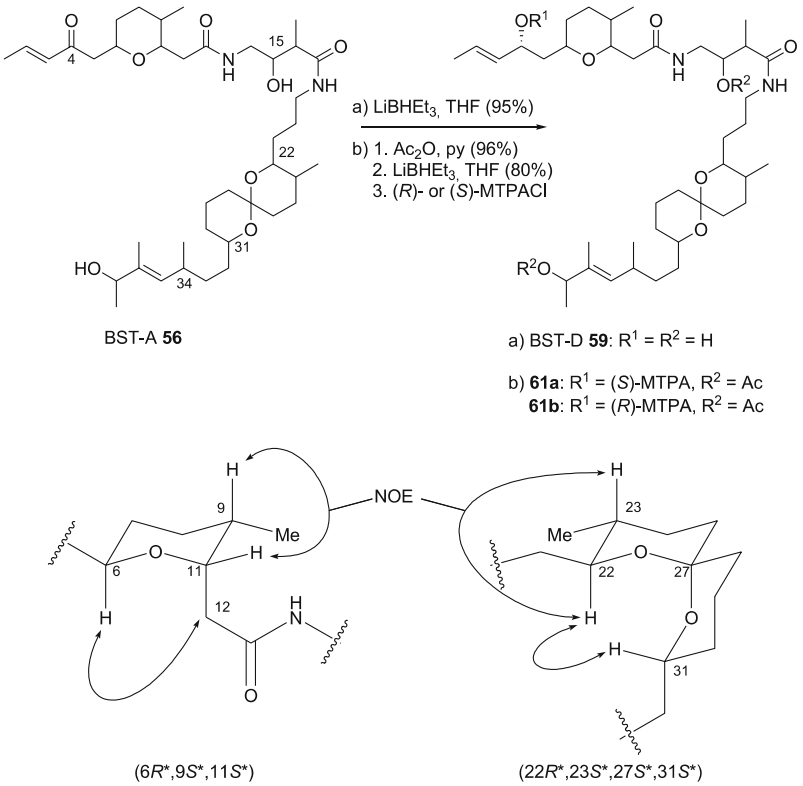


Scheme 5 Enders' synthesis of attenols A and B

tratum Sluiter [25–29]. These compounds showed cytotoxic activities against P388/dox, HL60, NSCLC-N6 cell lines etc. [30, 31], however, high toxicity prevents them from therapeutic use. Among them BST-D (**59**) and BST-K (**60**) are less toxic but far less abundant in nature. There are up to ten stereogenic centers present in bistramides and up to 1024 stereoisomers are candidates of the true structure. This had to be cleared up for further therapeutic studies of bistramides.

4.1 Solladié's Semisynthesis of Bistramide D

Solladié et al. converted highly toxic BST-A (**56**) into BST-D (**59**) and partly determined the absolute and relative configurations (Scheme 6) [32]. Several reagents were used for the reduction of **56**. The best result was obtained using $LiBHEt_3$ to give **59** in 95% yield. The stereochemistry of the 4-position was determined to be *R* by a modified Mosher method [10] by derivatization of **59**

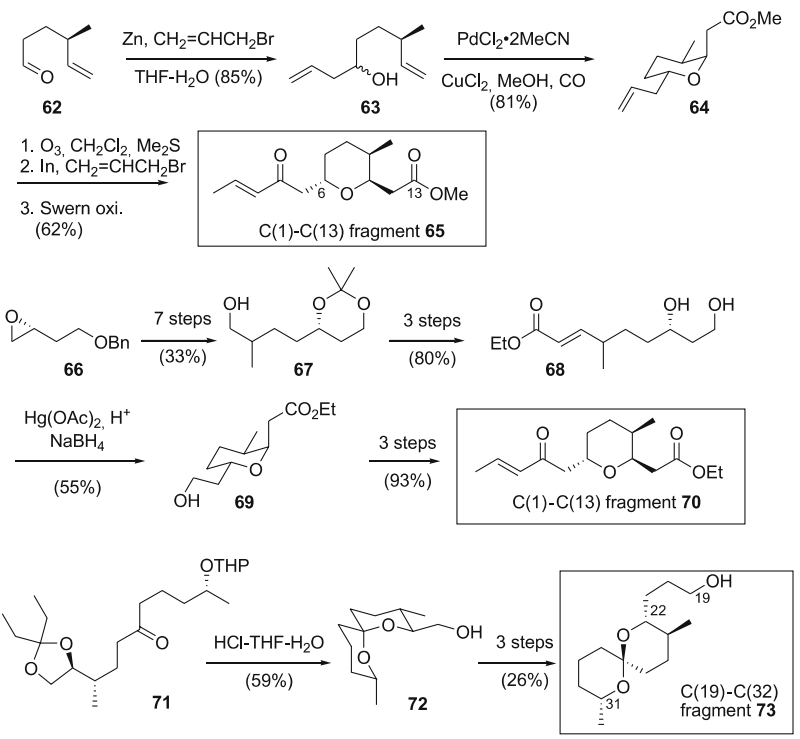


Scheme 6 Solladié's semisynthesis of bistramide D

into 15,39-di-*O*-acetyl-4-*O*-MTPA esters **61a** and **61b.** In addition, the NOESY spectrum of BST-A revealed the relative configurations of the tetrahydropyran and spiroacetal parts to be (6*R**,9*S**,11*S**) and (22*R**,23*S**,27*S**,31*S**), respectively.

4.2 Kitching's Synthetic Studies of Bistramides

Solladié's stereochemical assignments were followed by Kitching's partial synthesis of C(1)–C(13) and C(19)–C(32) fragments [33]. They applied mercury(II) or palladium(II) catalyzed cyclization for the construction of the tetrahydropyran moiety (Scheme 7). δ,ε-Unsaturated alcohol **63** derived from the known aldehyde **62** [34] was subjected to oxypalladation to give **64** as a diastereomeric mixture. This was converted to the C(1)–C(13) fragment **65** through Swern oxidation–isomerization. Oxymercuration was applied for conjugated ester **68** prepared from **66** [35] via **67**, to give **69**, which was converted to the fragment **70.** On the other hand, spiroacetal fragment **73** was synthesized from **71** [36]. Acidic treatment gave a spiroacetal **72,** which was



Scheme 7 Kitching's synthetic studies of bistramides

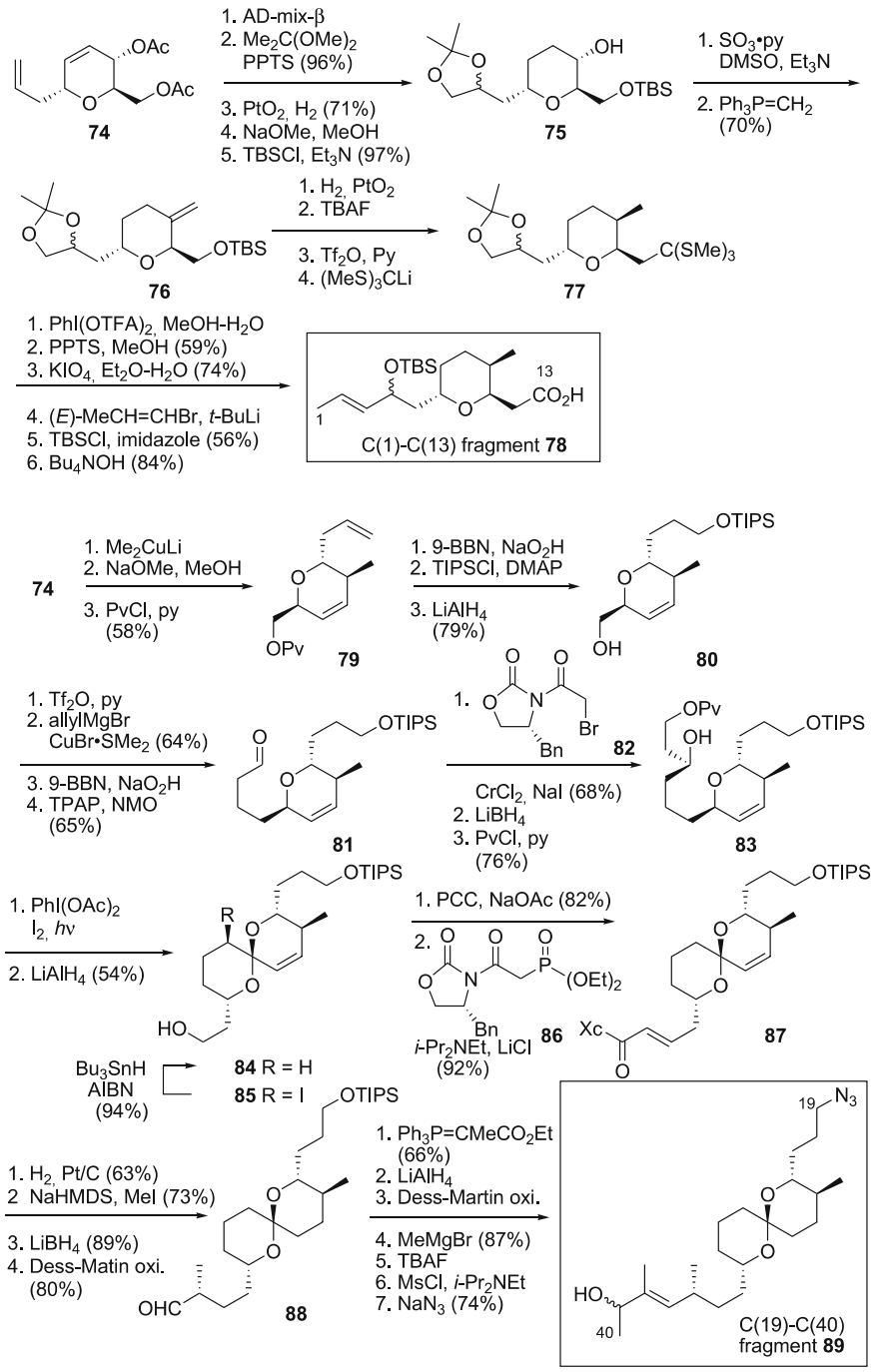
converted to the C(19)–C(32) fragment **73**. The ^{1}H- and ^{13}C-NMR spectral data of the fragments were in good agreement with those of BST-A (**56**).

4.3 Wipf's Total Synthesis of One Possible Stereoisomer of Bistramide C

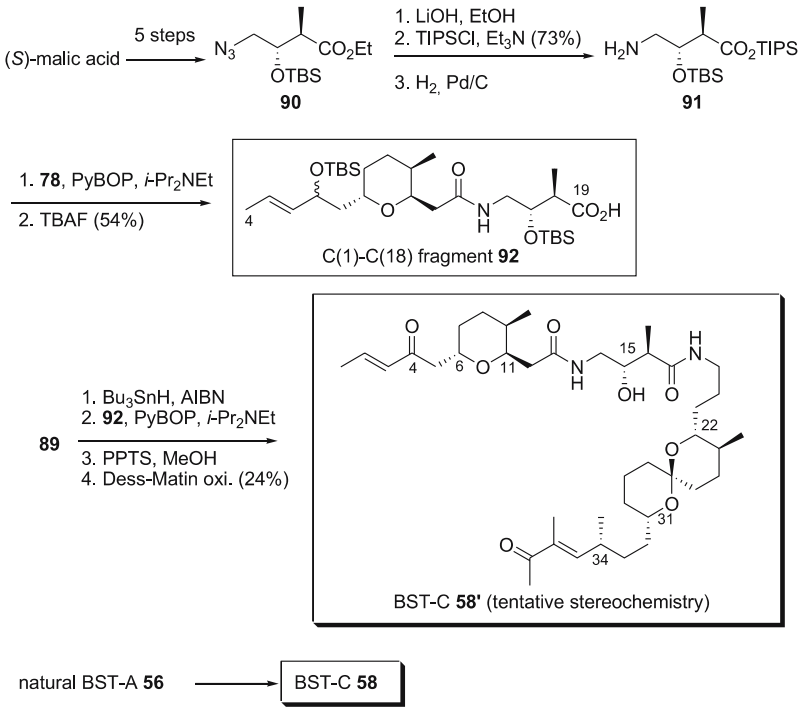
On the basis of Solladié's stereochemical work, Wipf et al. tried to assign the whole stereochemistry of BST-C (**58**) by a combination of total and partial syntheses [37].

Their synthesis used *C*-allyl glucal **74** for both cyclic fragments (Scheme 8). The double bond on the side chain was dihydroxylated using AD-mix β [38] and another double bond on the ring was hydrogenated to give **75**. Then a methyl substituent was introduced via the *exo* methylene moiety (**76**), and another side chain was elongated with tris(trimethylthio)methyllithium [39] to afford **77**. This compound was converted to carboxylic acid **78** [C(1)–C(13) fragment] in six steps. On the other hand, preparation of the spiroacetal fragment [C(19)–C(40)] started also from **74** via introduction of the methyl group by S_N2' reaction (**79**). Hydroboration–oxidation followed by removal of the pivaloyl group gave **80**. The formed hydroxyl group was converted to the corresponding triflate, which was coupled with allyl Grignard reagent. The second hydroboration–oxidation and TPAP oxidation gave aldehyde **81**. A Reformatzky reaction with the chromium enolate [40] generated from **82** introduced the secondary hydroxyl group. Reductive removal of the chiral auxiliary and the selective protection of the primary hydroxyl group afforded **83**. The key oxidative spirocyclization using iodobenzene diacetate and iodine was carried our under irradiation with a 250 W tungsten lamp [41] to give a 3.5 : 1 mixture of **84**, and iodide **85** which was easily converted to **84**. Introduction of Evans' chiral auxiliary **86** by the Wittig–Horner reaction [42] allowed the stereoselective construction of the 35-methyl group. The enone **87** was converted to aldehyde **88** in four steps. Chain elongation and introduction of an azide group gave the spiroacetal [C(19)–C(40)] fragment **89**.

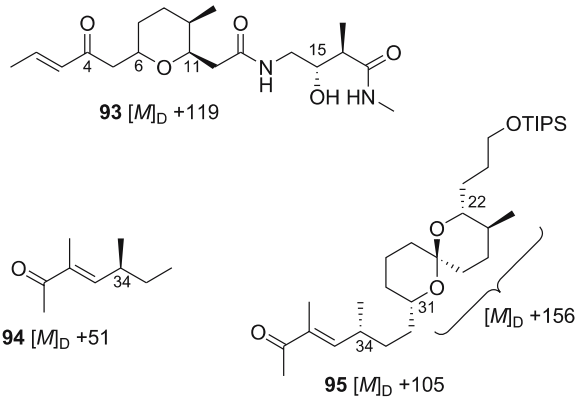
The *anti*-relationship of C(15) and C(16) substituents at the C(14)–C(18) amino acid fragment was deduced by a comparison of ^{1}H-NMR data of synthetic diastereomers. The *anti*-isomer **91** was prepared from L-(*S*)-malic acid via azide **90** (Scheme 9). Condensation of this amine **91** with the acid **78** using PyBOP followed by deprotection of the silyl group afforded the northern [C(1)–C(18)] fragment **92**. Then the southern fragment **89** was condensed with **92** to give the tentative target structure of BST-C (**58'**). They determined the relative stereochemistry of the northern fragment as above because the ^{1}H- and ^{13}C-NMR spectra of the C(1)–C(18) portions coincided with those of BST-C (**58**), prepared from natural BST-A (**56**) by MnO_2 oxidation. In addition, 31*R**,34*R**-relative configuration was deduced from the observation that the ^{13}C chemical shift at C(34) was significantly different from the natural BST-C. The remaining unknown points were the two sets



Scheme 8 Wipf's synthesis of one possible stereoisomer of bistramide C-1



Scheme 9 Wipf's synthesis of one possible stereoisomer of bistramide C-2

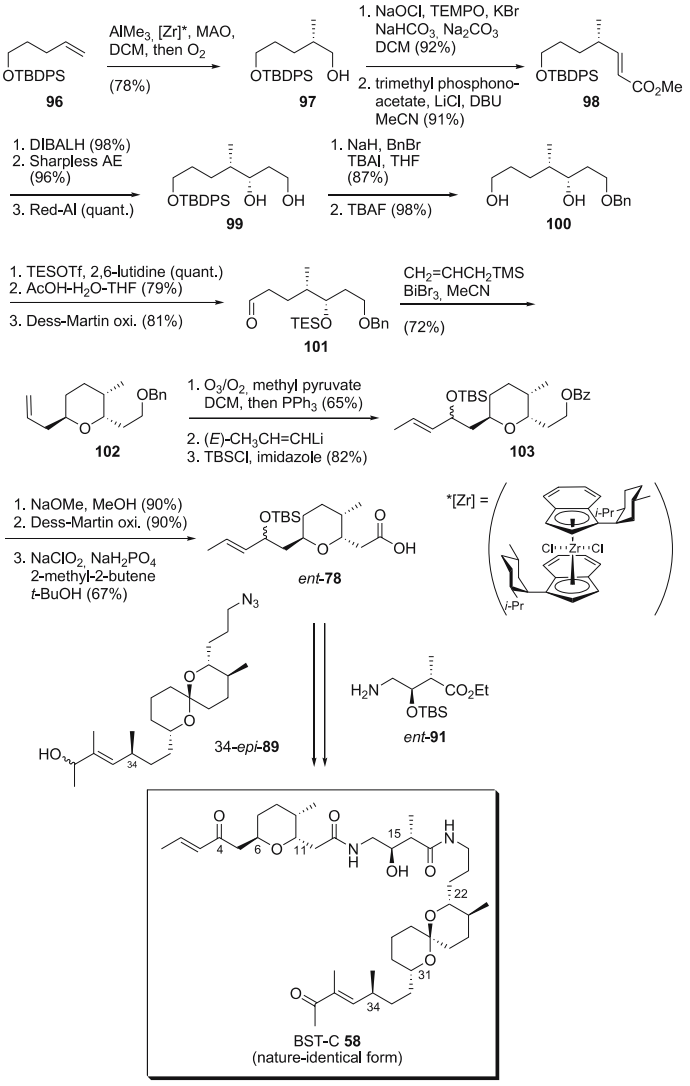


	measured	van`t Hoff sum values
synthetic **58'** (6*S*,9*R*,11*R*,15*S*,16*R*,22*R*,23*S*,27*S*,31*S*,34*R*)	$[M]_D$ +211	$[M]_D$ +224
natural **58** (6*R*,9*S*,11*S*,15*R*,16*S*,22*R*,23*S*,27*S*,31*S*,34*S*)	$[M]_D$ +70	$[M]_D$ +88
other 6 diastereomers	–	–326, –224, –88, –14, +14, +326

Fig. 4 Estimation of the absolute configuration of bistramide C

of the absolute stereochemistry: the northern fragment and the southern fragment. Accordingly, the number of possible stereostructures decreased to four.

Then they applied van't Hoff's principle of optical superposition [43–45]. The sum of the molecular rotation values of the three fragments **93, 94** [46] and **95** was calculated (Fig. 4). The results were applicable because the value of synthetic BST-C (**58**) (+211) was in good agreement with the calculated value



Scheme 10 Wipf's synthesis of bistramide C in nature-identical form

(+224). Finally, the whole absolute stereochemistry was determined to be 6*R*,9*S*,11*S*,15*R*,16*S*,22*R*,23*S*,27*S*,31*S*,34*S*: the values of natural and calculated molecular rotation were + 70 and + 88, respectively.

4.4
Wipf's Total Synthesis of Bistramide C with an Identical Form to that in Nature

Later, Wipf et al. synthesized BST-C (**58**) with the above absolute stereochemistry and confirmed their proposal [47]. As shown in Scheme 10, in their new synthesis the strategy towards the northern fragment *ent*-**78** was changed. Terminal alkene **96** was converted to alcohol **97** by MAO-mediated asymmetric methylalumination in the presence of Erker's chiral zirconocene (78%, 83% ee) [48]. Chain elongation using the Wittig–Horner reaction (**98**) and the interconversion of some functional groups via diols **99** and **100** gave aldehyde **101**. Then the construction of the *trans*-dihydropyran ring was achieved by the Evans' protocol using allyltrimethylsilane and bismuth tribromide to give **102** [49]. Ozonolysis of the double bond simultaneously oxidized the benzyl ether to benzoyl ester. Allylation of the resulting aldehyde gave **103**. This compound was converted to *ent*-**78** in three steps. Assembly of *ent*-**78**, *ent*-**91** and 34-*epi*-**89** afforded the desired bistramide C (**58**) with absolute chemistry and spectroscopic properties identical to that in nature.

5
Pinnatoxins

A series of macrocyclic compounds possessing a unique dispiroacetal {1,7,9-trioxadispiro[5.1.5.2]pentadecane} and a bicyclic acetal {6,8-dioxabi cyclo[3.2.1]octane} concomitant with a spirocyclic imine part were isolated from marine bivalves. Pinnatoxin A (**104**) was isolated from the Okinawan bivalve *Pinna muricata* [50, 51] and pinnatoxins B (**105**) and C (**106**) [52], and pteriatoxins A–C (**107–109**) were isolated from *Pinna penguin* [53]. These compounds seem to be responsible for *Pinna* shellfish poisonings in China and Japan, as Ca^{2+} activators [54]. In addition, analogous compounds without the bicyclic acetal, spirolides A–E (**110–114**), were produced by the dinoflagellate *Alexandrium ostenfeldii* [55, 56].

5.1
Ishihara–Murai's Synthetic Studies of Pinnatoxins

Several groups have made efforts to synthesize these unique natural products [57–59]. Ishihara and Murai's group constructed the BCD-tricyclic spiroacetal and the EF-bicyclic acetal simultaneously from a tetraketo precursor [60–63]. As shown in Scheme 11, a Julia-coupling reaction of **115** [60]

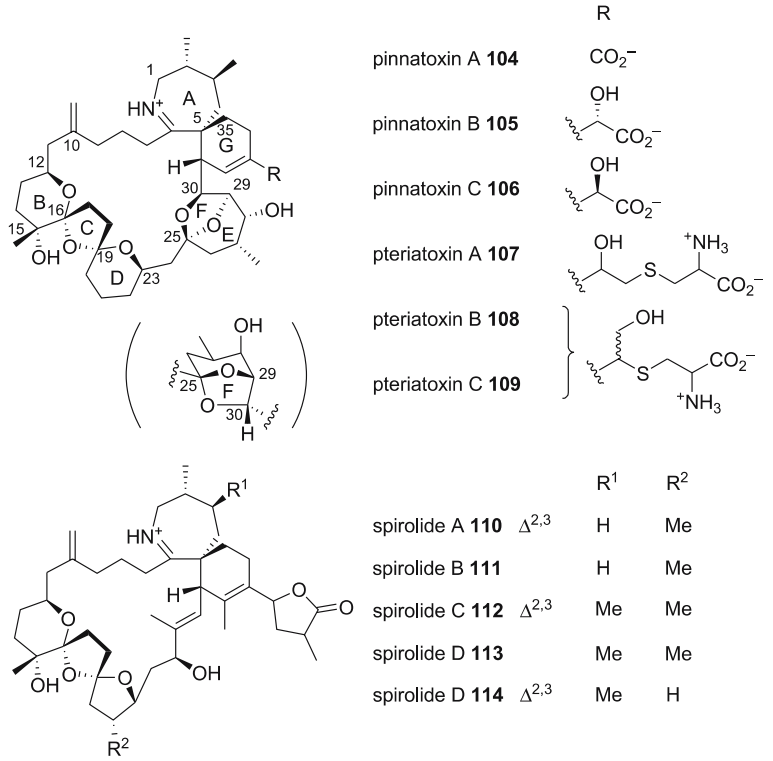


Fig. 5 Structures of pinnatoxins, pteriatoxins and spirolides

with **116** afforded **117**, which was again coupled with sulfone **118** [62] followed by perruthenate-mediated oxidation to give the tetraketo precursor **119.** Removal of four out of five silyl protecting groups using HF · pyridine complex in acetonitrile gave the desired pentacyclic compound **120** as a sole product [63]. Their previous studies concerning the construction of BCD-rings revealed that the configuration of the spirocyclic carbon belonging to the C and D-rings is influenced by protection of the hydroxyl group on the

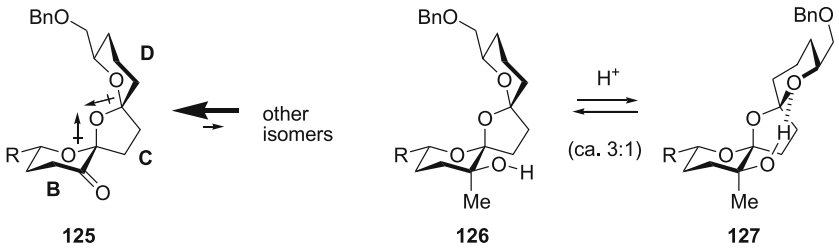
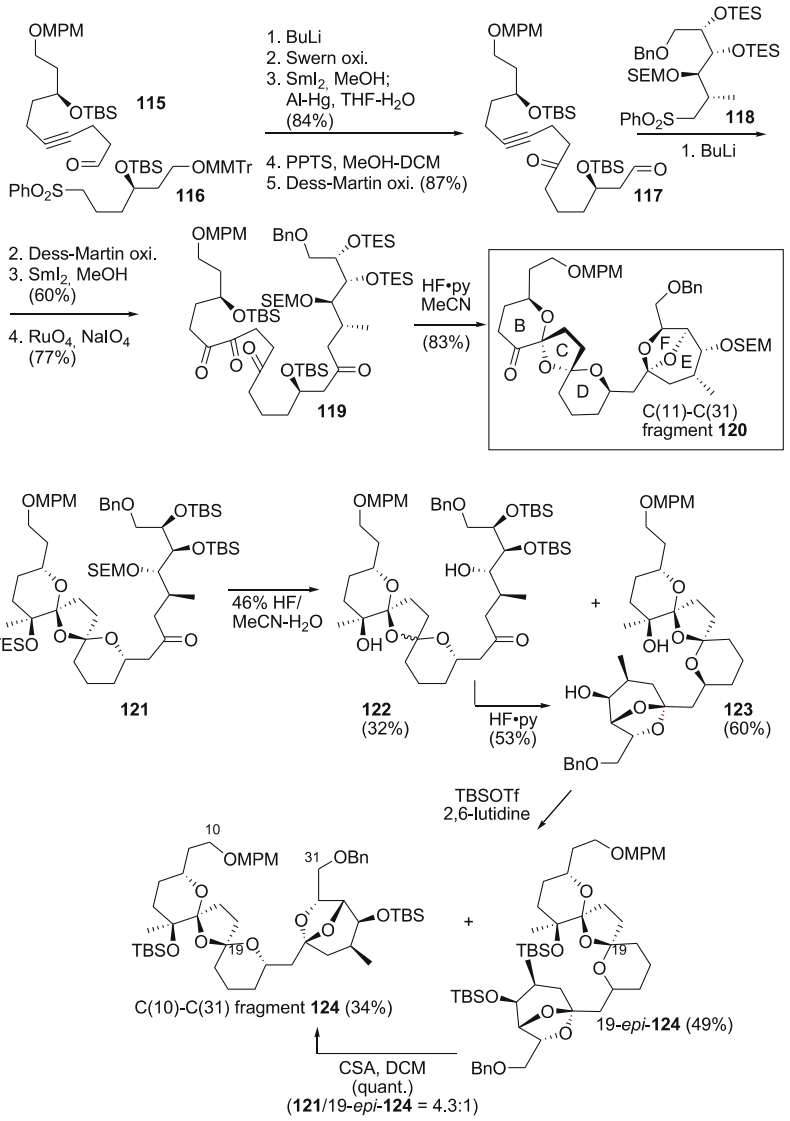


Fig. 6 Configurational studies of BCD-rings of pinnatoxins by Ishihara-Murai's group

B-ring [61]. Deprotection of the TES group on the B-ring of **121** resulted in epimerization at the C19 carbon to give a mixture of **122** and **123.** Complex **122** could be converted to **123.** Then, protection of the tertiary hydroxyl group on the B-ring again as TBS ether gave **124** and 19-*epi*-**124,** in 34% and 49% yield, respectively. Acidic treatment of 19-*epi*-**124** afforded a 4.3 : 1 mixture of **124** and 19-*epi*-**124.**

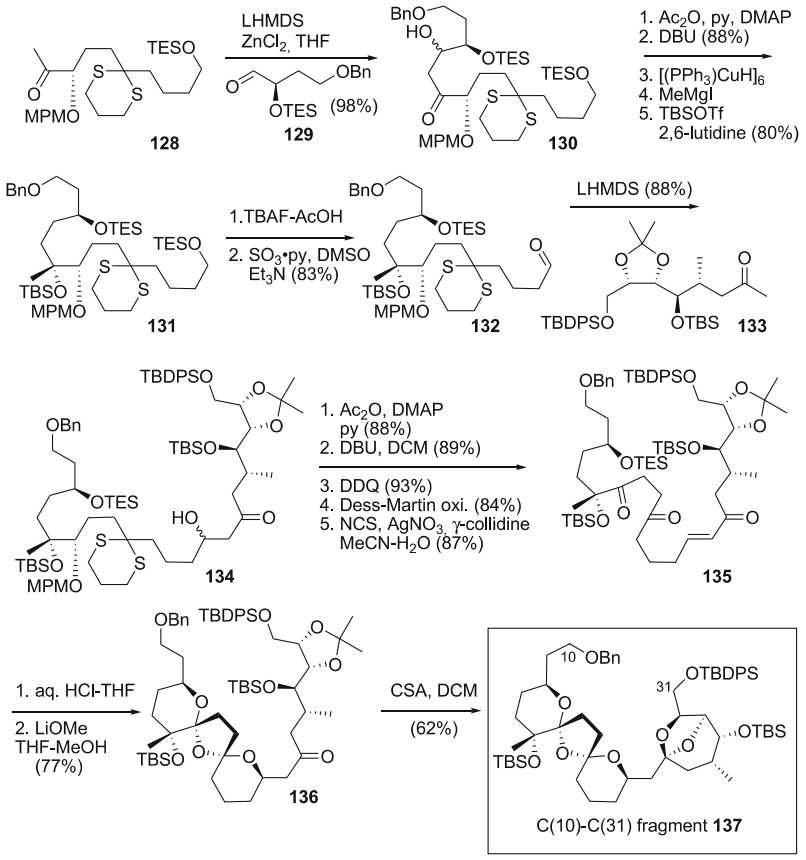


Scheme 11 Ishihara–Murai's preparation of BCDEF-rings of pinnatoxins

As shown in Fig. 6, the structure **125** was the most stable isomer due to the double anomeric effects from the C-ring oxygen atom. On the other hand, **126** partly epimerized to **127** due to the hydrogen bonding between the OH group and the D-ring oxygen atom [61]. These results were also confirmed by Hashimoto's group (vide infra).

5.2 Nakamura–Hashimoto's Synthetic Studies of Pinnatoxins

Nakamura and Hashimoto's group also prepared BCDEF-rings of pinnatoxins (Scheme 12) [64–66]. The aldol reaction of ketone **128** with aldehyde **129** afforded **130**. Removal of the formed hydroxyl group followed by introduction of a methyl group gave **131**, which was then converted to aldehyde **132**. A second aldol reaction with **133** afforded **134**. The aldol part was converted



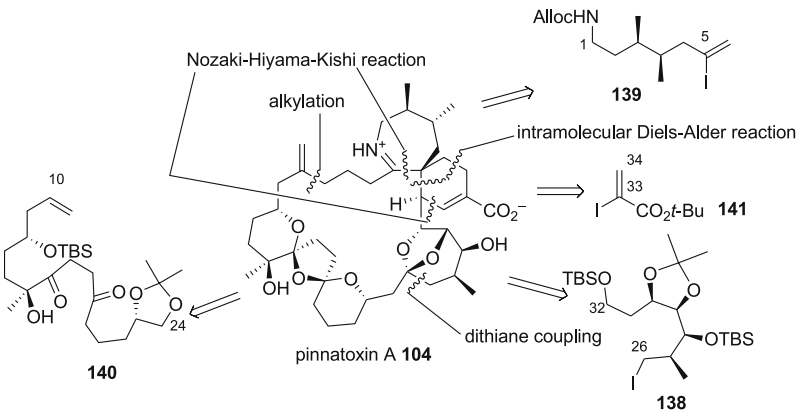
Scheme 12 Nakamura–Hashimoto's preparation of BCDEF-rings of pinnatoxins

to enone **135** as they planned to use a conjugate addition scheme to make the tricyclic spiroacetal. Removal of the TES group of **135**, a trigger of the ring closure of the BCD-ring (**136**), and following acidic treatment gave the desired compound **137** as a single isomer [66].

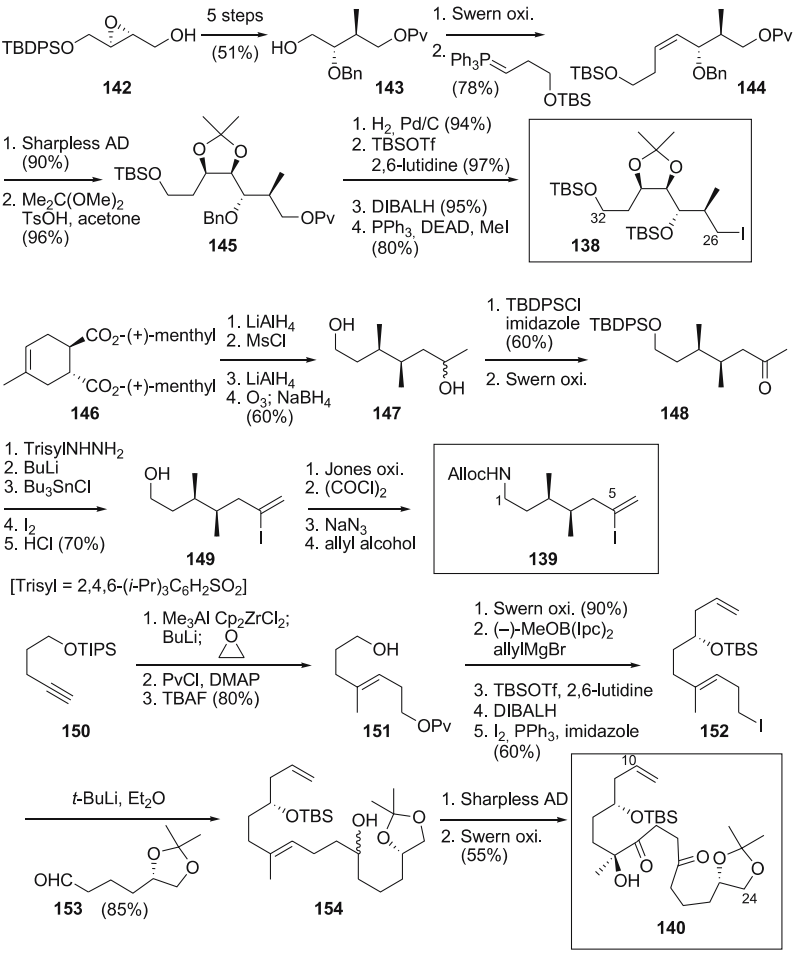
5.3 Kishi's First Total Synthesis of (+)- and (–)-Pinnatoxin A

The first total synthesis of pinnatoxin A (**104**) was completed by Kishi's group in 1998 [67, 68]. Their synthetic strategy is shown in Scheme 13. They planned to make the seven-membered iminium ring at the last stage, and the key macrocyclization was carried out by an intramolecular Diels–Alder reaction. Fragments **138–141** were coupled using the Nozaki–Hiyama–Kishi reaction, Julia coupling reaction etc.

The EF-ring fragment **138** was prepared from epoxide **142** (Scheme 14). Regioselective methylation (**143**) and the Wittig reaction afforded *cis*-olefin **144**. Then, two new asymmetric centers were introduced by Sharpless asymmetric dihydroxylation [39] and the corresponding acetonide **145** was converted to iodide **138**. The *syn*-dimethyl part of **139** was derived from di-(+)-menthyl ester **146** [69]. The ester moieties were reduced to methyls and the double bond was cleaved by ozonolysis to give diol **147**. The primary hydroxyl group was protected and another was oxidized to give **148**. The ketone was converted to vinyl iodide **149** by the Shapiro reaction [70], and a nitrogen function was introduced to another end to give the fragment **139**. Carboalumination of alkyne **150** followed by an attack on ethylene oxide gave **151** [71]. Asymmetric allylation using chiral borane reagent [72] and functional group manipulation afforded iodide **152**, which was coupled with aldehyde **153** derived from (*S*)-malic acid to give alcohol **154**. The introduction of a chiral



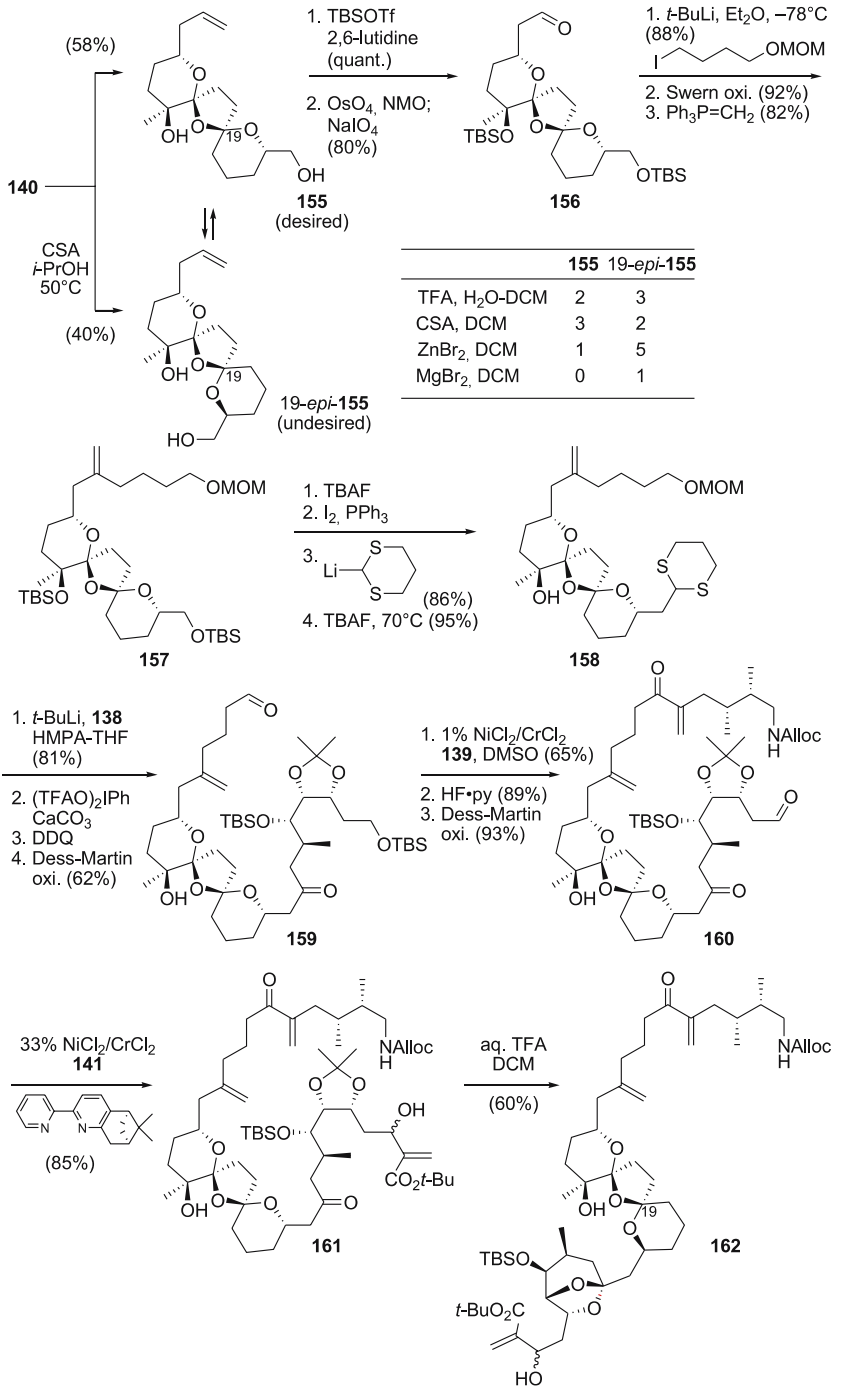
Scheme 13 Synthetic strategy of Kishi's first total synthesis of (+)- and (–)-pinnatoxins A



Scheme 14 Kishi's synthesis-1. Preparation of fragments

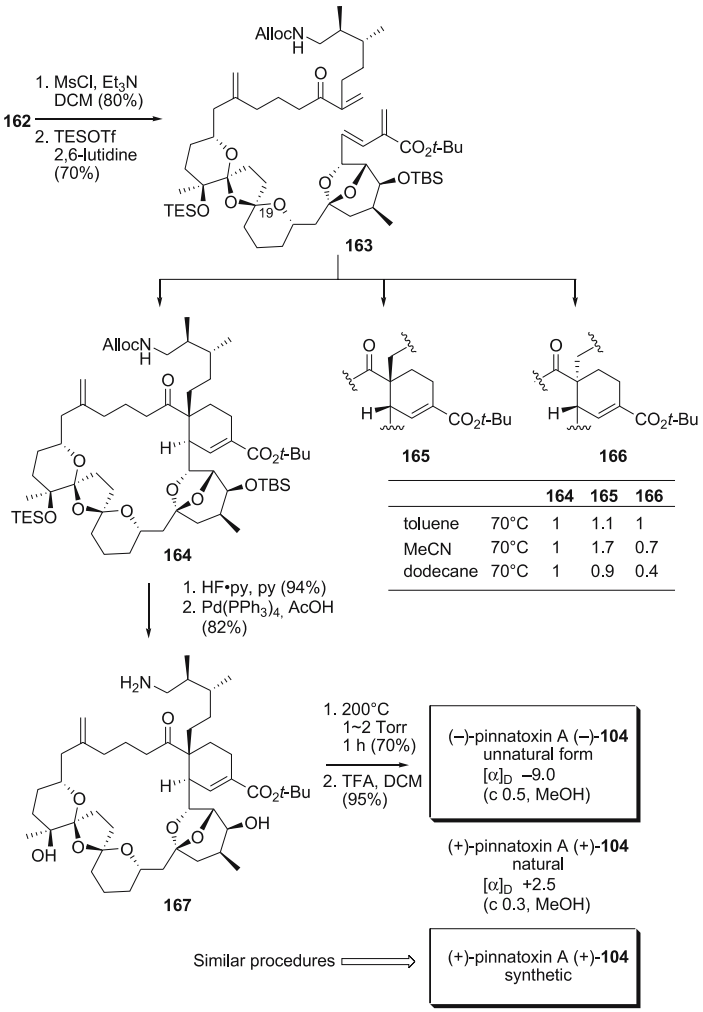
tertiary hydroxyl group at C15 was done using Sharpless asymmetric dihydroxylation (**140**).

The fragment **140** was then subjected to a BCD-ring closure experiment (Scheme 15). Deprotection of the TBS and acetonide group of **140** was carried out using CSA/*i*-PrOH to afford the desired tricyclic spiroacetal **155** and 19-*epi*-**155** in 58% and 40% yield, respectively. Formation of 19-epimer was due to the hydrogen bonding between the tertiary hydroxyl group and the D-ring oxygen as shown by Ishihara et al. (Fig. 6) [61]. These epimers were equilibrated under acidic conditions. Especially 19-*epi*-**155** was an exclusive product using $MgBr_2$, which may be due to its strong chelation effect. Both hydroxyl groups were then protected as TBS ethers and the double bond was cleaved to give aldehyde **156**. Four carbon chain elongation steps followed



Scheme 15 Kishi's synthesis-2. Preparation of BCD- and EF-rings

by Wittig olefination gave **157**. Another end was then converted to terminal dithioacetal **158**, which was then coupled with the iodide **138** to afford **159**. The large fragment **161** was prepared via **160** by successive Nozaki–Hiyama–Kishi reactions [73, 74] of aldehyde **159** with the iodide **139** followed by the iodide **141**. Deprotection of the acetonide group led to the formation of EF-rings to give **162** with a 19-epimerized form. However, this position was re-epimerized to the original form after protection of the 15-hydroxyl group as TES ether to afford **163**, which was a substrate for the key intramolecular Diels–Alder reaction (Scheme 16).



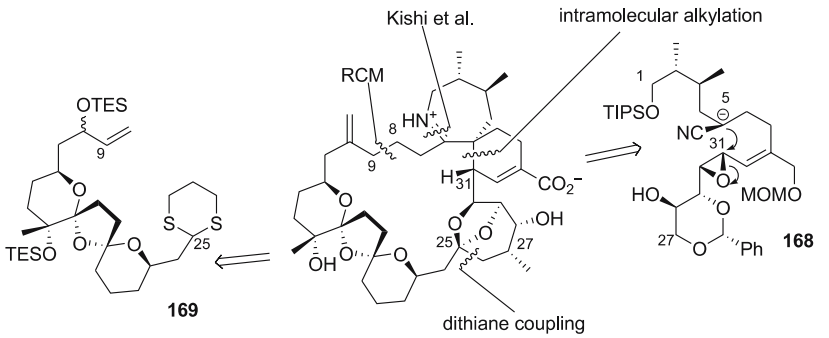
Scheme 16 Kishi's synthesis-3. Intramolecular Diels–Alder reaction and completion of the total synthesis

The intramolecular Diels–Alder reaction proceeded regioselectively, giving the desired **164** along with **165** and **166**. The best result was obtained using dodecane as a solvent. The TBS, TES and Alloc groups were then removed (**167**), and the spirocyclic iminium ring was formed under reduced pressure at 200 °C to remove water. Finally, acidic treatment gave (–)-pinnatoxin A [(–)-**104**]. The absolute stereochemistry of **104** was determined by comparison of the sign of the rotation values. They also synthesized the nature-identical form (+)-**104**.

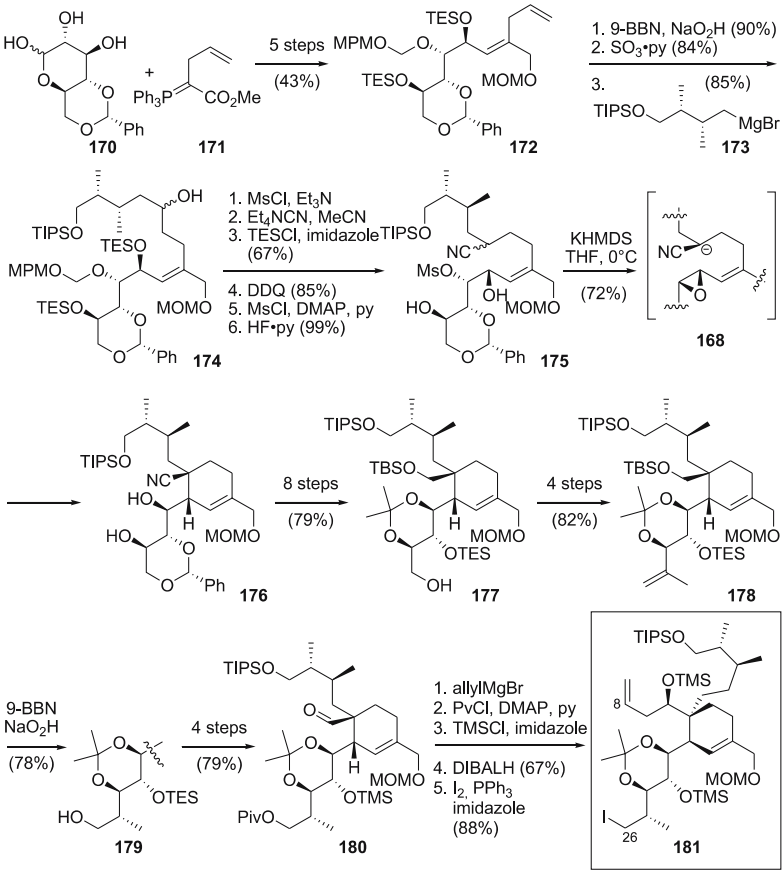
5.4 Inoue–Hirama's Synthesis of (+)-Pinnatoxin A

The key reaction of the second synthesis of (+)-**104** by Inoue–Hirama's group [75–79] was intramolecular alkylation of nitrile-epoxide **168** to form the G-ring, and dithiane coupling and olefin metathesis [80–82] with BCD-ring fragment **169** for macrocyclization (Scheme 17).

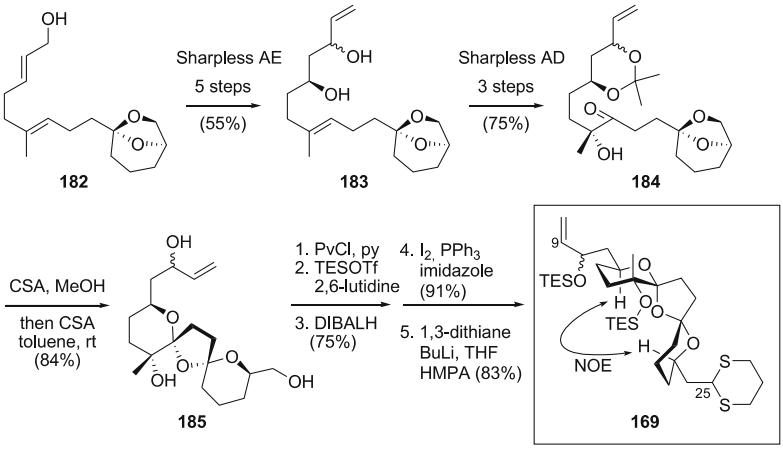
Starting from the Wittig reaction of the glucose derivative **170** [83] with phosphorane **171** [84] **172** was afforded. Hydroboration–oxidation of the terminal olefin followed by Grignard reaction with **173** [78] gave **174**, which was converted to nitrile **175**, the precursor of the intramolecular alkylation, in six steps. Treatment of the nitrile with 1,2-diol monomesylate **175** with KHMDS initially formed epoxide **168**, which was attacked by the carbanion α to the cyano group to give G-ring compound **176** in 72% yield as a sole isomer. Functional group interconversion in eight steps gave **177**, which was further converted to olefin **178**. Stereoselective hydroboration of the terminal double bond of **178** accomplished using 9-BBN and the product **179** was converted to aldehyde **180**. The right-hand fragment **181** was prepared from **180** in five steps.



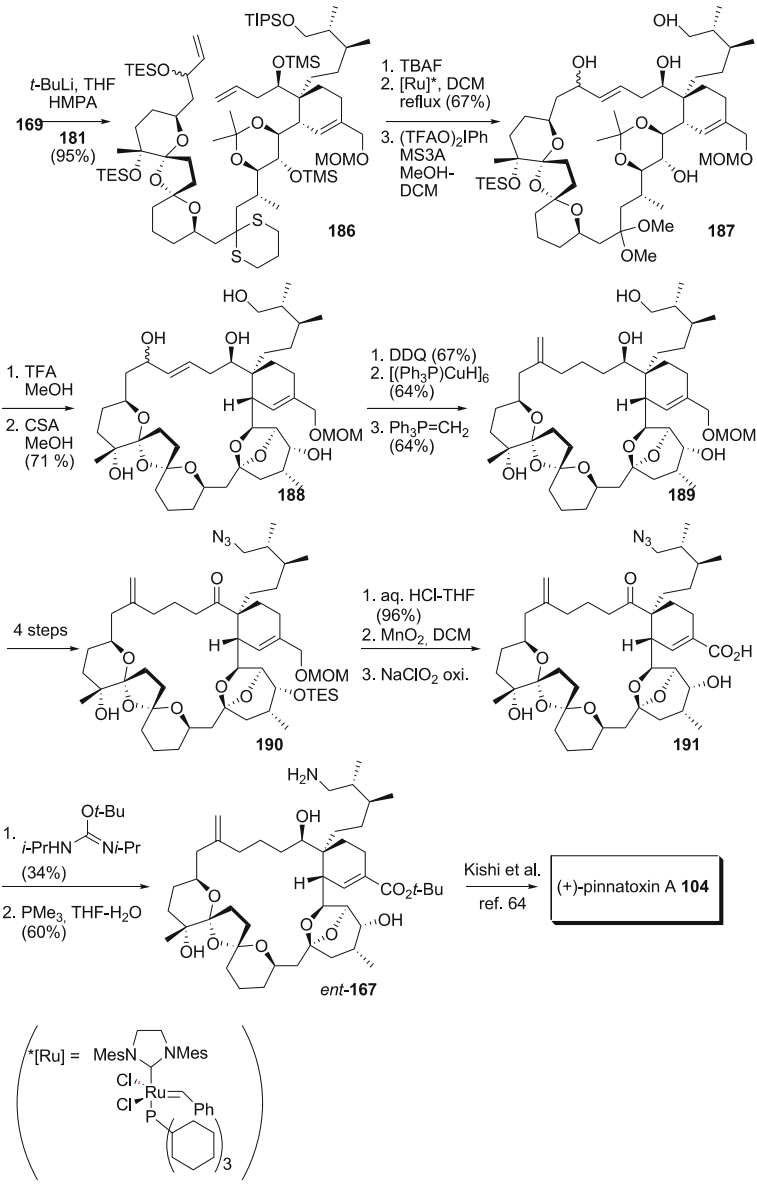
Scheme 17 Synthetic strategy of Inoue–Hirama's synthesis of (+)-pinnatoxin A



Scheme 18 Hirama's synthesis-1. Preparation of the G-ring



Scheme 19 Hirama's synthesis-2. Preparation of the BCD-rings



Scheme 20 Hirama's synthesis-3. Completion of the total synthesis

Preparation of another fragment began with **182** [75]. The asymmetry of the secondary hydroxyl groups of **183** and that of the tertiary one of **184** was derived from Sharpless epoxidation and Sharpless dihydroxylation. Acidic treatment to remove the acetonide group afforded tricyclic spiroacetal **185**. The stereochemistry was confirmed by NOE observed in the dithiane **169**.

Alkylation of dithiane **169** with **181** gave **186** in 95% yield. Macrocyclization by olefin metathesis using Grubbs' catalyst [85] successfully formed *E*-olefin and an acetal-exchange reaction [86] gave **187**. Removal of the TES and TIPS groups and acetonide exchange to form bicyclic EF-rings were accomplished in a two-step procedure (**188**). Then, the allylic hydroxyl group was converted to *exo*-olefin (**189**), and the primary hydroxyl group was transformed to an azide group (**190**). The MOM group was removed and the resulting allylic alcohol was oxidized to carboxylic acid **191**. The azide group of **191** was reduced to an amino group to afford Kishi's intermediate *ent*-**167**, which was converted to (+)-pinnatoxin A (**104**) according to Kishi [67] to complete the total synthesis.

6 Conclusion

Recent examples of synthetic studies of marine natural products with bicyclic and/or spirocyclic acetals have been described. There is an equilibrium between these acetals and their hydrate forms, dihydroxy ketones. Spiro carbons of spiroacetals in particular are prone to epimerize via oxonium cation intermediates even in the absence of water (or the presence of Lewis acid). Although these phenomena are undesirable for synthetic chemists, their study will shed light on the mechanism of acetal biological action and lead to the development of new medicines and agrochemicals.

References

1. Blunt JW, Copp BR, Munro MHG, Northcote PT, Prinsep MR (2003) Nat Prod Rep:1
2. Faulkner DJ (2002) Nat Prod Rep:1
3. Deslongchamps P, Rowan DD, Pothier N, Sauvé T, Saunders JK (1981) Can J Chem 59:1105
4. Vaillancourt V, Pratt NE, Perron F, Albizati KF (1992) The total synthesis of spiroketal-containing natural products. In: ApSimon J (ed) The total synthesis of natural products, vol 8. Wiley, New York, p 533
5. González N, Rodríguez J, Jiménez C (1999) J Org Chem 64:5705
6. Mitchell SS, Rhodes D, Bushman FD, Faulkner DJ (2000) Org Lett 2:1605
7. Kiyota H, Dixon DJ, Luscombe CK, Hettstedt S, Ley SV (2002) 4:3223
8. Garner P, Park JM (1987) J Org Chem 52:2361
9. Dixon DJ, Foster AC, Ley SV (2000) Org Lett 2:123
10. Ohtani I, Kusumi T, Kashman Y, Kakisawa H (1987) J Am Chem Soc 113:4092
11. Lidström P, Tierney J, Wathey B, Westman J (2001) Tetrahedron 57:9225
12. Takada N, Suenaga K, Yamada K, Zheng SZ, Chen HS, Uemura D (1999) Chem Lett 1025
13. Suenaga K, Araki K, Sengoku T, Uemura D (2001) Org Lett 3:527
14. Araki K, Suenaga K, Sengoku T, Uemura D (2002) Tetrahedron 58:1983

15. Evans DA, Chapman KT, Carreira EM (1988) J Am Chem Soc 110:3560
16. Van de Weghe P, Aoun D, Boitear JG, Eustache J (2002) Org Lett 4:4105
17. Evans PA, Murthy VS (1998) J Org Chem 63:6768
18. Rychnovsky SD, Griesgraber G, Zeller S, Skalizky DJ (1991) J Org Chem 56:5161
19. Oikawa M, Ueno T, Oikawa H, Ichihara A (1995) J Org Chem 60:5048
20. Bazan GC, Oskam JH, Cho HN, Park LY, Schrock RR (1990) J Am Chem Soc 112:8378
21. Carey JS, Coulter TS, Thomas EJ (1993) Tetrahedron Lett 34:3933
22. Enders D, Lenzen A (2003) Synlett:2185
23. Enders D, Jegelka U (1992) Synlett: 999
24. Job A, Janeck CF, Bettray W, Peters R, Enders D (2002) Tetrahedron 58:2253
25. Gouiffes D, Juge M, Grimaud N, Welin L, Sauviat MP, Barbin Y, Laurent D, Roussakis C, Henichart JP, Verbist JF (1988) Toxicon 26:1129
26. Gouiffés D, Moreau S, Helbecque N, Bernier JL, Hénichart JP, Barbin Y, Laurent D, Vervist JF (1988) Tetrahedron 44:451
27. Degnan BM, Hawkins CJ, Lavin MF, McCaffrey EJ, Parry DL, Watters DJ (1989) J Med Chem 32:1354
28. Foster MP, Mayne CL, Dunkel R, Pugmire RJ, Grant DM, Kornprobst JM, Verbist JF, Biard JF, Ireland CM (1992) J Am Chem Soc 114:1110
29. Biard JF, Roussakis C, Kornprobst JM, Verbist JF, Cotelle P, Foster MP, Ireland CM, Debitus C (1994) J Nat Prod 57:1336
30. Johnson WE, Watters D, Suniara RK, Brown G, Bruce CM (1999) Biochem Biophys Res Commun 260:80
31. Siavoshian S, Jacquot C, Biard JF, Briand G, Roussakis C (1999) Anticancer Res 19:5361
32. Solladié G, Bauder C, Biard JF (2000) Tetrahedron Lett 41:7747
33. Gallagher PO, McErlean CSP, Jacobs MF, Watters DJ, Kitching W (2002) Tetrahedron Lett 43:531
34. Banwell MG, Bui CT, Simpson GH (1988) J Chem Soc Perkin Trans 1:791
35. Frick JA, Klassen JB, Bathe A, Abrahamsons JM, Rappoport H (1992) Synthesis:621
36. Enders D, Gatzweiler W, Dederichs E (1990) Tetrahedron 46:4757
37. Wipf P, Uto Y, Yoshimura S (2002) Chem Eur J 8:1670
38. Kolb HC, VanNieuwenhze MS, Sharpless KB (1994) Chem Rev 94:2483
39. Damon RE, Schlessinger RH (1976) Tetrahedron Lett:1561
40. Wessjohann L, Gabriel T (1997) J Org Chem 62:3772
41. Danishefsky SJ, Armistead DM, Wincott FE, Selnick HG, Hungate R (1989) J Am Chem Soc 111:2967
42. Broka CA, Ehrler J (1991) Tetrahedron Lett 32:5907
43. Kondru RK, Wipf P, Beratan DN (1998) Science 282:2247
44. Kondru RK, Wipf P, Beratan DN (1998) J Am Chem Soc 120:2204
45. Ribe S, Kondru RK, Beratan DN, Wipf P (2000) J Am Chem Soc 122:4608
46. Martischonok V, Melikyan GG, Mineif A, Vostrowsky O, Bestmann HJ (1991) Synthesis:633
47. Wipf P, Hopkins TD (2005) Chem Commun 3421
48. Novak T, Tan Z, Liang B, Negishi E (2005) J Am Chem Soc 127:2838
49. Evans PA, Cue J, Gharpure SJ, Hinkle RJ (2003) J Am Chem Soc 125:11456
50. Uemura D, Chou T, Haino T, Nagatsu A, Fukuawa S, Zheng S, Chen H (1995) J Am Chem Soc 117:115
51. Chou T, Kamo O, Uemura D (1996) Tetrahedron Lett 37:4023
52. Takada N, Umemura N, Suenaga K, Chou T, Nagatsu A, Haino T, Yamada K, Uemura D (2001) Tetrahedron Lett 42:3491

53. Takada N, Umemura N, Suenaga K, Uemura D (2001) Tetrahedron Lett 42:3495
54. Zheng SH, Huang FL, Chen SC, Tan XF, Zuo JB, Peng J, Xie RW (1990) Chin J Mar Drugs 33:33
55. Hu T, Curtis JM, Walter JA, Watson-Wright WM, Wright JLC (1995) J Chem Soc Chem Commun:2159
56. Falk M, Burton IW, Hu T, Walter JA, Wright JLC (2001) Tetrahedron 57:8659
57. Suthers BD, Jacobs MF, Kitching W (1998) Tetrahedron Lett 39:2621
58. Pelc MJ, Zakarian A (2005) Org Lett 7:1629
59. Furkert DP, Brimble MA (2002) Org Lett 4:3655
60. Sugimoto T, Ishihara J, Murai A (1997) Tetrahedron Lett 38:7379
61. Ishihara J, Sugimoto T, Murai A (1998) Synlett:603
62. Sugimoto T, Ishihara J, Murai A (1999) Synlett:541
63. Ishihara J, Tojo S, Kamikawa A, Murai A (2001) Chem Commun:1392
64. Nakamura S, Inagaki J, Sugimoto T, Kudo M, Nakajima M, Hashimoto S (2001) Org Lett 3:4075
65. Nakamura S, Inagaki J, Kudo M, Sugimoto T, Obara K, Nakajima M, Hashimoto S (2002) Tetrahedron 58:10353
66. Nakamura S, Inagaki J, Sugimoto T, Ura Y, Hashimoto S (2002) Tetrahedron 58:10375
67. MacCauley JA, Nagasawa K, Lander PA, Mischke SG, Semones MA, Kishi Y (1988) J Am Chem Soc 120:7647
68. Nagasawa K (2000) J Synth Org Chem Jpn 58:877
69. Furuta K, Iwanaga K, Yamamoto H (1986) Tetrahedron Lett 27:4507
70. Chamberlin AR, Bloom SH (1990) Org React 39:1
71. Negishi E, Kihg AO, Klima WL (1980) J Org Chem 45:2526
72. Jadhav PK, Bhat KS, Perumal PT, Brown HC (1986) J Org Chem 51:432
73. Jin H, Uenishi J, Christ WJ, Kishi Y (1986) J Am Chem Soc 108:5644
74. Takai K, Tagashira M, Kuroda T, Oshima K, Utimoto K, Nozaki H (1986) J Am Chem Soc 108:6048
75. Noda T, Ishiwata A, Uemura S, Sakamoto S, Hirama M (1998) Synlett:298
76. Ishiwata A, Sakamoto S, Noda T, Hirama M (1999) Synlett:692
77. Nitta A, Ishiwata A, Noda T, Hirama M (1999) Synlett:695
78. Wang J, Sakamoto S, Kamada K, Nitta A, Noda T, Oguri H, Hirama M (2003) Synlett:891
79. Sakamoto S, Sakazaki H, Hagiwara K, Kamada K, Ishii K, Noda T, Inoue M, Hirama M (2004) Angew Chem Int Ed 43:6505
80. Grubbs RH, Chang S (1998) Tetrahedron 54:4413
81. Fürstner A (2000) Angew Chem Int Ed 39:3013
82. Trnka TM, Grubbs RH (2001) Acc Chem Res 24:18
83. Barili PL, Berti G, Catelani G, Cini C, D'Andrea F, Mastrorilli E (1995) Carbohydr Res 278:43
84. Bestmann HJ (1965) Angew Chem Int Ed Engl 4:645
85. Scholl M, Ding S, Lee CW, Grubbs RH (1999) Org Lett 1:953
86. Stork G, Zhao K (1989) Tetrahedron Lett 30:287

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Recent Advances in Total Synthesis of Marine Polycyclic Ethers

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Abstract The polycyclic ether class of marine natural products are some of the largest and most complex natural products. The fascinating molecular architectures and the extraordinarily potent biological activities of these molecules make them formidable and challenging synthetic targets. In the last few years, methodologies and strategies for the convergent synthesis of these large polycyclic ethers have made rapid progress, culminating in several total syntheses. This review highlights the recently completed total syntheses of polycyclic ether natural products.

Keywords Fragment coupling · Marine natural products · Polycyclic ethers · Total synthesis

Abbreviations

Cy	cyclohexyl
dba	dibenzylideneacetone
DMDO	dimethyl dioxirane
dppf	1,1′-bis(diphenylphosphino)ferrocene

dr	diastereomeric ratio
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
EE	ethoxyethyl
LDBB	lithium 4,4′-*tert*-butylbiphenylide
NAP	2-naphtylmethyl
NIS	*N*-iodosuccinimide
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide
PMB	*p*-methoxybenzyl
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
TES	triethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate

1 Introduction

Since the structure of brevetoxin-B (**1**, Fig. 1) was first reported by the Nakanishi group in 1981 [1], marine polycyclic ethers represent a growing class of naturally occurring substances with intriguing molecular architectures and potent biological properties [2–5]. These toxic metabolites, produced by marine unicellular algae, chiefly dinoflagellates, usually contain extended arrays of *trans*-fused cyclic (five- to nine-membered) ethers. Figure 1 shows a number of representative examples from this class of natural products, including brevetoxin-B (**1**) and A (**2**) [6, 7], hemibrevetoxin-B (**3**) [8], ciguatoxin (CTX, **4a**) [9–11], CTX3C (**4b**) [12], gambierol (**5**) [13, 14], gambieric acid A (**6**) [15–17] and gymnocin-A (**7**) [18]. Despite the common polycyclic ether structure motif, they show diverse biological activities with extreme potency, i.e. neurotoxicity, cytotoxicity and antifungal activity. However, the target receptor protein has only been identified for brevetoxins and ciguatoxins, which bind to voltage-sensitive sodium channels in the nervous system and inhibit depolarization [19–23], and the biological aspects of many of these molecules have not been fully investigated, mainly because of their limited availability from natural sources. Thus, chemical total synthesis plays an important role for production of useful quantities of these molecules and their structural analogues for detailed biological studies.

Under these circumstances, considerable efforts have been devoted toward their total syntheses over the past two decades [24–27]. In 1995, Nicolaou and co-workers completed the total synthesis of brevetoxin-B (**1**) after a 12-year endeavor, which is the first synthesis of a highly complex molecule of the polycyclic ether class [28–33]. This seminal work was followed by the synthesis of brevetoxin-A (**2**) by the same group in 1998 [34–38]. These outstanding achievements in the total synthesis of polycyclic ether natural products revealed the power of contemporary organic synthesis and, at the same time,

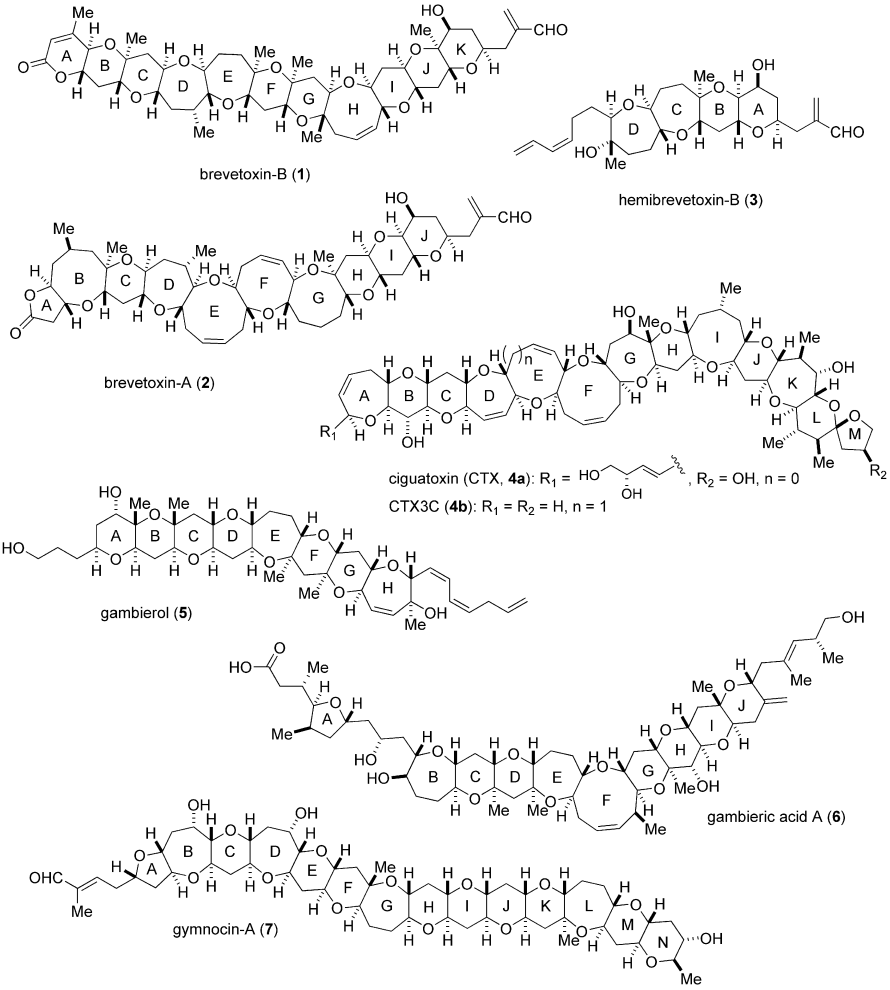


Fig. 1 Representative polycyclic ether marine natural products

its limitation in terms of efficiency and speed of delivery. In the past five years, the total syntheses of these large polycyclic ether natural products have made remarkable progress with the advance of synthetic methodologies and strategies, especially the development of an efficient method for convergent assembly of a polycyclic ether system, which is an obviously indispensable issue in this field. These efforts led to the total syntheses of CTX3C (**4b**) by the Hirama group in 2001 [39–42], gambierol (**5**) by the groups of Sasaki (2002) [43, 44], Yamamoto/Kadota (2003) [45, 46], and Rainier (2004) [47], gymnocin-A (**8**) by the Sasaki group (2003) [48, 49], and brevetoxin-B (**1**) by the Nakata (2004) [50] and Yamamoto/Kadota groups (2005) [51]. This review highlights these recently completed total syntheses of polycyclic ethers,

particularly focusing on the new methodologies and strategies developed for realizing the pivotal fragment couplings.

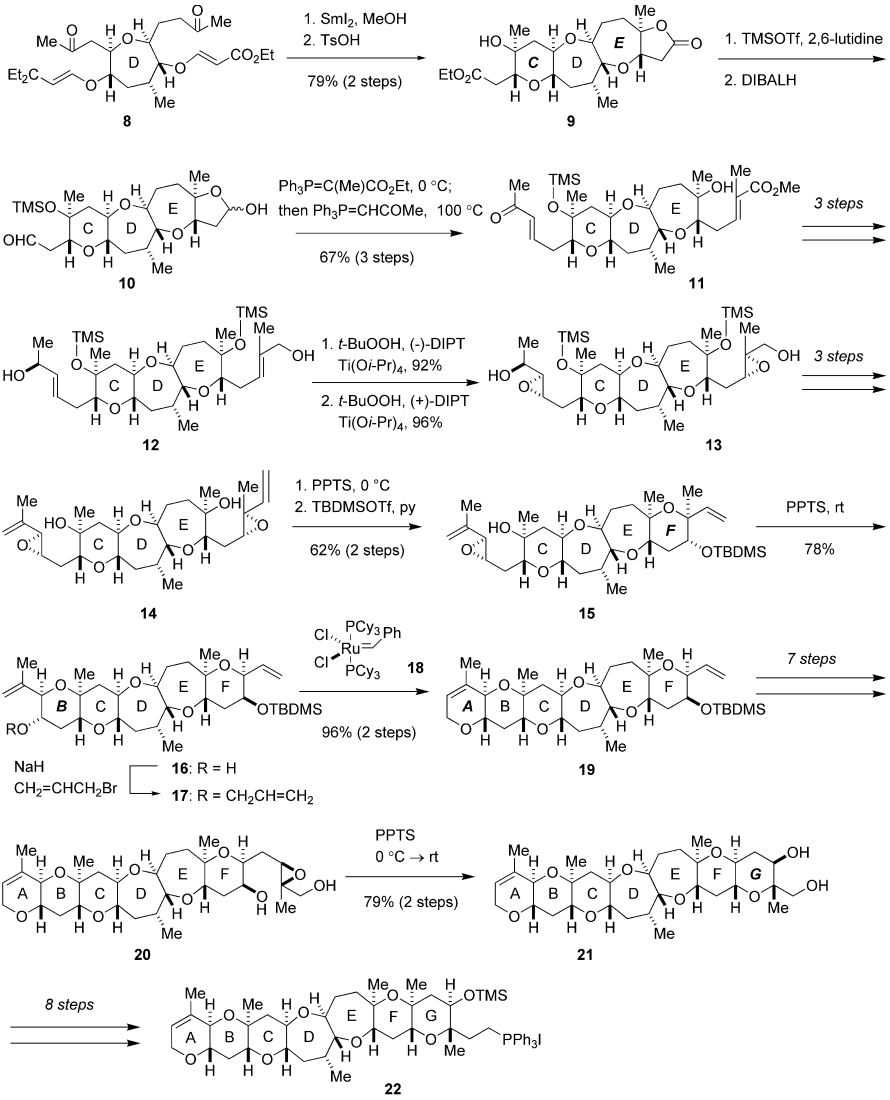
2
Total Synthesis of Brevetoxins

The dinoflagellate *Karenia brevis* (formerly *Gymnodinium breve*) is the red-tide causing organism responsible for massive fish kills and human intoxications including so-called neurotoxic shellfish poisoning (NSP) in the Gulf of Mexico and along the coast of Florida. Brevetoxins (**1**, **2**), the causative agents of the poisoning, are lipid soluble neurotoxins and the first members of polycyclic ethers to be structurally elucidated [1, 6, 7]. These molecules exhibit their potent neurotoxicity by binding to the voltage-sensitive sodium channels on excitable membranes [19–21]. The specific binding site on the channel proteins was reported to be shared by ciguatoxins [22, 23].

2.1
Nakata Synthesis of Brevetoxin-B

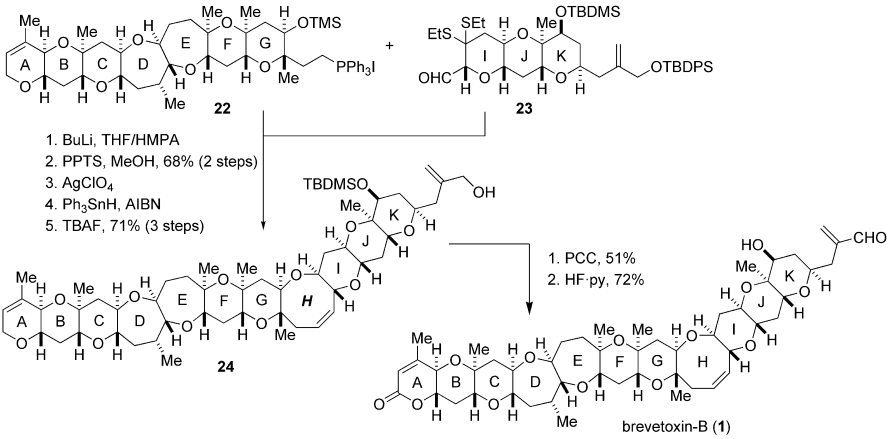
In 2004, Nakata and co-workers disclosed the second total synthesis of brevetoxin-B (**1**) nine years after the first synthesis by the Nicolaou group [50]. Their synthesis relied on the same key fragment coupling between the ABCDEFG- and IJK-rings as that developed in the pioneering work of Nicolaou et al. in their first total synthesis. A most elegant feature of the Nakata synthesis is a two-directional strategy for the construction of the ABCDEFG-ring fragment **22** [28, 31], which realized overall efficiency of their synthesis.

The synthesis of the ABCDEFG-ring **22** started with a two-directional cyclization of the D-ring **8**, derived from tri-*O*-acetyl-D-glucal (Scheme 1). Double reductive cyclization of **8** with samarium(II) iodide [52–55] proceeded with complete stereocontrol to form the C- and E-rings, leading to lactone **9** in high yield. Protection as the TMS ether followed by DIBALH reduction afforded aldehyde-lactol **10**, which was then subjected to one-pot, two-directional Wittig homologation. The first Wittig reagent, $Ph_3P=C(Me)CO_2Et$, predominantly reacted with the lactol moiety at 0 °C, and the second Wittig reagent, $Ph_3P=CHCOMe$, reacted with the aldehyde at elevated temperature to generate **11**. After a three-step sequence, the resultant bis(allyl alcohol) **12** was subjected to consecutive Sharpless asymmetric epoxidation; namely, treatment with *t*-BuOOH/(–)-DIPT/Ti(O*i*-Pr)$_4$ and then *t*-BuOOH/(+)-DIPT/Ti(O*i*-Pr)$_4$ effected epoxidation at the right and left sides, respectively, giving bis(α-epoxide) **13**. A further three-step double reaction converted **13** into bis(vinyl epoxide) **14**, which upon treatment with PPTS at 0 °C effected 6-*endo* cyclization at the right side to give **15**, after protection as the TBDMS ether. Subsequently, PPTS treatment of **15** at room



Scheme 1 Total synthesis of brevetoxin-B by Nakata and co-workers

temperature induced a second 6-*endo* cyclization at the left side to afford the BCDEF-ring system **16**. Following *O*-allylation, a ring-closing metathesis (RCM) reaction of the derived **17** with Grubbs catalyst **18** [56] proceeded smoothly to give **19**, which was then elaborated to epoxy diol **20** in seven steps. Exposure of **20** to PPTS effected 6-*endo* cyclization to give **21**, which was successfully transformed into phosphonium salt **22** [28, 31], representing the ABCDEFG-ring fragment, in an eight-step sequence.

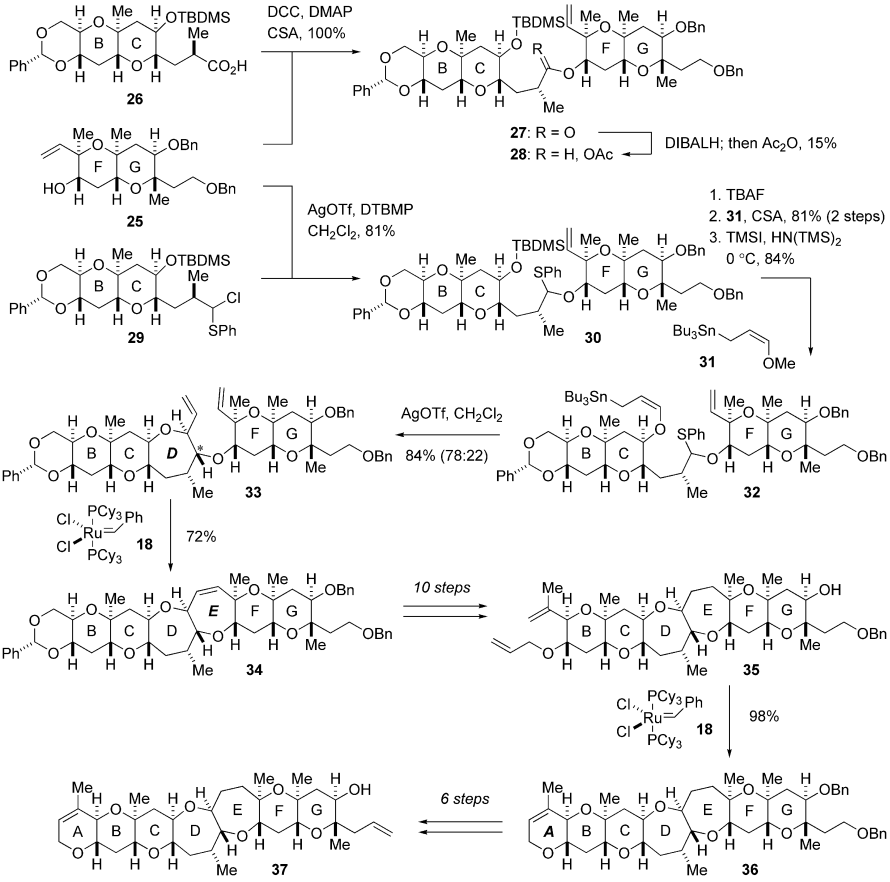


Scheme 2 Total synthesis of brevetoxin-B by Nakata and co-workers (continued)

Wittig reaction of **22** with the IJK-ring fragment **23** followed by closure of the H-ring was performed according to Nicolaou's procedure [29, 32, 57, 58] to generate the polycyclic ether skeleton **24**, after TBDPS deprotection (Scheme 2). Finally, simultaneous oxidation of allylic alcohol and the A-ring methylene with PCC, followed by deprotection, completed the total synthesis of brevetoxin-B (**1**). Thus, the present total synthesis was achieved in 59 steps as the longest linear sequence with an average of 93% yield for each step.

2.2 Yamamoto/Kadota Synthesis of Brevetoxin-B

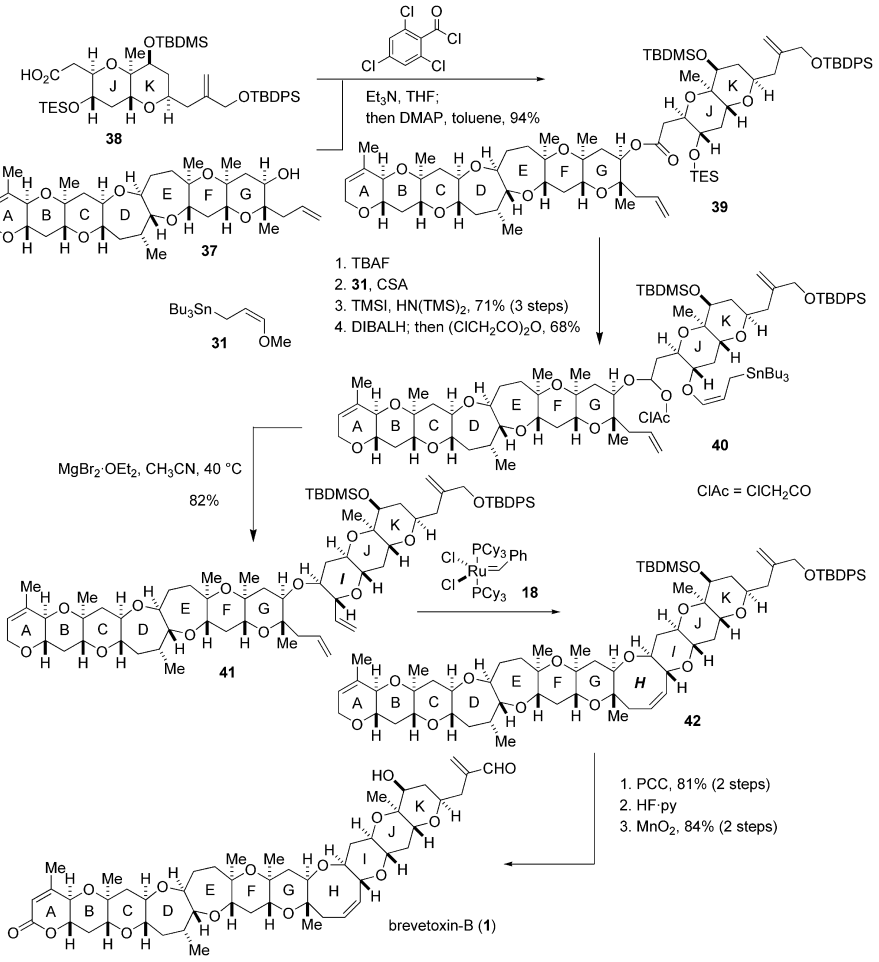
The Yamamoto/Kadota group disclosed a highly convergent total synthesis of brevetoxin-B (**1**) in 2005 [51]. The synthesis was based on their developed convergent approach to a polycyclic ether system using an intramolecular cyclization of γ-alkoxyallylstannanes with α-acyloxy ethers in conjunction with RCM [59, 60]. Alcohol **25** and carboxylic acid **26** were coupled through esterification to give **27** (Scheme 3). Reductive acetylation of **27** according to the method of Rychnovsky [61–63] resulted in over-reduction of the hemiacetal intermediate to give a poor yield (15%) of the desired α-acetoxy ether **28**. This problem was overcome by using the *O*,*S*-acetal method developed by the Hirama/Inoue group (vide infra) [64, 65]. Thus, α-chlorosulfide **29**, prepared from the precursor sulfide, was coupled with alcohol **25** using silver triflate (AgOTf) in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) to afford *O*,*S*-acetal **30** in high yield. After desilylation with TBAF, the resultant alcohol was reacted with γ-methoxyallylstannane **31** in the presence of catalytic amounts of CSA to produce a mixed acetal, which was then treated with iodotrimethylsilane and hexamethyldisilazane leading to γ-alkoxyallylstannane **32**. Upon treatment of **32** with AgOTf, the *O*,*S*-acetal



Scheme 3 Total synthesis of brevetoxin-B by the Yamamoto/Kadota group

worked as an electrophile and intramolecular cyclization proceeded to give oxepane **33** along with its diastereomer at C16 (dr = 78 : 22). Subsequently, the E-ring was formed by RCM to give the BCDEFG-ring system **34**. For the construction of the A-ring, **34** was converted into allyl ether **35** and subjected to RCM to afford **36**. A further six-step sequence of reactions was required to obtain the ABCDEFG-ring fragment **37**.

Condensation of **37** with the JK-ring carboxylic acid **38** under the Yamaguchi conditions provided ester **39** in high yield (Scheme 4). After selective removal of the triethylsilyl (TES) ether, the resultant alcohol was converted to the allylstannane by the standard procedure. DIBALH reduction of the ester followed by in situ esterification with chloroacetic anhydride/DMAP/pyridine delivered α-chloroacetoxy ether **40**. Intramolecular cyclization of **40** with magnesium bromide etherate in acetonitrile afforded the desired product **41** as a single stereoisomer in 82% yield. RCM reaction of **41** using **18** pro-

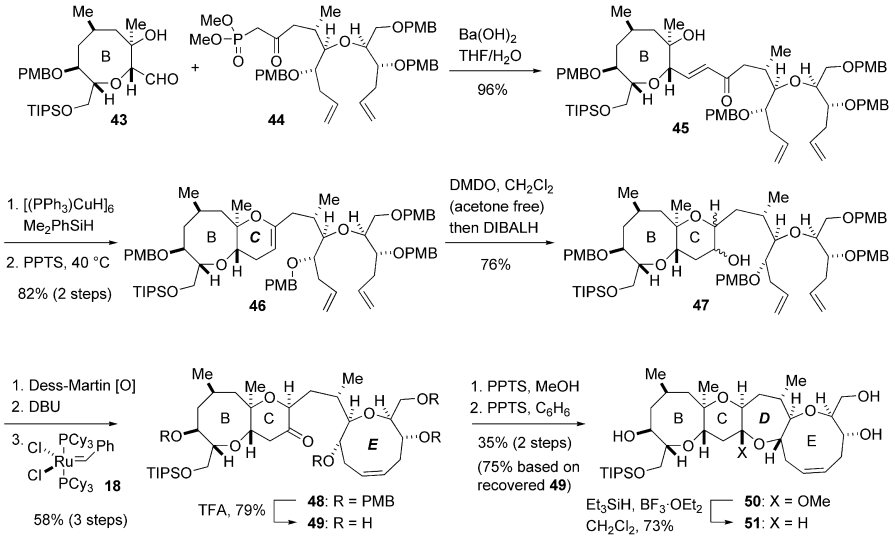


Scheme 4 Total synthesis of brevetoxin-B by the Yamamoto/Kadota group (continued)

vided the undecacyclic polyether skeleton **42**. Oxidation of the A-ring and desilylation, followed by oxidation of the resultant allylic alcohol, furnished brevetoxin-B (**1**). The longest linear sequence leading to **1** was 63 steps with 0.28% overall yield. The Yamamoto/Kadota synthesis demonstrated the utility of their intramolecular allylation/RCM strategy for the convergent synthesis of polycyclic ethers.

2.3 Crimmins Approach to Brevetoxin-A

Very recently, Crimmins and co-workers reported their convergent synthesis of the BCDE-ring fragment **51** of brevetoxin-A (**2**) (Scheme 5) [66]. The syn-



Scheme 5 Synthetic approach toward brevetoxin-A by Crimmins and co-workers

thesis features the Horner–Wadsworth–Emmons reaction to couple two complex fragments, cyclization/dehydration to form the six-membered C-ring as an endocyclic enol ether, and construction of the D-ring through reductive etherification.

The B-ring unit **43** and the E-ring precursor **44** were synthesized based on their established strategy for the synthesis of medium-ring ethers through RCM of diene fragments generated from chiral auxiliary-mediated aldol and alkylation reactions. The Horner–Wadsworth–Emmons coupling of **43** and **44** afforded enone **45**, which was subjected to 1,4-reduction using Stryker's reagent [67] to give the corresponding saturated ketone. Subsequent treatment with PPTS generated endocyclic enol ether **46** exclusively. Transformation of the C-ring enol ether to a suitable D-ring precursor was achieved by epoxidation using "acetone-free" dimethyl dioxirane (DMDO) followed by in situ DIBALH reduction. Although oxidation of the resultant alcohol **47** provided a 4 : 1 mixture of ketones with the undesired diastereomer predominating, isomerization of the undesired isomer was realized by exposure to DBU. Subsequently, the nine-membered E-ring was formed by RCM using Grubbs catalyst **18** to generate tricyclic ketone **48**. Selective removal of the *p*-methoxybenzyl (PMB) groups with trifluoroacetic acid gave keto alcohol **49**, ready for cyclization of the D-ring. A two-step procedure via the intermediary dimethyl ketal led to the desired mixed methyl ketal **50** albeit in modest yield. Finally, reduction of **50** with triethylsilane and boron trifluoride etherate completed the synthesis of the BCDE-ring fragment **51** of brevetoxin-A (**2**) as a single diastereomer.

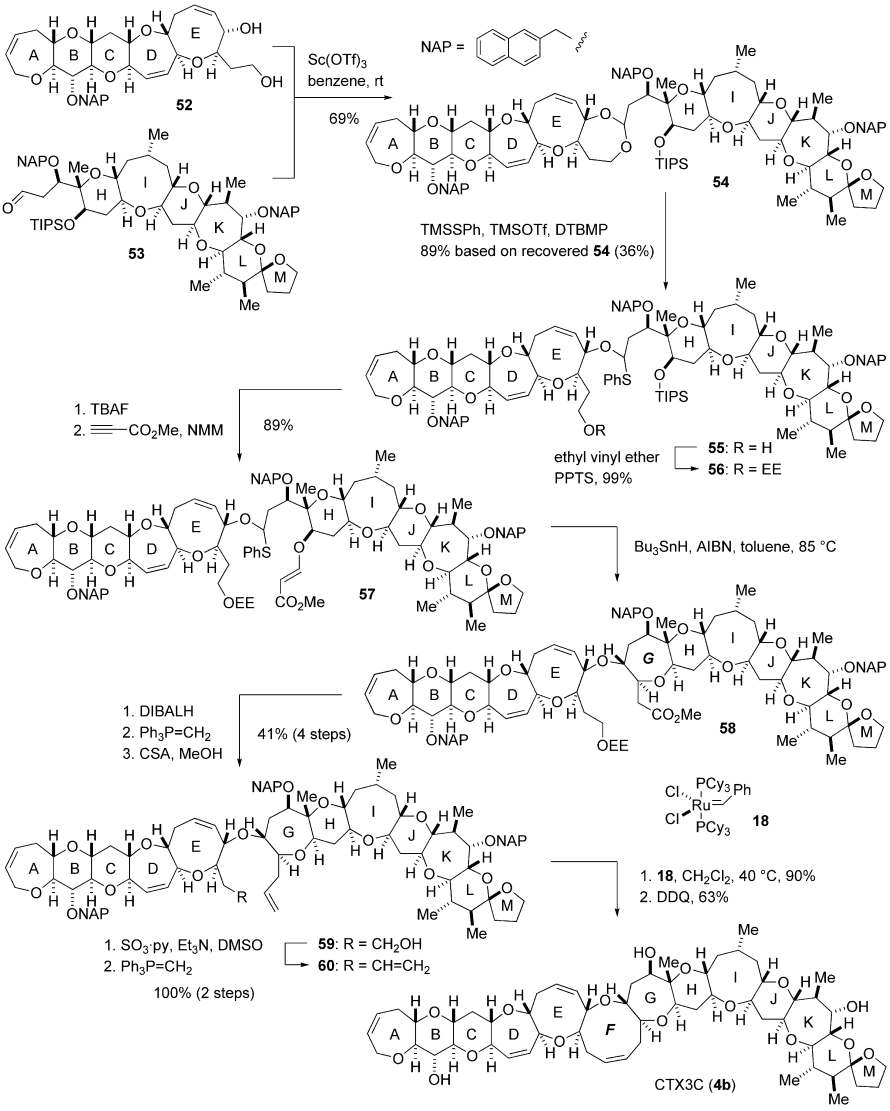
3
Total Synthesis of Ciguatoxins

Ciguatera is a seafood poison prevalent in tropical and subtropical areas with more than 20,000 victims annually and continues to be a serious public health problem [68]. The principal causative agents, ciguatoxin (CTX, **4a**) [9–11] and its congeners including CTX3C (**4b**) [12], are extremely potent neurotoxins that strongly bind to voltage-sensitive sodium channels and inhibit depolarization to allow inward Na^+ influx to continue [22, 23, 69].

In 2001, Hirama and co-workers reported the first total synthesis of CTX3C (**4b**) [39–42]. Their elegant and highly convergent synthesis exploited methodology originally developed in the Sasaki group [70–72] as the pivotal fragment coupling process [73]. Coupling of the ABCDE-ring diol **52** [74] and the HIJKLM-ring aldehyde **53** [75, 76] by the action of scandium(III) triflate delivered seven-membered acetal **54** (Scheme 6). A regioselective acetal cleavage reaction was realized using trimethylsilyl triflate and trimethyl(phenylthio)silane without affecting the spiroacetal LM-ring moiety [73]. The resultant alcohol **55** was protected as the ethoxyethyl (EE) ether to yield *O*,*S*-acetal **56**. Removal of the TIPS group was followed by attachment of the β-(*E*)-alkoxyacrylate unit to afford a cyclization precursor **57**. The crucial radical cyclization of **57** was achieved by treatment with tributyltin hydride and AIBN (toluene, 85 °C) to furnish the desired *O*-linked oxepane **58** as a single diastereomer.

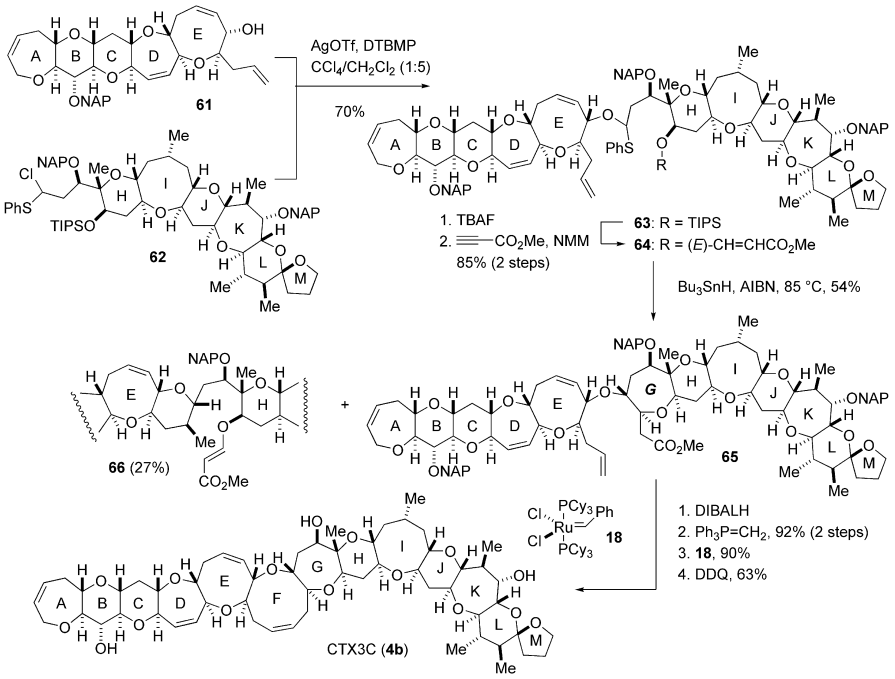
Cyclization of the remaining nine-membered F-ring was successfully performed by RCM reaction. Thus, DIBALH reduction of **58** followed by Wittig methylenation and removal of the EE group delivered alcohol **59**, which was then converted to the RCM substrate **60** via a two-step sequence. The chemoselective RCM reaction of pentaene **60** was successfully attained by the use of Grubbs catalyst **18**, leading to fully protected CTX3C. Finally, oxidative removal of the 2-naphtylmethyl (NAP) groups using DDQ completed the first total synthesis of CTX3C (**4b**).

The foregoing first-generation total synthesis of CTX3C (**4b**) demonstrated the power of the *O*,*S*-acetal strategy to build complex and large polycyclic ether structures. However, in order to synthesize ciguatoxin congeners with acid-sensitive functionalities, such as ciguatoxin (**4a**), a new approach to *O*,*S*-acetal without the need for strongly acidic conditions was required. Inoue and Hirama developed an alternative mild method for constructing *O*,*S*-acetals, which relied on the direct coupling of secondary alcohols with α-halosulfides using halophilic activators [64, 65], and successfully applied this methodology to the second-generation total synthesis of CTX3C (**4b**) in 2004 [77–79]. α-Chlorosulfide **62** was coupled with secondary alcohol **61** by the action of AgOTf and DTBMP to generate *O*,*S*-acetal **63** in 70% yield (Scheme 7). In a similar manner to the first-generation synthesis, compound **63** was converted to β-(*E*)-alkoxyacrylate **64** in two steps and subjected to radical



Scheme 6 First generation total synthesis of CTX3C by Hirama and co-workers

cyclization. The G-ring of **65** was formed stereoselectively in 54% yield, along with **66** arising from 6-*exo* cyclization on the terminal olefin. Although regioselectivity of the radical cyclization remained to be improved, the presence of the terminal olefin within **65** facilitated the synthesis of the substrate for the final RCM reaction. DIBALH reduction of **65** and ensuing Wittig methylenation provided a pentaene, which was subjected to RCM reaction and following global deprotection to furnish CTX3C (**4b**). Notably, this refined second-



Scheme 7 Second generation total synthesis of CTX3C by the Inoue/Hirama group

generation synthesis significantly reduced the number of steps required for the transformation from the fragment coupling to reach **4b**. In addition, the neutral nature and high chemoselectivity of the new coupling protocol based on *O*,*S*-acetal will enable the synthesis of other ciguatoxin congeners, including ciguatoxin (**4a**). The present total synthesis also allowed the supply of sufficient amounts of CTX3C (**4b**) for further physiological studies [80] and development of an immunoassay method to detect CTX3C (**4b**) [81, 82].

4
Total Synthesis of Gambierol

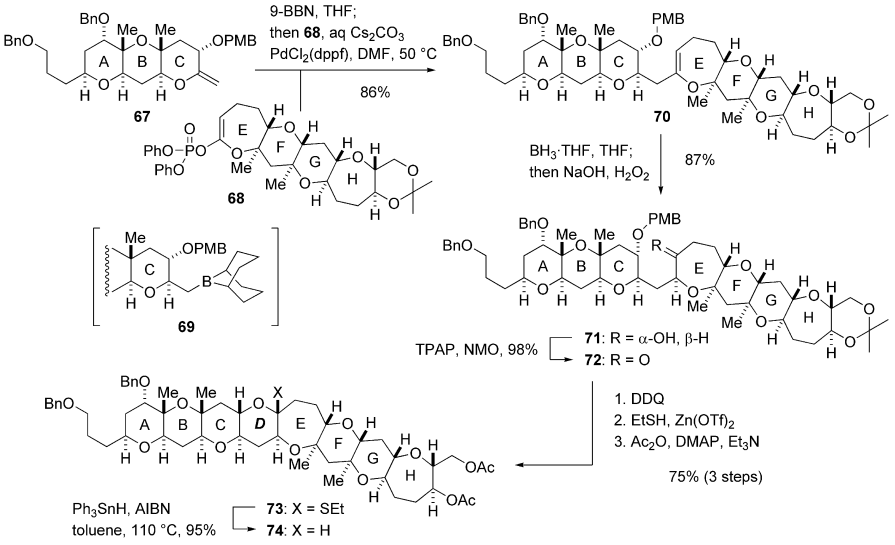
In 1993, Yasumoto and co-workers reported the isolation of gambierol (**5**) as a toxic constituent from the cultured cells of the ciguatera-causative dinoflagellate *Gambierdiscus toxicus*. Its gross structure including the relative stereochemistry has been revealed by extensive NMR studies [13]. Subsequently, the absolute configuration has been determined by derivatization and application of modified Mosher analysis [14]. The toxin molecule consists of an octacyclic polyether core and a partially skipped triene side chain including a conjugated (*Z*,*Z*)-diene system. Gambierol (**5**) exhibits potent neurotoxicity

against mice (minimum lethal dose = 50 $\mu g\,kg^{-1}$, ip) with symptoms resembling those shown by ciguatoxins, implying that gambierol (**5**) is also involved in ciguatera seafood poisoning. Very recently, Inoue et al. have described that gambierol (**5**) inhibits the binding of [^{3}H]dihydrobrevetoxin-B to voltage-sensitive sodium channels, although its binding affinity is significantly lower than that of brevetoxins and ciguatoxins [83].

4.1 Sasaki Synthesis of Gambierol

The first total synthesis of gambierol (**5**) was completed by the Sasaki group in 2002 [43, 44]. The synthesis features (i) convergent union of the ABC- and EFGH-ring fragments to form the octacyclic polyether core based on their developed *B*-alkyl Suzuki–Miyaura coupling chemistry [84–90]; and (ii) the stereoselective construction of the labile triene side chain via copper(I) chloride-accelerated Stille coupling at the final stage of the total synthesis.

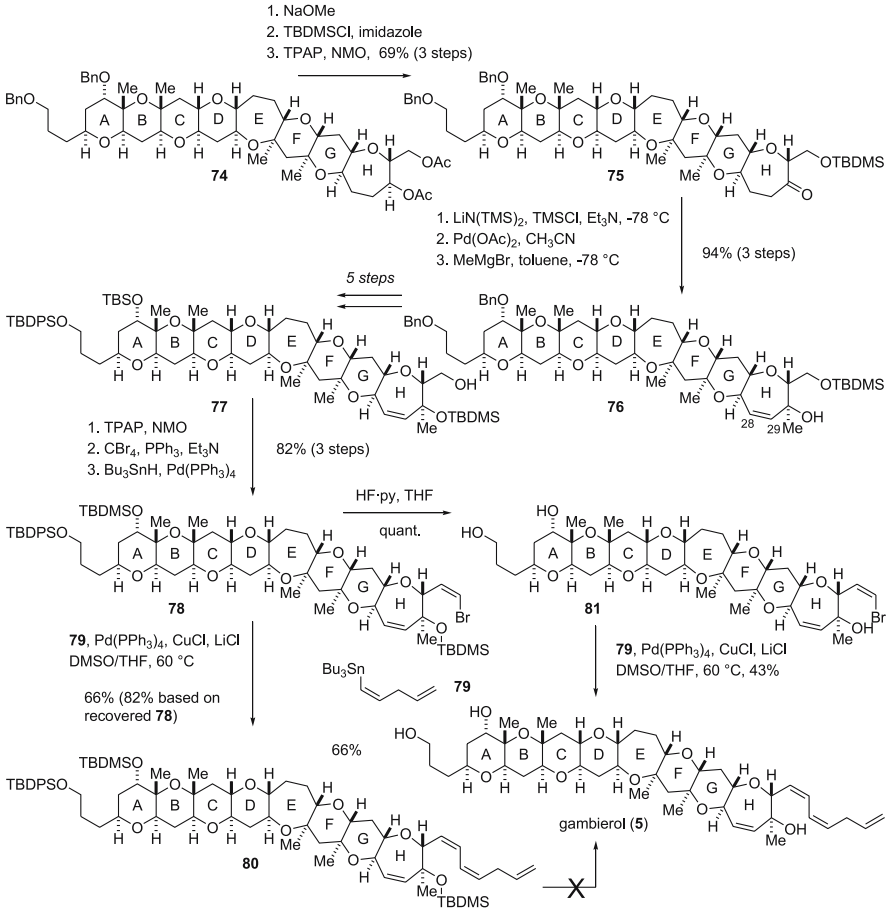
Hydroboration of the ABC-ring exocyclic enol ether **67** [44, 91] with 9-BBN generated the intermediate alkylborane **69**, which was in situ coupled with the EFGH-ring enol phosphate **68** [44, 92] in the presence of dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) [$PdCl_2$(dppf)] and aqueous cesium carbonate in THF/DMF at 50 °C (Scheme 8). The desired coupling product **70** was obtained in high yield. Ensuing hydroboration of endocyclic enol ether **70** with $BH_3 \cdot THF$ led stereoselectively to the desired alcohol **71**, which was oxidized with tetra-*n*-propylammonium perruthenate (TPAP) and



Scheme 8 Total synthesis of gambierol by the Sasaki group

N-methylmorpholine *N*-oxide (NMO) [93] to afford ketone **72.** Oxidative removal of the PMB group followed by treatment with ethanethiol and zinc triflate effected cyclization of the D-ring as the mixed thioketal to yield, after acetylation, **73.** Finally, desulfurization under radical reduction conditions (triphenyltin hydride, AIBN, toluene, 110 °C) [94] proceeded cleanly to furnish the octacyclic polyether core **74** in high yield. Thus, the synthesis of the octacycle **74** was achieved in just seven steps from the coupling of two advanced intermediates **67** and **68.**

Elaboration of **74** into ketone **75** set the stage for the functionalization of the H-ring (Scheme 9). Incorporation of the C28–C29 double bond was performed by means of the Ito–Saegusa protocol [95], and the resultant enone was treated with methylmagnesium bromide (toluene, – 78 °C) [96] to give tertiary alcohol **76** in high overall yield as a single stereoisomer. A five-step



Scheme 9 Total synthesis of gambierol by the Sasaki group (continued)

sequence of protective group manipulations from **76** afforded primary alcohol **77**. Oxidation followed by Corey–Fuchs reaction [97] and stereoselective reduction of the derived dibromoolefin by the Uenishi protocol [98] led to (*Z*)-vinyl bromide **78**, ready for installation of the triene side chain.

The final steps to complete the total synthesis were stereoselective construction of the triene side chain and global deprotection. However, both of these issues posed significant challenges. After extensive experimentation, it was finally found that the tetrakis(triphenylphosphine)palladium(0)/copper(I) chloride/lithium chloride-promoted modified Stille coupling conditions, developed by Corey and co-workers [99], were quite suitable for the present case. The Stille coupling of **78** with (*Z*)-vinyl stannane **79** gave rise to fully protected gambierol **80** in 66% yield (82% yield based on recovered **78**). However, all attempts to remove the silyl protective groups of **80** under various conditions were unsuccessful due to the labile nature of the triene side chain. This critical issue was overcome as follows. Exposure of (*Z*)-vinyl bromide **78** to excess HF · pyridine facilitated clean deprotection of the three silyl groups, giving triol **81** in excellent yield. Finally, the Stille coupling of unprotected **81** with **79** furnished (–)-gambierol (**5**) in 43% isolated yield. Thus, the first total synthesis of gambierol (**5**) was completed in 0.57% overall yield over a 71-step longest linear sequence. The present synthesis clearly demonstrated the utility of the *B*-alkyl Suzuki–Miyaura coupling chemistry for the fragment coupling process in polycyclic ether synthesis.

Now that ample quantities of gambierol (**5**) can be supplied by the Sasaki total synthesis, detailed studies aimed at understanding the molecular basis of the biological mode of action of this marine toxin were made possible [100]. Consequently, the molecular target of gambierol (**5**) was identified to be possibly the voltage-sensitive potassium channels by using taste cells [101]. In addition, by virtue of the established synthetic route to gambierol (**5**), a series of gambierol analogues were synthesized and investi-

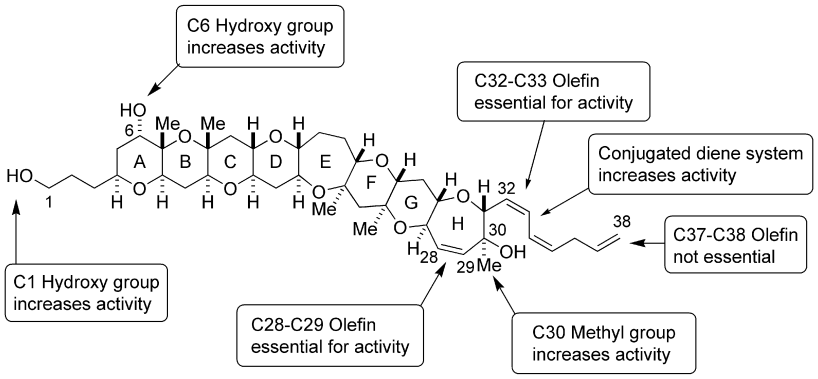
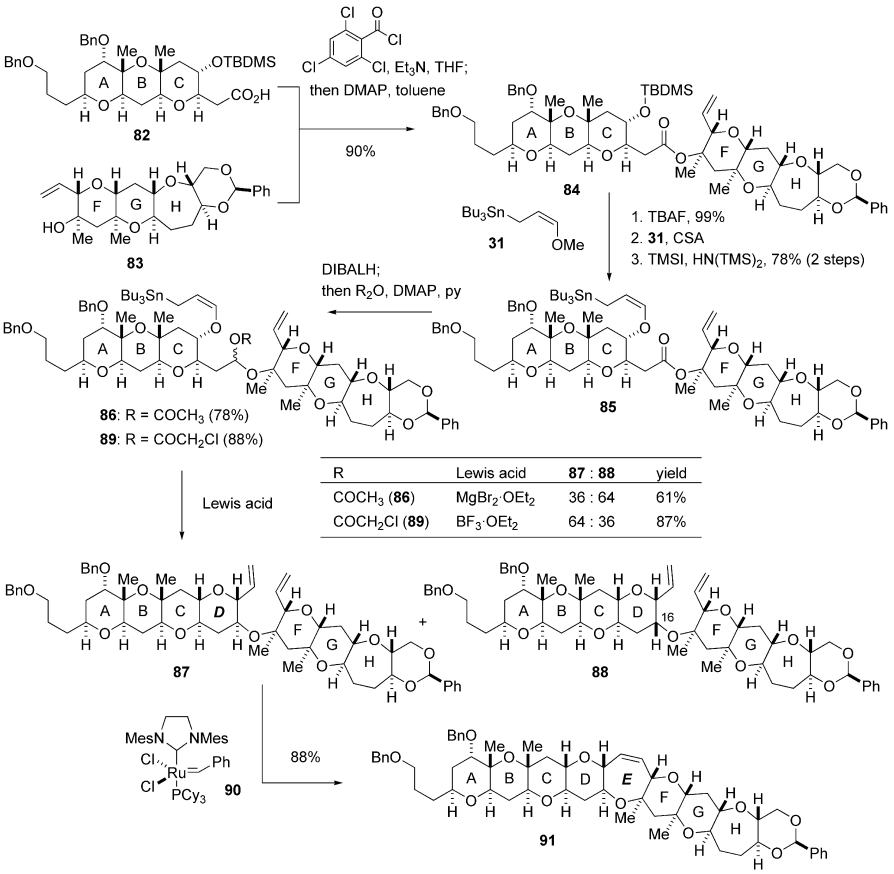


Fig. 2 Structure-activity relationships of gambierol

gated for their toxicity against mice. The systematic structure–activity relationship study revealed that the structural elements of gambierol (**5**) necessary for exhibiting potent toxicity are the H-ring double bond and the unsaturated side chain with an appropriate length. In contrast to these important structural elements, the C1 and C6 hydroxy groups, the C30 axial-oriented methyl group, and the C34–C35 double bond are not essential but are preferred functional groups for exhibiting potent toxicity (Fig. 2) [102, 103].

4.2 Yamamoto/Kadota Synthesis of Gambierol

In 2003, the Yamamoto and Kadota group reported the total synthesis of gambierol (**5**) based on their convergent strategy for a polycyclic ether system

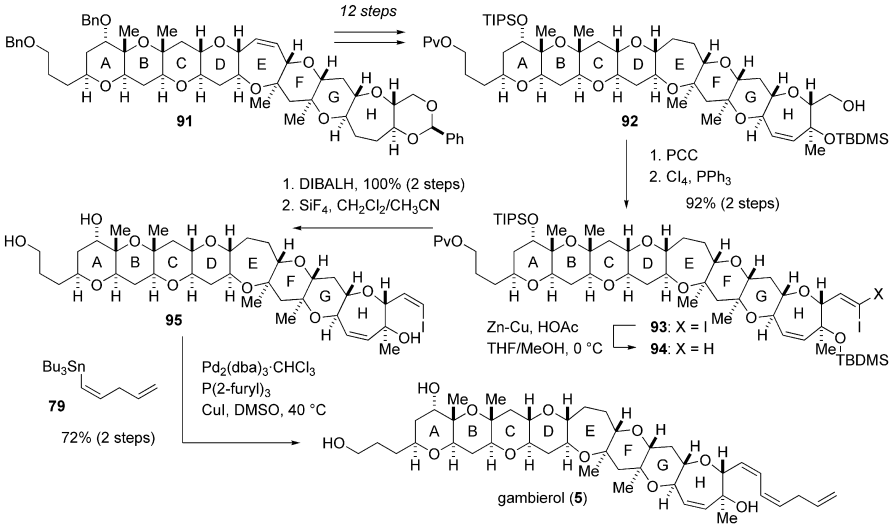


R	Lewis acid	87 : 88	yield
$COCH_3$ (**86**)	$MgBr_2{\cdot}OEt_2$	36 : 64	61%
$COCH_2Cl$ (**89**)	$BF_3{\cdot}OEt_2$	64 : 36	87%

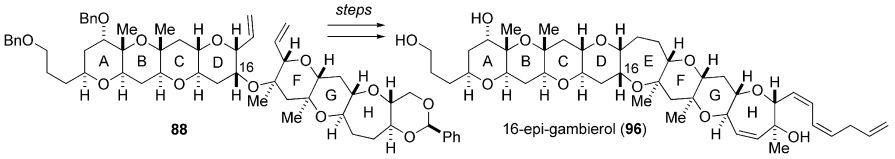
Scheme 10 Total synthesis of gambierol by the Yamamoto/Kadota group

described before [45, 46, 60]. The ABC- and FGH-ring fragments (**82** and **83**, respectively) were synthesized and coupled through esterification to give **84** (Scheme 10). Following removal of the TBDMS group, the allylic stannane moiety was attached by a two-step procedure to give **85**. The ester was then converted into α-acetoxy ether **86** through the Rychnovsky protocol [61–63]. Treatment of **86** with magnesium bromide etherate (CH_2Cl_2, room temperature) produced the undesired stereoisomer **88** as the major product (**87** : **88** = 36 : 64). In contrast, cyclization of α-chloroacetoxy ether **89** by the action of boron trifluoride etherate (20 : 1 CH_3CN/CH_2Cl_2, – 40 → 0 °C) led to the desired **87** predominantly (**87** : **88** = 64 : 37, 87% combined yield). This improved stereoselectivity is explained by the greater leaving ability of the chloroacetoxy group to form the oxonium cation intermediate compared to the acetoxy group. The obtained diene **87** was subjected to RCM reaction using the second-generation Grubbs catalyst **90** [104], giving rise to the octacyclic gambierol skeleton **91** in high yield.

Subsequently, compound **91** was elaborated to primary alcohol **92** with the H-ring functionality in a similar manner to the Sasaki synthesis (Scheme 11). For the introduction of the triene side chain, a simple and practical method for the stereoselective synthesis of (*Z*)-vinyl iodide, which is expected to be more reactive than the bromide counterpart, was developed [105]. Thus, PCC oxidation of alcohol **92** followed by treatment of the resultant aldehyde with tetraiodomethane and triphenylphosphine gave diiodoalkene **93**. Reduction of **93** with the zinc–copper couple in the presence of acetic acid provided (*Z*)-vinyl iodide **94** in high yield. Since deprotection of the fully protected



Scheme 11 Total synthesis of gambierol by the Yamamoto/Kadota group (continued)



Scheme 12 Synthesis of 16-epi-gambierol

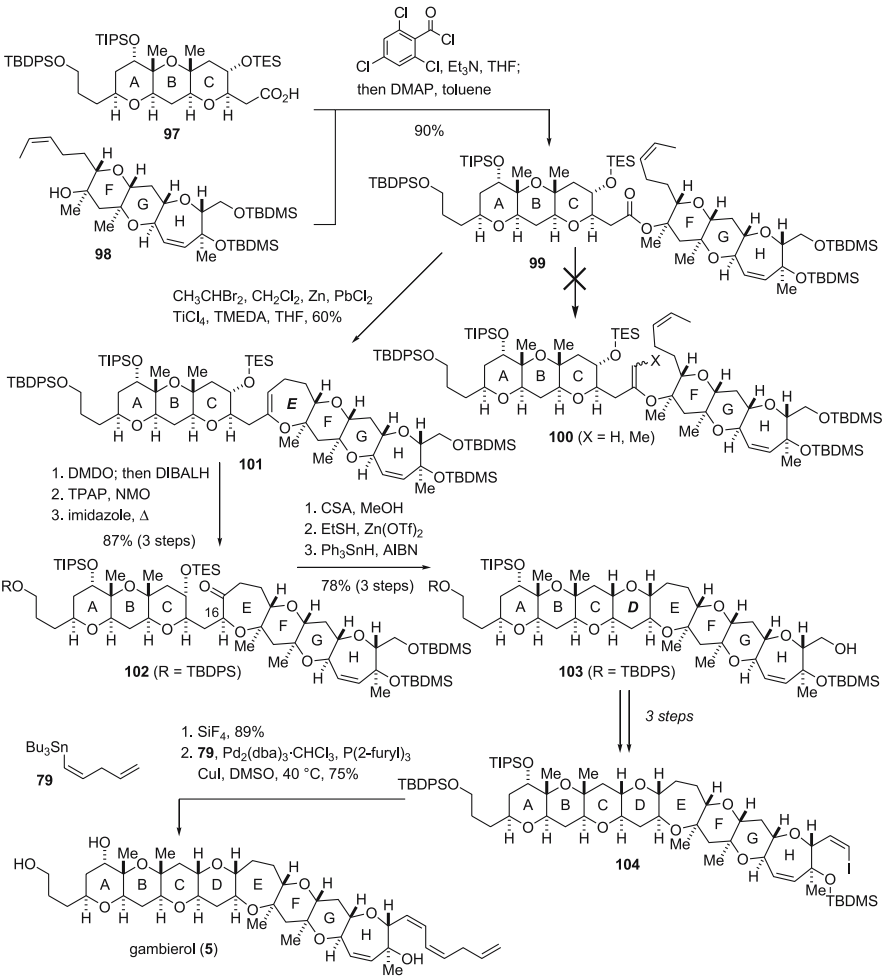
gambierol, prepared from the Stille coupling of **94** with **79**, was unsuccessful as in the case of the Sasaki synthesis, deprotection of **94** was carried out in a two-step procedure before constructing the triene side chain. As expected, iodoalkene **95** showed higher reactivity, and the modified Stille coupling reaction with **79** [tris(dibenzylideneacetone)dipalladium(0) · chloroform, tri(2-furyl)phosphine, copper(I) iodide, DMSO, 40 °C] proceeded smoothly to furnish gambierol (**5**) in 72% yield for the two steps. The longest linear sequence leading to **1** is 66 steps with 1.2% overall yield.

Similar transformation starting from the isomer **88** generated 16-epi-gambierol (**96**), a non-natural analogue (Scheme 12). Interestingly, the epimer **96** exhibited no toxicity against mice at higher dose (14 mg kg^{-1}), indicating that the *trans*-fused polycyclic ether framework is essential to the toxicity.

4.3 Rainier Synthesis of Gambierol

Very recently, Rainier and co-workers accomplished a more convergent total synthesis of gambierol (**5**) [47]. Their synthesis features (i) synthesis of *C*-glycoside from the coupling of cyclic enol ether with carbon nucleophile and; (ii) tandem methylenation/enol ether-olefin RCM. The synthesis started with convergent union of the ABC- and FGH-ring fragments (**97** and **98**, respectively) through esterification by the Yamaguchi method to afford **99** (Scheme 13). Initial attempts to convert ester **99** into acyclic enol ether metathesis precursor **100** (X = H) using the Takai–Utimoto titanium methylidene protocol [106, 107] were unsuccessful. After much experimentation, it was found that reaction of **99** with the titanium alkylidene reagent, generated from 1,1-dibromoethane, led to the formation of seven-membered enol ether **101** in 60% yield. Furthermore, the expected acyclic enol ether product **100** (X = Me) was also isolated in 30% yield, and could be converted to **101** in an unoptimized 60% yield by treating with the second-generation Grubbs catalyst **90**.

Oxidation of **101** with DMDO followed by one-pot reduction with DIBALH provided a 10 : 1 mixture of alcohols, in which the major isomer possessed the correct stereochemistry at C16. Oxidation of the alcohols gave ketone **102** and its C16 epimer, respectively. The minor diastereomer could be isomerized



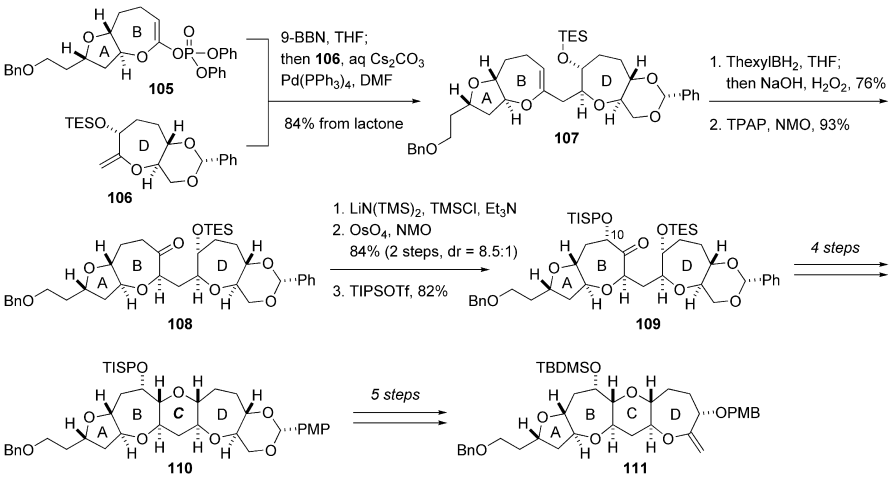
Scheme 13 Total synthesis of gambierol by Rainier and co-workers

to **102** by treating with imidazole at elevated temperature. The D-ring was constructed by a reductive cyclization sequence in the same way as that employed by the Sasaki group [44, 91], leading to a octacyclic polyether core **103**. Finally, the triene side chain was incorporated via (*Z*)-vinyl iodide **104** following Yamamoto's protocol [45, 46] to complete the total synthesis of natural product **5**. The convergence aspect of the Rainier synthesis is particularly noteworthy in light of the use of fragment **98** furnished with the H-ring functionality, thus the longest linear sequence to reach the target was 44 steps from D-glucal with 1.2% overall yield.

5
Total Synthesis of Gymnocin-A

Gymnocin-A (**7**) is a polycyclic ether toxin isolated by Satake and co-workers from the notorious red-tide dinoflagellate, *Karenia mikimotoi*, which is a representative species that causes devastating damages worldwide [18]. The toxin is a rare polycyclic ether that displays cytotoxicity against P388 leukemia cells (EC_{50} = 1.3 μg mL^{-1}). The structure of gymnocin-A (**7**), including the relative and absolute stereochemistry, has been established by a combination of extensive 2D-NMR analyses, FAB collision-induced dissociation MS/MS experiments, and a modified Mosher's method [18]. Structurally, gymnocin-A (**7**) is characterized by 14 contiguous ether rings, including two repeating 6/6/7/6/6 ring systems (the EFGHI and JKLMN rings), and a 2-methyl-2-butenal side chain.

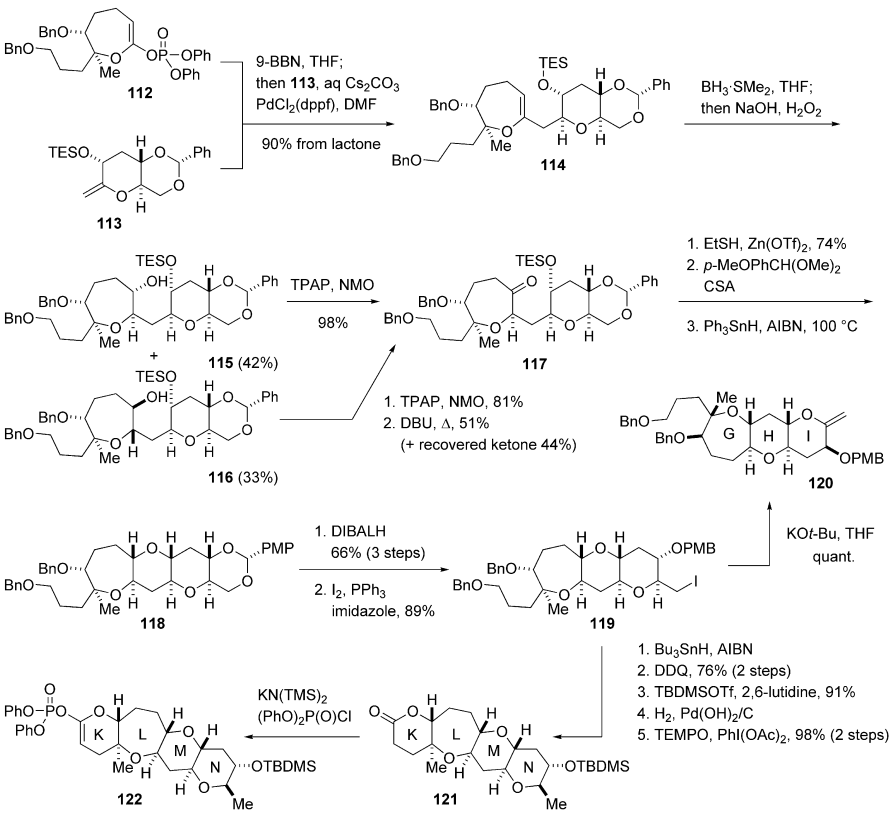
The most formidable challenge for the total synthesis of gymnocin-A (**7**) is apparently the construction of the large tetradecacyclic polyether skeleton. In 2003, the Sasaki group accomplished a highly convergent total synthesis of gymnocin-A (**7**) based on extensive use of the *B*-alkyl Suzuki–Miyaura coupling chemistry [48, 49]. Hydroboration of the D-ring exocyclic enol ether **106** with 9-BBN, followed by cross-coupling with the AB-ring enol phosphate **105**, afforded compound **107** in high yield (Scheme 14). Subsequent hydroboration and oxidation of the derived alcohol gave ketone **108**. For the stereoselective introduction of the C10 hydroxy group, ketone **108** was converted into the corresponding silyl enol ether, which was oxidized with OsO_4/NMO to give, after protection, α-siloxy ketone **109** with dr = 8.5 : 1. Construction



Scheme 14 Total synthesis of gymnocin-A by the Sasaki group (continued)

of the C-ring was carried out by reductive desulfurization of mixed thioketal to obtain **110**. A further five-step sequence was required to complete the synthesis of the ABCD-ring fragment **111**.

Given the repeating structural units, the GHI- and KLMN-ring fragments (**120** and **122**, respectively) were synthesized via a common precursor **119** (Scheme 15). Hydroboration of exocyclic enol ether **113** with 9-BBN and coupling with enol phosphate **112** gave **114** in high yield. Subsequent hydroboration produced a separable 4 : 3 mixture of the desired alcohol **115** and its diastereomer **116**. The poor stereoselectivity of this hydroboration is probably because of the steric hindrance of the pseudo-axial methyl group on the seven-membered ring. Oxidation of **115** gave ketone **117**, whereas the undesired **116** could be recycled by oxidation and base-induced isomerization. The obtained ketone **117** was subjected to ethanethiol and zinc triflate to generate a mixed thioketal, which was reprotected and reduced under radical conditions to afford tricyclic ether **118**. Reductive opening of the *p*-methoxybenzylidene acetal with DIBALH gave a primary alcohol,

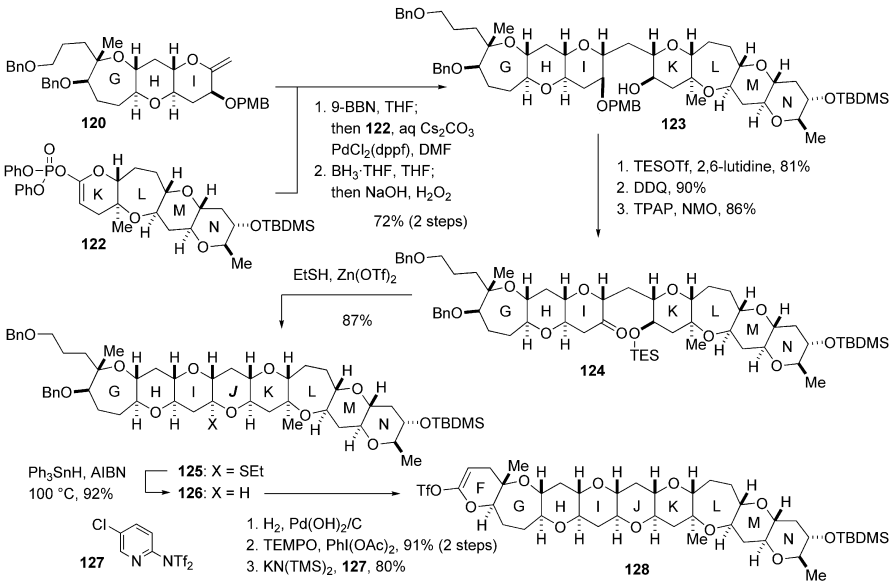


Scheme 15 Total synthesis of gymnocin-A by the Sasaki group (continued)

which was then iodinated to furnish the common intermediate **119**. Base-treatment of **119** generated the GHI-ring exocyclic enol ether **120**. On the other hand, radical reduction of **119** followed by protective group manipulations and oxidation of the 1,5-diol with 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO)/(diacetoxyiodo)benzene [108] provided lactone **121**, which was then converted to the KLMN-ring enol phosphate **122**.

Hydroboration of **120** with 9-BBN, followed by reaction with **122**, proceeded smoothly to give the cross-coupled product, which was then subjected to hydroboration leading exclusively to alcohol **123** in 72% overall yield (Scheme 16). A further three-step sequence of protective and functional group manipulations led to ketone **124**. Mixed thioketal **125** was formed by exposure to ethanethiol/zinc triflate, and then reduced under radical conditions to give octacyclic polyether **126**. Debenzylation followed by TEMPO oxidation of the resultant diol generated a δ-lactone, which was then converted to the FGHIJKLMN-ring enol triflate **128**, ready for the final cross-coupling reaction with **111**.

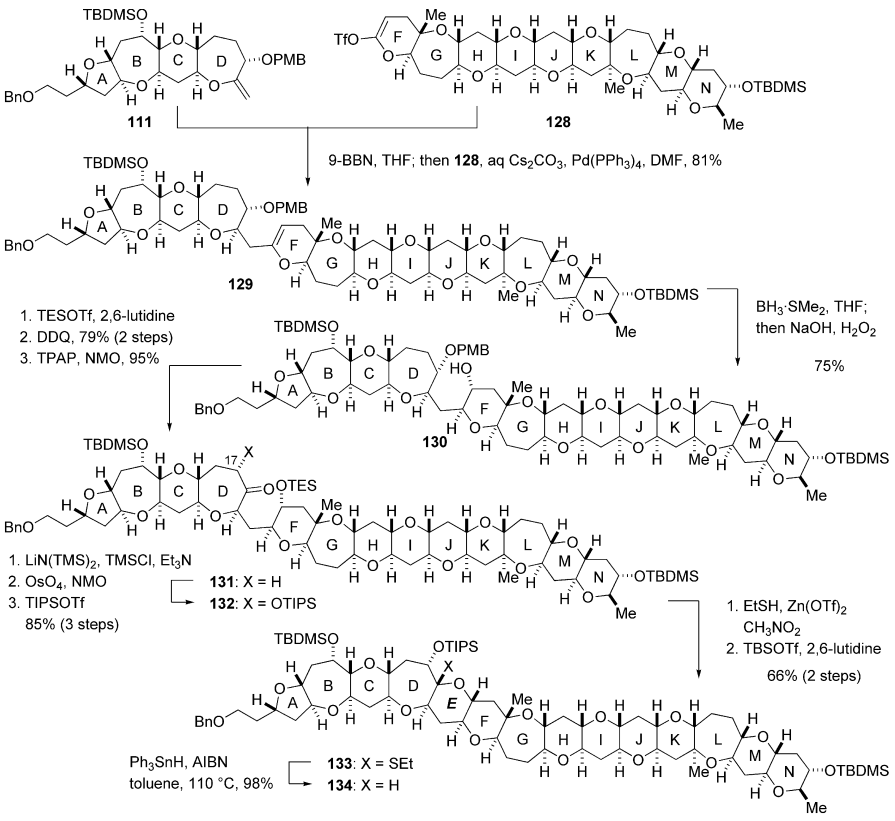
Hydroboration of exocyclic enol ether **111** with 9-BBN and following Suzuki–Miyaura reaction with enol triflate **128** proceeded smoothly to generate the cross-coupled product **129** in 81% yield (Scheme 17). Not unexpectedly, the corresponding enol phosphate of **128** proved to be a poor substrate for this complex fragment coupling. Given the structural complexity and sheer size of the respective fragments, this remarkable yield (81%) represents



Scheme 16 Total synthesis of gymnocin-A by the Sasaki group (continued)

the power and reliability of the Suzuki–Miyaura reaction as the fragment coupling process in polycyclic ether synthesis.

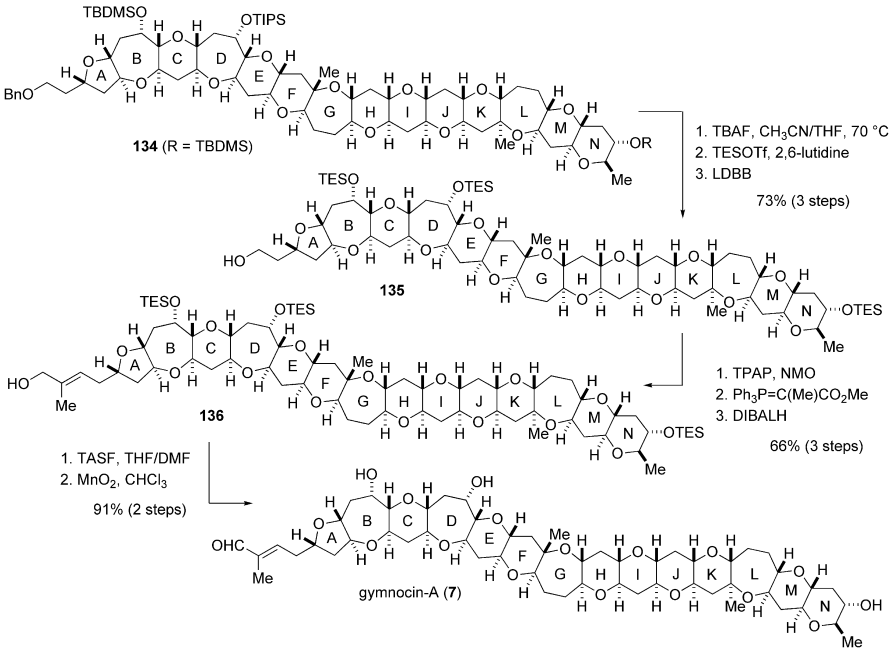
Coupling product **129** was then subjected to hydroboration using $BH_3 \cdot SMe_2$ to give alcohol **130** in 75% yield as the sole product. For the introduction of the C17 hydroxy group, **130** was elaborated to ketone **131** by a three-step sequence including TES protection, PMB deprotection and oxidation. Conversion of **130** to the corresponding enol silyl ether followed by oxidation with OsO_4/NMO installed the C17 hydroxy group with complete stereocontrol, to give, after protection, α-siloxy ketone **132**. Subsequent thioketal formation was best achieved by treatment of **132** with ethanethiol/zinc triflate in nitromethane; however, some of the C50 TBDMS group on the N-ring was cleaved. The choice of nitromethane instead of the usual dichloromethane as the solvent to mediate this reaction was crucial to the success of the cyclization. After reprotection, the desired thioketal **133** was obtained in 66% overall yield. Finally, reductive desulfurization proceeded cleanly to furnish the tetradecacyclic polyether skeleton **134** in excellent yield.



Scheme 17 Total synthesis of gymnocin-A by the Sasaki group (continued)

The last stage of the synthesis involved incorporation of the 2-methyl-2-butenal side chain. Initial attempts to remove the TBDMS and TIPS groups after introduction of the enal side chain or its equivalent were unsuccessful probably because of the labile nature of the side chain. Accordingly, the TBDMS and TIPS groups of **134** were replaced with more readily cleaved TES ethers (Scheme 18). Subsequent reductive removal of the benzyl group with lithium di-*tert*-butylbiphenylide (LDBB) [109] afforded alcohol **135**. Oxidation of **135** to the aldehyde followed by Wittig reaction with $Ph_3P=CHCO_2Me$ yielded the corresponding enoate, which was then reduced with DIBALH to give allylic alcohol **136**. Finally, global deprotection using tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) [110, 111] and following chemoselective oxidation of the allylic alcohol with manganese(IV) oxide completed the total synthesis of gymnocin-A (**7**).

The convergent synthetic entry to gymnocin-A (**7**) employing the three fragments of comparable complexity (**111**, **120** and **122**) is well-suited for the preparation of a diverse set of structural analogues to explore the structure-activity relationship profiles. Seven synthetic analogues were synthesized and tested against the P388 murine leukemia cell line. The structure-activity relationship study suggested that an electrophilic enal functionality of the side chain along with an appropriate molecular length of the polycyclic ether

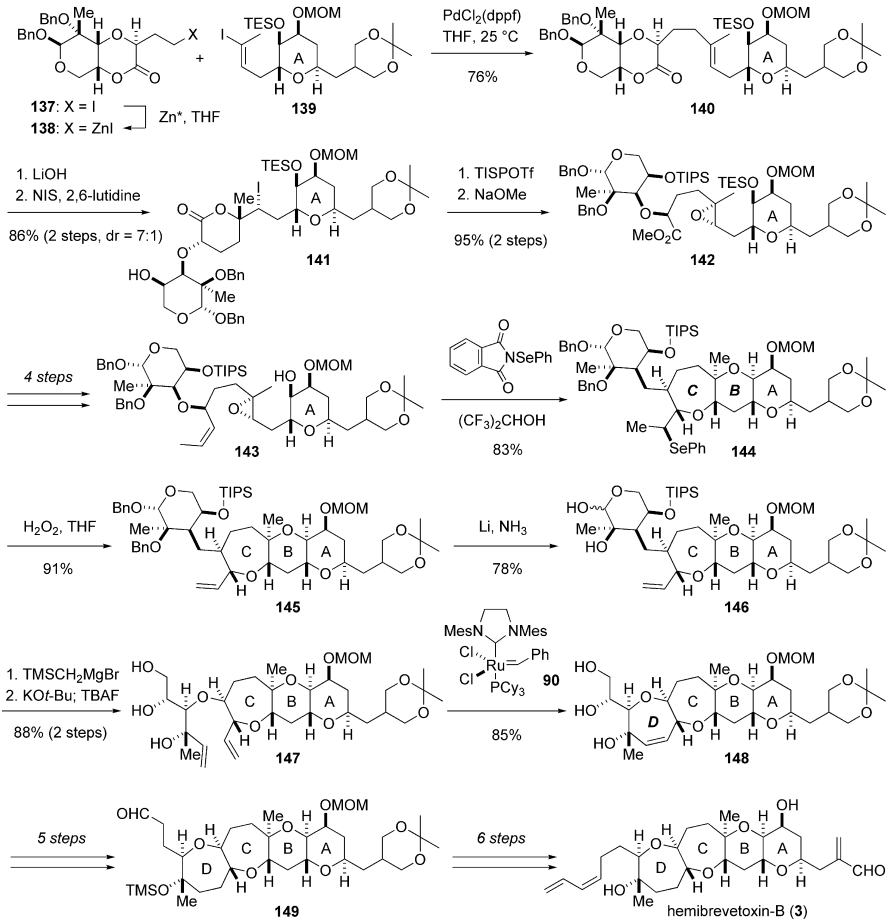


Scheme 18 Total synthesis of gymnocin-A by the Sasaki group (continued)

structure are necessary for exhibiting cytotoxic activity (Tsukano and Sasaki, 2005, personal communication) [49].

6
Total Synthesis of Hemibrevetoxin-B

Hemibrevetoxin-B (**3**), isolated from the cultured cells of the dinoflagellate *Karenia brevis* in 1989, is the smallest member of the polycyclic ethers and has a 7/7/5/6-tetracyclic structure with a molecular size about half that of brevetoxins [8]. So far, four total and three formal syntheses of hemibrevetoxin-B (**3**) have been reported [112–121].



Scheme 19 Total synthesis of hemibrevetoxin-B by Holton and co-workers

A cascade epoxy alcohol cyclization has been proposed for the biosynthesis of the polycyclic ether natural products [122–124]. In 2003, Holton and coworkers disclosed the first convergent total synthesis of hemibrevetoxin-B (**3**), in which a biomimetic epoxy alcohol cyclization has been successfully implemented [120].

Negishi cross-coupling of organozinc reagent **138**, prepared from iodide **137** using Rieke active zinc [125], with vinyl iodide **139**, representing the A-ring, provided alkene **140** (Scheme 19). Hydrolysis of lactone **140** produced a hydroxy acid, which upon treatment with *N*-iodosuccinimide (NIS) underwent diastereoselective iodolactonization to generate **141** along with its diastereomer (dr = 7 : 1). Protection of the hydroxy group as the TIPS ether followed by methanolysis produced epoxide **142**, which was then converted into the cascade cyclization precursor **143** in a four-step sequence. The crucial cyclization was realized by treatment of **143** with *N*-(phenylseleno)phthalimide in a highly polar solvent, 1,1,1,3,3,3-hexafluoro-2-propanol, giving rise to cyclization product **144** as a single diastereomer in 83% yield. Thus, the B- and C-rings were assembled in a single synthetic operation.

Oxidative elimination of the selenide within **144** gave terminal olefin **145** in high yield, but subsequent removal of the benzyl groups of **145** proved troublesome due to the sensitivity of the allylic ether. Finally, debenzylation was achieved by inverse addition of lithium in ammonia to a THF solution of **145**, leading to **146**. Peterson olefination was followed by desilylation to afford triol **147**. The D-ring was constructed by RCM reaction using the second-generation Grubbs catalyst **90** to give tetracyclic ether **148**, which was elaborated to aldehyde **149** in five steps. A further six-step sequence was required to complete the total synthesis of hemibrevetoxin-B (**3**). Thus, the convergent synthesis was accomplished in 39 steps and ca. 4% overall yield in the longest linear sequence from tri-*O*-acetyl-D-glucal.

7 Summary and Perspective

As demonstrated throughout this review, rapid progress has been made in the field of the total synthesis of polycyclic ether natural products. Particularly, most of these accomplishments were concentrated over the last five years. Convergent assembly of the polycyclic ether fragments is, of course, the key to successful construction of the large ladder-shaped polycyclic ether system. In this context, the completed total syntheses have benefited enormously from the transition-metal catalyzed carbon–carbon bond forming reactions, such as olefin metathesis and cross-coupling reactions. These powerful tools will undoubtedly enable even more impressive accomplishments in this field.

Since the isolation of these natural products from marine organisms is severely limited, chemical synthesis has been the only means to obtain sufficient amounts of these polycyclic ethers for future biological studies, including the detailed biological mechanism of action. Although the total syntheses described in this review are at the cutting edge of contemporary organic synthesis, the existing syntheses are currently limited to delivering several milligrams of these complex molecules. Therefore, development of even more efficient, practical and scalable synthetic routes to provide these compounds and their analogues in a shorter time will be a key challenge in the future. The authors believe that organic synthesis of polycyclic ethers will continue to be an exciting field of research.

References

1. Lin YY, Risk M, Ray SM, Van Engen D, Clardy J, Golik J, James JC, Nakanishi K (1981) J Am Chem Soc 103:6773
2. Yasumoto T, Murata M (1993) Chem Rev 93:1897
3. Scheuer PJ (1994) Tetrahedron 50:3
4. Murata M, Yasumoto T (2000) Nat Prod Rep:293
5. Yasumoto T (2001) Chem Rec 3:228
6. Shimizu Y, Chou HN, Van Duyne G, Clardy J (1986) J Am Chem Soc 108:514
7. Pawlak J, Tempesta MS, Golik J, Zagorski MG, Lee MS, Nakanishi K, Iwashita T, Gross MS, Tomer KB (1987) J Am Chem Soc 109:1144
8. Prasad AVK, Shimizu Y (1989) J Am Chem Soc 111:6476
9. Murata M, Legrand AM, Ishibashi M, Yasumoto T (1989) J Am Chem Soc 111:8929
10. Murata M, Legrand AM, Ishibashi M, Fukui M, Yasumoto T (1990) J Am Chem Soc 112:4380
11. Satake M, Morohashi A, Oguri H, Oishi T, Hirama M, Harada N, Yasumoto T (1997) J Am Chem Soc 119:11325
12. Satake M, Murata M, Yasumoto T (1993) Tetrahedron Lett 34:1975
13. Satake M, Murata M, Yasumoto T (1993) J Am Chem Soc 115:361
14. Morohashi A, Satake M, Yasumoto T (1998) Tetrahedron Lett 39:97
15. Nagai H, Torigoe K, Satake M, Murata M, Yasumoto T, Hirota H (1992) J Am Chem Soc 114:1102
16. Nagai H, Murata M, Torigoe K, Satake M, Yasumoto T (1992) J Org Chem 57:5448
17. Morohashi A, Satake M, Nagai H, Oshima Y, Yasumoto T (2000) Tetrahedron 56:8995
18. Satake M, Shoji M, Oshima Y, Naoki H, Fujita T, Yasumoto T (2002) Tetrahedron Lett 43:5829
19. Catterall WA, Risk M (1981) Mol Pharmacol 19:345
20. Poli MA, Mende TJ, Baden DG (1986) Mol Pharmacol 30:129
21. Baden DG (1989) FASEB J 3:1807
22. Lombet A, Bidard JN, Lazdanski M (1987) FEBS Lett 219:355
23. Dechraoui MY, Naar J, Pauillac S, Legrand AM (1999) Toxicon 37:125
24. Alvarez E, Candenas ML, Pérez R, Ravelo JL, Martín JD. Chem Rev 95:1953
25. Mori Y (1997) Chem Eur J 3:849
26. Marmsäter FP, West FG (2002) Chem Eur J 8:4347
27. Evans PA, Delouvrie B (2002) Curr Opin Drug Discov Devel 5:986

28. Nicolaou KC, Theodorakis EA, Rutjes FPJT, Tiebes J, Sato M, Untersteller E, Xiao XY (1995) J Am Chem Soc 117:1171
29. Nicolaou KC, Rutjes FPJT, Theodorakis E, Tiebes J, Sato M, Untersteller E (1995) J Am Chem Soc 117:1173
30. Nicolaou KC, Hwang CK, Duggan ME, Nugiel DA, Abe Y, Bal Reddy K, DeFrees SA, Reddy DR, Awartani RA, Conley SR, Rutjes FPJT, Theodorakis EA (1995) J Am Chem Soc 117:10227
31. Nicolaou KC, Theodorakis EA, Rutjes FPJT, Sato M, Tiebes J, Xiao XY, Hwang CK, Duggan ME, Yang Z, Couladouros EA, Sato F, Shin J, He HM, Bleckman T (1995) J Am Chem Soc 117:10239
32. Nicolaou KC, Rutjes FPJT, Theodorakis EA, Tiebes J, Sato M, Untersteller E (1995) J Am Chem Soc 117:10252
33. Niolaou KC (1996) Angew Chem Int Ed Engl 35:589
34. Nicolaou KC, Yang Z, Shi GQ, Gunzner JL, Agrios KA, Gärtner P (1998) Nature 392:264
35. Nicolaou KC, Bunnage ME, McGarry DG, Shi S, Somers PK, Wallace PA, Chu XJ, Agrios KA, Gunzner JL, Yang Z (1999) Chem Eur J 5:599
36. Nicolaou KC, Wallace PA, Shi S, Ouellette MA, Bunnage ME, Gunzner JL, Agrios KA, Shi GQ, Gärtner P, Yang Z (1999) Chem Eur J 5:618
37. Nicolaou KC, Shi GQ, Gunzner JL, Gärtner P, Wallace PA, Ouellete MA, Shi S, Nunnage ME, Agrios KA, Veale CA, Hwang CK, Hutchinson J, Prasad CVC, Ogilvie WW, Yang Z (1999) Chem Eur J 5:628
38. Nicolaou KC, Gunzner JL, Shi GQ, Agrios KA, Gärtner P, Yang Z (1999) Chem Eur J 5:646
39. Hirama M, Oishi T, Uehara H, Inoue M, Maruyama M, Oguri H, Satake M (2001) Nature 294:1904
40. Inoue M, Uehara H, Maruyama M, Hirama M (2002) Org Lett 4:4551
41. Inoue M, Hirama M (2004) Synlett 4:577
42. Inoue M (2004) Org Biol Chem 2:1811
43. Fuwa H, Sasaki M, Satake M, Tachibana K (2002) Org Lett 4:2981
44. Fuwa H, Kainuma N, Tachibana K, Sasaki M (2002) J Am Chem Soc 124:14983
45. Kadota I, Takamura H, Sato K, Ohno A, Mastuda K, Yamamoto Y (2003) J Am Chem Soc 125:46
46. Kadota I, Takamura H, Sato K, Ohno A, Matsuda K, Satake M, Yamamoto Y (2003) J Am Chem Soc 125:11893
47. Johnson HWB, Majumder U, Rainier JD (2004) J Am Chem Soc 127:848
48. Tsukano C, Sasaki M (2003) J Am Chem Soc 125:14294
49. Tsukano C, Ebine M, Sasaki M (2005) J Am Chem Soc 127:4326
50. Matsuo G, Kawamura K, Hori N, Matsukura H, Nakata T (2004) J Am Chem Soc 126:14374
51. Kadota I, Takamura H, Nishii H, Yamamoto Y (2005) J Am Chem Soc 127:9246
52. Hori N, Matsukura H, Matsuo G, Nakata T (1999) Tetrahedron Lett 40:2811
53. Hori N, Matsukura H, Nakata T (1999) Org Lett 1:1099
54. Matsuo G, Hori N, Nakata T (1999) Tetrahedron Lett 40:8859
55. Hori N, Matsukura H, Matsuo G, Nakata T (2002) Tetrahedron 58:1853
56. Sshwab P, Grubbs RH, Ziller JW (1996) J Am Chem Soc 118:100
57. Nicolaou KC, Duggan ME, Hwang CK (1986) J Am Chem Soc 108:2468
58. Nicolaou KC, Prasad CVC, Hwang CK, Duggan ME, Veale CA (1989) J Am Chem Soc 111:5321
59. Kadota I, Ohno A, Matsuda K, Yamamoto Y (2003) J Am Chem Soc 124:3562

60. Kadota I, Yamamoto Y (2005) Acc Chem Res 38:423
61. Dahanukar VH, Rychnovsky SD (1996) J Org Chem 61:8317
62. Kopecky DJ, Rychnovsky SD (2000) J Org Chem 65:191
63. Kopecky DJ, Rychnovsky SD (2003) Org Synth 80:177
64. Inoue M, Wang GX, Wang J, Hirama M (2002) Org Lett 4:3439
65. Inoue M, Yamashita S, Hirama M (2004) Tetrahedron Lett 45:2053
66. Crimmins MT, McDougall PJ (2005) Org Lett 7:4033
67. Mahoney WS, Brestensky DM, Stryker JM (1988) J Am Chem Soc 110:291
68. Scheuer PJ, Takahashi W, Tsutumi J, Yoshida T (1967) Science 155:1267
69. Bidard JN, Vijverberg HPM, Frelin C, Chungue E, Legrand AM, Bagnis R, Lazdanski M (1984) J Biol Chem 259:8353
70. Sasaki M, Inoue M, Noguchi T, Takeichi A, Tachibana K (1998) Tetrahedron Lett 39:2783
71. Sasaki M, Noguchi T, Tachibana K (1999) Tetrahedron Lett 40:1337
72. Sasaki M, Noguchi T, Tachibana K (2002) J Org Chem 67:3301
73. Imai H, Uehara H, Inoue M, Oguri H, Oishi T, Hirama M (2001) Tetrahedron Lett 42:6219
74. Maruyama M, Inoue M, Oishi T, Oguri H, Ogasawara Y, Shindo Y, Hirama M (2002) Tetrahedron 58:1835
75. Tatami A, Inoue M, Uehara H, Hirama M (2003) Tetrahedron Lett 44:5229
76. Inoue M, Yamashita S, Tatami A, Miyazaki K, Hirama M (2004) J Org Chem 69:2797
77. Inoue M, Miayazaki K, Uehara H, Maruyama M, Hirama M (2004) Proc Natl Acad Sci 101:12013
78. Inoue M, Hirama M (2004) Acc Chem Res 37:961
79. Hirama M (2005) Chem Rec 5:240
80. Yamaoka K, Inoue M, Miyahara H, Miyazaki K, Hirama M (2004) Br J Pharmacol 142:879
81. Oguri H, Hirama M, Tsumuraya T, Fujii I, Maruyama M, Uehara H, Nagumo Y (2003) J Am Chem Soc 125:7608
82. Nagumo Y, Gguri H, Tsumoto K, Shindo Y, Hirama M, Tsumuraya T, Fujii I, Tomioka Y, Mizugaki M, Kumagai I (2004) J Immunol Methods 289:137
83. Inoue M, Hirama M, Satake M, Sugiyama K, Yasumoto T (2003) Toxicon 41:469
84. Sasaki M, Fuwa H, Inoue M, Tachibana K (1998) Tetrahedron Lett 39:9027
85. Sasaki M, Fuwa H, Ishikawa M, Tachibana K (1999) Org Lett 1:1075
86. Sasaki M, Ishikawa M, Fuwa H, Tachibana K (2002) Tetrahedron 58:1889
87. Sasaki M, Fuwa H (2004) Synlett 1851
88. Miyaura N, Ishiyama T, Ishikawa M, Suzuki A (1986) Tetrahedron Lett 27:6369
89. Miyaura N, Ishiyama T, Sasaki H, Ishikawa M, Satoh M, Suzuki A (1989) J Am Chem Soc 111:314
90. Chemler SR, Trauner D, Danishefsky SJ (2001) Angew Chem Int Ed 40:4544
91. Fuwa H, Sasaki M, Tachibana K (2001) Org Lett 3:3549
92. Fuwa H, Sasaki M, Tachibana K (2001) Tetrahedron 57:3019
93. Ley SV, Norman J, Griffith WP, Marsden SP (1994) Synthesis 639
94. Nicolaou KC, Prasad CVC, Hwang CK, Duggan ME, Veale CA (1989) J Am Chem Soc 111:5321
95. Ito Y, Hirao T, Saegusa T (1978) J Org Chem 43:1011
96. Feng F, Murai A (1992) Chem Lett 1587
97. Corey EJ, Fuchs PL (1972) Tetrahedron Lett 13:3769
98. Uenishi J, Kawahama R, Yonemitsu O, Tsuji J (1998) J Org Chem 63:8965
99. Han X, Stolz BM, Corey EJ (1999) J Am Chem Soc 121:7600

100. Ito E, Suzuki-Toyota F, Toshimori K, Fuwa H, Tachibana K, Satake M, Sasaki M (2003) Toxicon 42:733
101. Ghiaroni V, Sasaki M, Fuwa H, Rossini GP, Scalera G, Yasumoto T, Pietra P, Bigiani A (2005) Toxicol Sci 85:657
102. Fuwa H, Kainuma N, Satake M, Sasaki M (2003) Bioorg Med Chem Lett 13:2519
103. Fuwa H, Kainuma N, Tachibana K, Tsukano C, Satake M, Sasaki M (2004) Chem Eur J 10:4894
104. Scholl M, Ding S, Lee CW, Grubbs RH (1999) Org Lett 1:953
105. Kadota I, Ueno H, Ohno A, Yamamoto Y (2003) Tetrahedron Lett 44:8645
106. Okazoe T, Takai K (1987) J Org Chem 52:4410
107. Takai K, Kakiuchi T, Kataoka Y, Utimoto K (1994) J Org Chem 59:2668
108. Hansen TM, Florence GI, Lugo-Mas P, Chen J, Adams JN, Forsyth CJ (2003) Tetrahedron Lett 44:57
109. Freeman PK, Hutchinson LL (1980) J Org Chem 45:1924
110. Noyori R, Nishida I, Sakata J, Nishizawa M (1980) J Am Chem Soc 102:1223
111. Scheidt KA, Chen H, Follows BC, Chemler SR, Coffey DS, Roush WR (1998) J Org Chem 63:6436
112. Nicolaou KC, Reddy KR, Skokotas G, Sato F, Xiao XY (1992) J Am Chem Soc 114:7935
113. Nicolaou KC, Reddy KR, Skokotas G, Sato F, Xiao XY, Hwang CK (1993) J Am Chem Soc 115:3558
114. Kadota I, Park JY, Koumura N, Pollaud G, Mitsukawa Y, Yamamoto Y (1995) Tetrahedron Lett 36:5777
115. Kadota I, Yamamoto Y (1998) J Org Chem 63:6597
116. Morimoto M, Mastukura H, Nakata T (1996) Tetrahedron Lett 37:6365
117. Mori Y, Yaegashi K, Furukawa H (1997) J Am Chem Soc 119:4557
118. Mori Y, Yaegashi K, Furukawa H (1998) J Org Chem 63:6200
119. Rainier J, Allwein SP, Cox JM (2001) J Org Chem 66:1380
120. Zakarian A, Batch A, Holton RA (2003) J Am Chem Soc 125:7822
121. Fujiwara K, Sato D, Watanabe M, Morishita H, Murai A, Kawai H, Suzuki T (2004) Tetrahedron Lett 45:5243
122. Nakanishi K (1985) Toxicon 23:473
123. Shimizu Y (1986) In: Harris JB (ed) Natural Toxins. Clarendon Press, Oxford, p 115
124. Fujiwara K, Murai A (2004) Bull Chem Soc Jpn 77:2129
125. Zhu L, Welmeyer RM, Rieke RD (1991) J Org Chem 56:1445

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Total Synthesis of Marine Macrolides

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Abstract Recent progress (2002–2005) of total syntheses of bioactive marine macrolides, lasonolide A, zampanolide, dactylolide, and leucascandrolide A, was described. The stereoselective construction of tetrahydropyrans, which are important units involved in these natural products, is also summarized.

Keywords Macrolide · Marine natural product · Tetrahydropyran · Total synthesis

Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
Ac_2O	acetic anhydride
AcOH	acetic acid
AIBN	2,2′-azobisisobutyronitrile
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
BINOL	1,1′-bi-2-naphthol
Bn	benzyl
cHex	cyclohexyl
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	(diethylamino)sulfur trifluoride
$Pd_2dba_3 \cdot CHCl_3$	tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBALH	diisobutylaluminum hydride
DIC	diisopropylcarbodiimide
DMAP	4-dimethylaminopyridine
DMB	3,4-dimethoxybenzyl
DMSO	dimethyl sulfoxide
EDCI	*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide
HMPA	hexamethylphosphoric triamide
HOBt	1-hydroxybenzotriazole
Ipc	isopinocamphenyl
KHMDS	potassium hexamethyldisilazide
LDBB	lithium 4,4′-di-*tert*-butylbiphenyl
mCPBA	*m*-chloroperoxybenzoic acid
Mes	mesityl
MPM	4-methoxybenzyl
MS4A	molecular sieves 4A
NBS	*N*-bromosuccinimide
NHMDS	sodium hexamethyldisilazide
NMM	4-methylmorpholine
NMO	4-methylmorpholine *N*-oxide
PCC	pyridinium chlorochromate
PMP	4-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
PS/DCC	polymer bound dicyclohexylcarbodiimide

Pv	pivaloyl
py	pyridine
Red-al	sodium bis(2-methoxyethoxy)aluminum hydride
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
Tf_2O	triflic anhydride
TFA	trifluoro acetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMANO	trimethylamine *N*-oxide
TMS	trimethylsilyl
tol	4-methylphenyl
TPAP	tetrapropylammoniiumu perruthenate
TsOH	4-toluenesulfonyl

1 Introduction

The term "macrolides" was initially proposed by Woodward in 1957 for macrocyclic lactone glycoside antibiotics [1], and presently the term seems to be used in a broader sense. Marine macrolides have stimulated organic chemists to make greater efforts in their syntheses because the macrolides possess synthetically challengeable unique structures. Total synthesis of these natural products is a showcase for new synthetic methodologies such as stereocontrolled carbon–carbon forming reactions, stereoselective and chemoselective functionalizations, macrolactonizations as well as new strategies of the construction of the carbon framework. Their various biological activities including cytotoxicity, neurotoxicity, antiviral, and antifungal activity has also attracted the attention of chemists. As most of marine macrolides are available in only tiny quantities from their natural sources, total synthesis has the potential for supplying sufficient quantities of the natural products for bioassay, and is helpful for the synthesis of their analogues for medicinal chemistry.

Total synthesis is also an important method for determining the stereochemistry of marine macrolides. In this review, the correct structures of lasonolide A and zampanolide have been determined by total synthesis.

Total synthesis of macrolides produced by terrestrial and marine organisms was reviewed by Nicolaou [2], Back [3], Paterson [4], and Nakata [5], and total synthesis of bioactive marine macrolides was reviewed by Pater-

son [6], and Yeung and Paterson [7]. More specialized reviews have also been published (for amphidinolides: [8]). This review is focused on recent developments (ca. 2002–2005) in the total synthesis of selected marine macrolides and related chemistry.

2
Stereoselective Construction of Substituted Tetrahydropyran Moiety

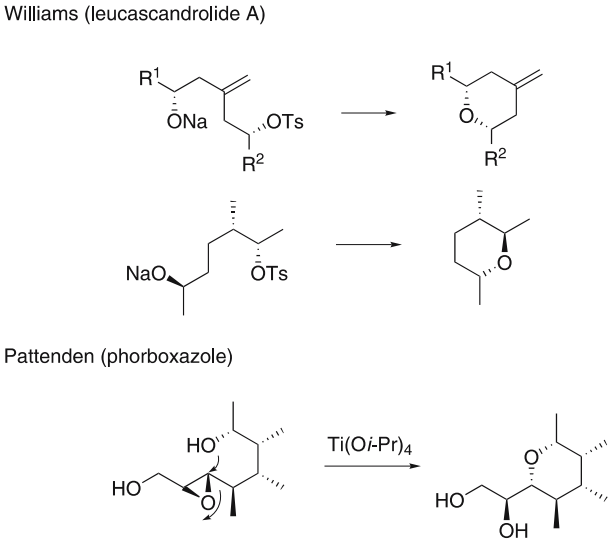
Marine macrolides have numerous asymmetric centers, oxygenated functionalities including alcohols, carbonyl groups, the tetrahydropyran moiety, di- and trisubstituted alkenes, and macrocyclic lactones. For completion of their total synthesis, efficient and stereoselective introduction of these characteristic units should be crucial. Recently, an excellent review on asymmetric synthesis of 1,3-diol, macrolactonization, and glycosidation in the syntheses of macrolides has been published by Nakata [5]. The multisubstituted tetrahydropyran moieties are often found in the marine macrolides, and the efficient preparation of these moieties is recognized as the key reaction in their total synthesis. In this decade, efficient methods for their stereoselective construction have been developed and used in the total synthesis of marine macrolides, wherein the relative configuration of 2- and 6-substituents is pivotal. In this section, recent progress in the preparation of tetrahydropyrans is described (for a previous review on the preparation of tetrahydropyrans, see: [9]).

2.1
Intramolecular S_N2 Reaction (6-*exo*-tet)

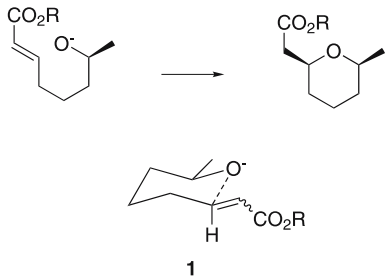
The intramolecular S_N2 reaction of alkoxide anions to alkyl halides or its equivalents is one of the fundamental methods for the synthesis of tetrahydropyrans (Scheme 1). The 1,5-diol should be prepared stereoselectively in both sites and one of the diols should be protected or tosylated. The stereochemistry of the product corresponds to that of the starting 1,5-diols. Williams used this method in the total synthesis of leucascandrolide A (Sect. 3.3.7), and Pattenden employed Lewis acid mediated ring-opening of epoxy alcohol in the total synthesis of phorboxazole [10, 11].

2.2
Intramolecular Michael Addition (6-*exo*-trig)

The intramolecular Michael addition of alkoxide anions to α,β-unsaturated esters is often seen in the preparation of tetrahydropyrans (Scheme 2). Usually, 2,6-*cis*-disubstituted tetrahydropyrans are obtained with high stereoselectivity via the 6-membered transition state model **1**. In the total syntheses



Scheme 1 Preparation of 2,6-*cis*-tetrahydropyrans via intramolecular S_N2 reaction

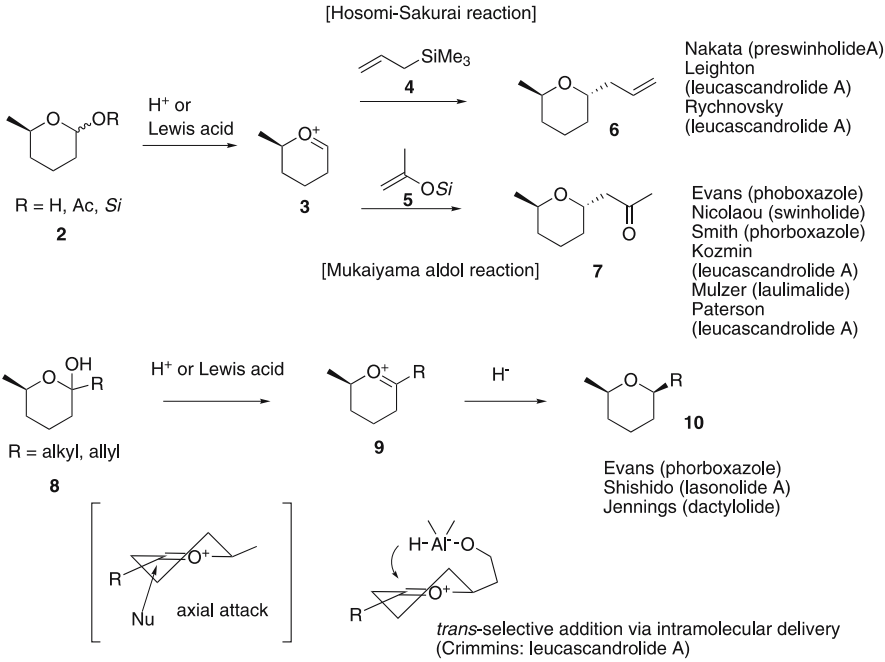


Scheme 2 Preparation of 2,6-*cis*-tetrahydropyrans via intramolecular Michael addition

of lasonolide A by Kang (Sect. 3.1.2) and Shishido (Sect. 3.1.3), leucascandrolide A by Carreira (Sect. 3.3.3) and Crimmins (Sect. 3.3.8), and phorboxazole by Forsyth [12], this method was used.

2.3 Nucleophilic Addition to Pyran Oxonium Cation

The δ-lactols and their acetylated derivatives (**2**, **8**) are activated by acid to form oxonium cation intermediates (**3**, **9**), which are attacked by nucleophiles to provide the substituted tetrahydropyrans with good stereoselectivity (Scheme 3) [13]. As the nucleophiles, allylsilane **4** (Hosomi–Sakurai reaction), silyl enol ethers **5** (Mukaiyama aldol) and Et_3SiH (reduction) have frequently been used. Since the axial attack of the nucleophiles determines the product's

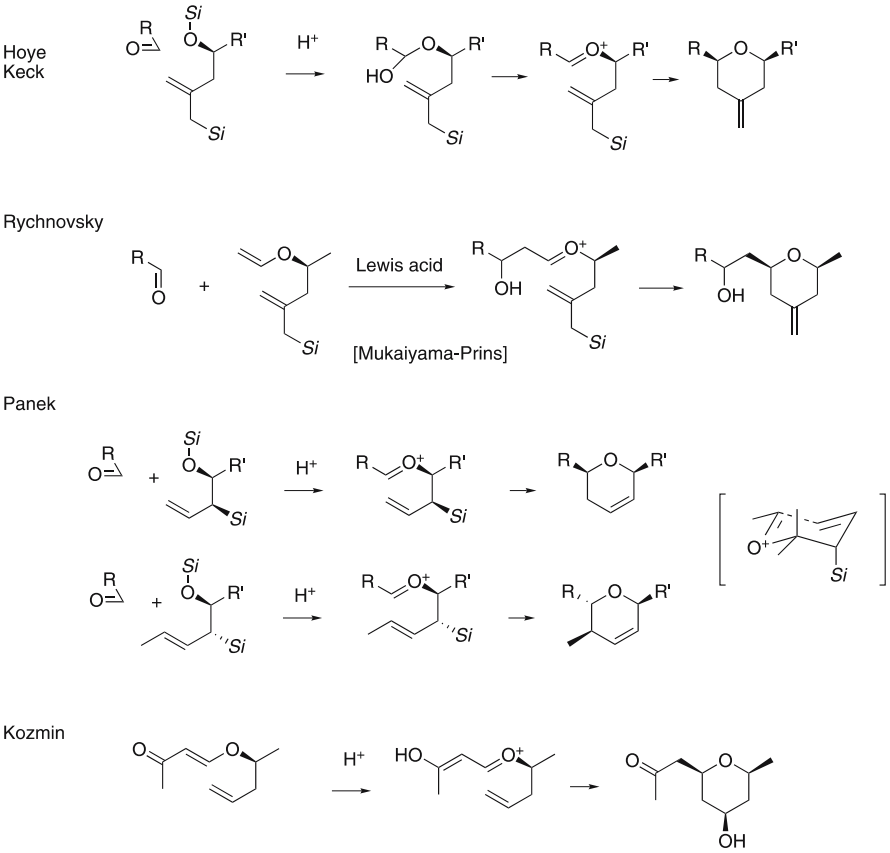


Scheme 3 Preparation of tetrahydropyrans through pyran oxonium cation

stereochemistry, in the reaction of carbon nucleophiles, the 2,6-*trans* products (**6**, **7**) are generated, and in the case of the hydride reduction, the 2,6-*cis* product (**10**) is usually produced. On the other hand, Crimmins reported the *cis*-reduction providing 2,6-*trans*-tetrahydropyran via the intramolecular delivery of hydride (Sect. 3.3.8).

2.4 Prins Reaction

The acid-promoted Prins reaction between a homoallylic alcohol and an aldehyde is a well-established synthesis of tetrahydropyrans (Scheme 4) [14, 15]. While substituted tetrahydropyrans are often assembled by cyclizations forming a C – O bond, the Prins reaction undergoes cyclization by C – C bond formation. The Prins reaction of the silyl-modified substrates [16], which can be regarded as the intramolecular Hosomi–Sakurai reaction, is effectively activated by the allylsilane unit. The stereochemistry of the 2,6-*cis*-form produced in the case of the *exo*-allylsilane unit is elucidated by the 6-membered transition state model. In the cyclization of the *endo*-allylsilane substrates, since the silyl group would be fixed on the axial position of the 6-membered transition states, the tetrahydropyrans with both 2,6-*cis* and *trans*-forms can be synthesized (Panek: Sect. 3.3.9). This type of cyclization was also



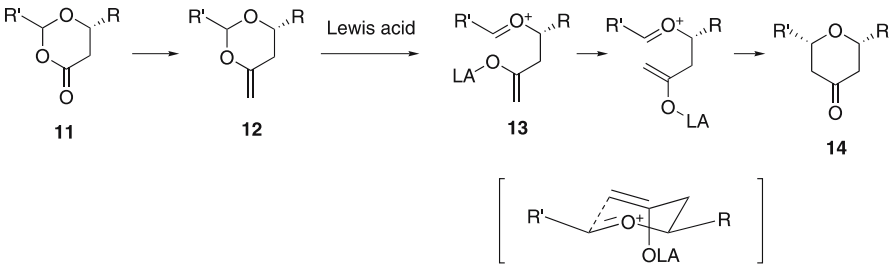
Scheme 4 Preparation of tetrahydropyrans via Prins reaction

used by Hoye (Sect. 3.2.2), Keck (Sect. 3.2.5), and Rychnovsky (Sect. 3.3.2) in the recent syntheses of marine macrolides. Kozmin reported that the Prins desymmetrization was performed using the enol-stabilized oxonium cation (Sect. 3.3.5).

2.5 Petasis–Ferrier Rearrangement

Smith utilized Petasis–Ferrier rearrangement [17] in the total syntheses of zampanolide (Sect. 3.2.1) and phorboxazole [18, 19]. The 1,3-dioxan-4-ones **11** are transformed into 4-methylene-1,3-dioxanes **12**, which are treated with Lewis acids to give oxonium intermediates **13**. Like the Prins reaction described above, the *cis*-2,6-disubstituted tetrahydropyran-3-ones **14** are preferentially synthesized via the C – C bond formation (Scheme 5).

Smith



Scheme 5 Preparation of tetrahydropyran via Petasis–Ferrier rearrangement

2.6 Oxymetallation, Oxycalcogenation

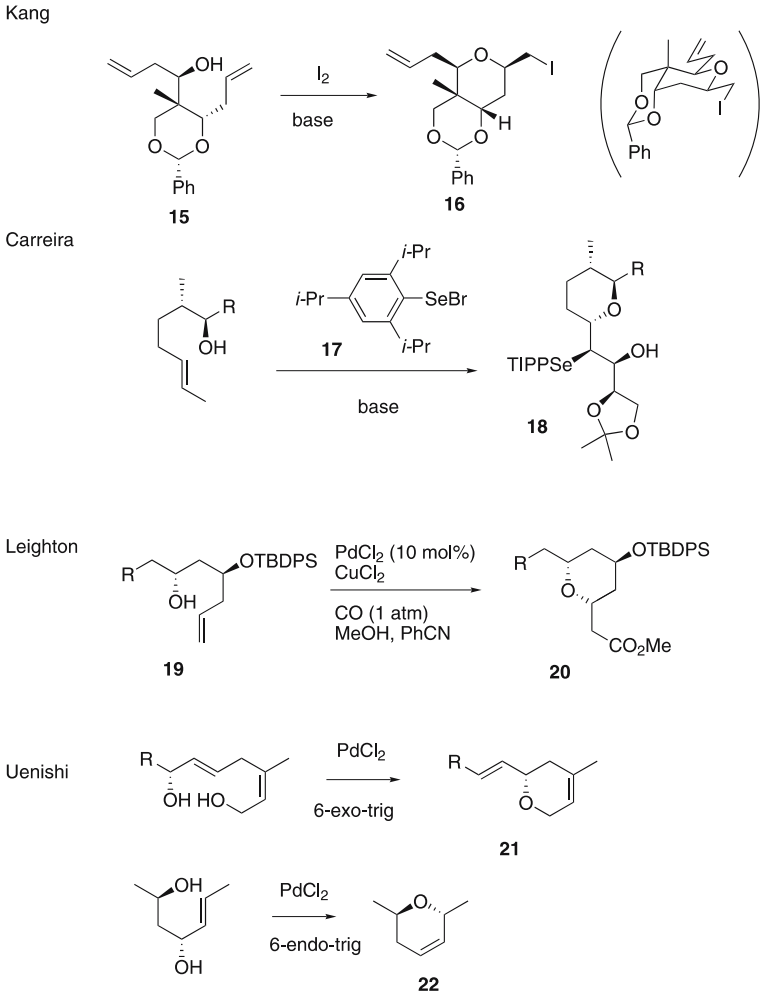
The strong electrophilic iodine and arylselenyl bromide activate a simple alkene, followed by the cyclization via addition of hydroxy group, to give tetrahydropyrans (Scheme 6). Kang achieved the highly selective cyclization giving the *cis*-2,6-disubstituted tetrahydropyran **16** using the conformationally fixed substrate **15** (Sect. 3.1.2). On the other hand, Carreira reported that the sterically hindered arylselenyl bromide **17** undergoes cyclization to the *trans*-2,6-disubstituted tetrahydropyran **18** (Sect. 3.3.3). Palladium catalyzed cyclization via oxymetallation was also reported. Leighton utilized Zemmelhak's alkoxy carbonylation of 5-hexenol unit **19** to obtain the *cis*-2,6-disubstituted tetrahydropyran **20** (Sect. 3.3.1). Uenishi found the allylic hydroxy group-assisted stereoselective construction of 5,6-dihydro[2H]pyrans (**21**, **22**) via formal *syn*-S_N2' reaction in the total synthesis of (–)-laulimalide [20].

2.7 Radical Reaction

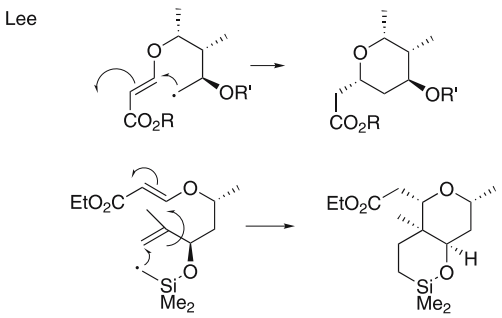
Lee synthesized 2,6-*cis*-disubstituted tetrahydropyrans via radical cyclization in the total synthesis of lasonolide A (Sect. 3.1.1). In this synthesis, Lee also achieved the 6-*endo*, 6-*exo* tandem radical cyclization constructing two contiguous asymmetric centers containing a quaternary carbon (Scheme 7).

2.8 Hetero Diels–Alder Reaction

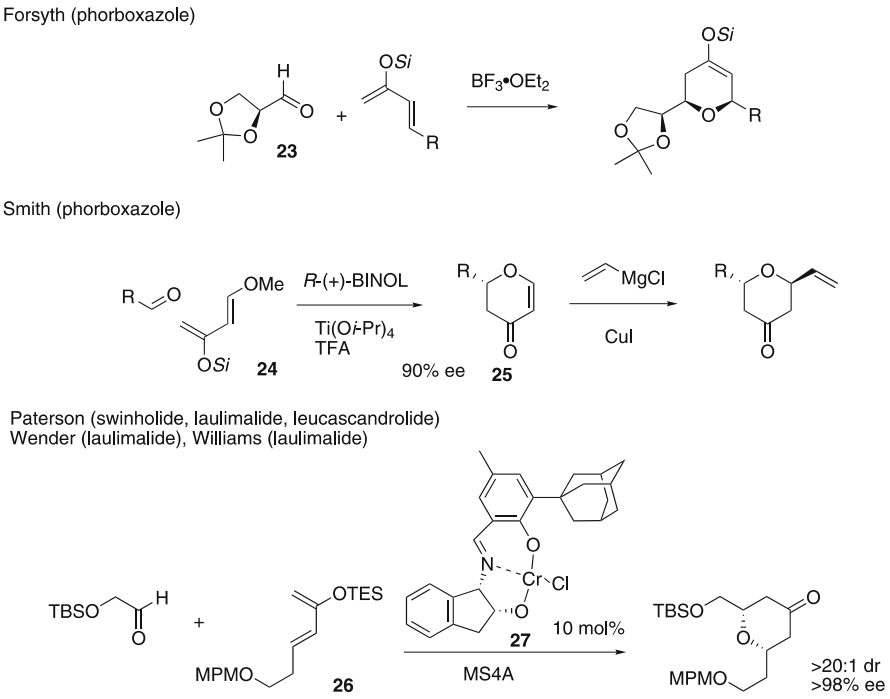
The hetero Diels–Alder reaction of activated dienes with aldehydes is a useful tool for the synthesis of dihydropyrans [21] (Scheme 8). In the synthesis of marine macrolides, for example, Forsyth reported the diastereoselective



Scheme 6 Preparation of tetrahydropyrans via iodoetherification and oxymetallation



Scheme 7 Preparation of tetrahydropyrans via radical reactions

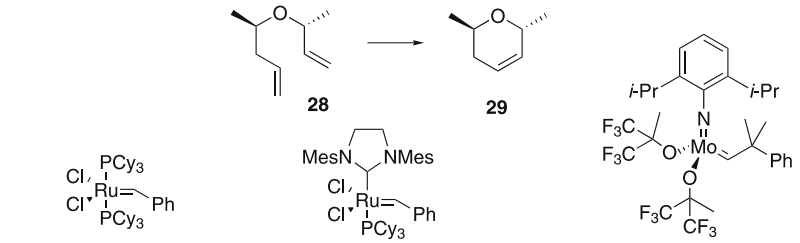


Scheme 8 Preparation of tetrahydropyranones via hetero Diels–Alder reaction

hetero Diels–Alder reaction using chiral aldehyde **23** [22]. Chiral Lewis acid catalyzed hetero Diels–Alder reaction [23] with Danishefsky's diene **24** [24] furnished dihydropyran **25** in 90% ee in the synthesis of phorboxazole by Smith [18, 19]. A more general catalytic enantioselective hetero Diels–Alder reaction has been achieved by Jacobsen [25]. Chiral tridentate Shiff base chromium(III) complex **27** catalyze the [4 + 2] cyclization of less nucleophilic dienes **26** than Danishefsky's dienes. Paterson [26], Wender [27], and Williams [28] have utilized the asymmetric reactions to obtain the tetrahydropyranones with high ee.

2.9 Ring-Closing Olefin Metathesis

In recent years, ring-closing olefin metathesis (RCM) has attracted organic chemists as a versatile cyclization method via carbon–carbon bond formation, and had a great impact on the synthesis of natural products [29, 30]. In the syntheses of dihydropyrans of marine macrolides, allyl homoallyl ethers **28** have been cyclized to dihydropyrans **29** via RCM. This methodology has been seen in the syntheses of laulimalide by Mulzer [31, 32], Crimmins [33], and Nelson [34] (Scheme 9).



Scheme 9 Preparation of dihydropyrans via RCM

3
Total Synthesis of Marine Macrolides

3.1
Total Synthesis of Lasonolide A

Lasonolide A is a novel cytotoxic 20-membered macrolide isolated in 1994 by McConnel from the shallow water Caribbean marine sponge *Forcepia* ap [35]. It displays a potent cytotoxin with IC_{50} values of 40 and 2 ng mL^{-1} against the A-549 human lung carcinoma and P388 murine leukemia cell lines, respectively, and inhibits cell adhesion in the EL-4IL2 cell line. McConnel's original proposed structure ((+)-**30**, Fig. 1), in which the stereochemistry at C28 was unknown, was found to be incorrect by Lee's synthetic studies. Finally, the structure of lasonolide A has been revised on the basis of Lee's total synthesis, and by its biological tests, (–)-form **31** has been found to be the biological active enantiomer (Fig. 2) [36].

Seven lasonolide series (A, B, C, D, E, F, G) [37] of natural products have been isolated to date, all of which possess the same C-1 through C-29 polyketide, but differ in the nature of the side-chain substituents (Fig. 2). The

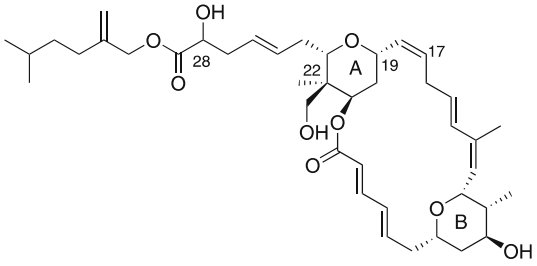
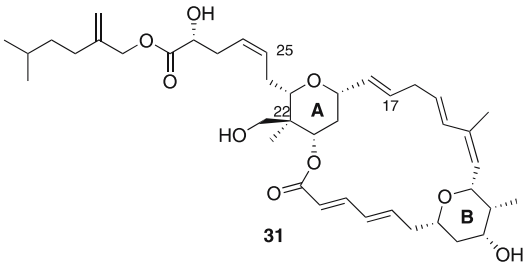


Fig. 1 McConnel's proposed structure of lasonolide A



(-)-Lasonolide A (the biologically active enantiomer)

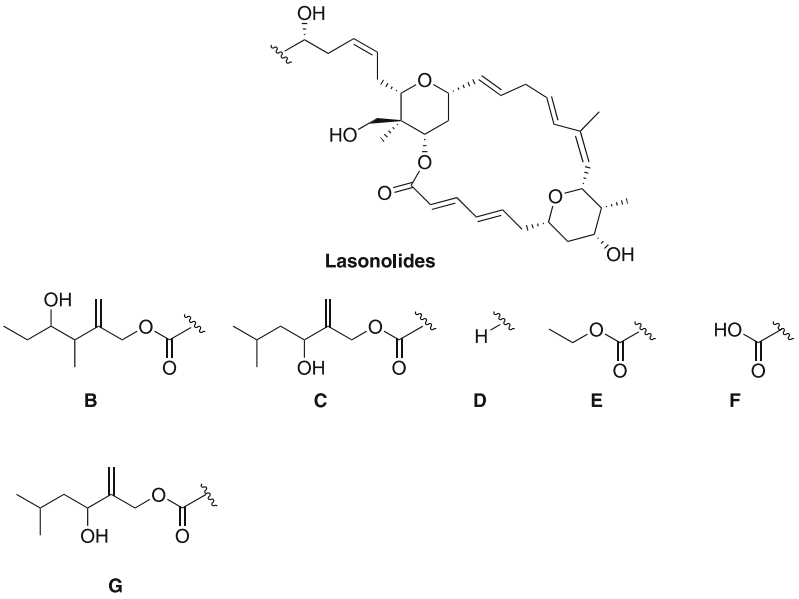


Fig. 2 Revised biologically active lasonolide A and other lasonolides

characteristic features in lasonopyran skeleton are the two *cis*-2,6-substituted tetrahydropyrans, one of which contains a quaternary stereogenic center at C-22. The intriguing structural features and significant biological activity of lasonolides A have stimulated synthetic organic chemists, and so far following Lee, Kang and Shishido have completed the total synthesis. In this section, these three total syntheses are described.

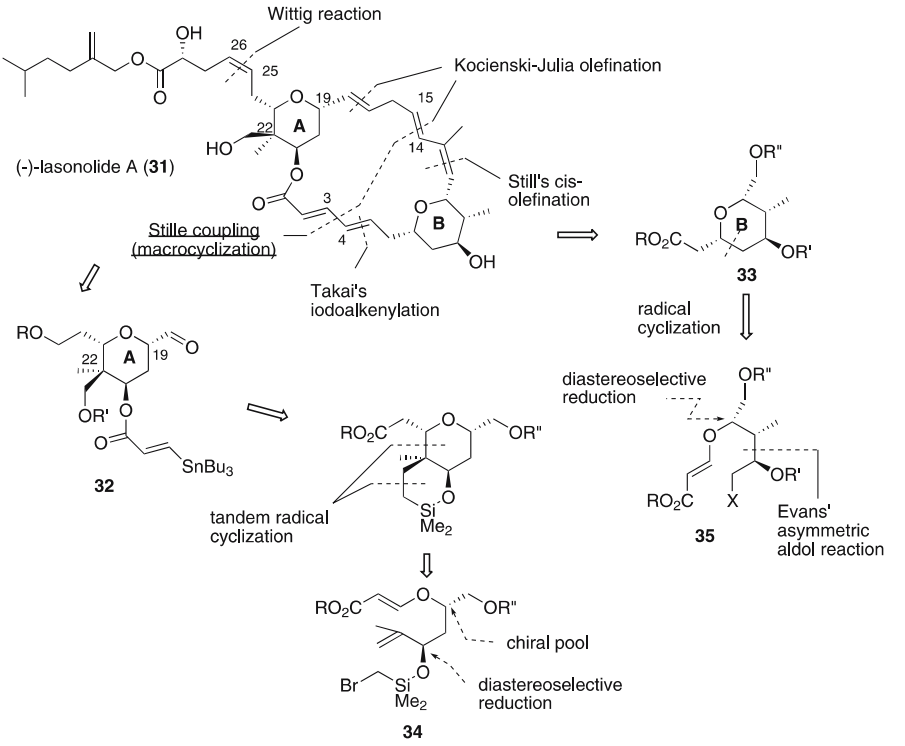
3.1.1 The First Total Synthesis of (+)- and (–)-Lasonolide A by Lee [38,39]

At first, Lee synthesized "lasonolide A" of McConnel's proposed structure **30**, which was not identical with the natural product. After Lee's synthesis of the

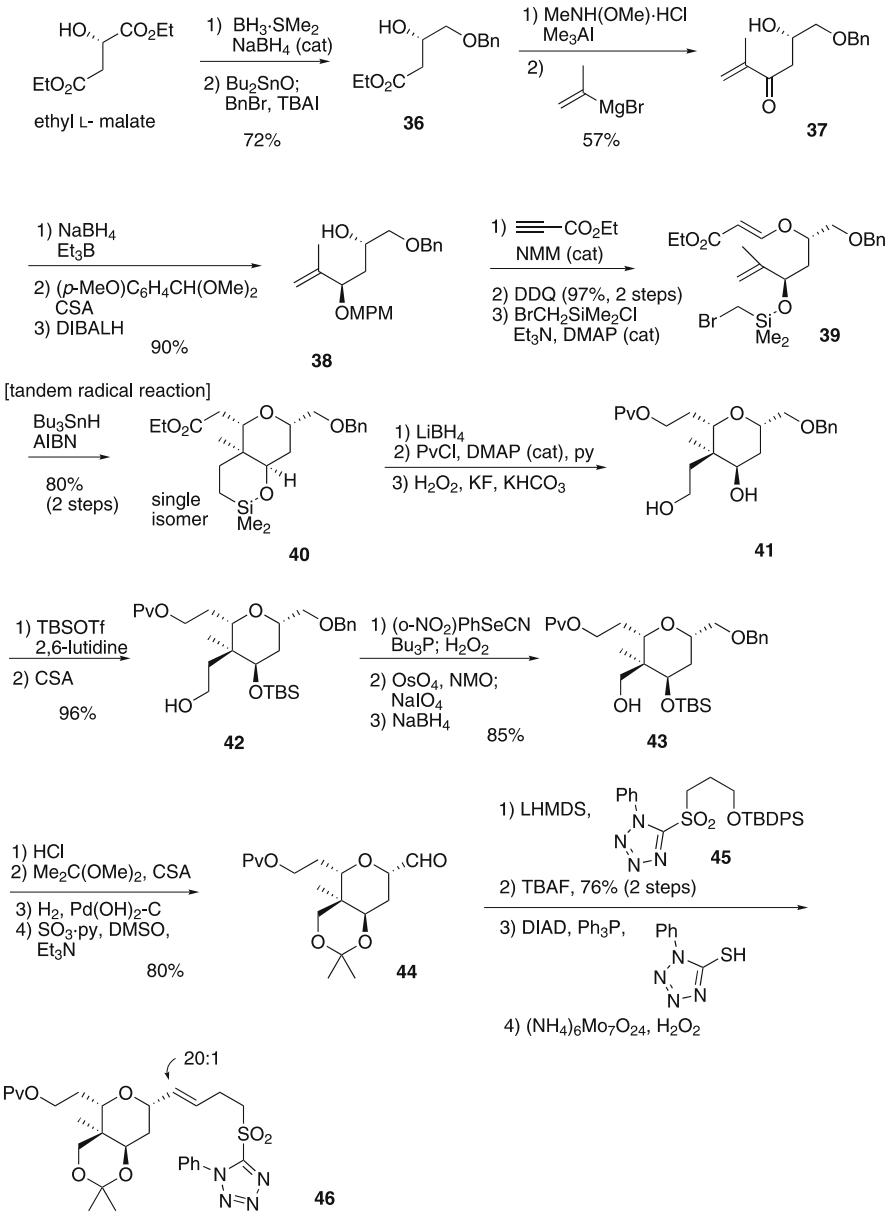
diastereomers and geometrical isomers of C-17 and C-25, (–)-**31** as shown in Fig. 2 has proved to be the biologically active lasonolide A, identical with the natural product except for optical rotation (the natural: $[\alpha]_{20}^{D}$ + 24.4; the synthetic biologically inactive: $[\alpha]_{20}^{D}$ + 24.2; the synthetic biologically active: $[\alpha]_{20}^{D}$ – 24.1). This discrepancy has not been resolved. In this section, Lee's first total synthesis of biologically active (–)-lasonolide A (**31**) is introduced.

Lee's strategy for the total synthesis is outlined in Scheme 10. The synthesis was based on side-chain bond formation (C25–C26) via the Wittig reaction, macrocyclization (C3–C4) via Stille coupling, and the connection of the A-ring unit **32** and the B-ring unit **33** via the Kociensky–Julia olefination [40]. The tetrahydropyrans in the A and B rings were constructed by radical cyclization of the chiral non-racemic β-alkoxyacrylates (**34**, **35**) which were derived from a chiral pool and an asymmetric aldol reaction, and in this radical reaction, the quaternary stereogenic center in the A-ring was also stereoselectively constructed.

Preparation of the A-ring unit (Scheme 11) started with ethyl L-malate, which was converted into the enone **37** through the Weinreb amide derived from the ester **36**. Stereoselective reduction [41] of **37** produced the syn



Scheme 10 Lee's retrosynthesis of bioactive lasonolide A



Scheme 11 Preparation of A-ring unit

diol, which was transformed into the mono-ol **38** via regioselective reduction [42] of the cyclic acetal. The Michael addition of **38** to ethyl propiolate, followed by deprotection of MPM, and bromomethylsilylation afforded the β-alkoxyacrylate **39**. Tandem radical cyclization of **39** proceeded smoothly to

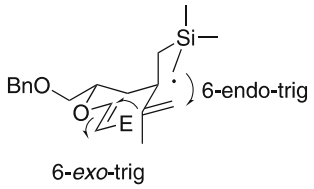


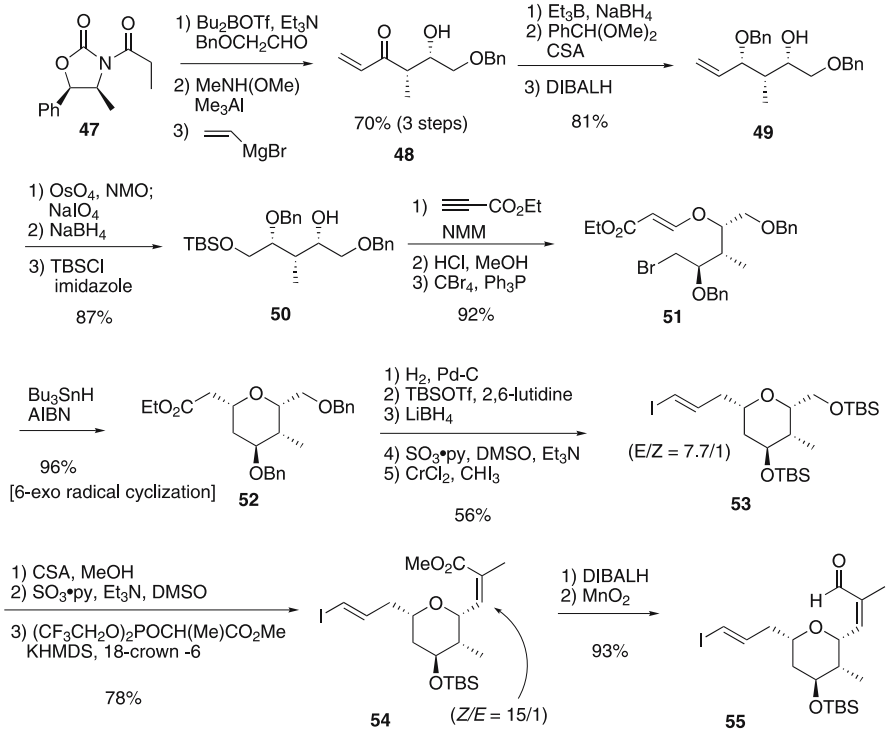
Fig. 3 Tetrahydropyran via stereoselective tandem radical cyclization

furnish the bicyclic product **40** as a single isomer (Sect. 2.7). The excellent stereoselectivity of the successive 6-*endo*, 6-*exo* radical reaction is elucidated by Fig. 3. After reduction of the ester moiety and protection, Tamao oxidation of the siloxane **40** provided the diol **41**, which was converted into the primary mono alcohol **42** via bis-silylation followed by selective desilylation. For removal of one carbon from the hydroxyethyl group, the dehydration of **42** via the selenylation/oxidation sequence [43], followed by the oxidative cleavage of the resulting terminal olefin, was employed to give **43**. After conversion of **43** to the aldehyde **44**, Kocienski–Julia olefination of the aldehyde **44** with **45**, followed by de-silylation and sulfonation, led to the 1-phenyl-1H-tetrazol-5-yl sulfone **46**.

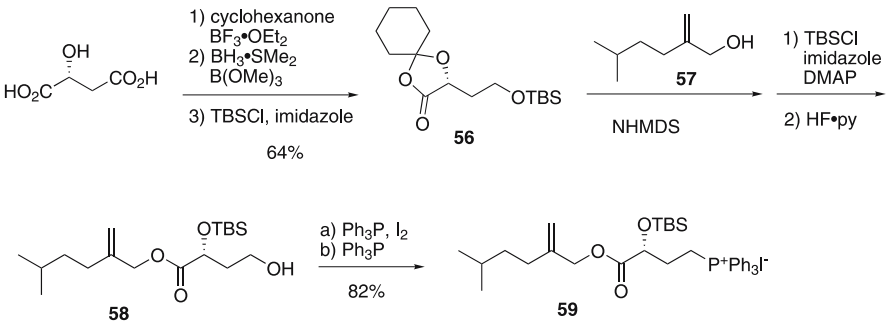
The B-ring unit was synthesized as illustrated in Scheme 12. The Evans asymmetric aldol reaction starting from chiral imide **47**, followed by vinyl Grignard reaction of the corresponding Weinreb amide, provided the hydroxy enone **48**. After stereoselective reduction of **48**, the resulting 1,3-diol was converted to the dibenzyl ether **49** via regioselective reduction of the corresponding benzylacetal. Oxidative cleavage of the terminal alkene of **49**, followed by reduction of the aldehyde and then protection of the primary alcohol, gave the secondary alcohol **50** bearing three contiguous stereogenic centers. The Michael addition of **50** to ethyl propiolate furnished the (*E*)-β-alkoxy acrylate, which was converted into the bromide **51**. The 6-*exo* radical cyclization of **51** proceeded to furnish the tetrahydropyran **52** in high yield with high stereoselectivity. **52** was converted into the (*E*)-iodoalkene **53** ($E/Z = 7.7$) via the Takai iodoalkenylation of the corresponding aldehyde. The selective TBS-deprotection of **53**, followed by oxidation, gave an aldehyde, which was olefinated by Still's modified Horner–Emmons reagent [44] to furnish the (*Z*)-enoate **54** ($Z/E = 15$). The ester moiety was transformed to the aldehyde **55**.

The side chain unit was prepared from L-malic acid in 8 steps as shown in Scheme 13. The cyclic acetal **56** was condensed with the alcohol **57** [45], to afford **58**, which was converted to the phosphonium salt **59**.

With the A-ring unit **46** and the B-ring unit **55** in hand, they were coupled via Kocienski–Julia olefination to provide the desired product **60** with high (*E*)-selectivity (Scheme 14). After deprotection of the acetonide and subsequent TBS-protection of the primary alcohol, esterification of the secondary alcohol with the acid **61** led to the preparation of the (*E*)-β-stannylacrylate **62**

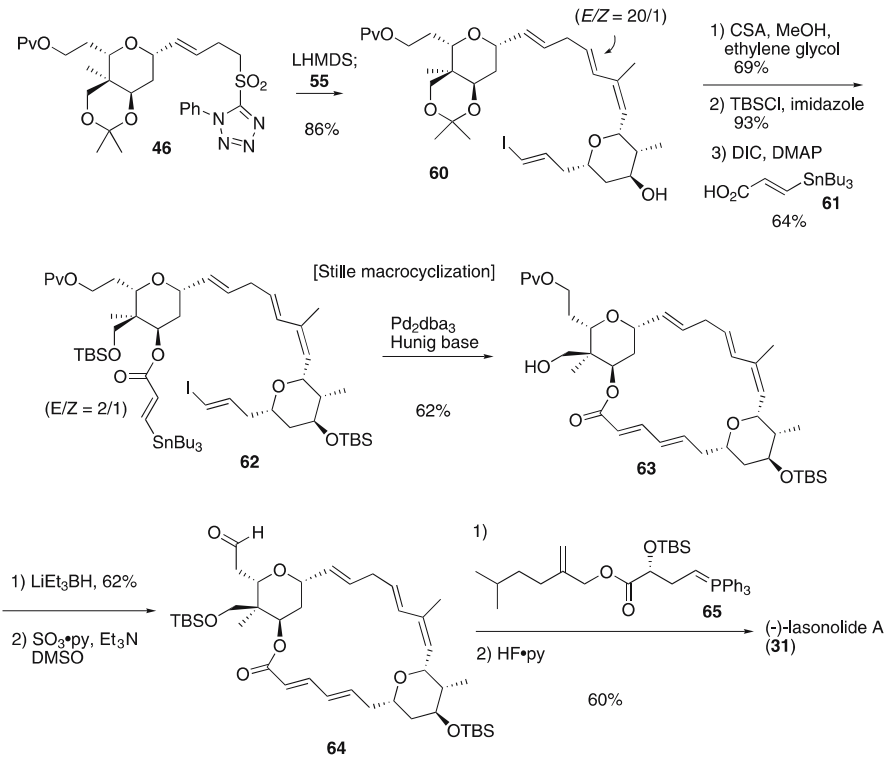


Scheme 12 Preparation of B-ring unit



Scheme 13 Preparation of side chain unit

along with the (*Z*)-isomer ($E/Z = 2/1$). The mixture was subjected to the intramolecular Stille coupling reaction to provide the macrolactone **63**. Finally, aldehyde **64**, prepared by reductive deprotection of the pival group and oxidation, was olefinated with the Wittig reagent **65**, derived from **59**, to yield, after deprotection, (+)-lasonolide A (**31**).

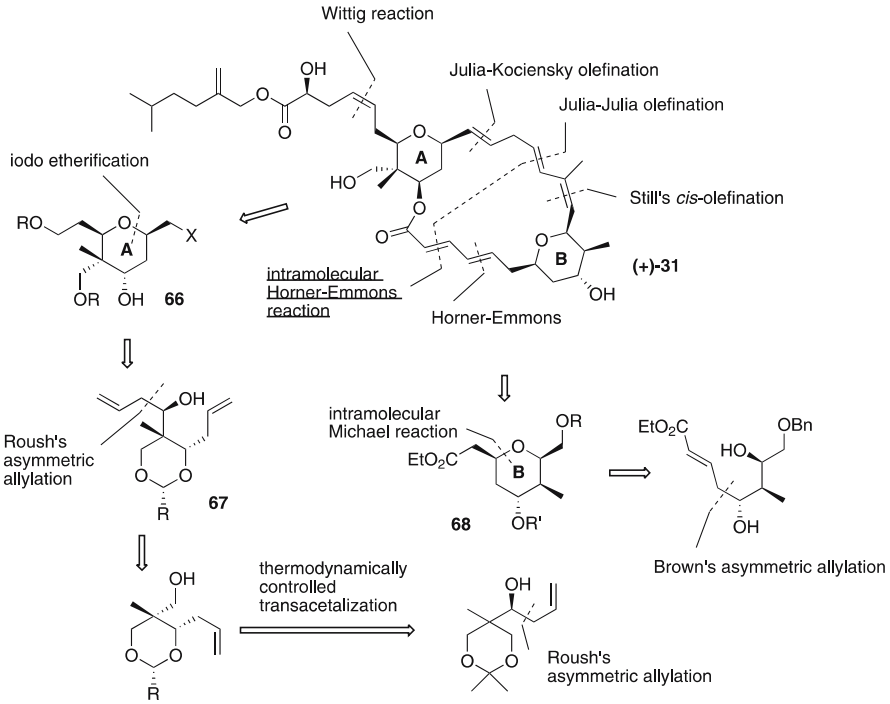


Scheme 14 Completion of total synthesis

From the biological tests, it was found that the (–)-enantiomer was more potent than the (+)-enantiomer, which was supposed to be the natural lasonolide A reported by McConnel. The original report on the optical rotation data for natural lasonolide A might be in error.

3.1.2 Kang's Total Synthesis of (+)-Lasonolide A [46]

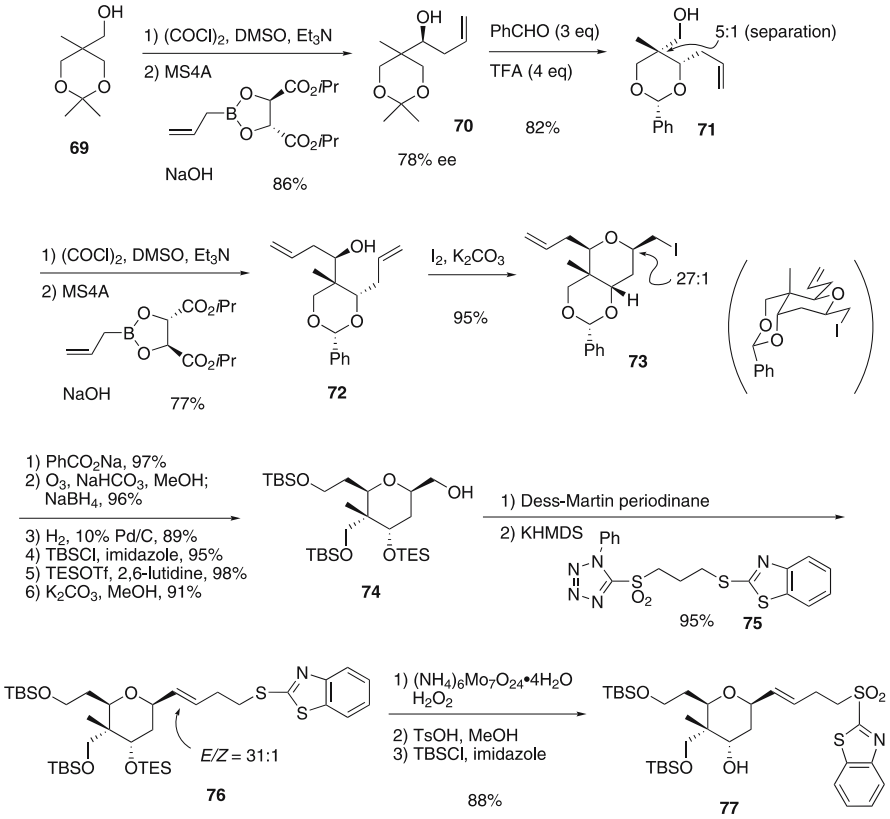
The strategy proposed by Kang for achieving a synthesis of lasonolide A is outlined in Scheme 15. For the introduction of the side chain, Lee's procedure was adopted. Macrocyclization was performed via the Horner–Emmons reaction, and the construction of the C12–C28 triene unit was similar to Lee's protocol using Julia-type olefination and Still's *cis*-olefination. The A-ring **66** was formed by iodoetherification of the alkenyl alcohol **67**, the tertially asymmetric centers of which were formed by asymmetric allylations. The construction of the key quaternary asymmetric carbon was carried out by the unique procedure of the thermodynamically controlled transacetalization. The B-ring **68**



Scheme 15 Kang's retrosynthesis

was cyclized by the intramolecular Michael addition, and the precursor was provided by asymmetric allylation.

The A-ring unit was synthesized as shown in Scheme 16. The alcohol **69** was oxidized and then allylated with Roush's chiral allylboronate to afford the homoallylic alcohol **70** with 78% ee. The key reaction constructing the quaternary carbon was performed via acidic transacetalization, in which the thermodynamically more stable diastereomer **71** was preferentially generated in a ratio of 5 : 1. It was elucidated that the selectivity was caused by hydrogen bonding between the axial hydroxymethyl group and the two oxygen atoms of the acetal as illustrated in Fig. 4. After separation of these diastereomers, the minor isomers of which can be recycled, the second asymmetric allylation of the corresponding aldehyde, prepared by oxidation of **71**, furnished the homoallylic alcohol **72**, which was subjected to iodoetherification to form the 2,6-*cis*-tetrahydropyran **73** bearing four asymmetric centers in a diastereomeric ratio of 27 : 1. The functionalization including oxidative cleavage of the alkene and the protecting group assembly led to the partially protected tetraol **74**. The aldehyde, prepared by oxidation of the primary alcohol of **74**, was subjected to Kocienski–Julia olefination with the disulfone equivalent **75**



Scheme 16 Preparation of the A-ring unit

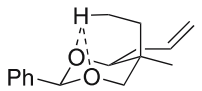
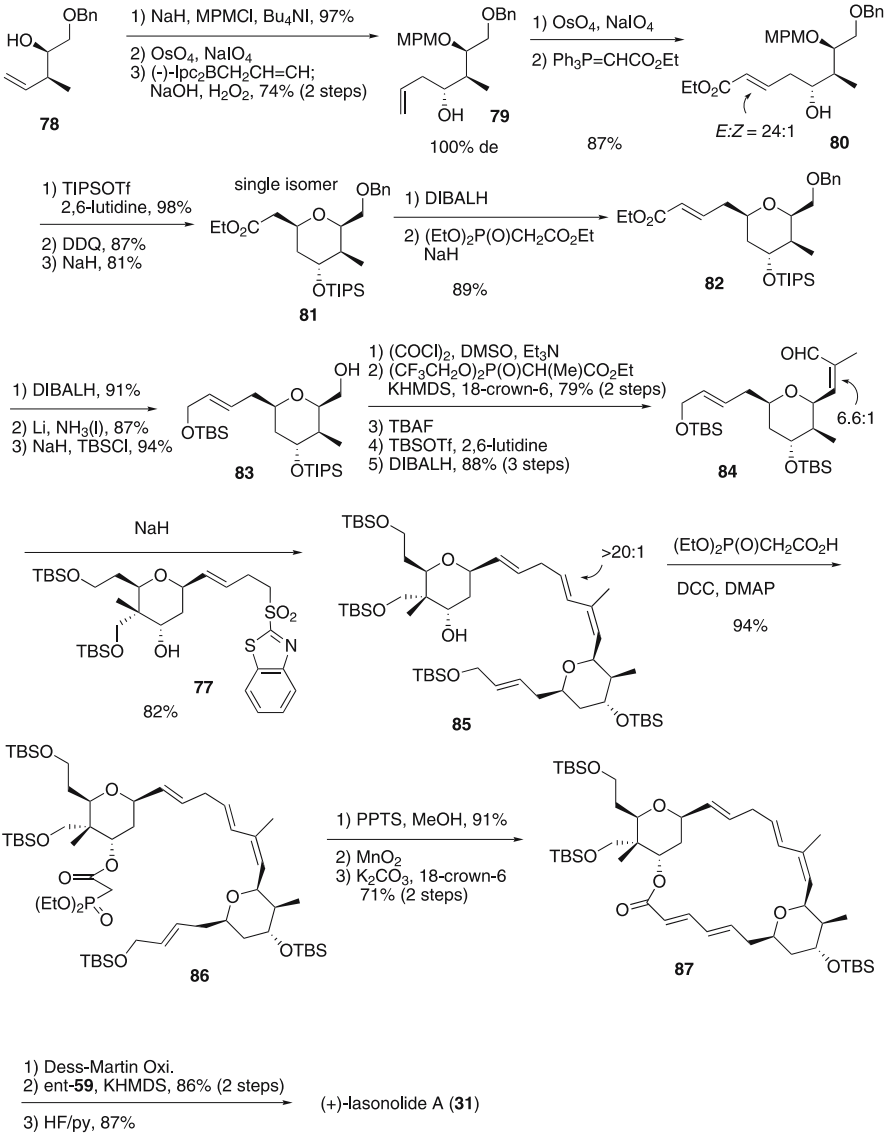


Fig. 4 Thermodynamic controlled construction of 1,3-dioxane stabilized by intramolecular hydrogen bonding

having three carbon units. The resulting product **76** was oxidized and selectively deprotected to give the sulfone **77**.

Scheme 17 illustrates the synthesis of the B-ring unit and the completion of total synthesis. The known homoallyl alcohol **78** [47] was protected and oxidatively cleaved to give an aldehyde, which was subjected to Brown's asymmetric allylation [48, 49] to give the alcohol **79** with excellent diastereoselectivity. Oxidative cleavage of **79**, followed by the Wittig reaction, provided (*E*)-unsaturated ester **80** ($E/Z = 24$), which has the B-ring frame work. After protecting group manipulation, the intramolecular Michael addition was performed to yield the 2,6-*cis*-tetrahydropyran **81** as a single isomer. Re-



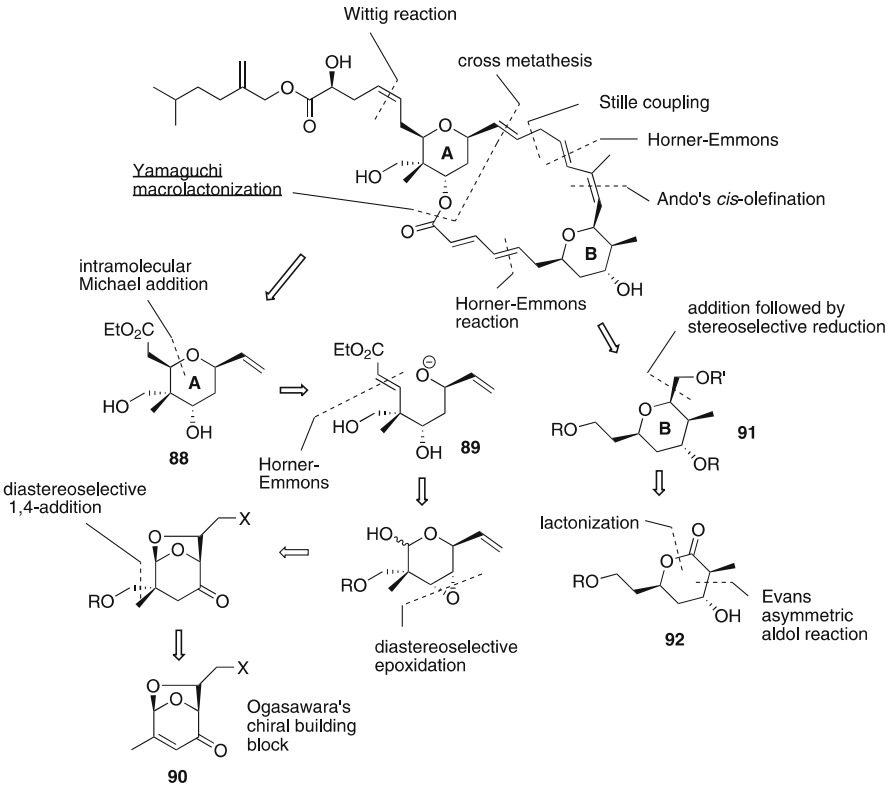
Scheme 17 Completion of total synthesis

duction of the ester, followed by Homer–Emmons homologation, furnished (*E*)-unsaturated ester **82,** which was converted into **83.** As can be seen in Lee's procedure, the Still's modified Horner–Emmons reaction was subjected to the aldehyde, derived from **83,** to construct the C12–C13 bond of the (*Z*)-olefin (*Z*/*E* = 6.6) **84,** after exchange of the protecting group from TBS to TIPS at the C-9 hydroxy group.

The coupling of **77** and **84** was performed via the Julia–Julia olefination [50] to construct the (*E*)-olefin **85** (E/Z => 20) at the C14–C15 bond. This approach is slightly more efficient than that of the Kocienski–Julia protocol in the case of Lee's synthesis. As a macrocyclization, the intramolecular Horner–Emmons reaction was adopted, because macrolactonization of the hydroxy (*E*, *E*)-dienylcarboxylic acid was difficult. The phosphonate **86**, derived from **85**, was exposed to K_2CO_3 and 18-crown-6 [51–53] to provide the macrolactone **87** in good yield. Finally, the side chain was introduced via the Wittig reaction like Lee's method, and the second total synthesis was accomplished.

3.1.3
Shishido's Total Synthesis of (+)-Lasonolide A [54]

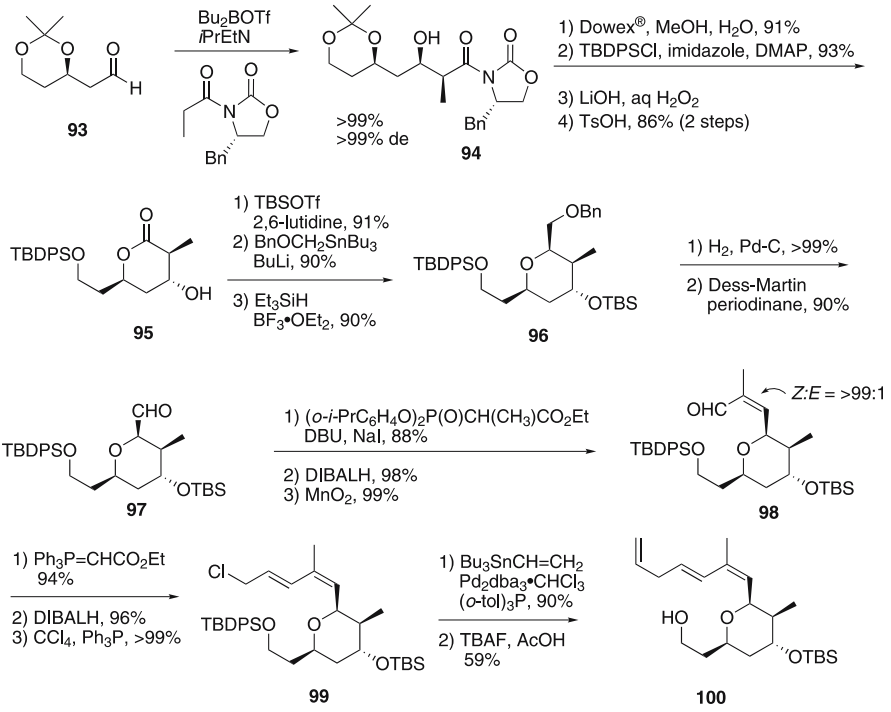
Recently, Shishido has achieved the third total synthesis of (+)-lasonolide A, and their synthetic strategy was based on the introduction of the side chain via Lee's protocol, the successful Yamaguchi macrolactonization, and the



Scheme 18 Shishido's retrosynthesis

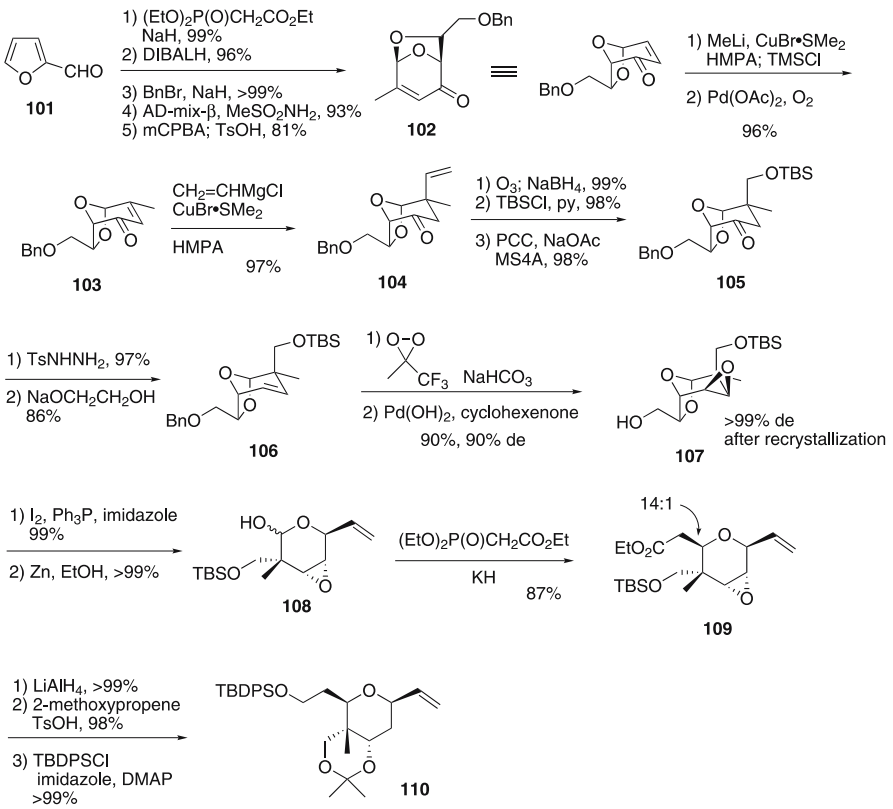
C1–C25 carbon framework construction by a sequence consisting of the cross metathesis between the A-ring unit and the B-ring unit, as shown in Scheme 18. The A-ring **88** was cyclized by the intramolecular Michael addition of the unsaturated hydroxy ester **89**, the asymmetric centers of which were constructed by diastereoselective epoxidation and 1,4-addition, starting from the Ogasawara's chiral building block **90** [55]. The B-ring **91** was formed by the stereoselective reduction of the pyran oxonium cation derived from the lactone **92.** The characteristic features in this synthesis are the cross metathesis and the construction of the quaternary asymmetric center.

The synthesis of the B-ring unit containing the skipped triene moiety was initiated from the Evans asymmetric aldol reaction of the optically pure aldehyde **93** [56] (Scheme 19). The resulting aldol **94** was converted to the lactone **95**, which was alkylated, followed by the treatment with Et_3SiH in the presence of BF_3OEt_2, to afford the B-ring **96** with excellent diastereoselectivity (Sect. 2.3). The reductive de-benzylation and oxidation led to the aldehyde **97**, which was olefinated by Ando's modified Horner–Emmons reaction [57], followed by reduction, to give the (*Z*)-aldehyde **98.** The dienyl chloride **99**, prepared from **98** in three steps, was subjected to Stille's coupling to yield the B-ring unit **100.**



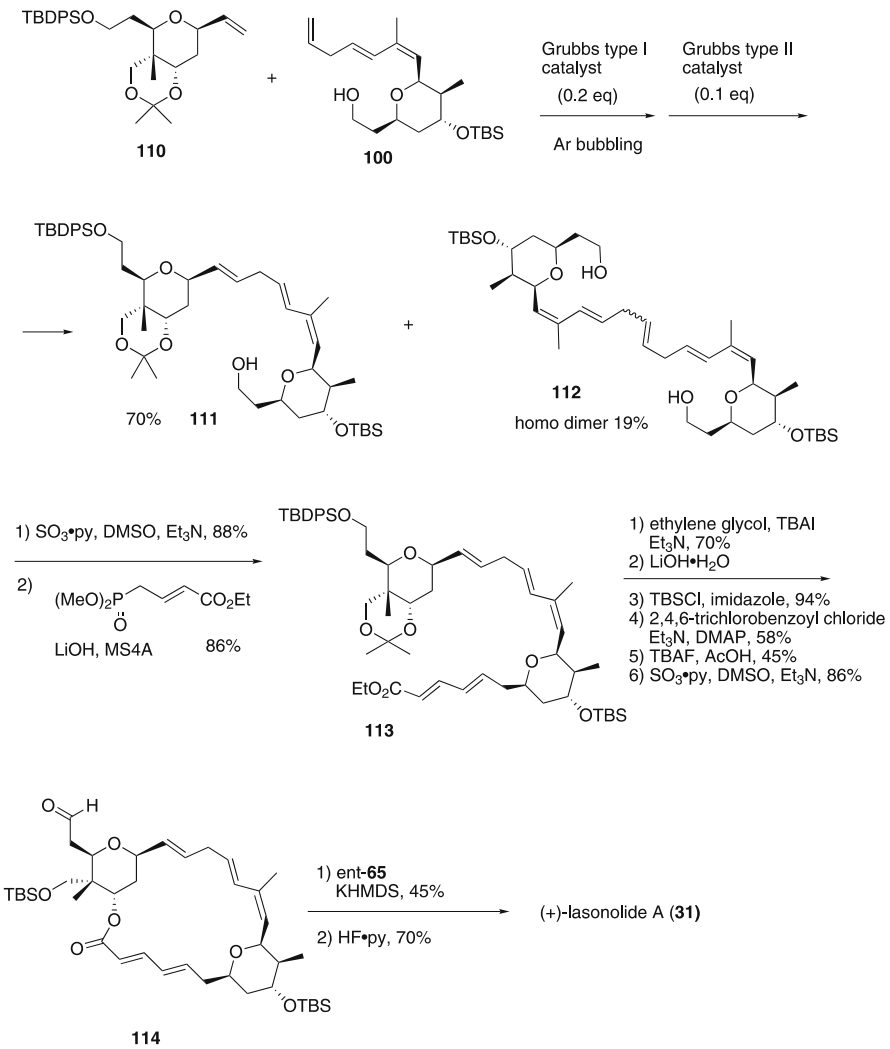
Scheme 19 Preparation of B-ring unit

The synthesis of the A-ring unit containing the quaternary stereogenic carbon was accomplished using Ogasawara's chiral building block **102**, prepared from furaldehyde (**101**) (Scheme 20). The convex face of the enone unit in the bicyclo[3.2.1]octane skeleton is efficiently reactive towards nucleophiles, and the concave face is blocked. Actually, the 1,4-addition of organocopper reagents to **103**, derived from **102** via oxidation [58] of the silyl enol ether, was achieved to afford **104** having the quaternary center at C-22 (lasonolide numbering) with excellent diastereoselectivity. The stereogenic center at C-21 was introduced via epoxidation of the dihydropyran **106**, prepared by the Bamford–Stevens reaction [59] of **105**, and the resulting epoxide **107** was obtained with 90% de. The lactol **108**, derived from **107** via iodination followed by zinc reduction, was treated with the Horner–Emmons reagent to afford the tetrahydropyran **109** in a ratio of 14 : 1 via successive olefination and the intramolecular Michael addition (Sect. 2.2). The epoxide in **109** was regioselectively ring-opened by $LiAlH_4$, and the resulting tetraol was protected to provide the A-ring unit **110** in excellent yield.



Scheme 20 Preparation of A-ring unit

Assembly of the A-ring and the B-ring units, and completion of the total synthesis of lasonolide A are outlined in Scheme 21. The strategy of cross metathesis between **110** and **100** had been problematic, because a considerable amount of the homodimer **112** was generated using Grubbs type II catalyst. After numerous experiments, it was found that sequential treatment of a mixture of **110** (3 equiv) and **100** with Grubbs type I catalyst for 24 h under argon bubbling for exhaust of ethylene and then with Grubbs type II catalyst for additional 24 h for conversion of **112** into **111** provided 70% of the desired product **111** along with 19% of **112**.



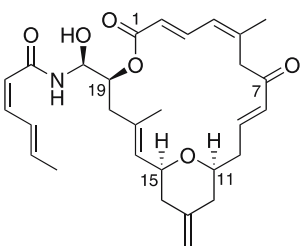
Scheme 21 Completion of total synthesis

After installation of the C1–C4 unit, the Yamaguchi macrolactonization [60] was subjected to the *seco*-acid derived from **113** to successfully yield the macrolactone **114**, although Kang's group failed. Finally, the side chain was introduced to the macrolactone via Lee's method to provide (+)-lasonolide A.

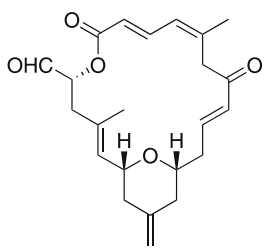
3.2 Total Synthesis of Zampanolide and Dactylolide

In 1996, Higa disclosed the isolation and partial structure elucidation of the novel macrolide (–)-zampanolide (**115**) [61] (Fig. 5), obtained from *Fasciospongia rimosa*, an Okinawan sponge that yielded four related macrolides of (+)-latrunculin A and S, (–)-laulimalide [62], and (–)-neolaulimalide [63]. Zampanolide exhibited significant cytotoxicity against the P388, HT29, A549, and MEL28 cell lines (IC_{50} 1–5 ng/mL), however, extensive biological tests have not been performed because of the lack of material. The structure of (–)-zampanolide include the highly unsaturated 20-membered macrolide incorporating a *cis*-2,6-disubstituted tetrahydropyran and the unusual *N*-acyl himiaminal side chain. The stereochemistry of the C-20 hydroxy group and the absolute stereochemistry, however, had not been determined until Smith's first total synthesis described in the following section.

In 2001, Riccio isolated a structurally related compound (+)-dactylolide (**116**) from the Vanuatu marine sponge *Dactylospongia* [64] (Fig. 5). Dactylolide is moderately cytotoxic toward L1210 and SK-OV-3 cells, causing 63% and 40% growth inhibition, respectively, at 3.2 μg/mL with respect to that of zampanolide. Smith concluded, on the basis of optical rotation data, that the common macrolide cores of dactylolide and zampanolide have opposite absolute configurations, upon completing the total syntheses of them.



natural **(-)-zampanolide** (**115**)



natural **(+)-dactylolide (116)**

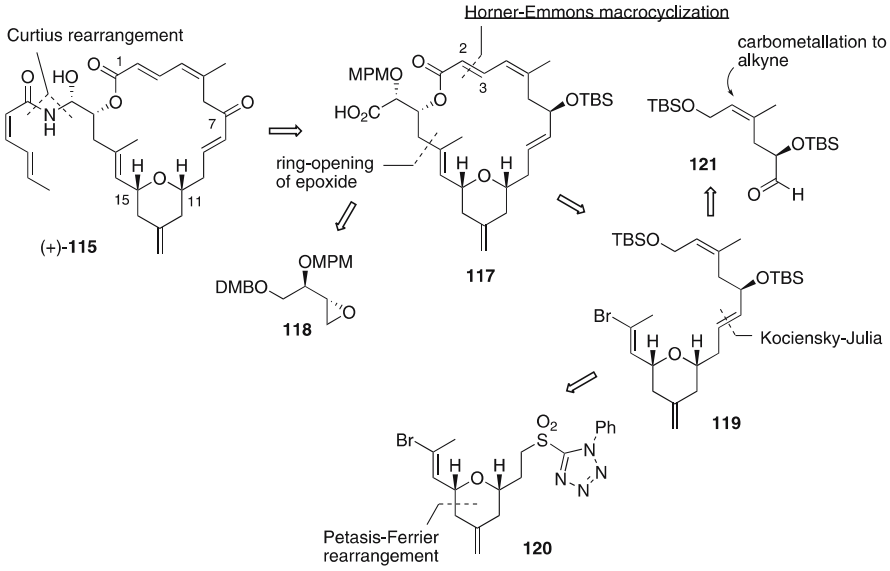
Fig. 5 Zampanolide and Dactylolide

3.2.1
The First Total Syntheses of Unnatural (+)-Zampanolide and Natural (+)-Dactylolide by Smith [65,66]

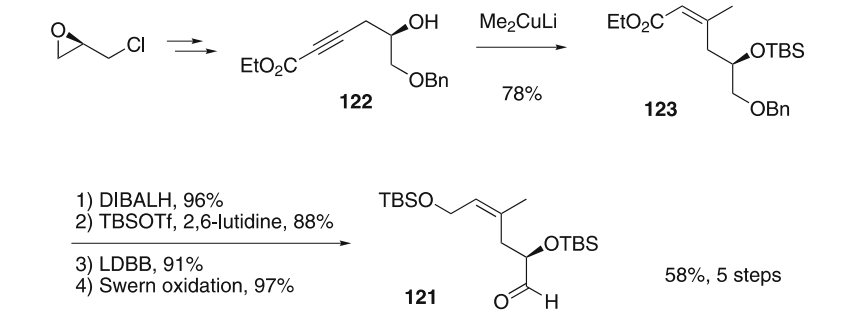
The retrosynthetic analysis is outlined in Scheme 22. The amide was introduced by the Curtius rearrangement, and the macrolide **117** was formed by Horner–Emmons macrocyclization at the C2–C3 bond. The C17–C18 bond was constructed by the ring-opening of epoxide **118**. **119** was formed via the Kocienski–Julia olefination at the C8–C9 bond. The *cis*-2,6-disubstituted tetrahydropyran in **120** was constructed by the Petasis–Ferrier rearrangement. The C4–C5 (*Z*)-trisubstituted alkene in **121** was formed by carbometallation to an alkyne.

Preparation of **121** is shown in Scheme 23. The known alkynolate **122** [67] was treated by a cuprate to give the (*Z*)-olefin **123** via the Michael-type carbometallation [68]. **123** was converted into **121** in four steps.

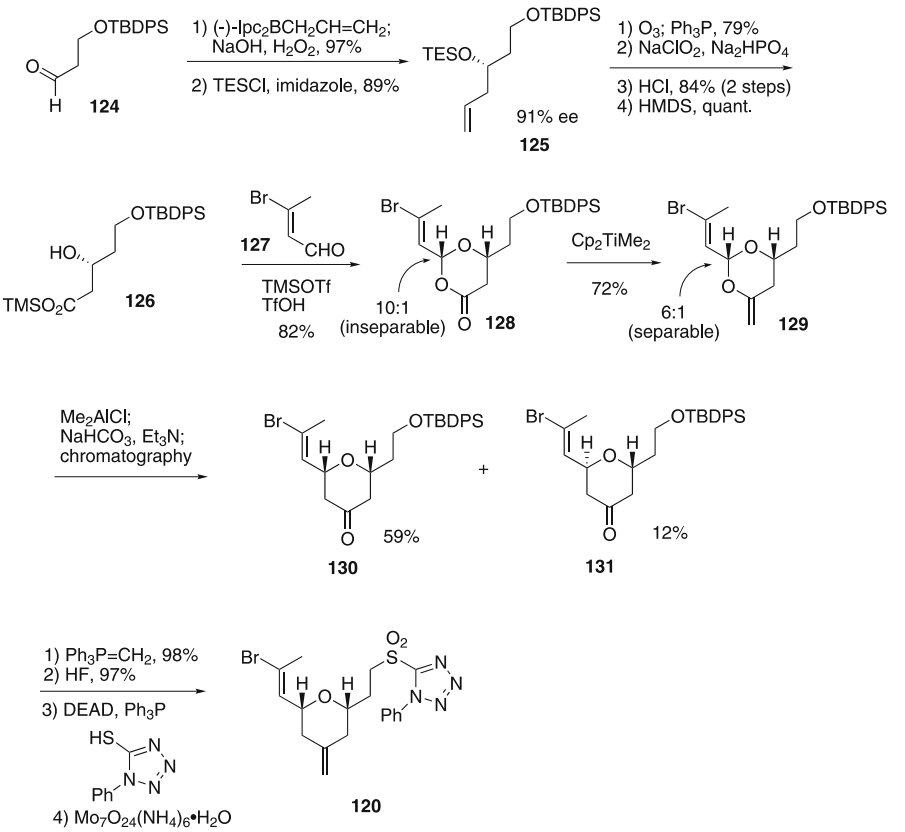
The key skeleton of **120** was constructed via the Petasis–Ferrier rearrangement [17], established by Smith as a powerful, stereocontrolled entry to *cis*-2,6-disubstituted tetrahydropyran (Scheme 24) [18, 19]. Brown asymmetric allylation of the known aldehyde **124** [69] installed the C-11 asymmetric center in 91% ee to give **125** after silylation. Oxidative cleavage of the terminal alkene, followed by silylation, delivered the β-hydroxy ester **126**, which was condensed with aldehyde **127** mediated by TMSOTf (but the actual catalyst was found to be TfOH) to furnish an inseparable mixture of the



Scheme 22 Smith's retrosynthesis of (+)-zampanolide



Scheme 23 Preparation of C3–C8 unit (**121**)



Scheme 24 Preparation of C9–C17 unit (**120**)

dioxanones **128** (10 : 1 at C-15). Presumably, this cyclization proceeds via the transition state as shown in Fig. 6, wherein the aldehyde side chain adopts a pseudoequatorial orientation. The Petasis–Tebbe methylenation of **128** pro-

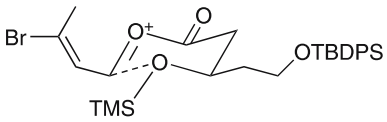


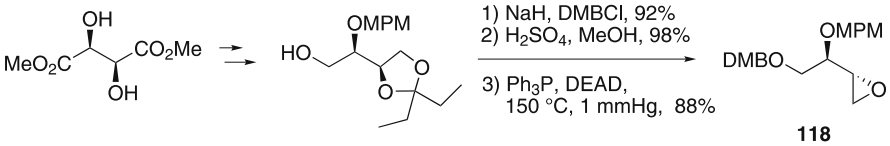
Fig. 6 Cyclic acetalization

vided a difficultly separable mixture of the cyclic enol ether **129** (6 : 1 at C-15). The Petasis–Ferrier rearrangement (Sect. 2.5) was carried out by treatment with Me_2AlCl (1 equiv) at – 78 °C to yield 2,6-*cis*-pyranone **130** in 59% and the *trans*-isomer **131** (12%). Synthesis of sulfone **120** was achieved by the Wittig methylenation, deprotection, the incorporation of the thiotetrazole via the Mitsunobu protocol, and oxidation.

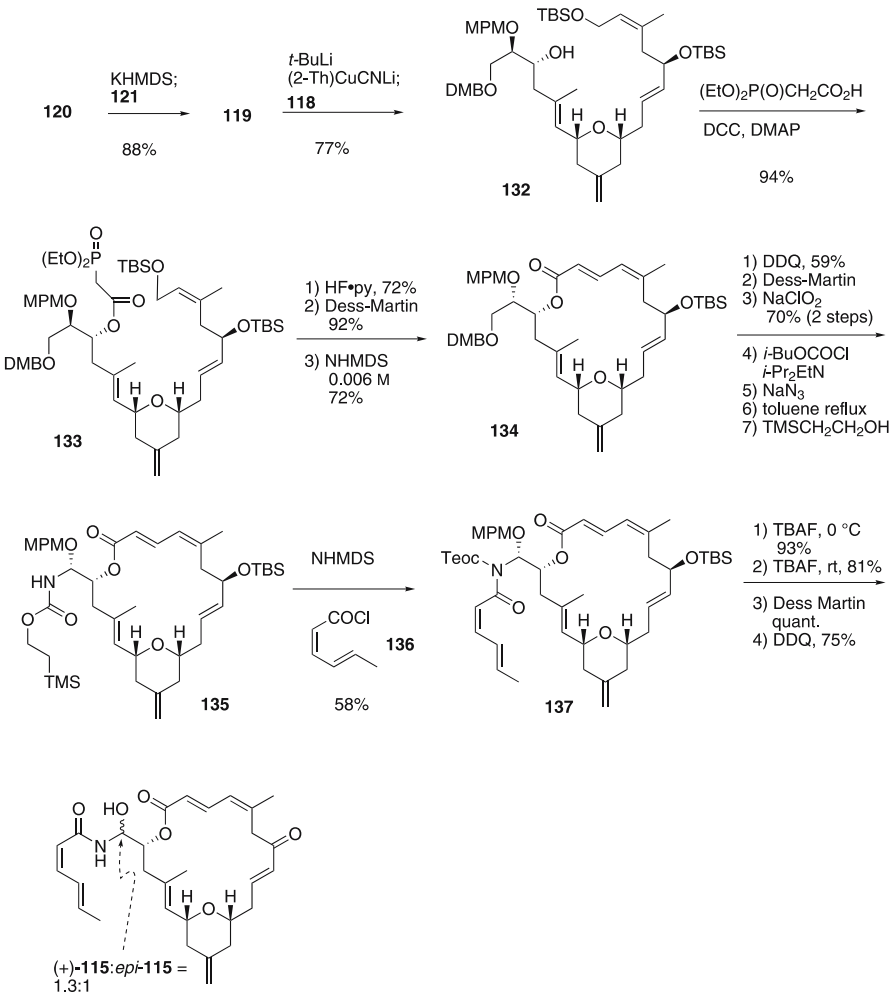
Epoxide **118** was prepared from (+)-diethyl tartrate in seven steps as shown in Scheme 25.

The final stage of the total synthesis is as shown in Scheme 26. The Kocienski–Julia olefination of the aldehyde **121** with the sulfone **120** forged the *trans*-C(8–9) double bond of **119**. The mixed cyano-Gilman cuprate, derived from vinyl bromide of **119** and lithium 2-thienylcyanocuprate [70], added to the epoxide **118** to give **132**. Diethylphosphonoacetic acid was condensed with **132** to give the phosphonoacetate **133**, which was subjected to the Horner–Emmons macrocyclization under high-diluted conditions, after transformation to aldehyde at C-3, to provide the macrocycle **134**. The carboxylic acid, derived from **134** via deprotection of DMB and oxidation, was converted into isocyanate via Curtius rearrangement to furnish the carbamate **135** after treatment with trimethylsilylethanol. Acylation with acid chloride **136** then gave the Teoc-protected amide **137**. Iterative removal of the Teoc, TBS, and MPM moiety provided (+)-zampanolide (**115**), which is identical to the spectral data for the natural product except for chiroptic properties (natural $[\alpha]_D$ – 101, synthetic $[\alpha]_D$ + 102), and C-20 epimer (1.3 : 1). At this point, the relative stereochemistry at C-20 in zampanolide remained unknown.

Because of potential instability of the *N*-acyl hemiaminal functionality, it was difficult to prevent epimerization upon deprotection of MPM. For assignment of the C-20 relative configuration, synthetic (+)-zampanolide and the C-20 epimer were again protected with the MPM group via Hanessian's pro-



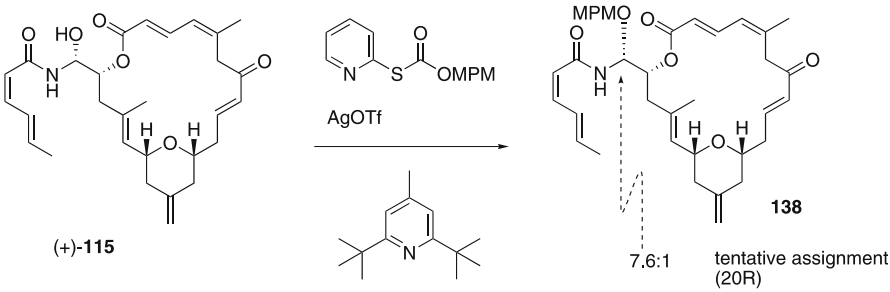
Scheme 25 Preparation of C18–C21 unit (**118**)



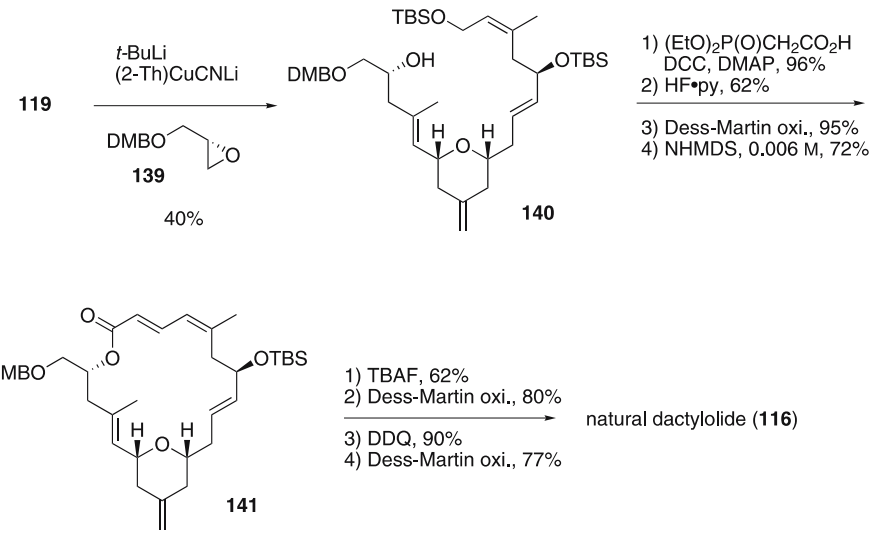
Scheme 26 Total synthesis of (+)-zampanolide

tocol (Scheme 27) [71]. (+)-Zampanolide afforded **138** and its C-20 epimer in a 7.6 : 1 ratio, and the C-20 epimer of (+)-zampanolide afforded a 1 : 3.7 mixture of **138** and its C-20 epimer. From these results including UV spectra, Smith assigned tentatively the relative and absolute stereochemistry of (+)-zampanolide as 20R.

Smith also completed the total synthesis of (+)-dactylolide as shown in Scheme 28. As with zampanolide, **119** in Scheme 26 was converted into the mixed cyanocuprate, which reacted with epoxide **139** to afford **140**. Esterification with phosphonoacetic acid, macrocyclization provided the macrolide **141**, which was deprotected to yield (+)-dactylolide (**116**). The spectral and



Scheme 27 Tentative assignment of C-20 stereochemistry



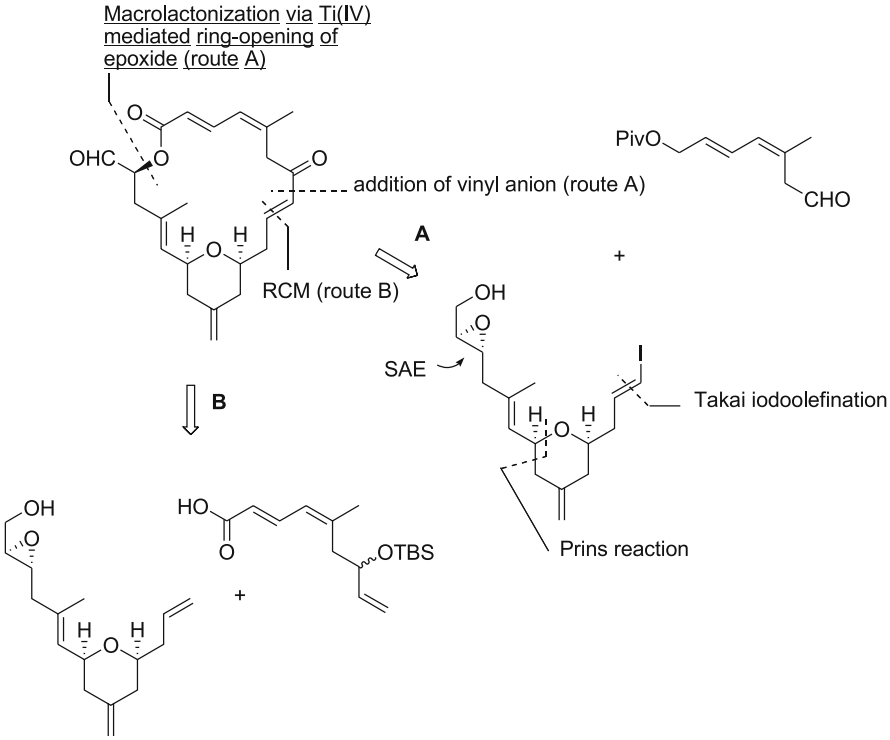
Scheme 28 Total synthesis of (+)-dactylolide

chiroptic data for synthetic (+)-dactylolide proved identical in all respects with those of the natural product.

The total syntheses of (+)-zampanolide and (+)-dactylolide reveal the macrocyclic domain of natural zampanolide is enantiomeric compared with that of natural dactylolide.

3.2.2 Hoye's Total Synthesis of (–)-Dactylolide [72]

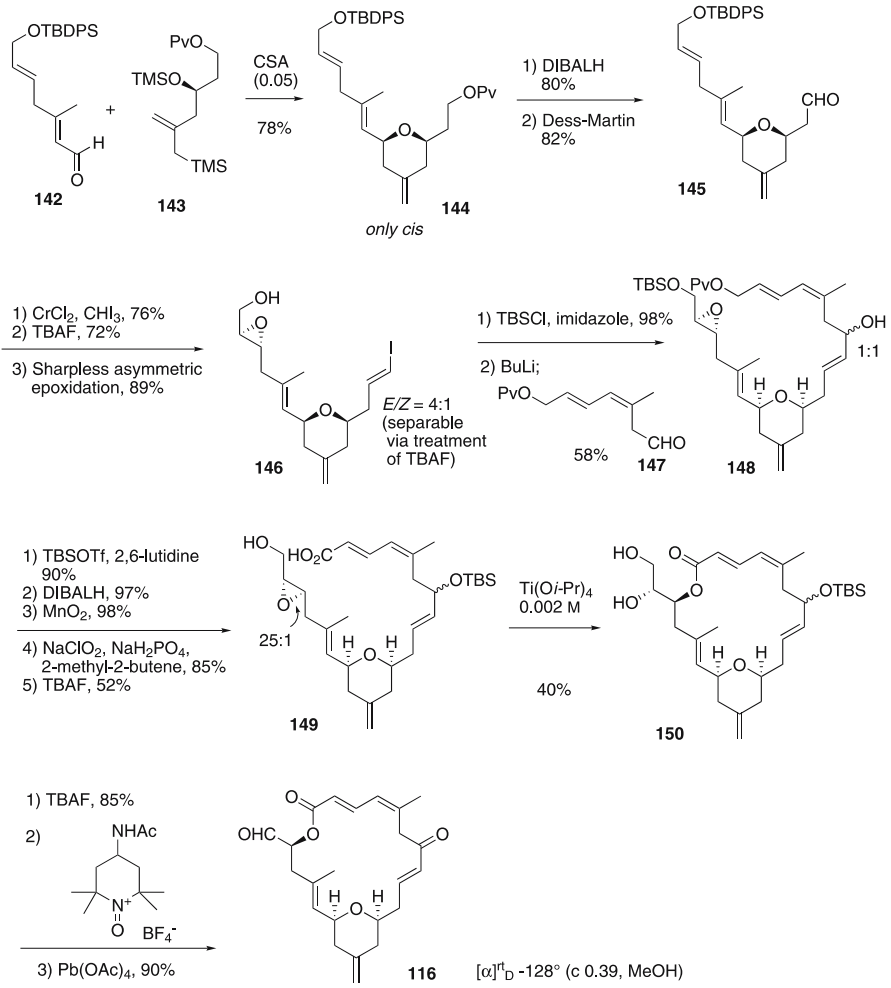
Hoye achieved the total synthesis of (–)-dactylolide via two distinct macrocyclization strategies, involving Ti(IV)-mediated macrolactonization of an epoxy-acid (route A) and a RCM macrocyclization (route B) (Scheme 29). The *cis*-2,6-disubstituted-4-methylene tetrahydropyran was constructed by Prins



Scheme 29 Hoye's retrosynthesis

reaction taking advantage of an intramolecular Hosomi–Sakurai cyclization between an enal and an allyl silane (Sect. 2.4).

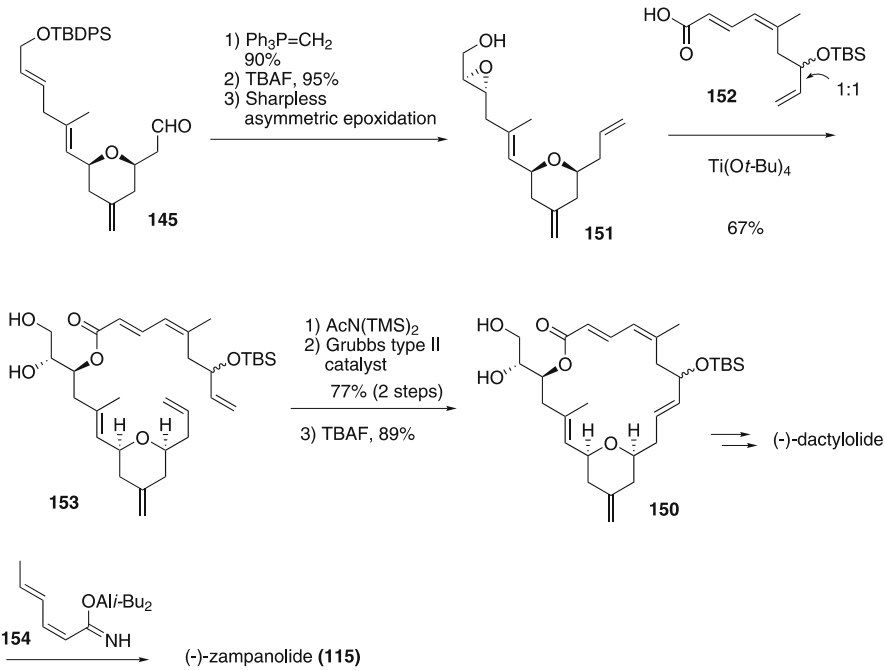
The Hosomi–Sakurai–Prins reaction of the easily available enal **142** and allylsilane **143** was performed in the presence of Lewis acids to give the 4-methylene-tetrahydropyran with poor *cis-trans* selectivity ($\sim 2:1$), however, the protic acid provided only *cis*-**144**, which was converted into the aldehyde **145**. The Takai iodoalkenylation, followed by desilylation and Sharpless asymmetric epoxidation, provided **146** with a 4 : 1 ratio of E/Z, which was separable via the treatment of TBAF. After protection of the primary alcohol, the alkenyllithium derived from the iodoalkene, reacted with aldehyde **147** to form **148**, which was converted into epoxy-carboxylic acid **149** in five steps. The key macrocyclization was performed by the treatment of **149** with Ti(O*i*-Pr)$_4$ [73] under high diluted conditions (2 mM) at 75 °C to provide the macrolactone **150** in moderate yield with 30% of the starting material recovery. After desilylation, the chemoselective oxidation of the allyl alcohol with 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate, followed by oxidative cleavage of the C20–C21 diol, produced (–)-dactylolide (Scheme 30).



Scheme 30 Total synthesis of (–)-dactylolide

The alternative synthesis is shown in Scheme 31. The epoxide **151**, prepared from **145**, and the trienoic acid **152** were coupled with Ti(O*t*-Bu)$_4$ to provide **153**. After protection of the vicinal diol, the ring closing metathesis was carried out using Grubbs catalyst to provide the macrolactone **150** with a single C8–C9 alkene of *E*-geometry. Finally, (–)-dactylolide was converted into zampanolide by the aza-aldol addition of **154**.

The value of the specific rotation of (–)-**116** ($[\alpha]_D^{rt}$ – 128° (c 0.39, MeOH)) differed from values for both natural ($[\alpha]_D^{rt}$ + 30° (c 1.0, MeOH)) and Smith's synthetic ($[\alpha]_D^{rt}$ + 235° (c 0.52, MeOH)) dactylolide, presumably due to the formation of stable hemiacetal with methanol.



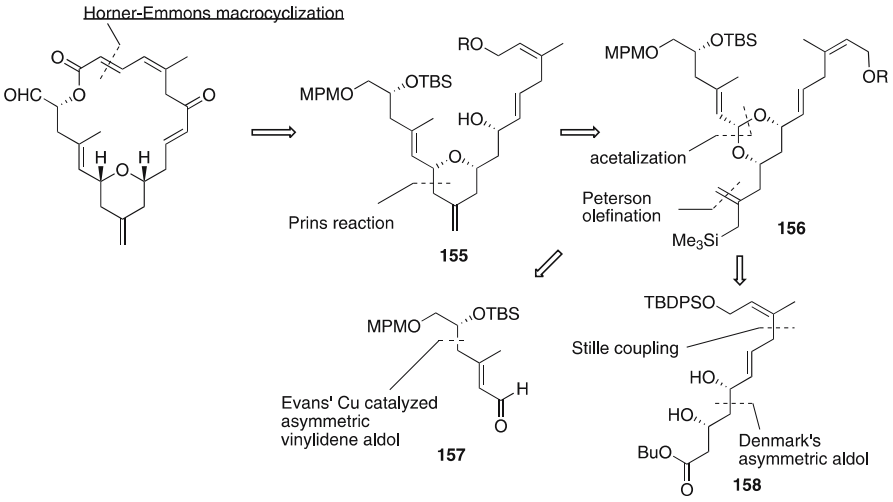
Scheme 31 Alternative synthesis of (–)-dactylolide

3.2.3
Floreancig's Total Synthesis of (+)-Dactylolide [74]

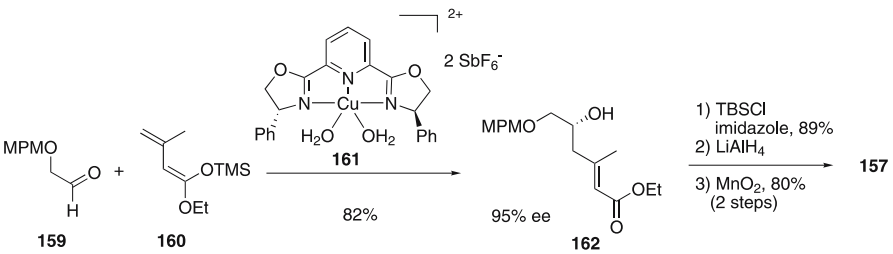
Floreancig completed the total synthesis of (+)-dactylolide via a sequential Peterson olefination and an intramolecular Hosomi–Sakurai–Prins cyclization of the acetal-linked substrate (Scheme 32). Macrocyclization was performed by Horner–Emmons olefination as Smith did (Sect. 3.2.1). The key element of 2,6-*cis*-tetrahydropyran in **155** was constructed via the sequential cyclization starting from acetal **156**, which involved aldehyde **157** and 1,3-diol **158**, synthesized via Denmark's asymmetric aldol reaction and Stille coupling.

The aldehyde **157** was prepared according to the sequence in the synthesis of Evans' total synthesis of callipeltoside A (Scheme 33) [75]. The vinylidene asymmetric Mukaiyama aldol reaction of α-oxy aldehyde **159** and silyl ketene acetal **160** catalyzed by Cu-pybox complex **161** [76] furnished δ-hydroxy-α, β-unsaturated ester **162** in 95% ee, which was reduced to yield **157**.

The 1,3-diol unit **158** was synthesized as shown in Scheme 34. The (*Z*)-vinyl stannane **164**, prepared by hydroalumination of **163** followed by stannylation, was coupled with bromide **165** to give skipped dienal **166**, after hydrolysis. The next vinylidene asymmetric Mukaiyama aldol reaction of



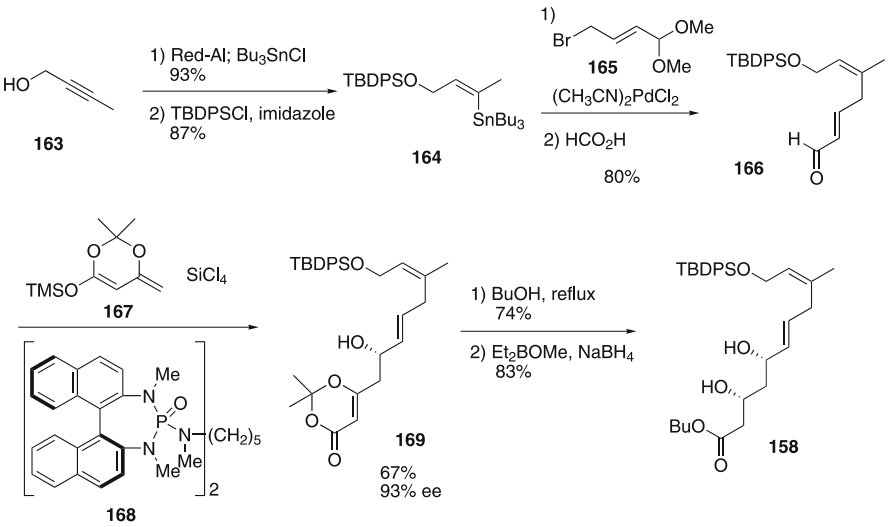
Scheme 32 Floreancig's retrosynthesis



Scheme 33

the dienal **166** with silyl dienol ether **167** was performed using Denmark's bisphosphoramide catalyst **168** [77] and $SiCl_4$ to provide **169** in 93% ee. Esterification of **169**, followed by stereoselective reduction, afforded the diol **158.**

The acetal **170** was prepared by using the bis-trimethylsilyl ether of **158** and the aldehyde **157** mediated by TMSOTf without isomerization. Peterson olefination to **170** with excess TMSMgCl and $CeCl_3$ afforded the allyl silane **171**, which was subjected to the Hosomi–Sakurai–Prins cyclization by using pyridinium triflate and $MgSO_4$ to yield 2,6-*cis*-tetrahydropyran **172.** Since a kinetically facile 6-*endo* pathway was dominant rather than 8-*endo* pathway, cyclization would be the product-determining step rather than ionization. Transposition of the C9 hydroxy group to the C7 position was achieved by a selenium variant of the Mislow–Evans rearrangement [78], that is, the hydroxy group at C9 was converted into the phenylselenyl group, and the oxidation of the selenide induced to provide **173** after protection of the resulting hydroxy group. Selective oxidation of the primary allylic alcohol, and then esterification of the C19 hydroxy group with phosphono acetic acid led



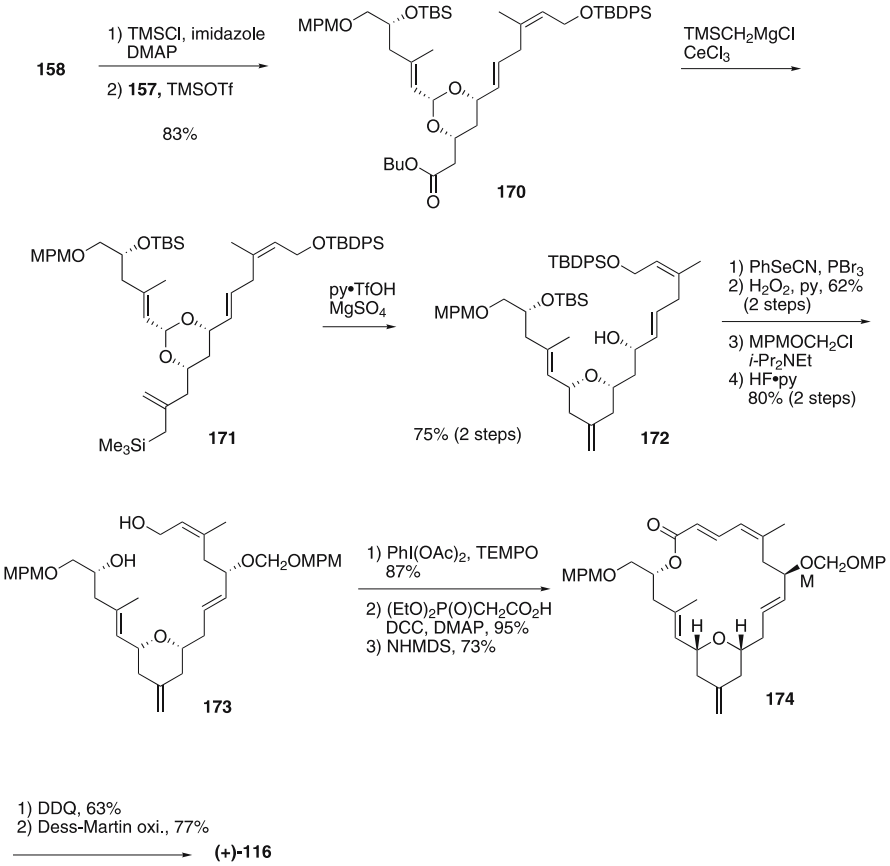
Scheme 34

to the corresponding phosphonoacetate, which was treated with base to yield macrolactone **174** via intramolecular Horner–Emmons olefination. Finally, deprotection, followed by oxidation, furnished (+)-dactylolide ($[\alpha]_D^{rt}$ + 163° (c 0.29, MeOH)) (Scheme 35).

3.2.4 Jennings' Total Synthesis of (–)-Dactylolide [79]

Jennings' strategy for obtaining the macrolide skeleton was Yamaguchi esterification and ring closing metathesis (RCM) with **175** and **176** (Scheme 36). Construction of the key 2,6-*cis*-tetrahydropyran in **176** was carried out via diastereoselective axial reduction of an oxonium cation. The precursor, a pyranone, was prepared via RCM of divinyl ester **177**. An asymmetric center was made by Brown's asymmetric allylation.

The alkynyl ester **179**, prepared from glycidol **178** in four steps, was subjected to Michael addition of thiolate, followed by copper-mediated 1,4-addition–elimination of MeMgBr, afforded (*Z*)-unsaturated ester, which was reduced to enal **180**. Asymmetric allylation of **180** using Brown's reagent gave the homoallylic alcohol with 90% de, which was converted to the acrylate ester **177**. A ring-closing olefin metathesis of **177** furnished unsaturated lactone **181**, which was subjected to epoxidation, followed by reduction by PhSeH to provide hydroxy lactone **182**. The nucleophilic addition-diastereoselective reduction of oxonium cation furnished the 2,6-*cis*-tetrahydropyran **183**. Oxidation of the hydroxy group, followed by methylenation, and the protecting group manipulation provided **176** (Scheme 37).

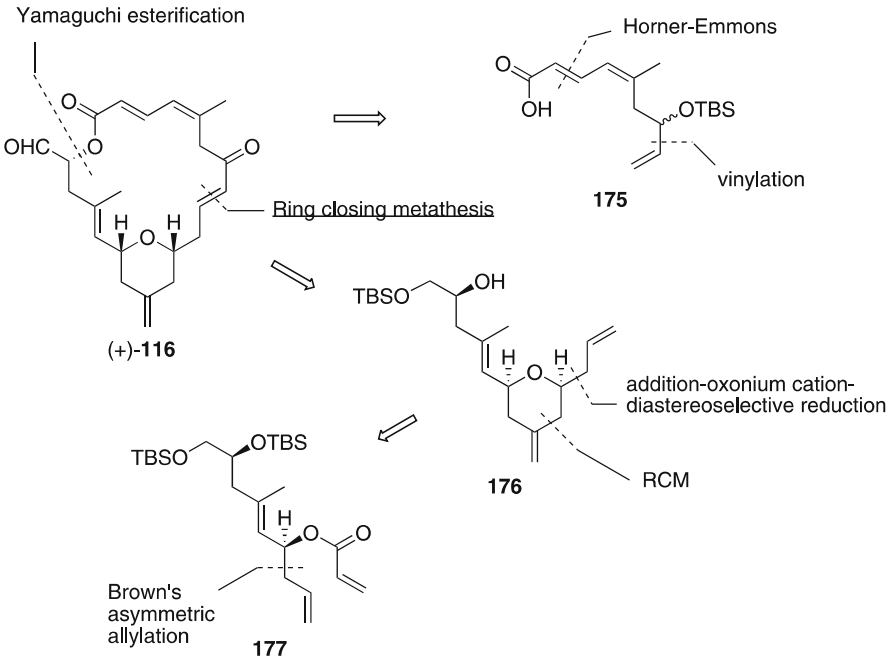


Scheme 35 Total synthesis of (+)-dactylolide

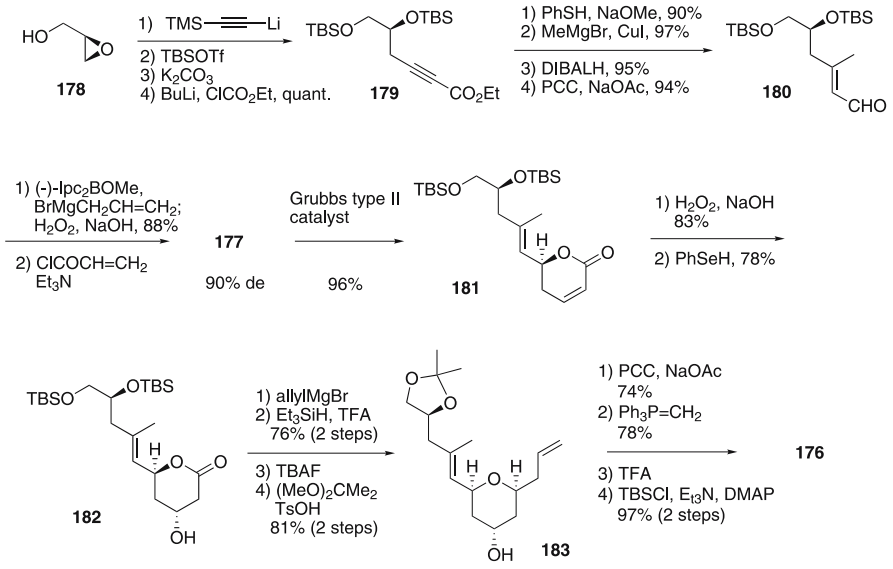
Esterification of **176** with two equiv. of the triene carboxylic acid **175**, prepared from unsaturated lactone **184** in nine steps [80], proceeded under the Yamaguchi protocol to give **185** in good yield. After deprotection, the corresponding diol was subjected to Grubbs catalyst to convert to the desired macrolactone with only one alkene geometry. Finally, the hydroxy group was oxidized by the Dess–Martin reagent to yield (–)-dactylolide ($[\alpha]_D^{20}$ – 136° (c 1.2, MeOH)) (Scheme 38).

3.2.5
Keck's Total Synthesis of (+)-Dactylolide [81]

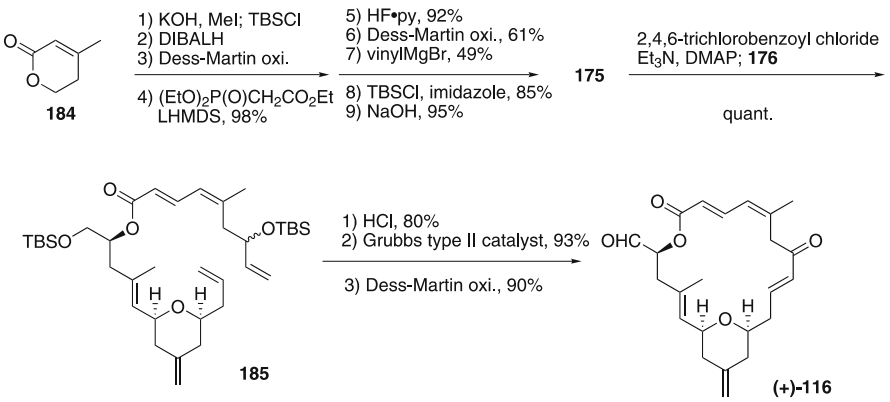
Keck reported a total synthesis of (+)-dactylolide, based on Horner–Emmons macrocyclization and the Hosomi–Sakurai–Prins reaction. The point is construction of two asymmetric centers via Keck's catalytic asymmetric ally-



Scheme 36 Jennings' retrosynthesis



Scheme 37

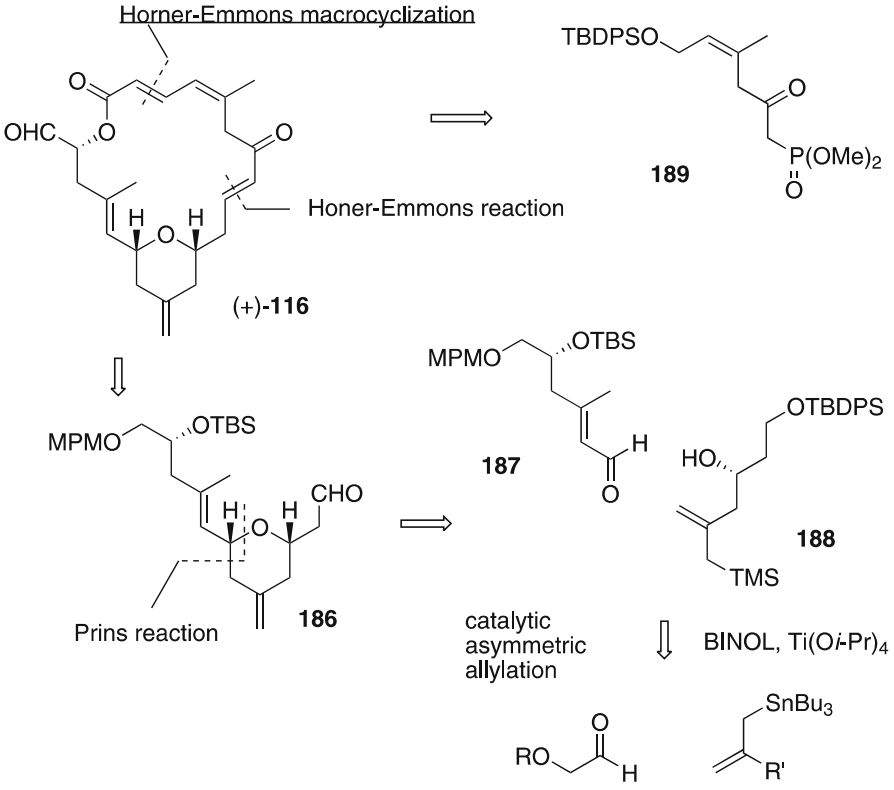


Scheme 38 Total synthesis of (–)-dactylolide

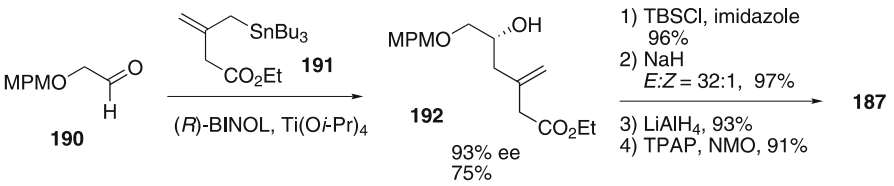
lation, followed by a short step synthesis of pyran **186** from enal **187** and hydroxy allylsilane **188** (Scheme 39).

The preparation of the enal **187** commenced with the asymmetric allylation of aldehyde **190** with allylstannane **191** catalyzed by BINOL titanium tetraisopropoxide (BITIP) [82] to give the (*R*)-homoallylic alcohol **192** in 93% ee. After protection of the hydroxy group, a "kinetic" isomerization was employed to secure (*E*)-unsaturated ester (32 : 1), which was converted to the enal **187** in good yield (Scheme 40). The *E*/*Z* selectivity in the isomerization was lower in the case of using DBU.

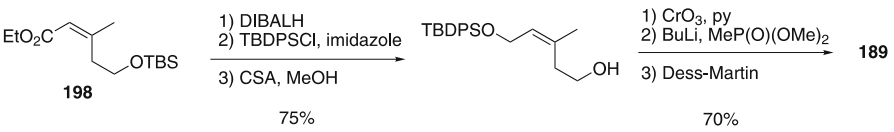
The hydroxy allylsilane **188** was prepared via an asymmetric allylation using allyl stannane **194** and **193** catalyzed by (*S*)-BITIP in 95% ee only in one step [83]. The pyran annulation between **187** and **188** via the Hosomi–Sakurai–Prins reaction afforded the 2,6-*cis*-dihydropyran **195** as a single isomer. Deprotection, followed by TPAP oxidation led to aldehyde **186**, which was subjected to Horner–Emmons olefination with **189**, prepared from (*Z*)-unsaturated ester **198** in six steps (Scheme 41), under Peterson's conditions [84] to provide (*E*)-enone **196**. To preclude enolization of C7 ketone, because of the high acidity of C6–H, the ketone was reduced and the resulting hydroxy group was protected by MPM ether. Selective deprotection and esterification gave phosphonoacetate **197**, which was deprotected and oxidized. The resulting phosphono aldehyde was exposed to NHMDS to provide the macrocycle in 60% yield. Finally, deprotection of both MPM, followed by double oxidation with Dess–Martin reagent afforded (+)-dactylolide ($[\alpha]_D^{20}$ + 134° (c 0.065, MeOH)) (Scheme 42). Keck described that the deviation in optical rotation should be due to the highly conjugated and enolizable ketone at C7.



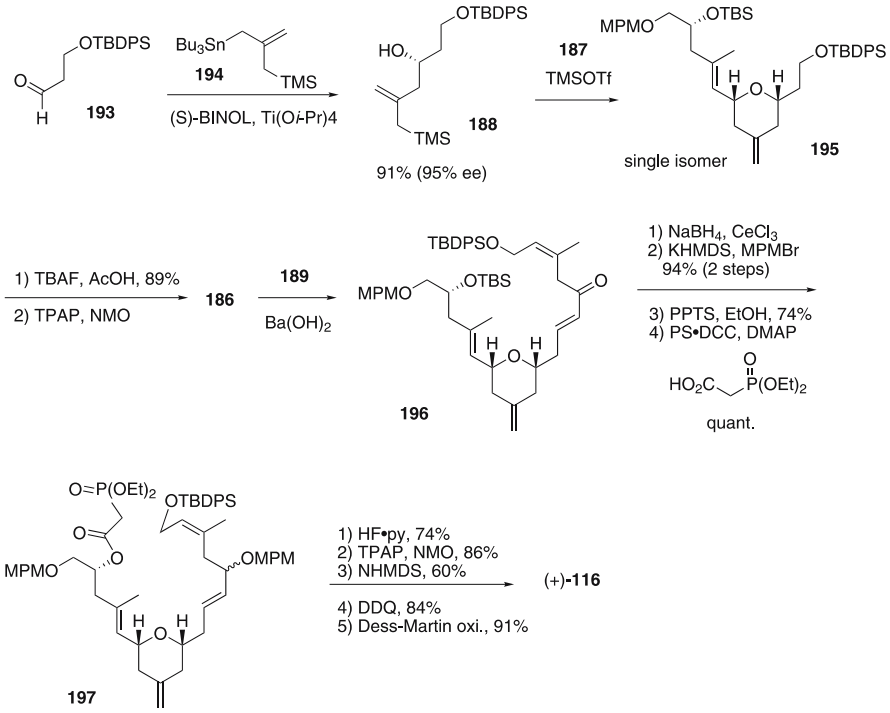
Scheme 39 Keck's retrosynthesis of (+)-dactylolide



Scheme 40



Scheme 41



Scheme 42 Completion of total synthesis

3.3
Total Synthesis of Leucascandrolide A

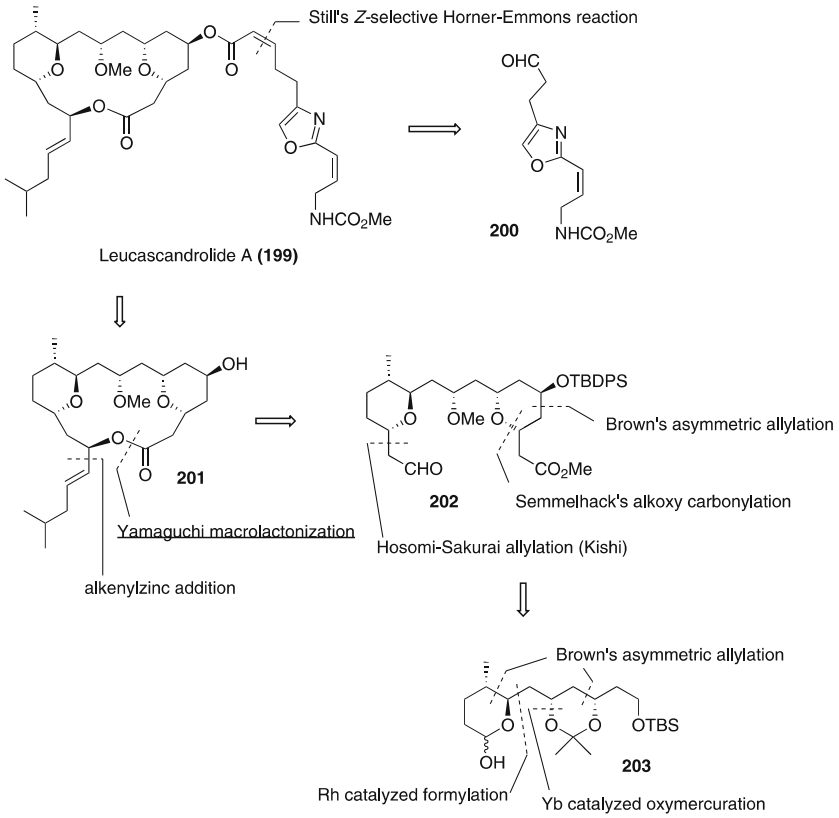
Leucascandrolide A is a bioactive macrolide of a new structural type isolated in 1996 from a calcareous sponge *Leucascandra caveolata* collected along the east coast of New Caledonia, Coral Sea, by Pietra [85]. In preliminary cell-based studies, leucascandrolide A displayed strong cytotoxic activity in vitro on human KB and P388 cancer cell lines (IC_{50} = 50 and 250 ng mL^{-1}, respectively) as well as powerful antifungal activity against the pathogenic yeast *Candida abicans*. Subsequent reisolation attempts proved unsuccessful which indicates that leucascandrolie A may be derived from opportunistic microbial colonization of the sponge, as evidenced by the large amounts of dead tissue in the initial harvest of the sponge [86]. Since the natural supply of leucascandrolide A is unavailable, and thus the full biological potential of the compound has not been established, efficient chemical synthesis represented the only option for the production of the natural product. Leucascandrolide A possesses a polyoxygenated 18-membered macrolide ring that includes two 2,6-*cis*- and 2,6-*trans*-trisubstituted tetrahydropyran rings and an unusual oxazole-containing side chain that possesses two (*Z*)-olefins. The complexity of the

structure, potent biological activities combined with the uncertainty of the biogenetic origin has attracted considerable synthetic attention.

Since Leighton's first total synthesis, total syntheses of leucascandrolide A have been achieved by Rychnovsky (formal), Carreira, Wipf (formal), Kozmin (racemic), Paterson, Williams (formal), Crimmins (formal), and Panek. In this section, these syntheses are briefly introduced.

3.3.1 The First Total Synthesis of Leucascandrolide A by Leighton [87]

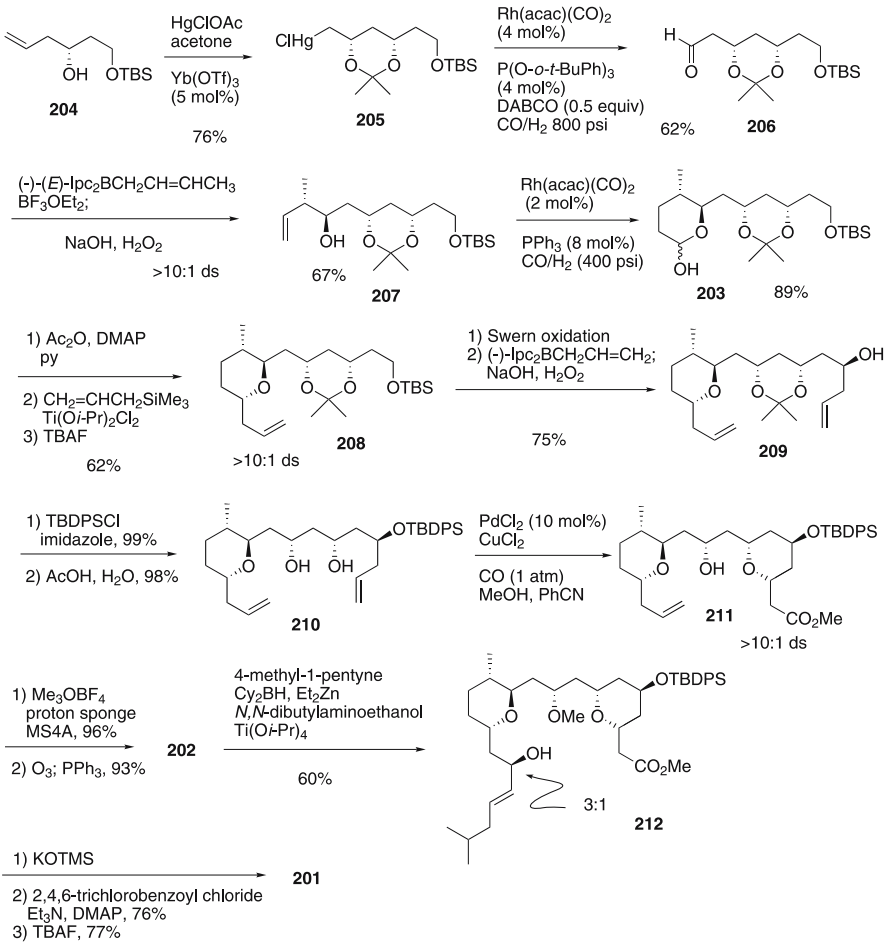
Leighton's synthetic strategy is shown in Scheme 43. Side chain **200** was introduced by the Still-modified (*Z*)-selective Honer–Emmons reaction forming the C2′–C3′ double bond. Macrolactonization leading to **201** was carried out by using the Yamaguchi procedure, and C17 asymmetric carbon was constructed by alkenylzinc addition to an aldehyde in **202**. The 2,6-*trans*-tetrahyderopyran was synthesized by the Hosomi–Sakurai reaction to a lactol,



Scheme 43 Leighton's retrosynthesis

and the 2,6-*cis*-tetrahydropyran was cyclized via Semmelhack's alkoxy carbonylation. The asymmetric centers at C5, C7, C11 and C12 were constructed via three allylation reactions using Brown's chiral allyl borane reagent, and the catalyzed oxymercuration–formylation sequence developed by Leighton introduced the C9 asymmetric carbon in **203.** In the synthesis, three different metal-catalyzed carbonylations were used.

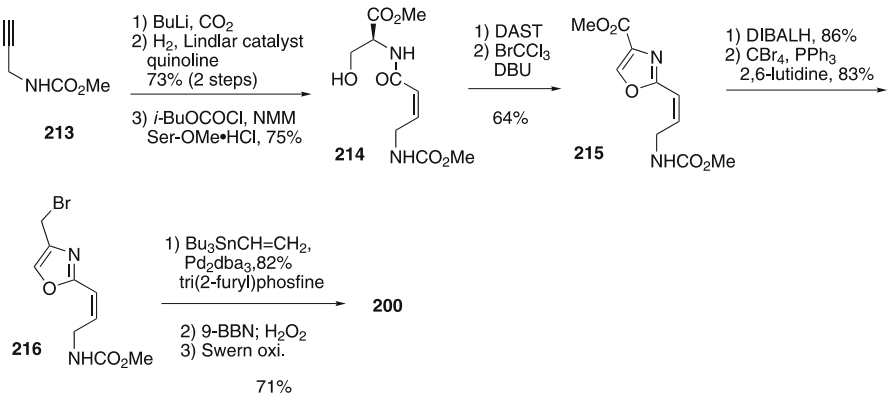
The synthesis began with $Yb(OTf)_3$-catalyzed oxymercuration [88] of homoallylic alcohol **204** [89], prepared by asymmetric allylation with Brown's reagent, to generate organomercury chloride **205.** Rh(I)-catalyzed formylation [90] of **205** in the presence of DABCO (0.5 equiv.) furnished aldehyde **206.** Stereoselective crotylation of **206** via Brown's reagent, followed by regioselective Rh(I)-catalyzed hydroformylation provided lactol **203.** Dia-



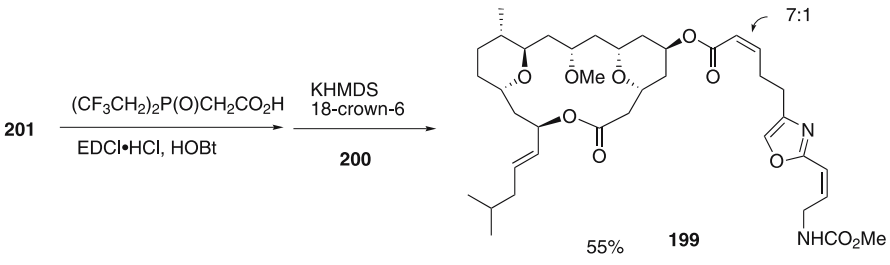
Scheme 44

stereoselective Hosomi–Sakurai allylation of the lactol **203** yielded 2,6-*trans*-tetrahydropyran **208** (> 10 : 1 ds), after desilylation. Brown's asymmetric allylation of an aldehyde, derived from **208**, afforded homoallylic C – 5 alcohol **209** in > 10 : 1 ds. The second pyran synthesis was performed by Semmelhack alkoxy carbonylation [91] to the deprotected diol **210** to give the desired 2,6-*cis*-tetrahydropyran **211** with high diastereoselectivity. It is noteworthy that, without protection of C9-hydroxy and C17-alkyenyl groups, only the desired reaction proceeded. Aldehyde **202**, prepared from **211** in two steps, was subjected to alkenylation by alkenyltitanium [92], derived from alkenylzinc via transmetallation from alkenylboron [93], to yield a 3 : 1 mixture of the allylic alcohol **212**. The corresponding *seco*-acid was subjected to Yonemitsu-modified Yamaguchi macrolactonization [94] to afford macrolide **201**, after desilylation (Scheme 44).

The side chain unit was prepared as shown in Scheme 45. Carbamate **213** was carboxylated, reduced by the Lindlar catalyst, and condensed with serine methyl ester to give β-hydroxyamide amide **214**, which was readily converted to oxazole **215** via the one-pot procedure with DAST-DBU-$BrCCl_3$ [95]. The



Scheme 45 Preparation of side chain unit



Scheme 46 Completion of the first total synthesis

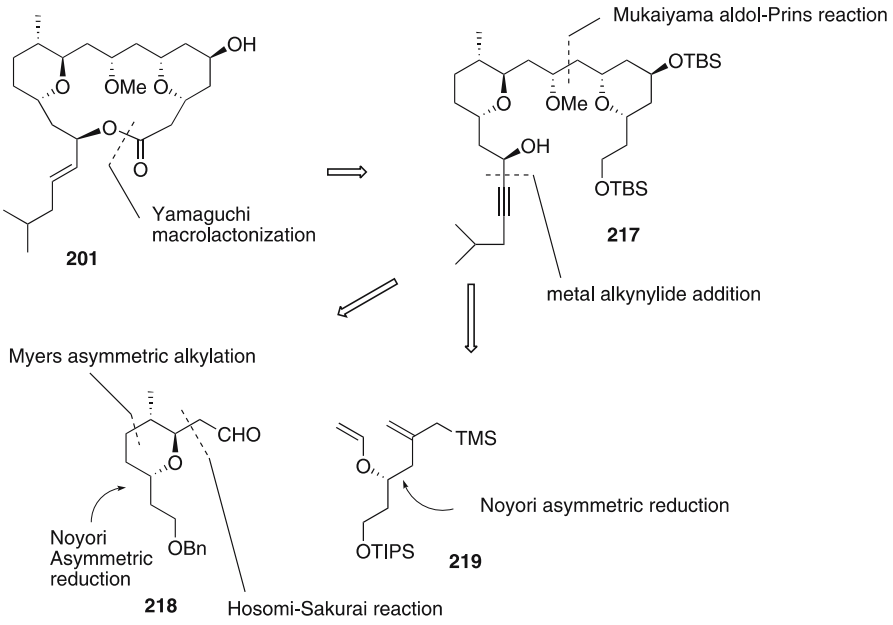
ester **215** was converted to **216**, which was two-carbon elongated via Stille coupling, followed by hydroboration and oxidation, to afford **202.**

Finally, **201** was acylated and then the resulting Still's modified Horner–Emmons phosphonate was subjected to olefination with aldehyde **200** to provide leucascandrolide A, along with (*E*)-isomer in a ratio 7 : 1 (Scheme 46).

3.3.2 Rychnovsky's Formal Synthesis of Leucascandrolide A [96]

Rychnovsky reported synthesis of Leighton's macrolide **201** of leucascandrolide A, wherein the key reaction is the Mukaiyama aldol-Prins cascade reaction (Sect. 2.4). In this cascade reaction, oxonium cation, required for the Prins reaction, is prepared by a Lewis acid-mediated Mukaiyama aldol reaction of alkyl vinyl ether with aldehyde. Usually, alkyl vinyl ethers are not suitable for Mukaiyama-aldol, because of oligomerization of the resulting oxonium cation. Rychnovsky resolved this issue by trapping the cation with an intramolecular nucleophile, which resulted in Prins cyclization.

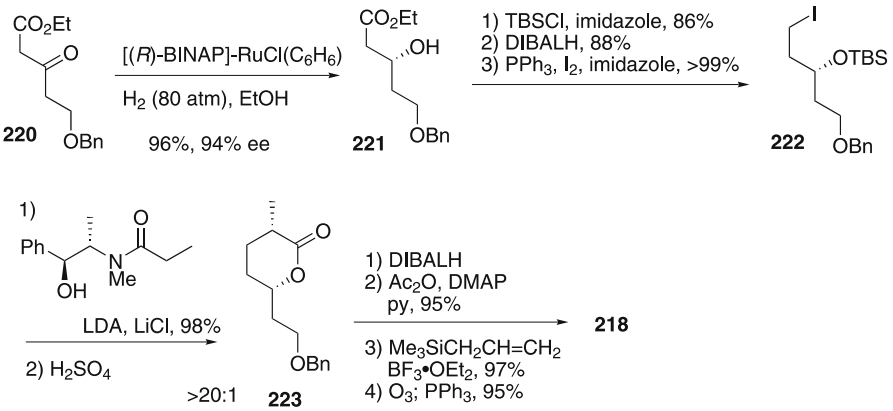
The synthetic strategy is based on Yamaguchi macrolactonization, metal alkynylide addition at C17, Mukaiyama-aldol Prins reaction of vinyl ether **219** with aldehyde **218** forming 2,6-*cis*-tetrahydropyran, Hosomi–Sakurai reaction giving 2,6-*trans*-tetrahydropyran, asymmetric center formation via Myers alkylation at C12 and Noyori reduction at C15 and C3 (Scheme 47).



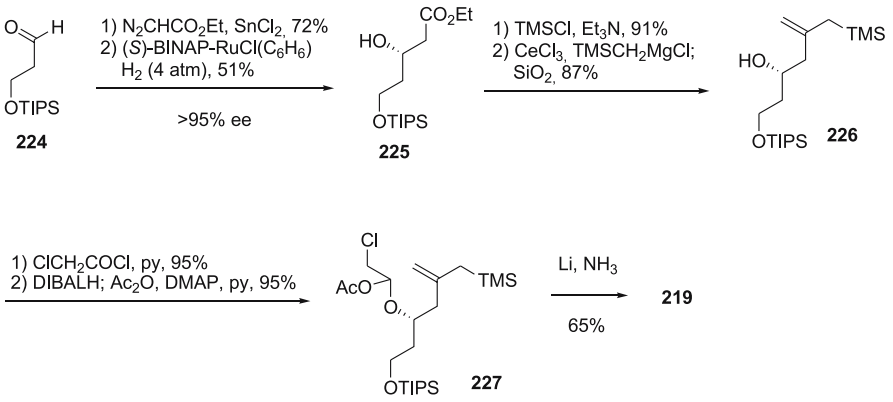
Scheme 47 Rechnovsky's retrosynthesis

The aldehyde **218** possessing 2,6-*trans*-tetrahydropyran, was synthesized as shown in Scheme 48. β-Keto ester **220** was reduced by Noyori hydrogenation [97] to give β-hydroxy ester **221** in 94% ee, which was converted into iodide **222.** Asymmetric alkylation using Myers chiral auxiliary [98] with **222,** followed by acid treatment, furnished δ-lactone **223** with high stereoselectivity. Reductive acetylation, axial allylation by the Hosomi–Sakurai reaction, and ozonolysis completed the synthesis of **218.**

The vinyl ether **219** was synthesized as shown in Scheme 49. Noyori asymmetric hydrogenation of a β-keto ester derived from **224** generated the stereogenic center in **225** with > 95% ee. According to Bunnelle's method [99], **225** was converted into allylsilane **226.** Rychnovsky developed a new method for preparing vinyl ether, because of its sensitivity: chloroacetylation and



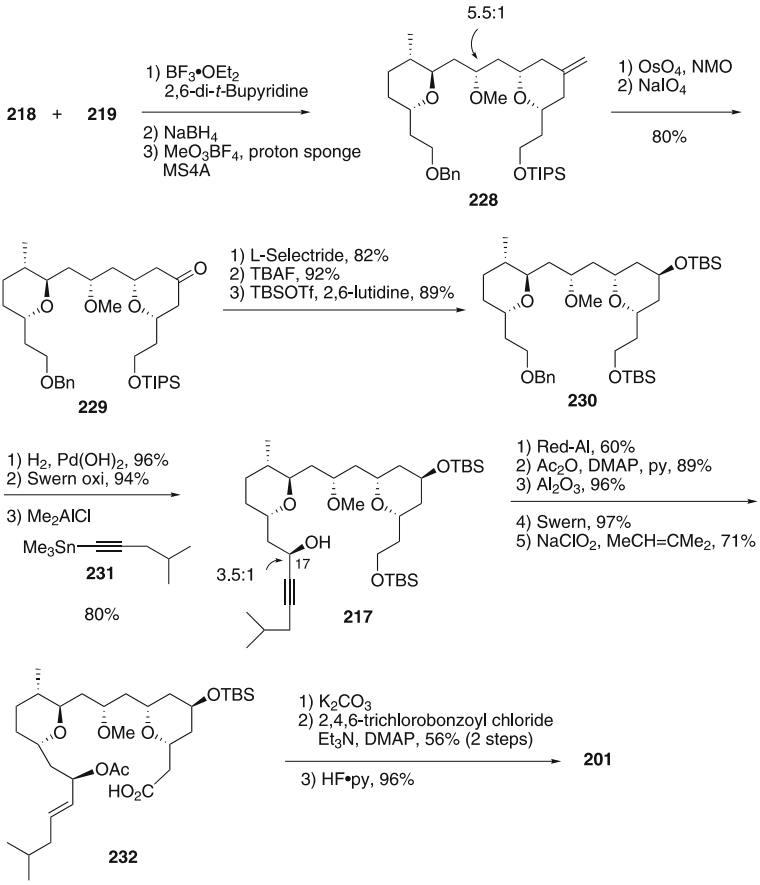
Scheme 48



Scheme 49

then reductive acetylation gave **227**, which was exposed to Li/NH_3 to afford vinyl ether **219**.

The Mukaiyama aldol-Prins cascade reaction was carried out by utilizing the aldehyde **218** and the vinyl ether **219** in the presence of $BF_3 \cdot OEt_2$ to provide 2,6-*cis*-tetrahyderopyran **228** and the epimer at C9 in a ratio of 5.5 : 1, after methyl etherification. Oxidative cleavage of the *exo*-methylene giving ketone **229**, reduction, and protection afforded **230** bearing an axial siloxy group at C5. Debenzylation and Swern oxidation gave an aldehyde, which reacted with alkynylstannane **231** to afford C17 alcohol **217** in a ratio of 3.5 : 1, being at a similar level to that of addition of alkenylzinc found in Leighton's synthesis. After Red-Al reduction of alkyne on **230**, it was converted to *seco*-acid **232**, which was subjected to Yamaguchi macrolactonization to provide Leighton's intermediate **201** (Scheme 50).

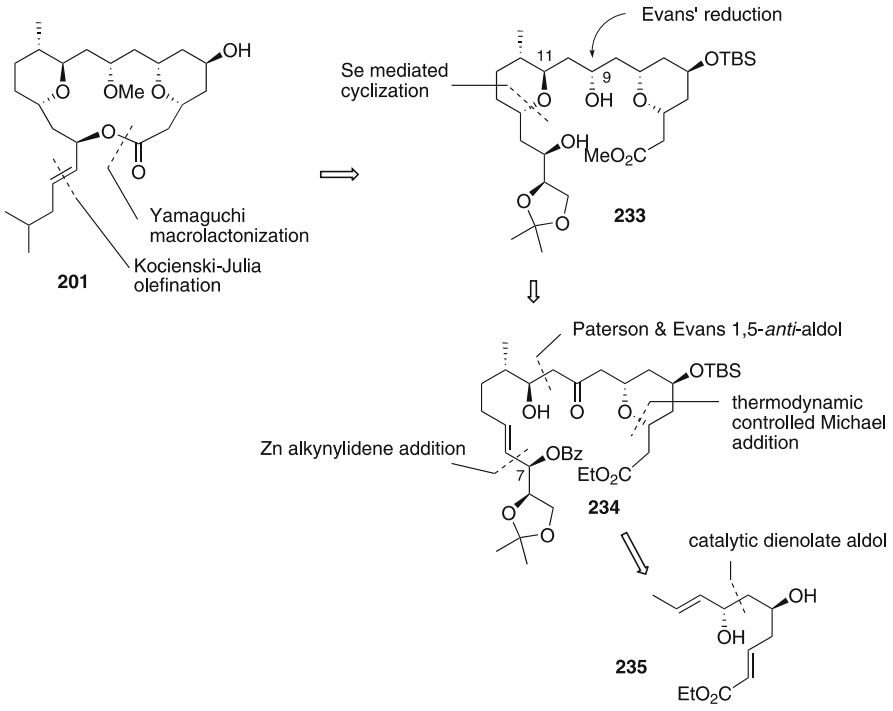


Scheme 50 Formal total synthesis

3.3.3
Carreira's Total Synthesis of Leucascandrolide A [100]

Carreira's methodological features are catalytic asymmetric dienolate aldol, zinc alkynilide addition, and selenium-mediated 2,6-*trans* tetrahydropyran cyclization. The strategy is shown in Scheme 51. Macrolactonization was according to the Yamaguchi method, and selenium-mediated cyclization generated 2,6-*trans*-tetrahydropyran. Asymmetric centers at C9 and C11 in **233** were constructed by stereoselective reduction and 1,5-*anti*-aldol reaction, respectively. The 2,6-*cis*-tetrahydropyran in **234** was synthesized by Michael addition. The C17 stereogenic center was installed by alkynilide addition in the early stage. The C7-stereogenic center in **235** was constructed by catalytic dienolate addition.

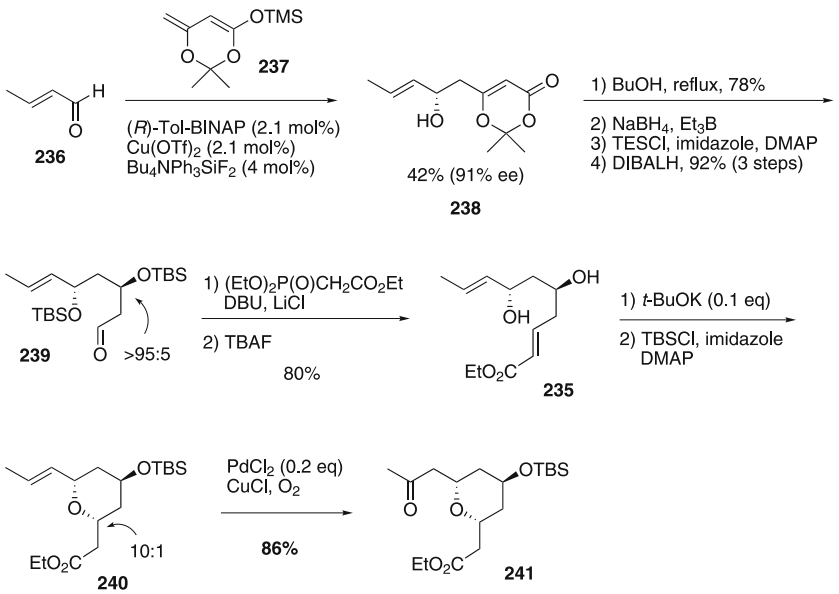
The synthesis of ketone **242** commences with the enantioselective addition of silyl dienolate **237** to crotonaldehyde **236** catalyzed by Carreira's asymmetric complex [101] to give adduct **238** in 91% ee and 42% yield, albeit with a susceptibility towards polymerization. Transesterification, *syn*-reduction, protection of the corresponding diol, and reduction of the ester afforded aldehyde **239**, which was subjected to Horner–Emmons olefination



Scheme 51 Carreira's strategy

under Masamune–Roush conditions to give **235**, after deprotection. The base-catalyzed intramolecular Michael addition of the dihydroxy ester, followed by protection of the remaining alcohol, provided the thermodynamically favored 2,6-*cis*-tetrahydropyran **240**. The remarkable regioselective efficient Wacker oxidation to **240** gave **241** in high yield (Scheme 52).

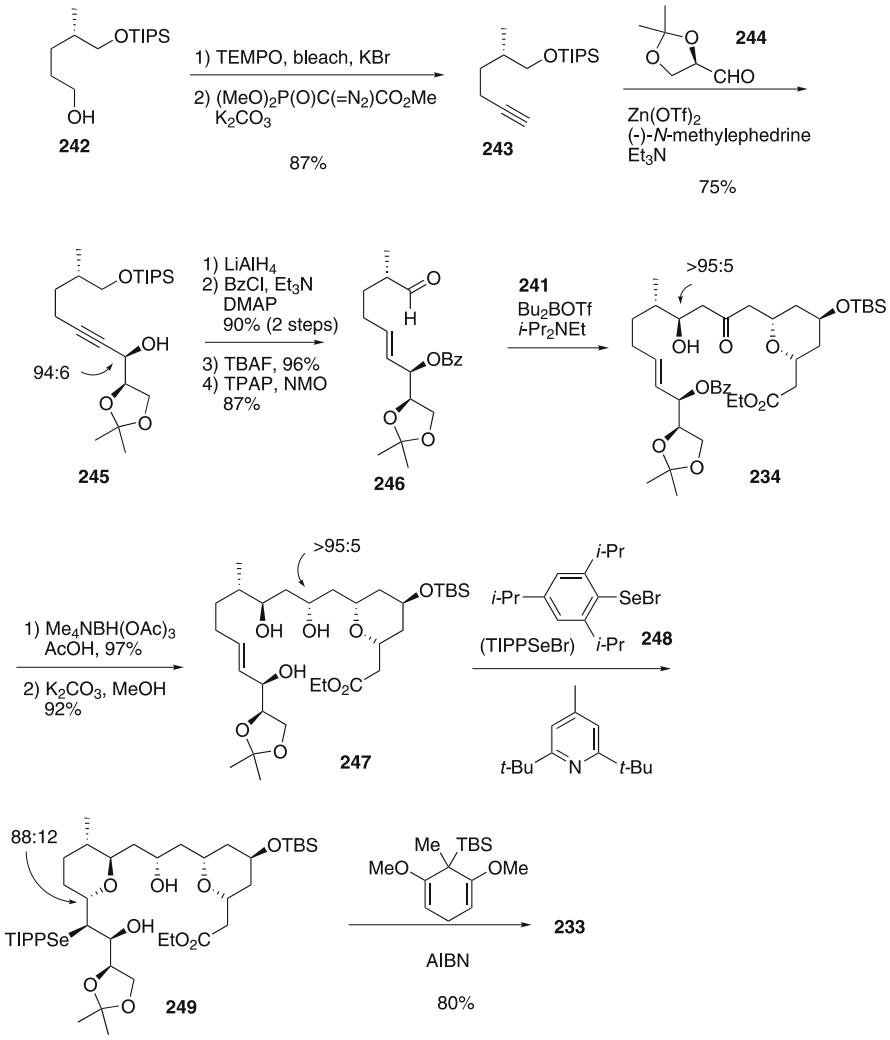
Alcohol **242**, derived from Myers' asymmetric alkylation, was oxidized by TEMPO to give an aldehyde, which was converted to terminal alkyne **243** via the Bestmann protocol [102]. The zinc-alkynilide addition to chiral aldehyde **244** mediated by (–)-*N*-methylephedrine [103] was executed to give propargylic alcohol **245** with 94 : 6 diastereoselectivity. The installation of the asymmetric carbon at C17 in the early stage of total synthesis would achieve this high selectivity, in contrast to moderate selectivities in the syntheses by Leighton, Rychnovski, and Kozmin. After reduction of alkyne, aldehyde **246** was obtained by several functional group transformations. The boron-enolate aldol reaction of the methyl ketone **241** with aldehyde **246** gave hydroxy ketone **234** as a single isomer. This remote 1,5-stereoinduction is based on the pioneering works by Paterson [104] and Evans [105]. Stereoselective reduction of C9-ketone was successfully carried out by using $Me_4NBH(OAc)_3$, followed by methanolysis, to generate **247** [106], although the Tishchenko method failed. Electrophile-mediated cyclization of **247** was executed by using sterically hindered triisopropylphenylselenyl bromide to provide 2,6-*trans*-tetrahydropyran **249** in a ratio



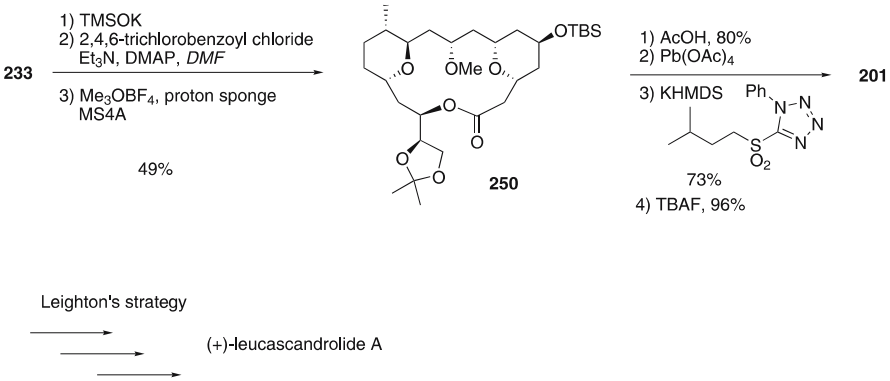
Scheme 52

of 88 : 12. Reductive radical deselenylation of **249** to **233** was achieved under Studer's tin-free conditions (Scheme 53) [107].

Yamaguchi macrolactonization of the corresponding C9, C17-dihydroxy *seco*-acid, prepared by hydrolysis of **233**, was unsuccessful under the standard conditions, probably due to the unfavorable hydrogen-bonded network including C9–OH. To disrupt the hydrogen-bonding, a polar solvent, DMF, was used to lead to macrocycle **250**, after methyl etherification. Finally, hydrolysis of the acetonide and oxidative cleavage of the glycol gave the corresponding aldehyde, which was subjected to Kocienski–Julia olefination, followed



Scheme 53



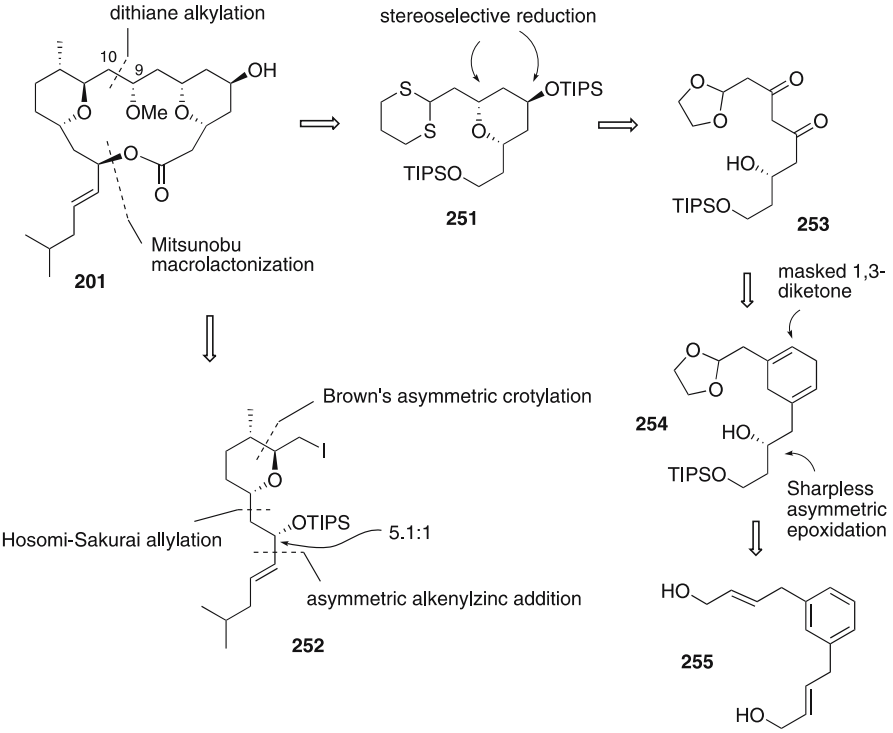
Scheme 54 Completion of total synthesis

by desilylation, to provide Leighton's intermediate **201** as a single isomer (Scheme 54). Total synthesis of leucascandrolide A was completed according to Leighton's method (Sect. 3.3.1).

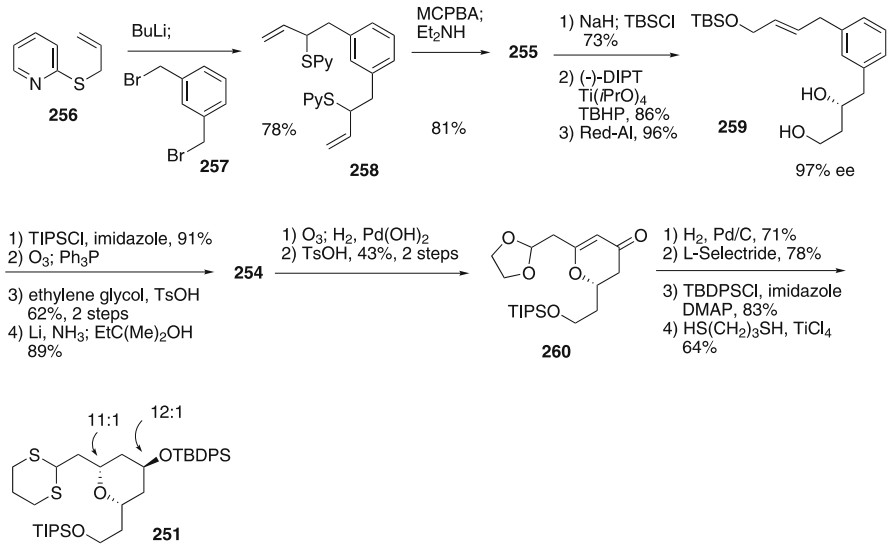
3.3.4 Wipf's Formal Synthesis of (+)-Leucascandrolide A [108]

Wipf reported the convergent synthesis of Leighton's macrolide intermediate **201** as shown in Scheme 55. Macrocyclization was carried out by using the Mitsunobu reaction, and the *seco*-acid was divided into two fragments **251** and **252** with the disconnection at the C9–C10 bond. These fragments were coupled by dithiane anion alkylation. The stereogenic centers on **251** were assembled by reductions via intramolecular stereoinduction oriented from the C3 stereocenter on **253**, which was constructed by Sharpless asymmetric epoxidation of **255**. The special feature in the synthesis of this fragment is that the *m*-disubstituted arene works as masked 1,3-diketone. The preparation of **252** is based on Brown's asymmetric allylation, Hosomi–Sakurai axial allylation forming 2,6-*trans*-tetrahydropyran, and Wipf's asymmetric alkenylzinc addition. Wipf also separately reported the synthesis of a side chain of leucascandrolide A in 2001 [109] that is skipped in this review.

Lithiated allyl sulfide **256**-Li reacted with *m*-xylylene dibromide **257** to afford the bis-sulfide **258**. A double Mislow–Evans rearrangement of **258** and subsequent reductive trapping of the sulfenate ester provided the symmetric *trans*-diol **255**. Monoprotection, Sharpless asymmetric epoxidation, and reductive ring-opening of the epoxide gave 1,3-diol **259** in 97% ee. After several functionalizations, the arene was subjected to Birch reduction to provide 1,4-cyclohexadiene **254**. Ozonolysis of the diene, followed by reductive workup and treatment of the resulting 1,3-diketone with acid furnished pyra-



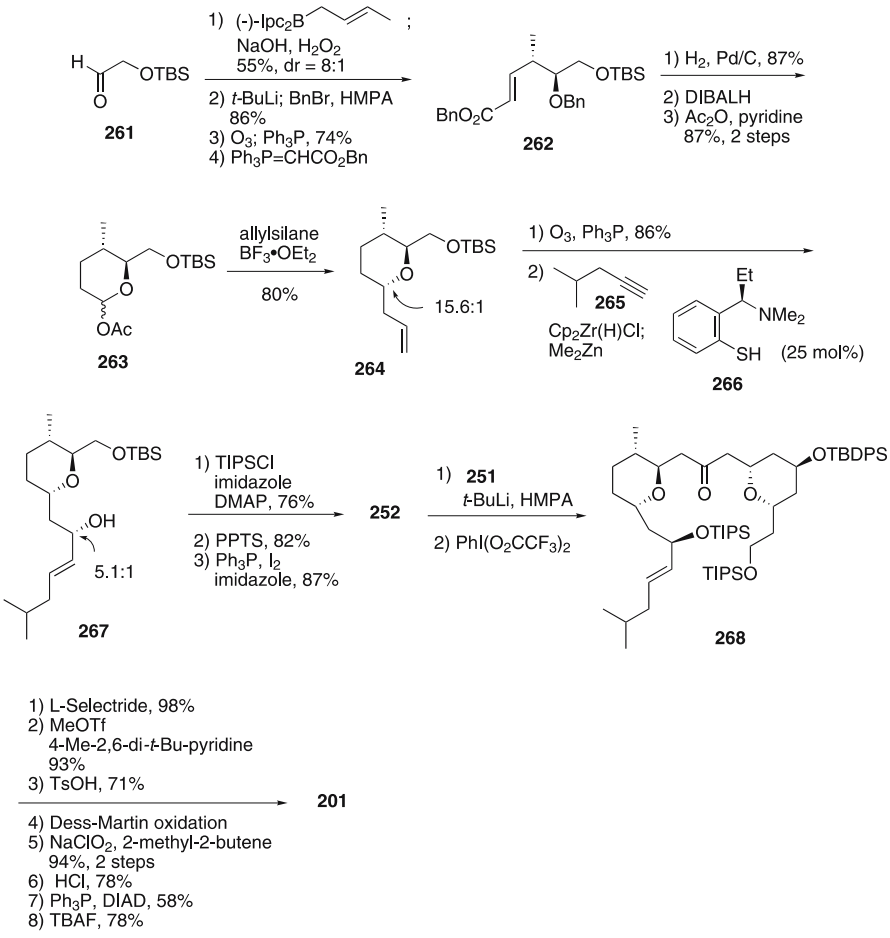
Scheme 55 Wipf's strategy



Scheme 56

none **260**. Stereoselective hydrogenation and reduction, followed by protecting group manipulation, gave dithiane **251** (Scheme 56).

The synthesis of **252** began with Brown's asymmetric crotylation to aldehyde **261**. The resulting homoallyl alcohol was converted benzyl ester **262**, which was reduced to give lactol acetate **263**. Axial allylation to **263** formed 2,6-*trans*-tetrahydropyran **264**, which was subjected to ozonolysis to give an aldehyde. Addition of alkenylzinc, prepared by hydrozirconation of an alkyne **265**, to the aldehyde mediated by chiral ligand **266** yielded allyl alcohol **267** with a 5.1 : 1 diastereoselectivity [110]. The stereochemistry of the major isomer was found, unexpectedly, to be the *S*-form at C17, which rendered the macrolactonization to adopt the Mitsunobu reaction. The iodide **252**, prepared from **267** in three steps, reacted with

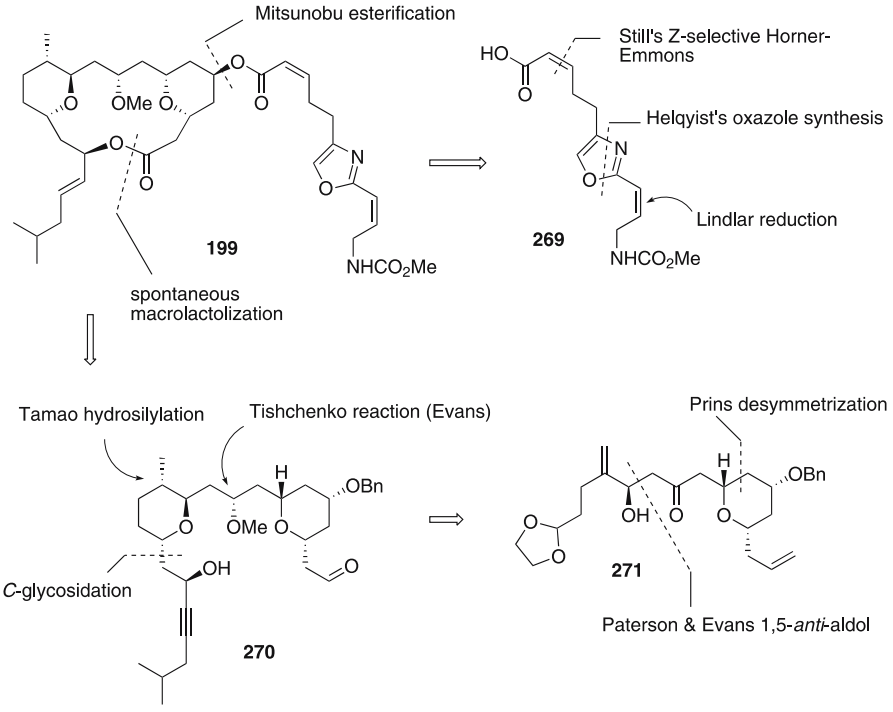


Scheme 57 Completion of total synthesis

lithiated dithiane **251**-Li, and subsequent oxidative hydrolysis of dithiane provided **268**. Finally, stereoselective reduction and several functionalizations gave *seco*-acid, which was subjected to Mitsunobu macrocyclization to yield the macrocycle **201** (Scheme 57).

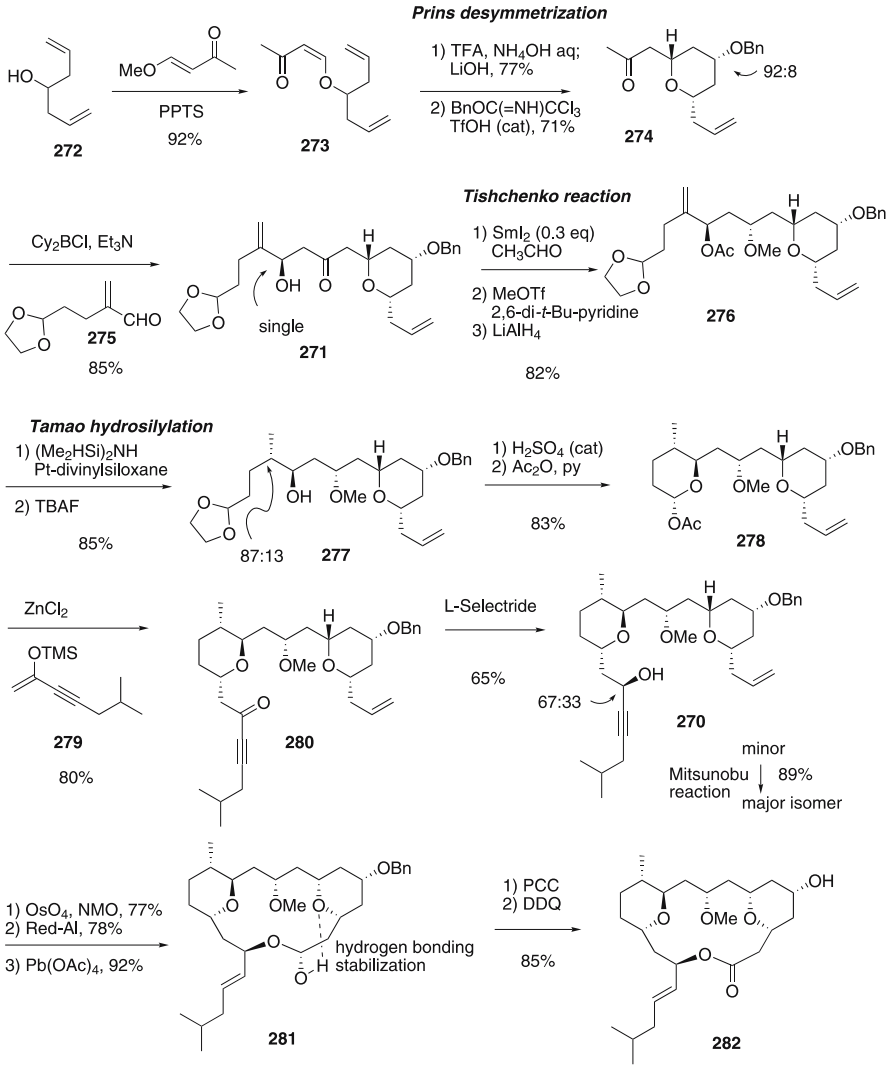
3.3.5 Kozmin's Total Synthesis of (±)-Leucascandrolide A [111,112]

Kozmin's synthetic strategy is illustrated in Scheme 58. Oxazole-containing subunit **269**, prepared by using Helqyist's Rh-catalyzed oxazole synthesis, was introduced via the Mitsunobu reaction. A spontaneous intramolecular *macrolactolization*, which would be assisted by intramolecular hydrogen bonding, is an unprecedented route to macrolides. *C*-Glycidation (axial attack) of an enol silane to a lactol acetate constructed 2,6-*trans*-tetrahydropyran. The asymmetric centers at C12, C11, and C9 on **270** were constructed by Tamao hydrosilylation, the Paterson–Evans 1,5-*anti*-aldol reaction, as Carreira did, and the Tishchnko reaction, respectively. The 2,6-*cis*-tetrahydropyran (C3–C7) was synthesized by Prins desymmetrization, which is also characteristic in this synthesis.



Scheme 58 Kozmin's retrosynthesis

The synthesis began with Prins cyclization of the symmetric vinylogous ester **273**, prepared from heptadienol **272**, followed by hydrolysis of the resulting trifluoroacetate and benzylation, to afford the desired 2,6-*cis*-tetrahydropyran **274** with 92 : 8 diastereoselection at C5 [113]. By this novel desymmetrization, 2,4,6-all-*cis* trisubstituted pyran was efficiently provided. Boron-enolate aldol reaction, as Carreira did, of the methyl ketone **274** with aldehyde **275** gave hydroxy ketone **271** as a single isomer. In contrast to Carreira's result, samarium-catalyzed intramolecular Tishchenko reduction [114]



Scheme 59

of the β-hydroxy ketone **271** established the C9-stereogenic center, and then methyl etherification, followed by reductive removal of acetate, afforded **276.** A chemo and diastereoselective installation of the C12 stereogenic center was achieved via Pt-catalyzed Tamao hydrosilylation [115] to give **277** (87 : 13) after protodesilylation. The stereochemical outcome can be rationalized by considering minimization of the $A^{1,2}$ strain between R^1 and R^2 in the substrate (Fig. 7).

C-Glycosidation of enol silane **279** to lactol acetate **278**, prepared from **277** in two steps, furnished ynone **280** as a single isomer. Reduction of the ketone with L-selectride furnished alcohol **270** with poor selectivity, but the minor isomer can be converted into the desired isomer via the Mitsunobu protocol. Dihydroxylation of the terminal alkene, reduction of alkyne, and oxidative cleavage of the resulting triol gave the intermediate hydroxy aldehyde, which was spontaneously transformed into macrolactol **281** as a single diastereomer.

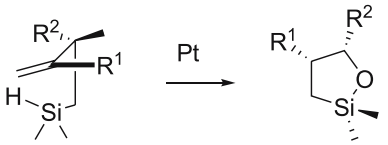
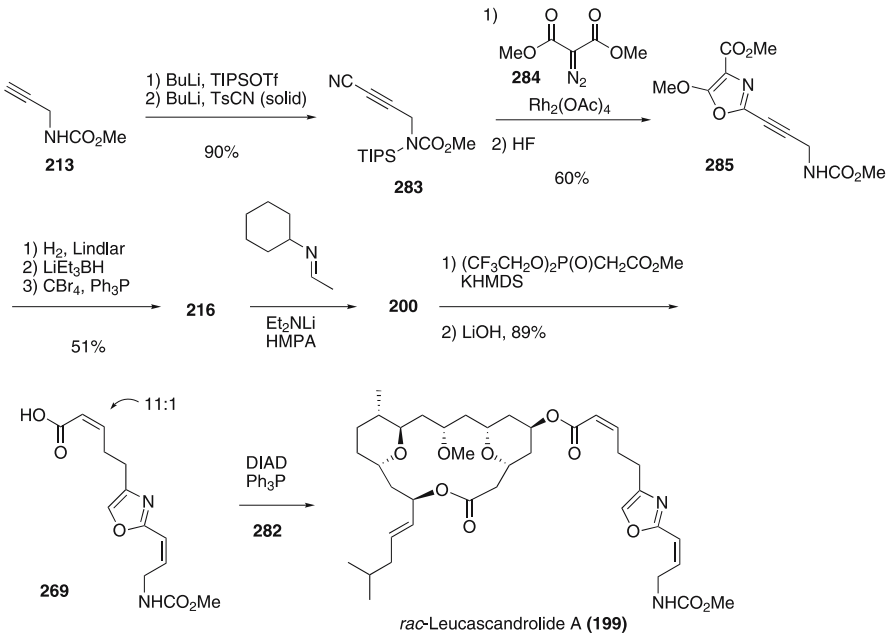


Fig. 7 Pt-catalyzed Tamao hydrosilylation



Scheme 60 Completion of total synthesis

The conformational study revealed that the intramolecular hydrogen bonding provided additional stabilization for the thermodynamically favored lactol formation. PCC oxidation of the lactol, followed by deprotection, gave the macrolide subunit **282** (Scheme 59).

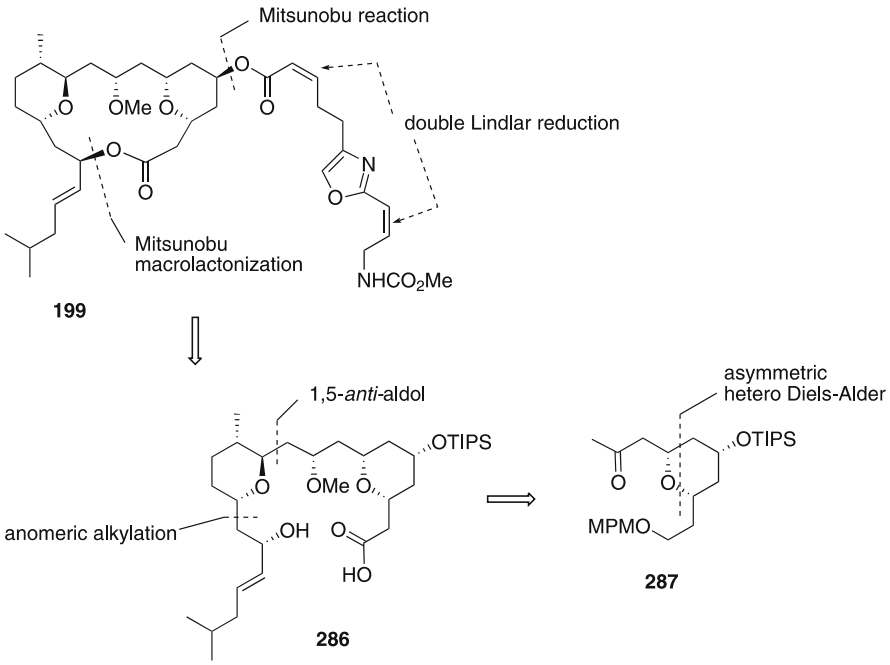
Kozmin's synthesis of the side chain was more efficient than Leighton's method (Scheme 60). Oxazole **285** was synthesized by Rh-catalyzed condensation of alkynyl nitrile **283** with diazo malonate **284** using the Helquist protocol [116]. Lindlar reduction of alkyne, reduction by Super-H, and bromination afforded bromide **216**, which was employed for the alkylation of metalloenamine to afford the aldehyde **200**. Subsequent (*Z*)-olefination and saponification furnished the side chain subunit **269**.

Finally, Mitsunobu reaction of alcohol **282** with acid **269** provided *rac*-leucascandrolide A (**199**) in good yield, despite the significant steric congestion at the reaction site. The racemic mixture can be separated with HPLC using a Daicel Chiralcel AD-H chiral column.

3.3.6
Paterson's Total Synthesis of (+)-Leucascandrolide A [117]

Paterson reported a total synthesis of (+)-leucascandrolide A (**199**) in which essentially complete control over all of the stereochemistry is achieved. As outlined in Scheme 61, two Mitsunobu reactions were employed for macrocyclization and installation of the side chain. The two *cis*-alkenes in the side chain were introduced by double Lindlar hydrogenation in the final stage. The oxygenated stereogenic centers on *seco*-acid **286** were constructed by reduction at C17 and C9, C-glycosidation at C15, and 1,5-*anti*-aldol reaction at C11, all of which were by using substrate control. The 2,6-*cis*-tetrahydropyran in **287** was synthesized by the asymmetric hetero Diels–Alder reaction.

An asymmetric hetero Diels–Alder reaction of aldehyde **288** and siloxydiene **289**, catalyzed by Jacobsen's chromium catalyst **290** provided 2,6-*cis*-tetrahydropyran **291** with excellent selectivity (Scheme 62). After stereoselective reduction of ketone at C5, the resulting alcohol **292** was converted to methyl ketone **287** via alkynylation followed by oxymercuration. The 1,5-*anti*-aldol reaction of **287** with aldehyde **293**, followed by stereoselective reduction, provided diol **294**. The corresponding triol, derived from **294** via acid treatment, was subjected to chemoselective oxidative lactonization by TEMPO – $PhI(OAc)_2$ to yield lactone **295**, after methyl etherification. The lactone **295** was reduced to lactol, which reacted with silyl dienol ether **296** in the presence of $ZnBr_2$ to provide 2,6-*trans*-tetrahydropyran **297**. Reduction of ketone at C17 was employed by using $LiAlH(O\textit{t}\text{-}Bu)_3$ to afford (17*S*)-**298** with high selectivity. The fact that addition of $ZnBr_2$ decreased the selectivity suggests the non-chelation model rather than the chelation one. It is in contrast to the moderate selectivity in the synthesis by Kozmin giving the 17*R*-form.



Scheme 61 Paterson's strategy

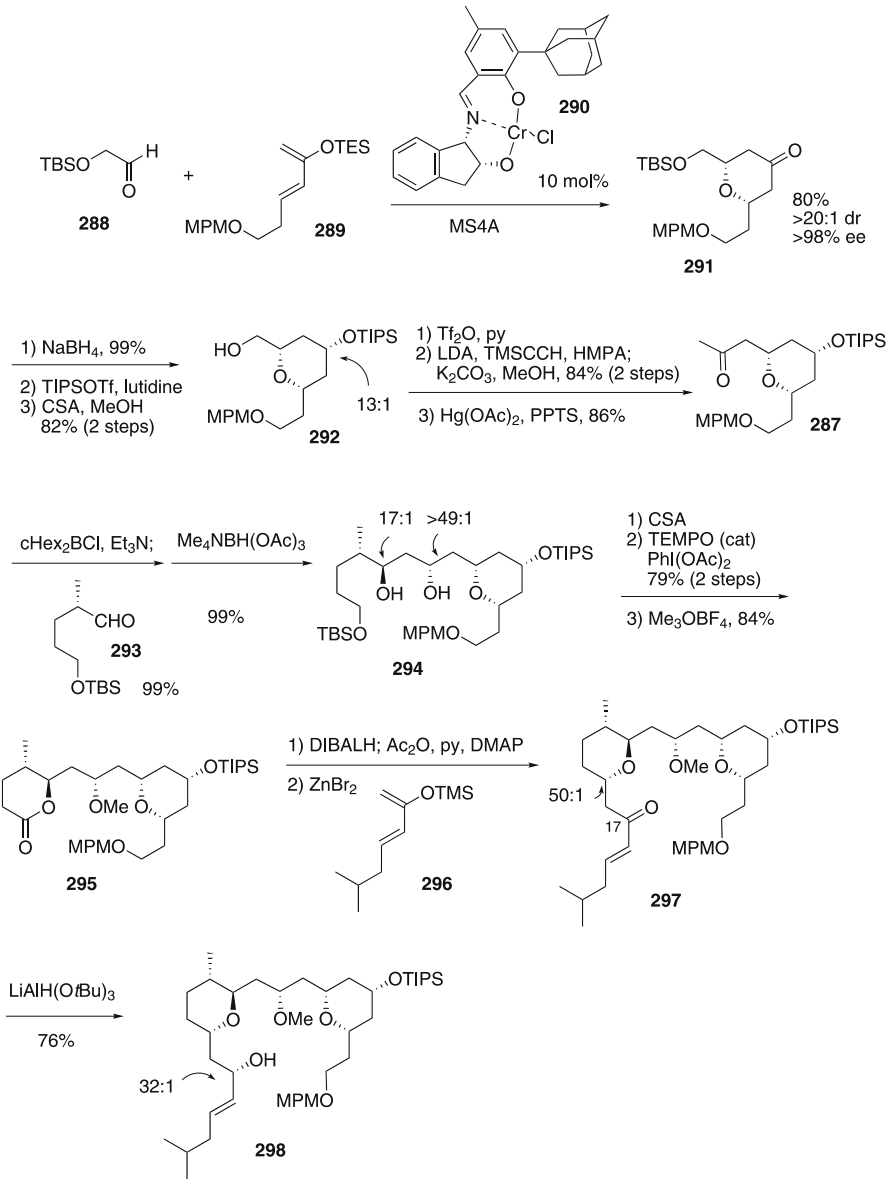
The *seco*-acid **286**, prepared from **298** in five steps, was subjected to Mitsunobu macrolactonization to provide the desired macrolactone in 65% yield with clean inversion of configuration. Deprotection of TIPS group afforded **282** with equatorial C5–OH for installation of the side chain (Scheme 63).

The bis-alkyne side chain was synthesized as outlined in Scheme 64. Hydrazone **300** was alkylated, followed by hydrolysis, to give α-hydroxy ketone **301**, which was converted to oxazolone by treatment with trichloroacetyl isocyanate. The oxazolyl triflate **302**, prepared by reaction of the oxazolone with triflic anhydride, was coupled with alkyne **213** under Sonogashira conditions as reported by Panek [118], followed by deprotection of MPM and oxidation, to furnish the side chain precursor bisalkynyloxazole **299.**

Finally, Mitsunobu reaction of macrocycle **282** with the acid **299** afforded the axial ester, which was hydrogenated using Lindlar catalyst to yield (+)-leucascandrolide A (**199**) (Scheme 64).

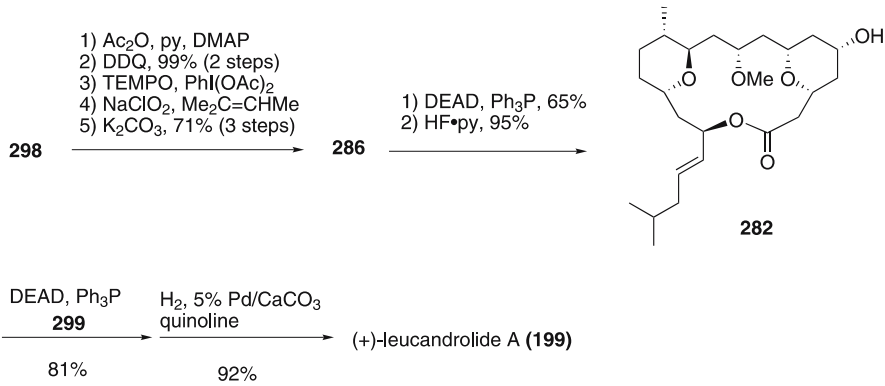
3.3.7
Williams' Formal Synthesis of Leucascandrolide A [119]

Williams reported the synthesis of Leighton's macrolide intermediate (**201**). The strategy for synthesis of two tetrahydropyrans is based on intramolecu-

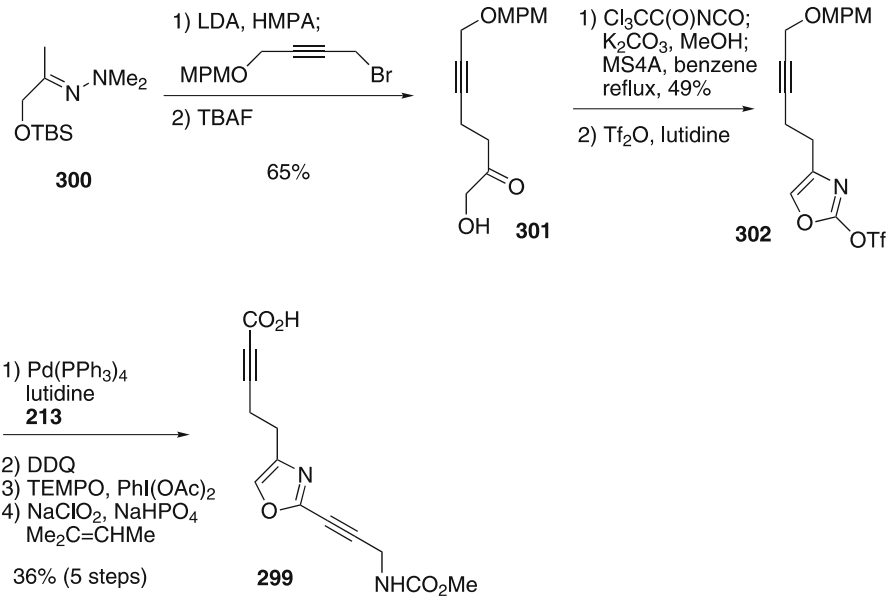


Scheme 62

lar S_N2 reaction, thus the stereogenic centers at C3, C7, C11, and C15 should be fully assembled prior to cyclization of the pyrans. As shown in Scheme 65, the asymmetric centers at C9, C11, and C15 were derived from the chiral pool, and C3 and C9 were constructed via asymmetric allylations. C11 and C17 were introduced by asymmetric reductions.

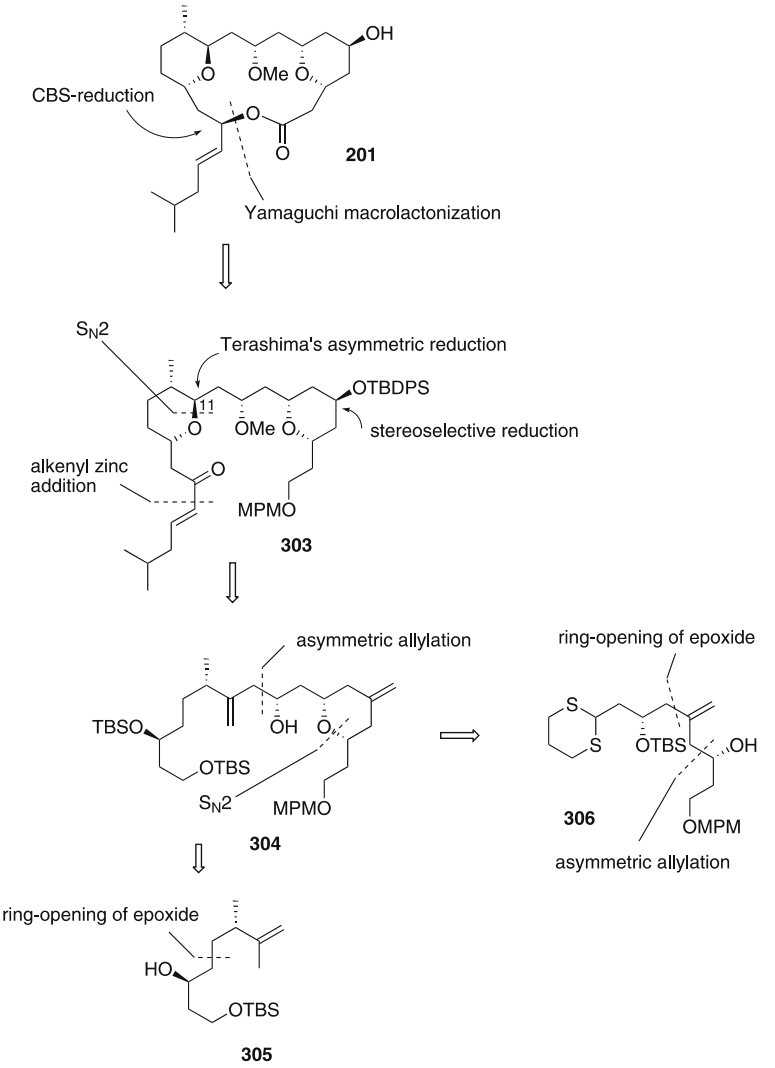


Scheme 63 Completion of total synthesis



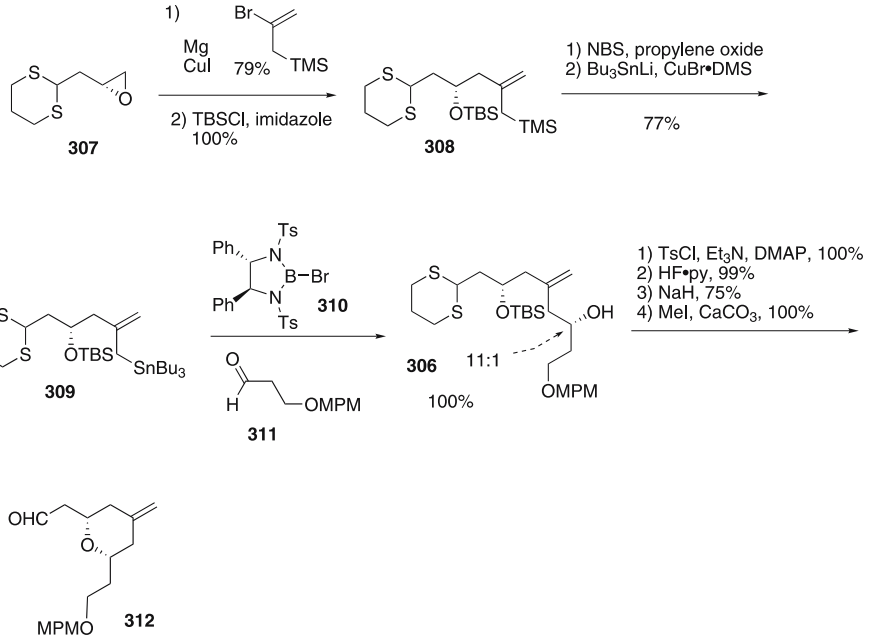
Scheme 64

Non-racemic epoxide **307**, prepared from (+)-epichlorohydrin, was alkenylated to give allyl silane **308**, which was converted into allyl stannane **309**. Corey's chiral boron reagent-mediated asymmetric allylation [120] to aldehyde **311** provided homoallylic alcohol **306** with a 11 : 1 diastereomer ratio. Intramolecular S_N2 cyclization of the corresponding 7-hydroxy-3-TsO unit derived from **306**, followed by hydrolysis of the dithiane, afforded aldehyde **312** (Scheme 66).



Scheme 65 Williams' strategy

Homoallyl bromide **314**, prepared from readily available non-racemic ester **313**, was converted to the Grignard reagent, which reacted with non-racemic epoxide, derived from D-malic acid, to afford the alcohol **305**. Ozonolysis of the alkene gave a ketone, which was converted into enol triflate **316**. Ni-catalyzed cross coupling with trimethylsilylmethyl magnesium chloride afforded the allyl silane, which was converted into the allyl stannane **317**. The asymmetric allylation of **313** with **317** provided **304** with a ration of 8.5 : 1. Methyl etherification and oxidative cleavage of *exo*-methylene



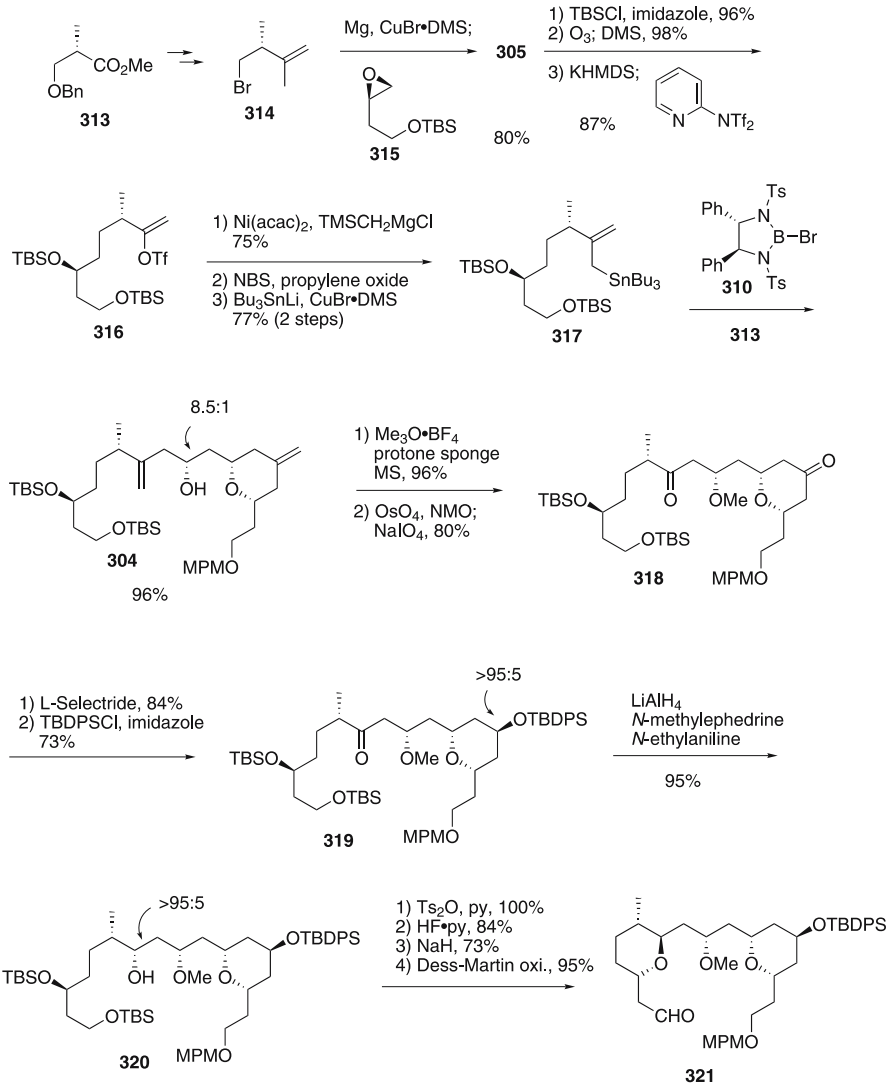
Scheme 66

gave ketone **318,** which was subjected to stereoselective reduction to give **319.** Asymmetric reduction of C11-ketone was successfully achieved by using Terashima's aluminum reagent to afford **320.** The synthesis of the second pyran was also performed by S_N2 reaction to provide **321** (Scheme 67).

Addition of alkenylzinc **322** to the aldehyde **321** resulted in a diastereomer mixture (1 : 1) of allylic alcohol, which was oxidized to afford ketone **303.** Although Terashima's asymmetric aluminum reagent did not give the desired alcohol, the asymmetric borohydride reduction catalyzed by the Corey–Bakshi–Shibata reagent gave a 5 : 1 mixture of separable diastereomers, in favor of the (17*R*)-alcohol **323.** Finally, protective group manipulation and oxidations led to a seco-acid, which was subjected to Yonemitsu-modified Yamaguchi macrolactonization to yield the macrocycle (**201**) (Scheme 68).

3.3.8
Crimmins' Formal Synthesis of (+)-Leucascandroloide A [121]

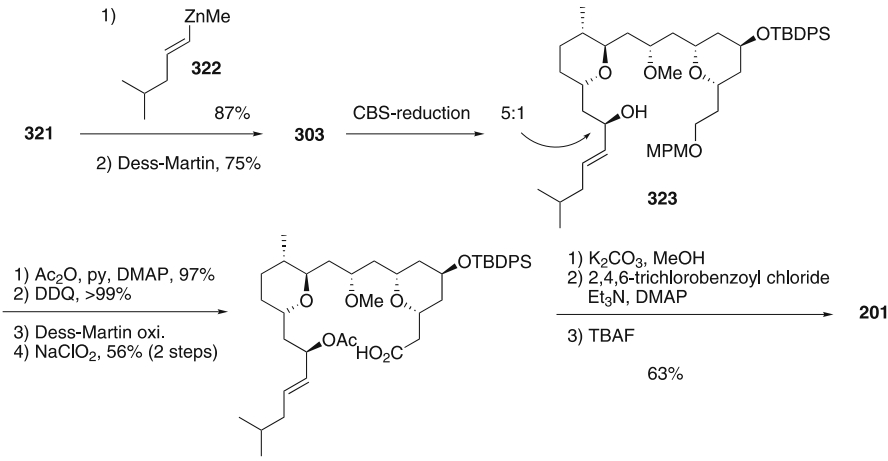
Crimmins reported synthesis of Leighton's macrolide intermediate (Scheme 69). The key steps are a reductive cleavage of bicyclic acetal to form 2,6-*trans*-tetrahydropyran **325**, that is essentially reduction of pyran oxonium cation, and a diastereoselective 1,5-*anti*-aldol reaction of the boron enolate to establish a stereogenic center at C7 by generating a C7–C8 bond, that is in contrast to the 1,5-*anti*-aldol forming C10–C11 bond (Carreira



Scheme 67

and Kozmin). Stereogenic centers at C5, C11, and C17 were constructed by Evans' asymmetric alkylation, Brown's asymmetric allylation, and stereoselective aldol reactions mediated by Nagao's auxiliary and a boron enolate, respectively. Cyclizations of macrolactone and 2,6-*cis*-tetrahydropyran were achieved by Yamaguchi macrolactonization, intramolecular Michael addition, respectively.

The C8–C22 unit was synthesized as shown in Scheme 70. Brown crotylation of aldehyde **328**, oxidative acetalization, and oxidative cleavage of alkene



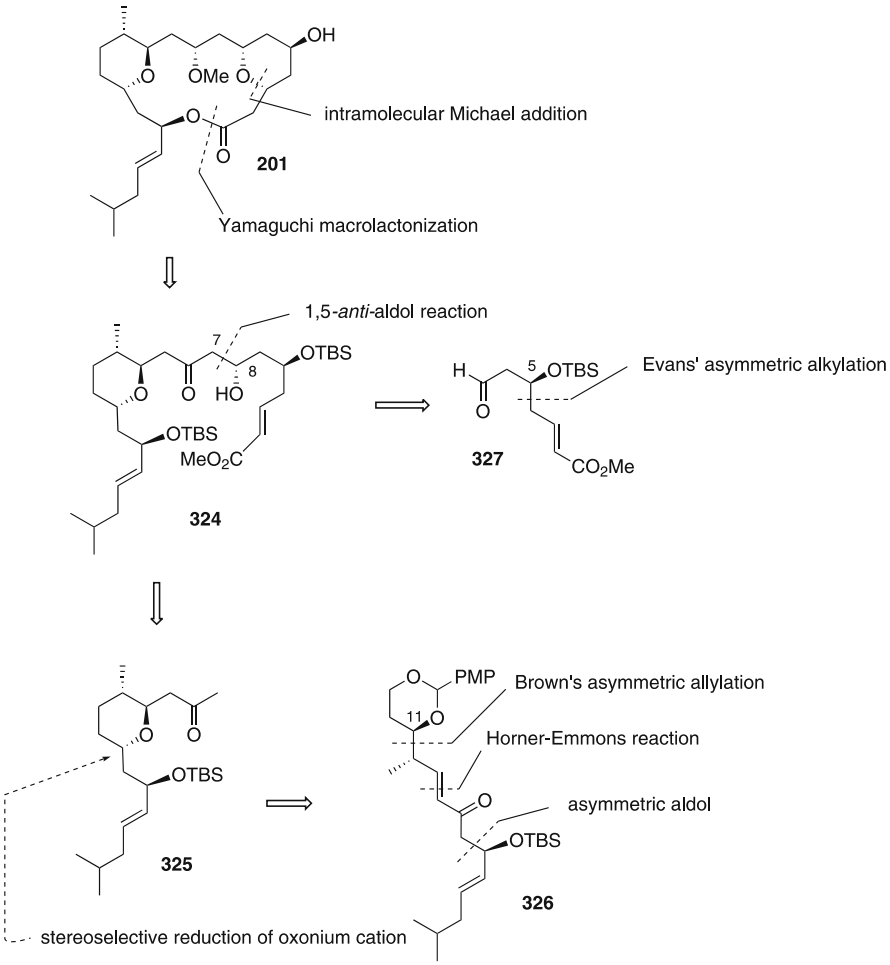
Scheme 68

afforded aldehyde **329**, which was subjected to the Horner–Emmons reaction under Paterson's conditions [84] with phophonate **330**, prepared via asymmetric aldol reaction using the chiral thiazolidinethione auxiliary as outlined in Scheme 71, to give enone **326**. Selective 1,4-reduction of **326** with DIBALH in the presence of HMPA [122], followed by two-step acetalization including mixed methyl acetalization and subsequent bridged acetalization, to furnish the bicyclic acetal **331**. Treatment of **331** with DIBALH under Kotsuki's conditions [123] delivered the 2,6-*trans*-tetrahydropyran **332** with a 15 : 1 ratio of diastereomers. Crimmins explained this selectivity for the intramolecular delivery of hydride by coordination of DIBALH to the acetal oxygen (Sect. 2.3). The primary alcohol in **332** was converted to methyl ketone **325**.

The 1,5-*anti*-aldol reaction was performed with chiral boron enolate of **325** and aldehyde **327**, prepared by Evans' asymmetric alkylation, cross metathesis, and Wittig homologation (Scheme 72), to afford **324** with a 96 : 4 diastereoselectivity. Stereoselective reduction of C9-ketone provided the *syn*-1,3-diol, which was exposed to catalytic *t*-BuOK to give 2,6-*cis*-tetrahyderopyran **333** via an intramolecular Michael reaction. Finally, methyl etherification, deprotection, hydrolysis of ester, and Yamaguchi macrolactonization yielded the leucascandrolide macrolide **201** (Scheme 73).

3.3.9
Panek's Total Synthesis of (+)-Leucascandrolide A [124]

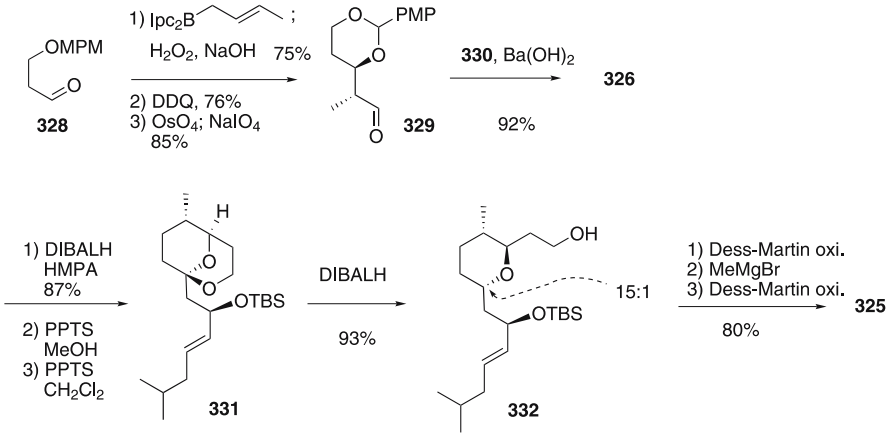
Panek's synthesis is highlighted by the efficient construction of a *cis*- and *trans*-2,6-disubstituted tetrahydropyran ring. As described in Sect. 2.4, Panek's annulation between aldehydes and chiral allylsilanes can be regarded as a Hosomi–Sakurai–Prins reaction, in which the stereochemistry of *cis*-



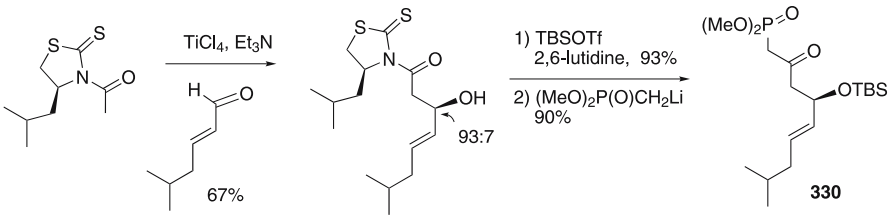
Scheme 69 Crimmins' retrosynthesis

and *trans*-pyrans can be controlled by the stereochemistry of the allylsilanes. The strategy of the synthesis is illustrated in Scheme 74. Side chain **334**, prepared by his original method [125], was introduced to the macrocycle via the Mitsunobu esterification. The macrocyclization was initiated by macrolactolization previously reported by Kozmin (Sect. 3.3.5). The asymmetric center at C17 was constructed by addition of alkenylzinc.

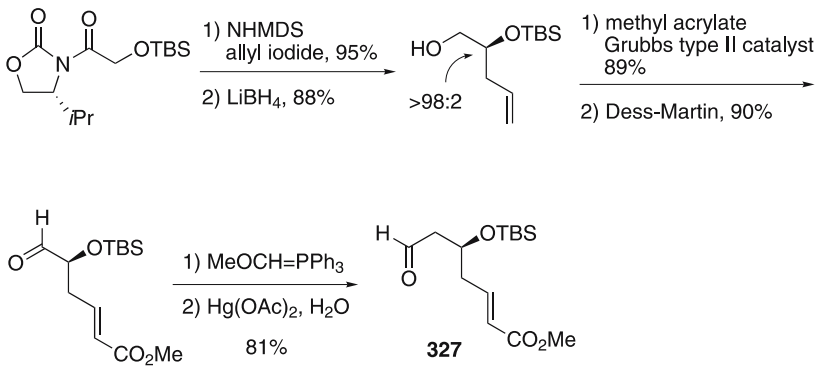
The 2,6-*cis*-dihydropyran **340** was synthesized by the Panek-modified Prins reaction between the chiral aldehyde **338** and the chiral *syn*-allylsilane **339** mediated by triflic acid. The key point of the stereoselectivity is the sterically hindered electron-withdrawing mesylsulfonate, which induced the chair-like transition state **341**. Cyanation, regioselective oxymercuration, and



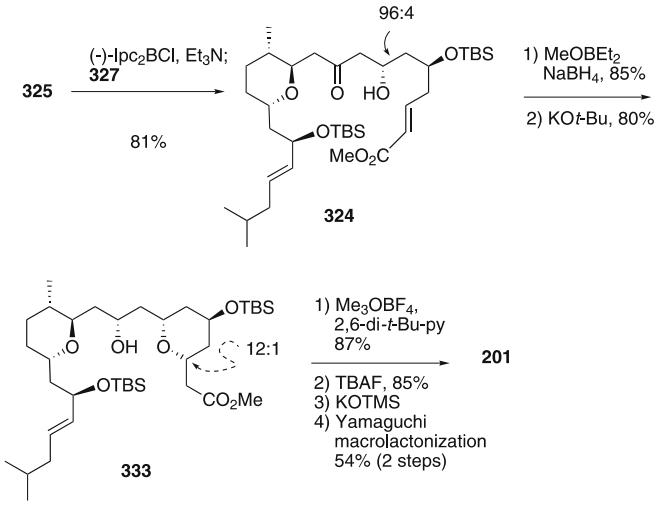
Scheme 70



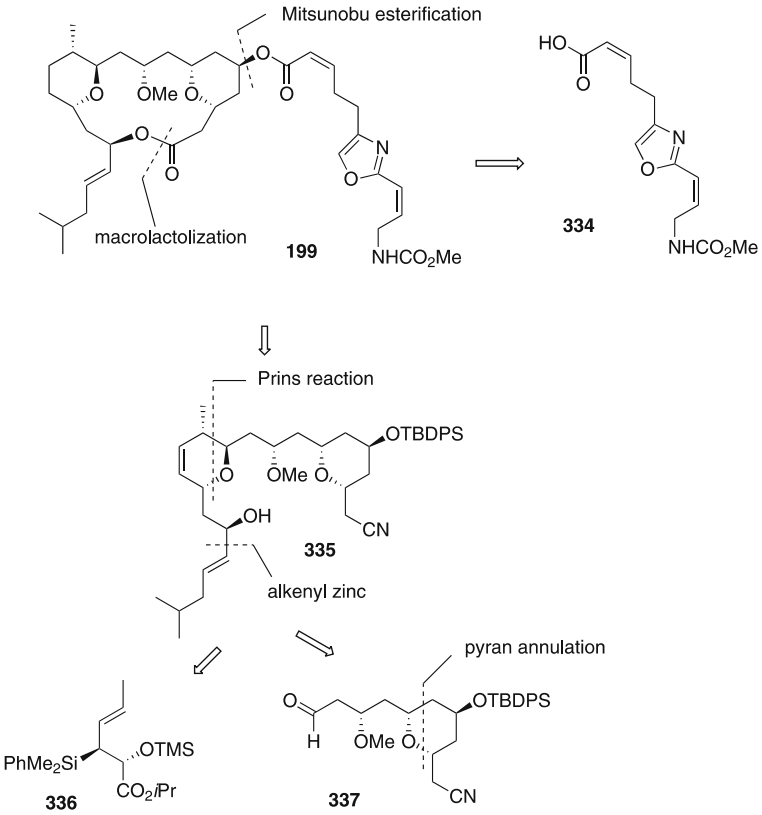
Scheme 71



Scheme 72

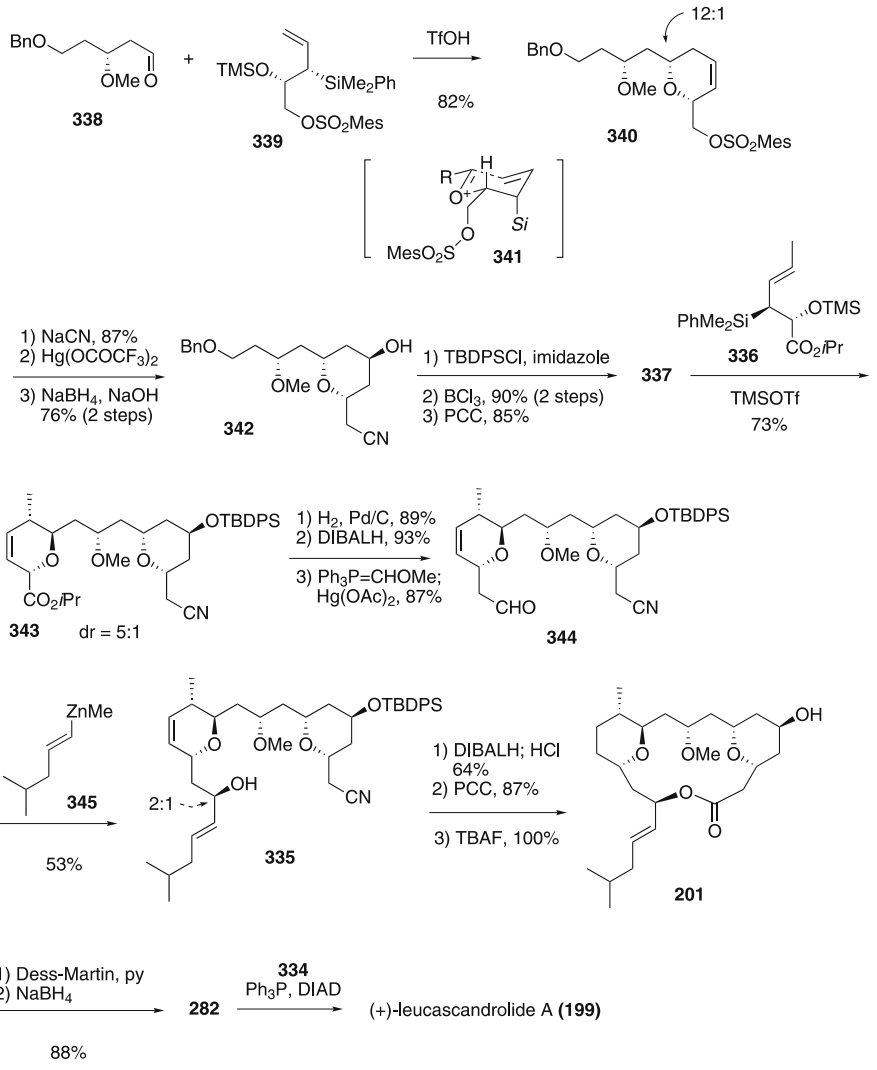


Scheme 73

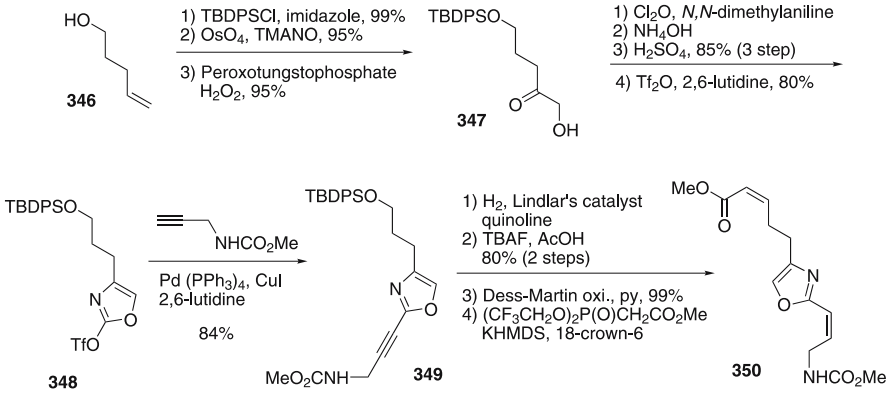


Scheme 74 Panek's retrosynthesis

stereoselective reduction led to tetrahydropyran **342,** which was converted into aldehyde **337** in three steps. The second Panek-modified Prins reaction between the aldehyde **337** with the chiral *anti*-allylsilane **336** afforded 2,6-*trans*-dihydropyran **343** with a 5 : 1 ratio of diastereomers. Addition of an alkenylzinc **345** to aldehyde **344**, prepared from **343** in three steps, furnished allylic alcohol **335** with poor selectivity. Reduction of nitrile of **335** led to a transient hydroxyaldehyde which spontaneously cyclized into the macrolac-



Scheme 75



Scheme 76

tol, that is a similar transformation to Kozmin's protocol. The PCC oxidation of the lactol provided macrolide **201** in good yield (Scheme 75).

The synthesis of the side chain was illustrated in Scheme 76. 4-Penten-1-ol **346** was converted into hydroxy ketone **347**, which was treated with phosgene, followed by exposure to aqueous ammonia to give oxazolone, after acidification. Triflyloxazole **348**, which was prepared from the oxazolone by Tf_2O and lutidine, was subjected to Sonogashira coupling to provide **349**, which was converted into the side chain unit **350** via Lindlar hydrogenation, desilylation, oxidation, and the Still's modified Horner–Emmons reaction.

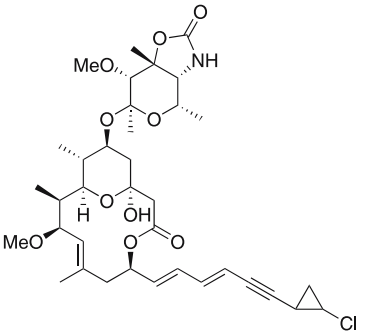
For the Mitsunobu esterification, the configuration at C-5 of **201** was inverted via an oxidation–reduction sequence. Finally, the resulting alcohol **282** and acid of **350** was united under the Mitsunobu conditions to conclude the total synthesis of leucascandrolide A.

3.4
Other Marine Macrolides

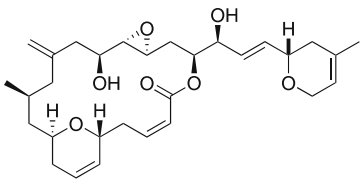
In addition to the total syntheses of marine macrolides described in this review, several total syntheses of other marine macrolides have been achieved in recent years. Figures 8–10 show the structures of the representative examples.

4
Concluding Remarks

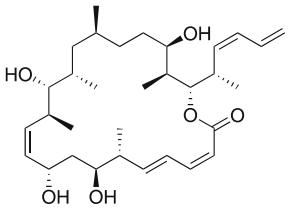
Recent progress in the total syntheses of marine natural products has been described. These synthetic studies revealed the correct structures including absolute configurations of the natural products. They also taught us not only



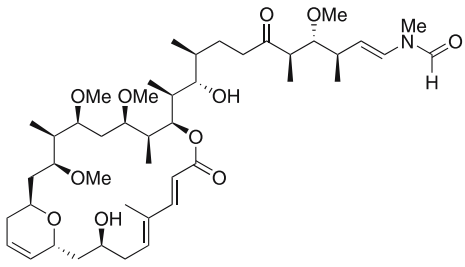
callipeltoside A
Trost (2002)[116]
Evans (2002)[65]
Paterson (2003)[117]
Panek (2004)[118]



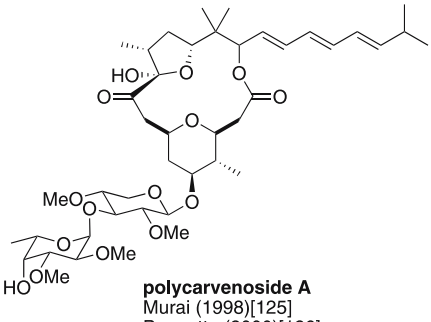
laulimalide
Ghosh (2000)[119]
Paterson (2001)[23]
Mulzer (2001)[27]
Wender (2002)[24]
Crimmins (2002)[28]
Williams (2002)[25]
Nelson (2002)[29]
Gallagher, Jr. (2004)[120]
Uenishi (2005)[17]



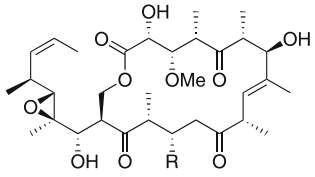
dictyostatin
Paterson (2004)[121]
Curran (2004)[122]



scytophycin C
Paterson (1997)[123]
Miyashita (2003)[124]



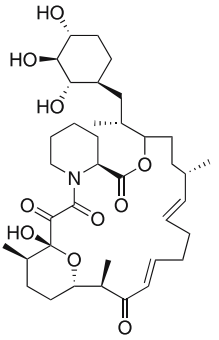
polycarvenoside A
Murai (1998)[125]
Paquette (2000)[126]
White (2001)[127]



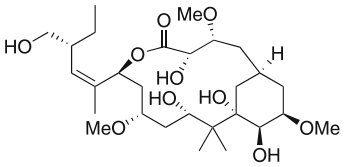
tedanolide (R = OH)
Smith III (2004)[128]
13-deoxytedanolide (R = H)
A. B. Smith (2004)[128]
W. R. Roush (2005)[129]

Fig. 8 The marine macrolides that have been synthesized in recent years

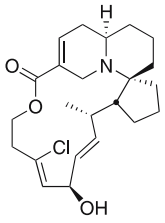
how to construct the molecules but also how to use the known reactions, and moreover how to develop new synthetic methodology. These results represent remarkable contributions to organic chemistry.



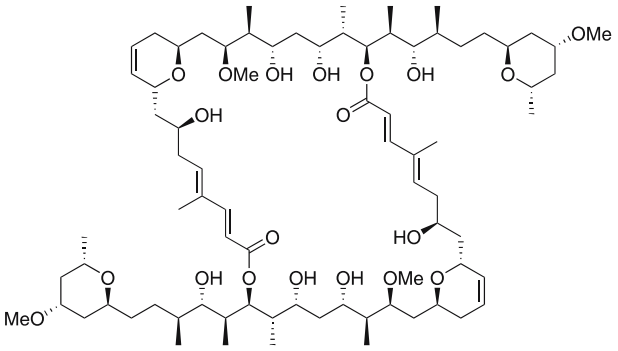
antascomicin B
Ley (2005)[130]



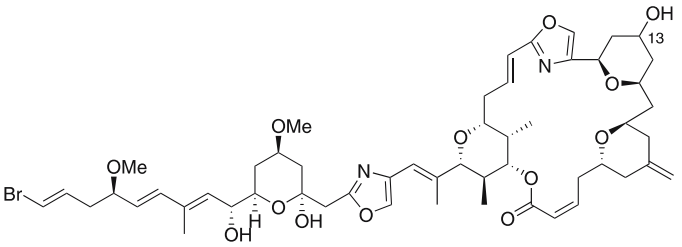
(+)-peloruside A
(-)-form: Brabander (2003)[131]
(+)-form: Taylor (2005)[132]



(+)-halichlorine
(+)-form: Danishefski (1999)[133]
dl-form (formal): Kibayashi (2004)[134]
dl-form: Heathcock (2004)[135]
formal: Zhao (2005)[136]



swinholide A
Paterson (1994)[137]
Nicolaou (1996)[138]



phorboxazole A (C13-α-OH)
phorboxazole B (C13-β-OH)
Forsyth (1998)[139]
Evans (2000)[140]
Smith (2001)[141]
Pattenden (2003)[142]
Williams (2003)[143]

Fig. 9 The marine macrolides that have been synthesized in recent years

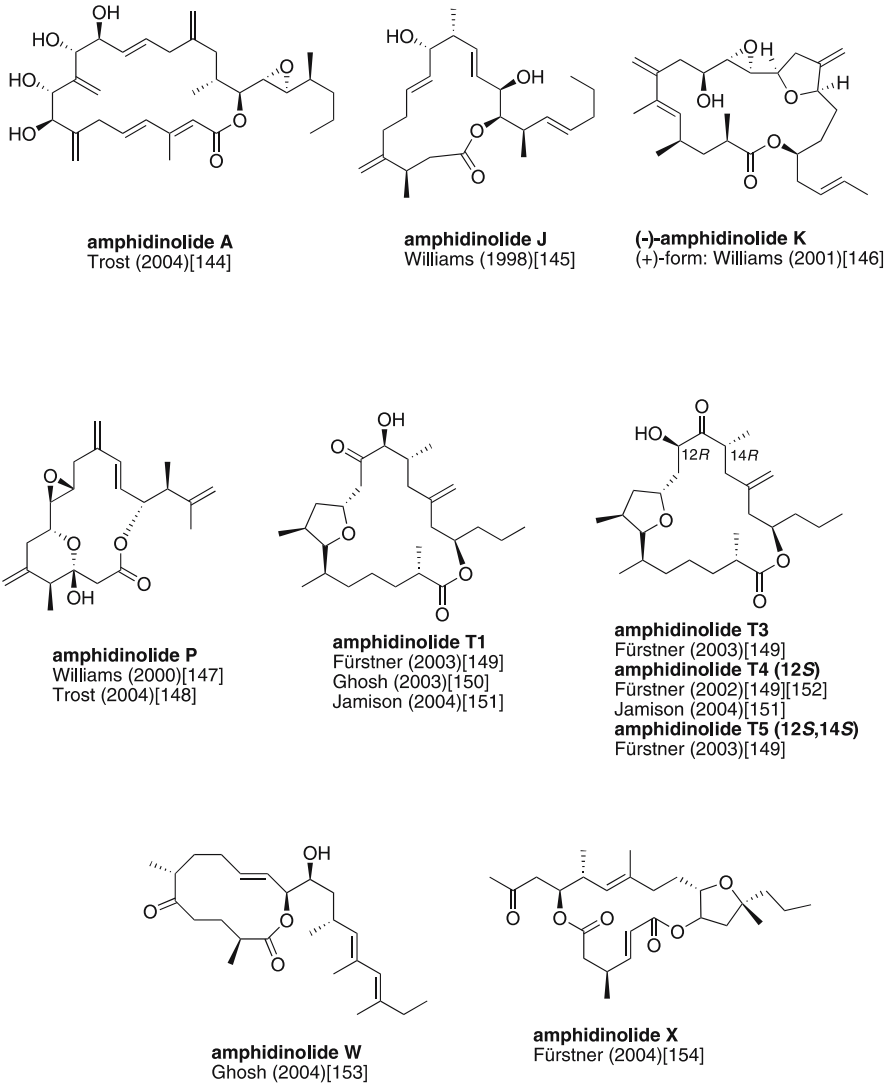


Fig. 10 The amphidinolides that have been synthesized in these years

Many marine natural products have significant bioactivities, that will be highly useful for biosciences. Sufficient amount of pure synthetic materials should be supplied via total synthesis in near future, in order to contribute to a broader area of science. It is a challenge of the next stage of synthetic organic chemistry.

References

1. Woodward RB (1957) Angew Chem 69:50
2. Nicolaou KC (1977) Tetrahedron 33:683
3. Back T (1977) Tetrahedron 33:3041
4. Paterson I, Mansuri MM (1985) Tetrahedron 41:3569
5. Nakata T (2002) Total synthesis of macrolides. In: Omura S (ed) Macrolide antibiotics. Academic Press, San Diego, chap 4
6. Norcross RD, Paterson I (1995) Chem Rev 95:2041
7. Yeung KS, Paterson I (2002) Angew Chem Int Ed 41:4632
8. Kobayashi J, Tsuda M (2004) Nat Prod Rep 21:77
9. Boivin TLB (1987) Tetrahedron 43:3309
10. Gonzalez MA, Pattenden G (2003) Angew Chem Int Ed 42:1255
11. Pattenden G, Gonzalez MA, Little PB, Millan DS, Plowright AT, Tornos JA, Ye T (2003) Org Biomol Chem 1:4173
12. Forsyth CJ, Ahmed F, Cink RD, Lee CS (1998) J Am Chem Soc 120:5597
13. Lewis DL, Cha JK, Kishi Y (1982) J Am Chem Soc 104:4976
14. For reviews, see: Adams DR, Bhatnagar SP (1977) Synthesis:661
15. Snider BB (1991) The Prins and carbonyl ene reactions. In: Trost BM (ed) Comprehensive Organic Synthesis, vol 2. Pergamon Press, Oxford, p 527
16. Mekhalfia A, Marko IE, Adams H (1991) Tetrahedron Lett 32:4783
17. Petasis NA, Lu SP (1996) Tetrahedron Lett 37:141
18. Smith AB III, Verhoest PR, Minbiole KP, Schelhaas M (2001) J Am Chem Soc 123:4834
19. Smith AB III, Minbiole KP, Verhoest PR, Schelhaas M (2001) J Am Chem Soc 123:10942
20. Uenishi J, Ohmi M (2005) Angew Chem Int Ed 44:2756
21. For a review, see: Bednarski MD, Lyssikatos JP (1991) Reactions of Activated Dienes with Aldehydes. In: Trost BM (ed) Comprehensive Organic Synthesis, vol 2. Pergamon Press, Oxford, p 661
22. Cink RD, Forsyth CJ (1997) J Org Chem 62:5672
23. Keck GE, Li XY, Krishnamurthy D (1995) J Org Chem 60:5998
24. Danishefsky (1981) Acc Chem Res 14:400
25. Dossetter AG, Jamison TF, Jacobsen EN (1999) Angew Chem Int Ed 38:2398
26. Paterson I, Savi CD, Tudge M (2001) Org Lett 3:3149
27. Wender PA, Hegde SG, Hubbard RD, Zhang L (2002) J Am Chem Soc 124:4956
28. Williams DR, Mi L, Mullins RJ, Stites RE (2002) 43:4841
29. For reviews, see: Trnka TM, Grubbs RH (2001) Acc Chem Res 34:18
30. Fürstner A (2000) Angew Chem Int Ed 39:3012; (c) Schuster M, Blechert S (1997) Angew Chem Int Ed Engl 36:2036
31. Mulzer J, Ohler E (2001) Angew Chem Int Ed 40:3842
32. Mulzer J, Martin HJ (2004) Chemical Record 3:258
33. Crimmins MT, Stanton MG, Allwein SP (2002) J Am Chem Soc 124:5958
34. Nelson SG, Cheung WS, Kassick AJ, Hilfiker MA (2002) J Am Chem Soc 124:13654
35. Horton PA, Koehn FE, Longley RE, McConnell OJ (1994) J Am Chem Soc 116:6015
36. Lee E, Song HY, Joo JM, Kang JW, Kim DS, Jung CK, Hong CY, Jeong SW, Jeon K (2002) Bioorg Med Chem Lett 12:3519
37. Wright AE, Chen Y, Winder PL, Pitts TP, Pomponi SA, Longley RE (2004) J Nat Prod 67:1351
38. Lee E, Song HY, Kang JW, Kim DS, Jung CK, Joo JM (2002) J Am Chem Soc 124:384

39. Song HY, Joo JM, Kang JW, Kim DS, Jung CK, Kwak HS, Park JH, Lee E, Hong CY, Jeong SW, Jeon K, Park JH (2003) J Org Chem 68:8080
40. Blakemore PR, Cole WJ, Kocienski PJ, Morley A (1998) Synlett 26
41. Chen KM, Gunderson KG, Hardtmann GE, Prasad K, Repic O, Shapiro MJ (1987) Chem Lett 1923
42. Takano S, Akiyama M, Sato S, Ogasawara K (1983) Chem Lett 1593
43. Grieco PA, Gilman S, Nishizawa MJ (1976) J Org Chem 41:1485
44. Still WC, Gennari C (1983) Tetrahedron Lett 24:4405
45. Fleming I, Patterson I, Pearce A (1981) J Chem Soc Perkin Trans 1 256
46. Kang SH, Kang SY, Kim CM, Choi H, Jun HS, Lee BM, Park CM, Jeong JW (2003) Angew Chem Int Ed 42:4779
47. Nicolaou KC, Patron AP, Ajito K, Richter PK, Khatuya H, Bertinato P, Miller RA, Tomaszawski MJ (1996) Chem Eur J 2:847
48. Brown HC, Jadhav PK (1983) J Am Chem Soc 105:2092
49. Brown HC, Bhat KS (1986) J Am Chem Soc 108:293
50. Baudin JB, Hareau G, Julia SA, Ruel O (1991) Tetrahedron Lett 32:1175
51. Aristoff PA (1981) J Org Chem 46:1954
52. Nicolaou KC, Seitz SP, Pavia MR (1982) J Am Chem Soc 104:2030
53. Norin-Fox ML, Lipton MA (1993) Tetrahedron Lett 34:7899
54. Yoshimura T, Yakushiji F, Kondo S, Wu X, Shindo M, Shishido K (2006) Org Lett 8:475
55. Takeuchi M, Taniguchi T, Ogasawara K (1999) Synthesis:341
56. Deba T, Yakushiji F, Shindo M, Shishido K (2003) Synlett:1500
57. Ando K (1997) J Org Chem 62:1934
58. Larock RC, Hightower TR, Kraus GA, Zheng D (1995) Tetrahedron Lett 36:2423
59. Shapiro RH (1976) Org React 23:405
60. Inanaga J, Hirata K, Saeki H, Katsuki T, Yamaguchi M (1979) Bull Chem Soc Jpn 52:1989
61. Tanaka J, Higa T (1996) Tetrahedron Lett 37:5535
62. Jefford CW, Bernardinelli G, Tanaka J, Higa T (1996) Tetrahedron Lett 37:159
63. Tanaka J, Higa T, Bernardinelli G, Jefford CW (1996) Chem Lett:255
64. Cutignano A, Bruno I, Bifulco G, Casapllo A, Debitus C, Gomez-Paloma L, Riccio R (2001) Eur J Org Chem:775
65. Smith III AB, Safonov IG, Corbett RM (2001) J Am Chem Soc 123:12426
66. Smith AB III, Safonov IG, Corbett (2002) J Am Chem Soc 124:11102
67. Oizumi M, Takahashi M, Ogasawara K (1997) Synlett:1111
68. Corey EJ, Katzenellenbogen J (1969) J Am Chem Soc 91:1851
69. Boechman RK Jr, Charette AB, Asberom T, Jonston BH (1987) J Am Chem Soc 109:7553
70. Lipshutz BH, Kozlowski JA, Parker DA, Nguyen SL, McCarthy KE (1985) J Organomet Chem 285:437
71. Hanessian S, Huynh HK (1999) Tetrahedron Lett 40:671
72. Hoye TR, Hu M (2003) J Am Chem Soc 125:9576
73. Caron M, Sharpless KB (1985) J Org Chem 50:1557
74. Aubele DL, Wan S, Floreancig PE (2005) Angew Chem Int Ed 44:3485
75. Evans DA, Hu E, Burch JD, Jaeschke G (2002) J Am Chem Soc 124:5654
76. Evans DA, Kozlowski MC, Murry JA, Burgey CS, Campos KR, Connell BT, Staples RJ (1999) J Am Chem Soc 121:669
77. Denmark SE, Wynn T, Beutner GL (2002) J Am Chem Soc 124:13405
78. Evans DA, Andrews GC (1974) Acc Chem Res 7:147

79. Ding F, Jennings MP (2005) Org Lett 7:2321
80. Mclaughlin MJ, Hsung RP (2001) J Org Chem 66:1049
81. Keck GE, Sanchez CC (2005) Org Lett 7:3053
82. Keck GE, Yu T (1999) Org Lett 1:289
83. Keck GE, Covel JA, Schiff T, Yu T (2002) Org Lett 4:1189
84. Paterson I, Yeung KS, Smaill JB (1993) Synlett:774
85. D'Ambrosio M, Guerriero A, Debitus C, Pietra F (1996) Helv Chim Acta 79:51
86. D'Ambrosio M, Tato M, Pocsfalvi G, Debitus C, Pietra F (1999) Helv Chim Acta 82:347
87. Hornberger KR, Hamblett CL, Leighton JL (2000) J Am Chem Soc 122:12894
88. Dreher SD, Hornberger KR, Sarraf ST, Leighton JL (2000) Org Lett 2:3197
89. Paterson I, Wallace D, Gibson KR (1997) Tetrahedron Lett 38:8911
90. Sarraf ST, Leighton JL (2000) Org Lett 2:3205
91. Semmelhack MF, Bodurow C (1984) J Am Chem Soc 106:1496
92. Yoshioka M, Kawakita T, Ohno M (1989) Tetrahedron Lett 30:1657
93. Srebnik M (1991) Tetrahedrin Lett 32:2449
94. Hikota M, Sakurai Y, Horita K, Yonemitsu O (1990) Tetrahedron Lett 31:6367
95. Phillips AJ, Uto Y, Wipf P, Reno MJ, Williams DR (2000) Org Lett 2:1165
96. Kopecky DJ, Rychnovsky SD (2001) J Am Chem Soc 123:8420
97. Noyori R, Ohkuma T, Kitamura M, Takaya H, Sayo N, Kumobayashi H, Akutagawa S (1987) J Am Chem Soc 109:5856
98. Myers AG, Yang BH, Chen H, McKinstry L, Kopecky DJ, Gleason JL (1997) J Am Chem Soc 119:6496
99. Narayanan BA, Bunnelle WH (1987) Tetrahedron Lett 28:6261
100. Fettes A, Carreira EM (2002) Angew Chem Int Ed 41:4098
101. Krüger J, Carreira EM (1998) J Am Chem Soc 120:837
102. Muller S, Liepold B, Roth GJ, Bestmann HJ (1996) Synlett:521
103. Frantz DE, Fässler R, Carreira EM (2000) J Am Chem Soc 122:1806
104. Paterson I, Gibson KR, Oballa RM (1996) Tetrahydron Lett 37:8585
105. Evans DA, Coleman PJ, Cote B (1997) J Org Chem 62:788
106. Evans DA, Chapman KT, Carreira EM (1988) J Am Chem Soc 110:3560
107. Studer A, Amrein S (2000) Angew Chem Int Ed 39:3080
108. Wipf P, Reeves JT (2002) Chem Commun:2066
109. Wipf P, Graham TH (2001) J Org Chem 66:3242
110. Wipf P, Ribe S (1998) J Org Chem 63:6454
111. Wang Y, Janjic J, Kozmin SA (2002) J Am Chem Soc 124:13670
112. Wang Y, Janjic J, Kozmin SA (2005) Pure Appl Chem 77:1161
113. Kozmin SA (2001) Org Lett 3:755
114. Evans DA, Hoveyda AH (1990) J Am Chem Soc 112:6447
115. Tamao K, Nakajima T, Sumiya R, Arai H, Higuchi N, Ito Y (1986) J Am Chem Soc 108:6090
116. Connell R, Scavo F, Helquist P, Akermark B (1986) Tetrahedron Lett 27:5559
117. Paterson I, Tudge M (2003) Angew Chem Int Ed 42:343
118. Langille NF, Dakin LA, Panek JS (2002) Org Lett 4:2485
119. Williams DR, Plummer SV, Patnaik S (2003) Angew Chem Int Ed 42:3934
120. Corey EJ, Yu CM, Kim SS (1989) J Am Chem Soc 111:5495
121. Crimmins MT, Siliphaivanh P (2003) Org Lett 5:4641
122. Tsuda T, Hayashi T, Satomi H, Kawamoto T, Saegusa T (1986) J Org Chem 51:537
123. Kotsuki H (1992) Synlett:97
124. Su Q, Panek JS (2005) Angew Chem Int Ed 44:1223

125. Dakin LA, Langille NF, Panek JS (2002) J Org Chem 67:6812
126. Deschlorocallipeltoside: Trost BM (2001) J Am Chem Soc 123:9449
127. Total synthesis: Trost BM, Dirat O, Gunzner JL (2002) Angew Chem Int Ed 41:841
128. Trost BM, Gunzner JL, Dirat O, Rhee YH (2002) J Am Chem Soc 124:10396
129. Aglycon: Paterson I, Davies RDM, Marquez R (2001) Angew Chem Int Ed 40:603
130. Total synthesis: Paterson I, Davies RDM, Heimann AC, Marquez R, Meyer A (2003) Org Lett 5:4477
131. Huang H, Panek JS (2004) Org Lett 6:4383
132. Ghosh AK, Wang Y (2000) J Am Chem Soc 122:11027
133. Gallagher BM Jr, Fang FG, Johannes CW, Pesant M, Tremblay MR, Zhao H, Akasaka K, LiX, Liu J, Littlefield BA (2004) Tetrahedron Lett 14:575
134. Paterson I, Britton R, Delgado O, Meyer A, Poullennec KG (2004) Tetrahedron Lett 43:4629
135. Shin Y, Fournier JH, Fukui Y, Bruckner AM, Curran DP (2004) Tetrahedron Lett 43:4634
136. Paterson I, Watson C, Yeung KS, Wallace PA, Ward RA (1997) J Org Chem 62:452
137. Nakamura R, Tanino K, Miyashita M (2003) Org Lett 5:3579,3583
138. Fujiwara K, Murai A, Yotsu-Yamashita M, Yasumoto T (1998) J Am Chem Soc 120:10770
139. Paquette LA, Barriault L, Pissarnitski D, Johnston JN (2000) J Am Chem Soc 122:619
140. White JD, Blakemore PR, Browder CC, Hong J, Lincoln M, Nagornyy PA, Robarge LA, Wardrop DJ (2001) J Am Chem Soc 123:8593
141. White JD, Blakemore PR, Browder CC, Hong J, Lincoln M, Nagornyy PA, Robarge LA, Wardrop DJ (2005) J Org Chem 70:5449
142. Smith III AB, Adams CM, Barbosa SAL, Degnan AP (2004) Proc Natl Acad Sci USA 101:12042
143. Julian LD, Newcom JS, Roush WR (2005) J Am Chem Soc 127:6186
144. Brittain DE, Griffiths-Jones CM, Linder MR, Smith MD, McCusker C, Barlow JS, Akiyama R, Yasuda K, Ley SV (2005) Angew Chem Int Ed 44:2732
145. Liao X, Wu Y, De Brabander JK (2003) Angew Chem Int Ed 42:1648
146. Jin M, Taylor RE (2005) Org Lett 7:1303
147. Trauner D, Schwarz JB, Danishefsky SJ (1999) Tetrahedron Lett 38:3542
148. Matsumura Y, Aoyagi S, Kibayashi C (2004) Org Lett 6:965
149. Christie HS, Heathcock CH (2004) Proc Natl Acad Sci USA 101:12079
150. Zhang HL, Zhao G, Ding Y, Wu B (2005) J Org Chem 70:4954
151. Paterson I, Yeung KS, Ward RA, Cumming JG, Smith JD (1994) J Am Chem Soc 116:9391
152. Nicolaou KC, Ajito K, Patron AP, Khatuya PH, Richter PK, Bertinato P (1996) J Am Chem Soc 118:3059
153. Forsyth CJ, Ahmed F, Cink RD, Lee CS (1998) J Am Chem Soc 120:5597
154. Evans DA, Cee VJ, Smith TE, Fitch DM, Cho PS (2000) Angew Chem Int Ed 39:2533
155. Evans DA, Fitch DM, Smith TE, Cee VJ (2000) J Am Chem Soc 122:10033
156. Smith AB III, Verhoest PR, Minbiole KP, Schelhaas M (2001) J Am Chem Soc 123:4834
157. Smith AB III, Minbiole KP, Verhoest PR, Schelhaas M (2001) J Am Chem Soc 123:10942
158. Gonzalez MA, Pattenden G (2003) Angew Chem Int Ed 42:1255
159. Pattenden G, Gonzalez MA, Little PB, Millan DS, Plowright AT, Tornos JA, Ye T (2003) Org Biomol Chem 1:4173

160. Williams DR, Kiryanov AA, Emde U, Clark MP, Berliner MA, Reeves JT (2003) Angew Chem Int Ed 42:1258
161. Trost BM, Harrington PE (2004) J Am Chem Soc 126:5028; Trost BM, Harrington PE, Chisholm JD, Wrobleski ST (2005) J Am Chem Soc 127:13598
162. Trost BM, Wrobleski ST, Chisholm JD, Harrington PE, Jung M (2005) J Am Chem Soc 127:13589
163. Williams DR, Kissel WS (1998) J Am Chem Soc 120:11198
164. Williams DR, Meyer KG (2001) J Am Chem Soc 123:765
165. Williams DR, Myers BJ, Mi L (2000) Org Lett 2:945
166. Trost BM, Papillon PN (2004) J Am Chem Soc 126:13618
167. Aissa C, Riveiros R, Ragot J, Fürstner A (2003) J Am Chem Soc 125:15512
168. Ghosh AK, Liu C (2003) J Am Chem Soc 125:2374
169. Colby EA, O'Brien KC, Jamison TF (2004) J Am Chem Soc 126:998
170. Colby EA, O'Brien KC, Jamison TF (2005) J Am Chem Soc 127:4297
171. Fürstner A, Aissa C, Riveiros R, Ragot J (2002) Angew Chem Int Ed 41:4763
172. Ghosh AK, Gong G (2004) J Am Chem Soc 126:3704
173. Lepage O, Kattning E, Fürstner A (2004) J Am Chem Soc 126:15970

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Strategies for the Synthesis of Manzamine Alkaloids

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Abstract Recent advances in strategies for the synthesis of manzamine-related alkaloids are summarized and discussed. We particularly focus on strategies for the formation of a complex central ring core, especially substituted hydroquinoline, and the formation of medium and large azacycles.

Keywords Manzamine · Marine alkaloid · Natural product · Total synthesis · Strategy

Abbreviations

Bs	Benzenesulfonyl
Cy	Cyclohexyl
DA	Diels–Alder
DCM	Dichloromethane
DHP	Dihydropyran
DMDO	Dimethyldioxirane
DMP	Dess–Martin periodinane
DPPA	Diphenoxyphosphinyl azide
DPPB	1,4-(Bisdiphenylphosphino)butane
DPPF	1,1′-Bis(diphenylphosphino)ferrocene
DPS	*t*-Butyldiphenylsilyl
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
HOBt	1-Hydroxybenzotriazole
HWE	Horner–Wadsworth–Emmons
IBX	*o*-Iodoxybenzoic acid
Imid	Imidazole
IPA	Isopropyl alcohol
LAH	Lithium aluminium hydride
MPM	(*p*-Methoxyphenyl)methyl
NaHMDS	Sodium hexamethyldisilazane
Ns	*p*-Nitrobenzenesulfonyl
Ox	Oxidation
PMP	*p*-Methoxyphenyl
PTSA	*p*-Toluenesulfonic acid
RCM	Ring-closing metathesis
Re	Reduction
SES	(2-Trimethylsilylethyl)sulfonyl
TASF	Tris(diethylamino)sulfonium difluorotrimethylsilicate
TBS	*t*-Butyldimethylsilyl
TES	Triethylsilyl
TPAP	Tetrapropylammonium perruthenate
TRIS	Tris(hydroxymethyl)aminomethane

1 Introduction

Ever since the first manzamine alkaloid, manzamine A (**1**), was isolated and its unique structure was determined by Higa and coworkers in 1986 [1], more than 70 compounds have been isolated and these constitute a large group of alkaloids [2–4] (Fig. 1). Due to their unique and diverse structures, manzamine alkaloids have been an attractive target for biogenetic [5], pharmacological [6], and synthetic studies [2–4, 7], and more than 180 papers have been published. Among these numerous studies on manzamine alkaloids, in this chapter we will discuss recent progress in synthetic studies with a focus on strategies for ring formation.

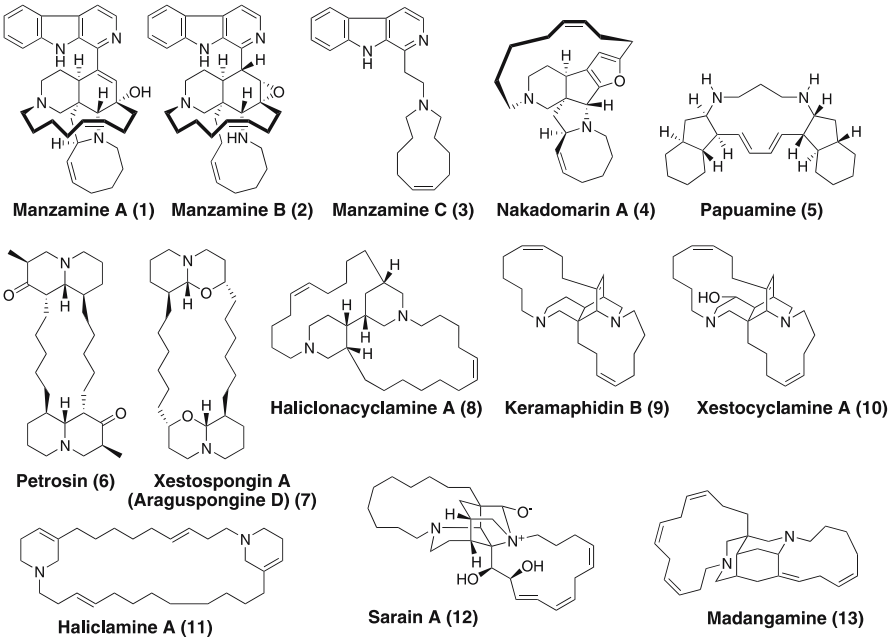


Fig. 1 Representative manzamine alkaloids

2 General Aspects

The structure of manzamine and related alkaloids is characterized by a highly substituted central skeleton, which includes nitrogen-containing heterocycles and fuses to two medium or large rings with (*Z*)- and/or (*E*)-olefins. In considering these structural features, the synthesis of manzamine and related compounds can be divided into two parts (Fig. 2): (1) the preparation of substituted central cores, and (2) the construction of medium and large rings.

Before 1995, these medium and large rings were mainly constructed using the Yamaguchi lactamization methodology [8, 9]. However, with the development of stable metal carbene catalysts by Grubbs in the 1990s, there has been a shift toward the use of ring-closing metathesis (RCM) [10–13]. Although poor *E*/*Z* selectivity is sometimes a serious problem, RCM is a powerful method for preparing large rings because it is easy to synthesize a diene structure (**14**) as a RCM precursor. However, since the construction of a medium or large ring generally requires high-dilution conditions, these transformations occur in a late stage of total synthesis.

RCM of tetraenes, **16** and **20**, to prepare two unsaturated rings by a single operation at the same time is an interesting issue (Scheme 1). However, this approach was unsuccessful in the syntheses of a key intermediate of manza-

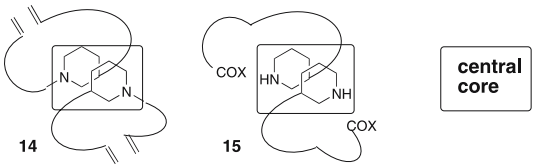


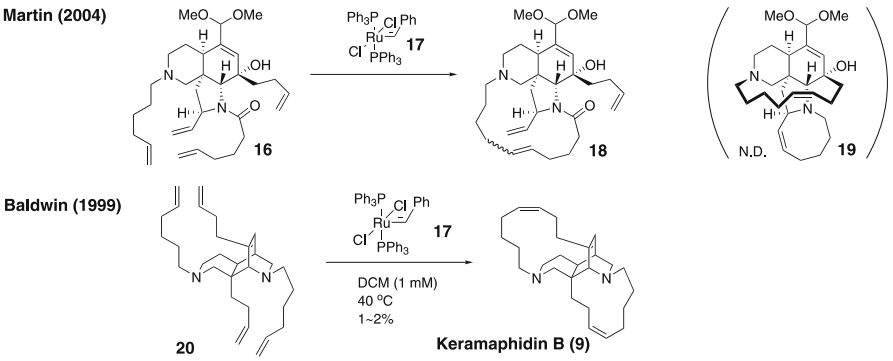
Fig. 2 Basic strategies for the synthesis of manzamine; RCM vs macro-lactamization

mine A (**19**) [14] and keramaphidin B (**9**) [15] as a result of the unsuitable reactivity of alkenes and/or the wrong orientation of olefinic side chains. Stepwise formation of these medium and large rings after the construction of a highly functionalized central core should be an efficient methodology.

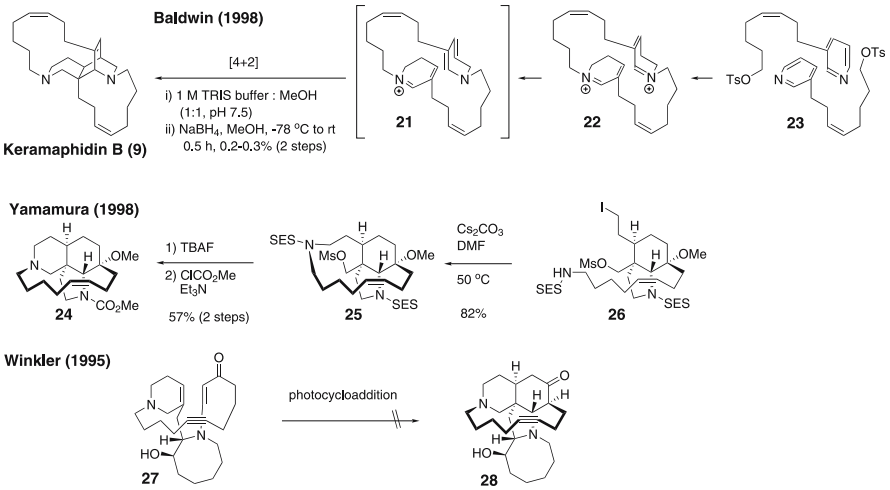
Synthesis of the central core after the formation of a large ring might be an entropically favorable process. Both Baldwin [16] and Yamamura [17] showed successful transformations by this methodology (Scheme 2). However, in an early synthetic study on manzamine A by Winkler [18, 19], the photocyclization of **27** to **28** was unsuccessful, although they completed the total synthesis using a different substrate, which will be discussed later in Scheme 14.

The masking and unmasking of tertiary amines are also critical issues in the total synthesis. Recently, Overman reported a synthesis of the western part of sarain A (**12**) (Scheme 3) [20]. In their synthesis, protonation of the pyrrolidine nitrogen in **29** promoted the rearrangement via aziridinium cation under mildly acidic conditions. Structural reorganization of protonated tetracyclic diol (**29**) resulted in the formation of tetracyclic amino-ether (**30**). Amide-lactam (**31**) prepared by Cha might be a suitable intermediate for preventing such an undesirable transformation [21].

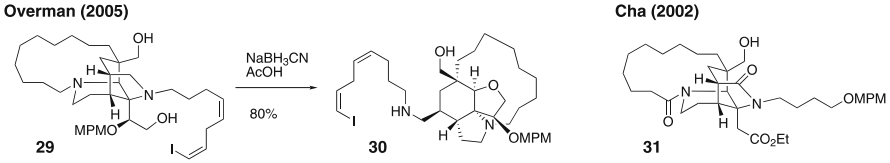
Efficient construction of a highly condensed central core structure while controlling the reactivity of functional groups is another key point for the synthetic strategy. Since the 1990s, [4 + 2] cyclization such as the Diels–Alder reaction [22, 23] has been used as a key step to prepare a *cis*-



Scheme 1 Double RCM in manzamine synthesis



Scheme 2 Synthesis of the central core after the formation of macrocycles



Scheme 3 Rearrangement of the sarain A core under mild acidic conditions

hydroisoquinoline skeleton. After 2000, [3 + 2] cyclization [24, 25] has been recognized as an efficient method for synthesizing a pyrrolidine-containing unit.

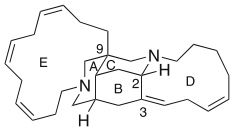
Due to these difficulties, only seven manzamine alkaloids, including manzamine A (**1**) (containing ircinol A, ircinal A, and manzamine D, two reports) [18, 19, 26, 27], keramaphidin B (**9**) (two reports) [15, 16], papuamine (**5**) (two reports) [28, 29], nakadomarin A (**4**) (two reports from the same group) [30, 31], and less complex manzamine C (**3**) [32–36], and haliclamine A (**11**) (two reports) [37–40], have been synthesized. In this review, we summarize the strategies for the synthesis of each manzamine alkaloid, especially those with more than three condensed ring skeletons, from recent papers.

Basically, the synthetic schemes are arranged from right to left to clarify the final product. For comparison, synthetic schemes that describe a common structure of two alkaloids will be presented in each section. When the synthetic studies cover a racemic target or each enantiomer, we show the synthetic schemes using a single enantiomeric form for comparison.

3
Strategies for the Synthesis of Representative Alkaloids

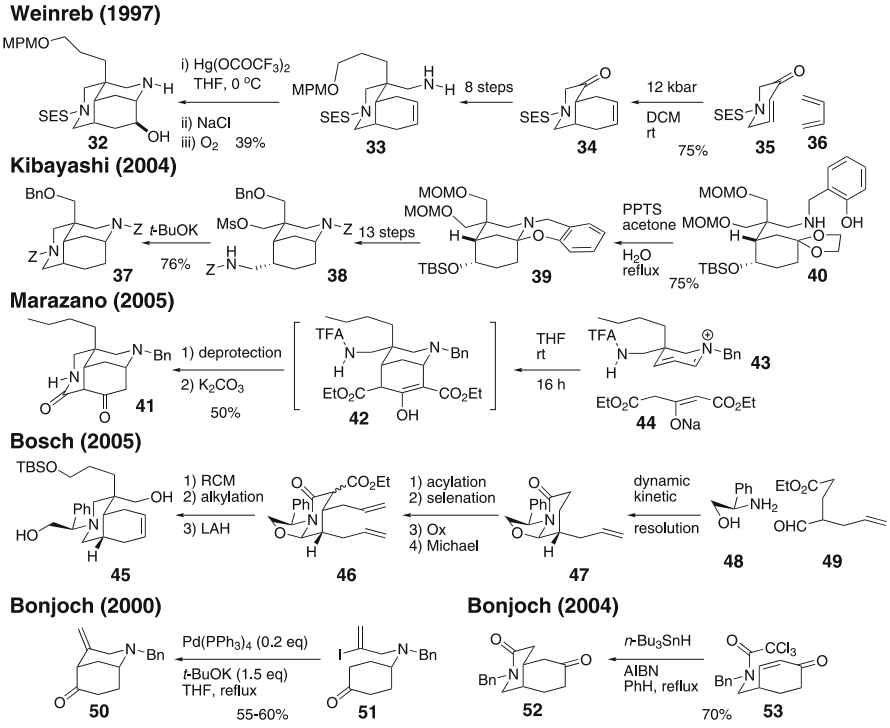
3.1
Madangamine A

Madangamine A (**13**) (Fig. 3), which was isolated from *Xestospongia ingens* by Andersen et al. in 1994, has a 2,6-diazatricyclo[6.2.2.0^{4,9}]dodecane skeleton [41, 42]. Weinreb prepared this skeleton from a *cis*-fused hydroisoquinoline derivative (**33**) by amino-merculation [43]. Diels–Alder reaction [43],



Madangamine A (13)

Fig. 3 Madangamine A



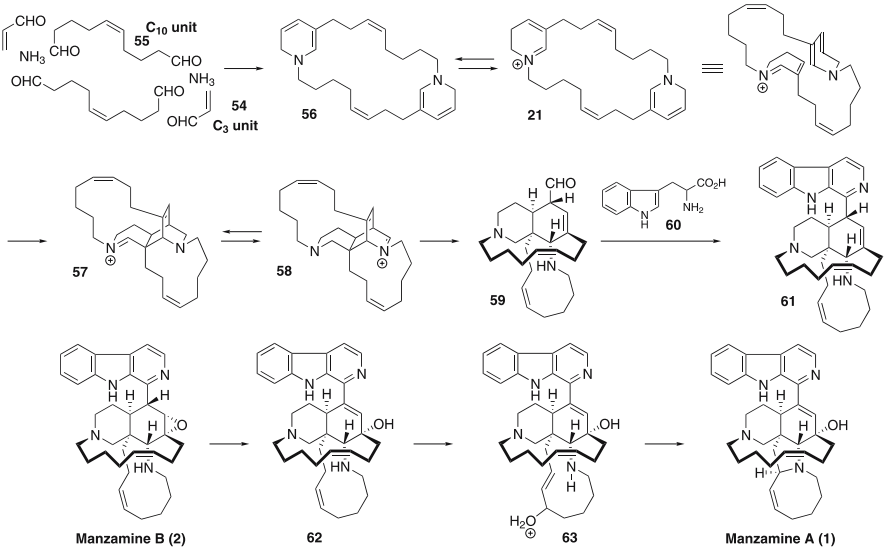
Scheme 4 Strategies for the synthesis of madangamine A

radical cyclization [44], and RCM [45] were used to synthesize the *cis*-hydroisoquinoline derivatives (**34**, **52** and **45**) (Scheme 4). An optically active intermediate (45) was prepared by Bosch [45] using dynamic kinetic resolution.

On the other hand, Kibayashi [46] and Marazano [47] first prepared the diazabicyclo[3.3.1]nonane system and converted it to a 2,6-diazatricyclo[6.2.2.$0^{4,9}$]dodecane skeleton (**37** and **41**) by intramolecular alkylation or acylation. Bonjoch [48] also reported a synthesis of diazabicyclo[3.3.1]nonane (**50**) by a palladium-mediated intramolecular coupling reaction. It is still difficult to construct polyunsaturated 11- and 15-membered rings.

3.2
Keramaphidin B and Xestrocyclamine A

Baldwin and Whitehead proposed an amazing biogenetic pathway for manzamine A and related alkaloids which is based on the intramolecular Diels–Alder reaction of dihydropyridinium cation **21** (Scheme 5) [49]. This proposed pathway stimulated many scientists to focus on the isolation and synthesis of manzamine-related alkaloids. In 1994, Kobayashi [50–52] reported the isolation and structure determination of keramaphidin B (**9**) (Fig. 4) from *Anphimedon* sp., which had exactly the same skeleton as was proposed based on a biogenetic pathway via the Diels–Alder reaction [49].



Scheme 5 Biosynthesis of manzamine A proposed by Baldwin and Whitehead

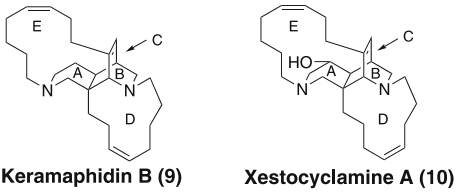
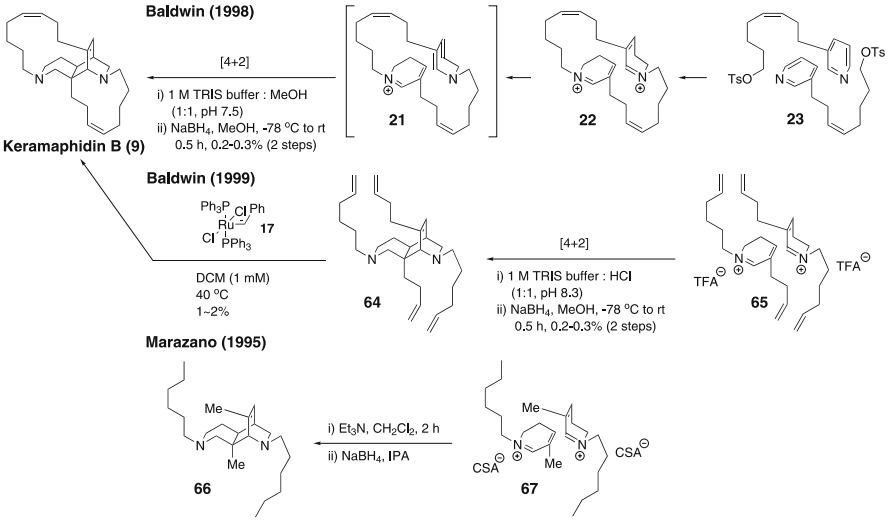


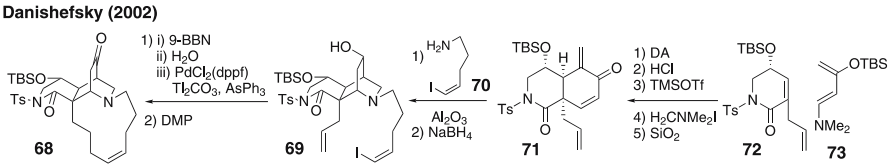
Fig. 4 Keramaphidin B and xestocyclamine A

This central core has been synthesized by Baldwin [16] and Marazano [53] using the inter- or intramolecular Diels–Alder reaction of dihydropyridinium cations, **21** and **67** (Scheme 6). Baldwin also reported a total synthesis of **9** using double RCM of **64** [15].

Xestocyclamine A (Fig. 4) [54, 55] has the same skeleton as keramaphidin B and the position of a (*Z*)-double bond is different from that in related alkaloids. A synthetic study of xestocyclamine has been reported by Danishefsky (Scheme 7) [56]. The Diels–Alder reaction of activated dihydropyridinone



Scheme 6 Strategies for the synthesis of keramaphidin B



Scheme 7 Strategies for the synthesis of xestocyclamine A

(**72**) and siloxyaminodiene (**73**) afforded a *cis*-fused isoquinolone derivative (**71**). A double-Michael reaction using iodoalkenylamine (**70**) gave the desired central core (**69**). The palladium-catalyzed *B*-alkyl Suzuki coupling of (*Z*)-iodoalkene (**69**) to give (*Z*)-diazaundecene (**68**) is also interesting.

3.3 Sarain A

Sarain A (**12**) (Fig. 5) was isolated by Cimino et al. from the sponge *Reniera sarai* in 1989 [57] and has a unique 2,8-diazatricyclo[5.4.0.0^{4,11}]undecane skeleton in which the tertiary amine of a pyrrolidine ring (ring B) interacts with an adjacent aldehyde.

A saturated macrocyclic ring of sarain was constructed by RCM followed by hydrogenation (Scheme 8). Substituted pyrrolidone (**80**) was first prepared stereoselectively by Overman [58, 59]. Intramolecular amidation of **80** followed by iminium-cation cyclization of **77** gave the central tricyclic core (**76**), which was converted to tetracyclic intermediate (**74**) by RCM. On the other hand, Cha [60] started his synthesis from an azabicyclo[3.3.1]nonane ring

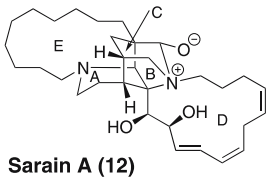
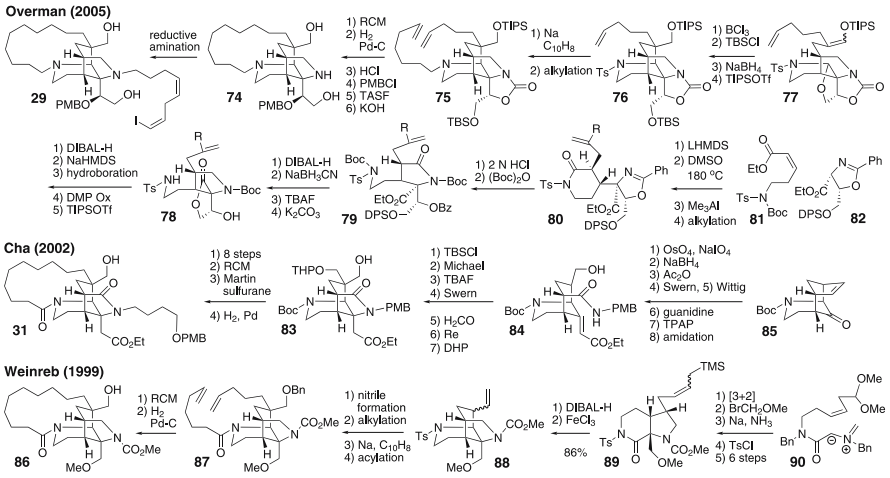
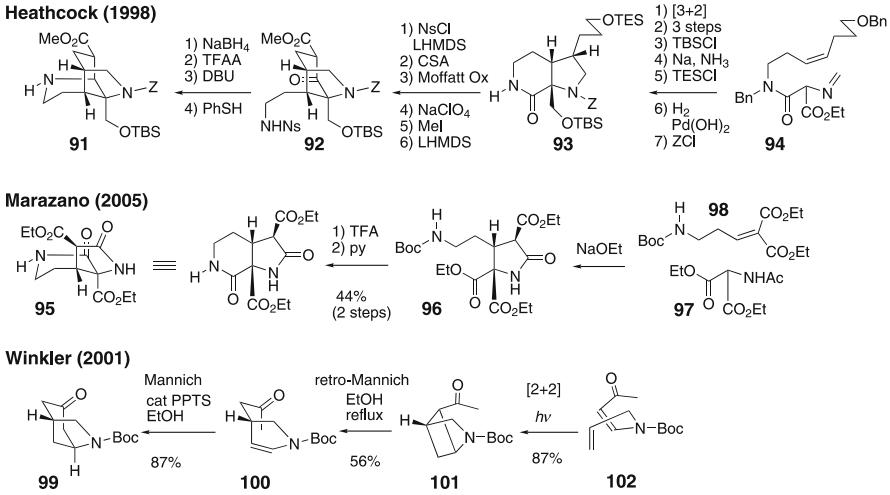


Fig. 5 Sarain A



Scheme 8 Strategies for the synthesis of sarain A (part 1)



Scheme 9 Strategies for the synthesis of sarain A (part 2)

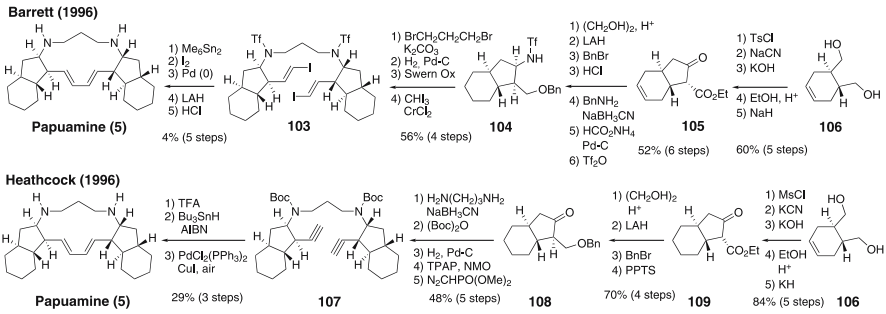
system (**84**). The pyrrolidine ring B was constructed by an intramolecular Michael reaction. Weinreb and coworkers [61] also prepared the same type of bicyclic system (**89**) via a stereospecific [3 + 2] azomethine ylide/olefin cycloaddition, and this was converted to 2,8-diazatricyclo[5.4.0.0^{4,11}]undecane (**88**) by an allylsilane/*N*-sulfonyliminium ion cyclization catalyzed by $FeCl_3$.

Heathcock [62] synthesized the central core (**91**) of sarains by intramolecular [3+2] azomethine ylide cyclization followed by Dieckmann-type cyclization of sulfonyllactam to prepare ring C, and an intramolecular Michael reaction to prepare ring A (Scheme 9). Methods for preparing the partial structures of the core (**95** and **99**) were also reported by Marazano [63] and Winkler [64].

3.4 Papuamine and Haliclonadiamine

The C_2-symmetric, pentacyclic alkaloid papuamine (**5**) (Scheme 10) was isolated from *Haliclona* sp., a thin red sponge that overgrows and kills coral reefs, which was collected by Scheuer and coworkers off the coast of Papua, New Guinea, in 1988 [65]. Faulkner and coworkers isolated haliclonadiamine, a diastereoisomer of papuamine, as the major metabolite, along with a minor amount of papuamine, from *Haliclona* sp. obtained from Palau [66].

Papuamine (**5**) contains a central 13-membered ring and has a C_2-symmetry axis that passes through the central methylene of the diaminopropane bridge and bisects the (*E*,*E*)-diene. Barrett and Heathcock completed an asymmetric synthesis of papuamine (Scheme 10) [28, 29]. Both groups started their synthesis from C_2-symmetric diol (**106**) and con-



Scheme 10 Strategies for the synthesis of papuamine

verted it to a bicyclic[4.3.0]nonane system (**105** and **109**). This carbocyclic unit was connected by a diamino-tether. The 13-membered ring was constructed by palladium-catalyzed cross-coupling reactions with the formation of a (*E*,*E*)-diene system.

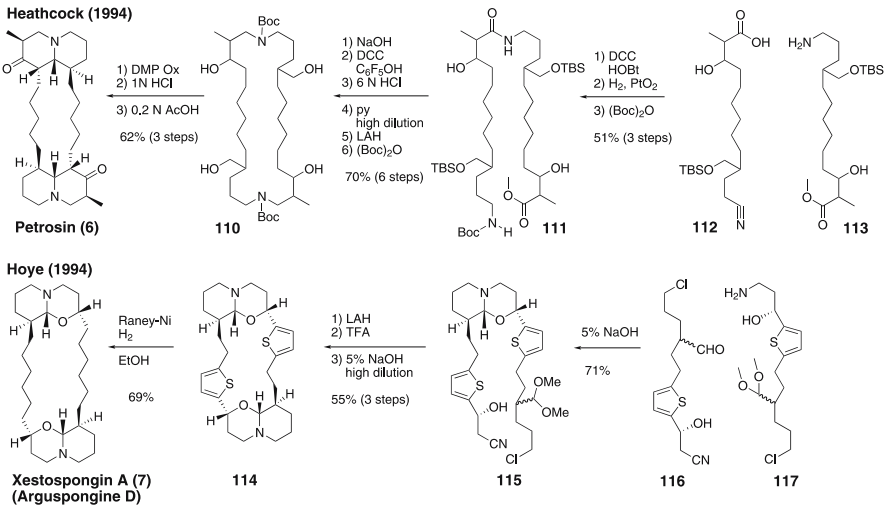
3.5
Petrosins and Xestospongin A (Araguspongine D)

Petrosin alkaloids (Scheme 11) were isolated from the sponge *Petrosia seriata*, which was collected near Papua, New Guinea, in the 1980s [67–69]. In the racemic synthesis of petrosin, Heathcock et al. synthesized dimeric diazamacrocycle (**110**) by lactamization of **111** [70]. The oxidation of two hydroxyl groups of **110** with Dess-Martin periodinane and the removal of Boc groups led to double Mannich cyclization to give petrosins as a mixture of diastereoisomers. The desired petrosin (**6**) was isolated from the mixture in 23% yield by crystallization.

Xestospongin A (Araguspongine D) (**7**) (Scheme 11) was isolated from the marine sponge *Xestospongia exigua* in 1984 [71–74]. Its structure contains a pair of oxaquinolizidine moieties connected to each other by two 6-carbon tethers that form a 20-membered ring. The first synthesis was accomplished by Hoye et al. [75, 76] (Scheme 11). Suitably functionalized chiral half units (**116**, **117**) were cyclized to give an oxaquinolizidine (**115**), in which the stereochemistry was controlled thermodynamically (2.3 : 1). The same cyclization followed by Raney Ni reduction gave (+)-xestospongin A [(+)-araguspongine D] (**7**). In this synthesis, two thiophene rings were used as a four-carbon unit and also as a rigidifier for macrocyclization.

3.6
Manzamine A

Manzamine A (**1**) (Fig. 6) was isolated by Higa and coworkers from the Okinawan marine sponge *Haliclona* sp. in 1986 [1]. Its unique structure consists



Scheme 11 Strategies for the synthesis of petrosins and xestospongin A (araguspongine D)

of a β-carboline attached to a novel diazapentacyclic core (6/6/5/8/13). Its novel biosynthetic pathway has been proposed by Baldwin and Whitehead via an intramolecular Diels–Alder reaction as described above (Scheme 5) [49].

Extensive effort has been applied to realize the total synthesis of manzamine A (**1**) because of its unprecedented structure and its strong biological activity. In addition to the synthesis of unsaturated medium and large heterocycles, a highly functionalized and *cis*-fused pyrrolo-hydroisoquinoline ring, the central core of manzamine A, was recognized to be a synthetic challenge. Until now, only two groups have completed the total synthesis.

The first total synthesis of manzamine A was reported by Winkler and Axten in 1998 [18, 19]. In their synthesis, a unique [2 + 2] photocycloaddition followed by retro Mannich/Mannich rearrangement furnished a 6/6/5/8 ring system in a highly stereospecific manner. The 13-membered ring was prepared by standard cyclization.

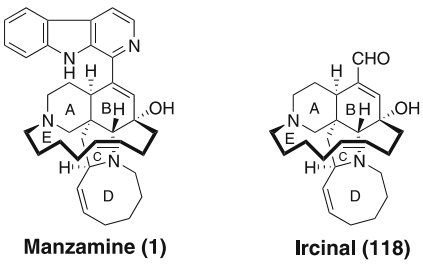


Fig. 6 Manzamine A and ircinal A

In 1999, Martin et al. reported a second total synthesis of manzamine A [26, 27]. The stereoselective synthesis of a fully functionalized central core by an intramolecular Diels–Alder reaction is a highlight of their synthesis. Use of the RCM methodology for the synthesis of eight- and 13-membered rings with (*Z*)-olefin was established by Pandit [77–79] and Martin.

Methods for the synthesis of central hydroisoquinolines or pyrrolohydroisoquinolines of manzamine A can be classified into 11 types of reactions: (1) intermolecular Diels–Alder reaction, (2) intramolecular Diels–Alder reaction, (3) photochemical reaction, (4) radical reaction, (5) ionic cyclization, (6) intramolecular Michael reaction, (7) intramolecular Mannich reaction, (8) intramolecular [3 + 2] cycloaddition, (9) intermolecular [3 + 2] cycloaddition, (10) Pauson-Khand reaction, and (11) eneyne metathesis.

3.6.1 Intermolecular Diels–Alder Reaction

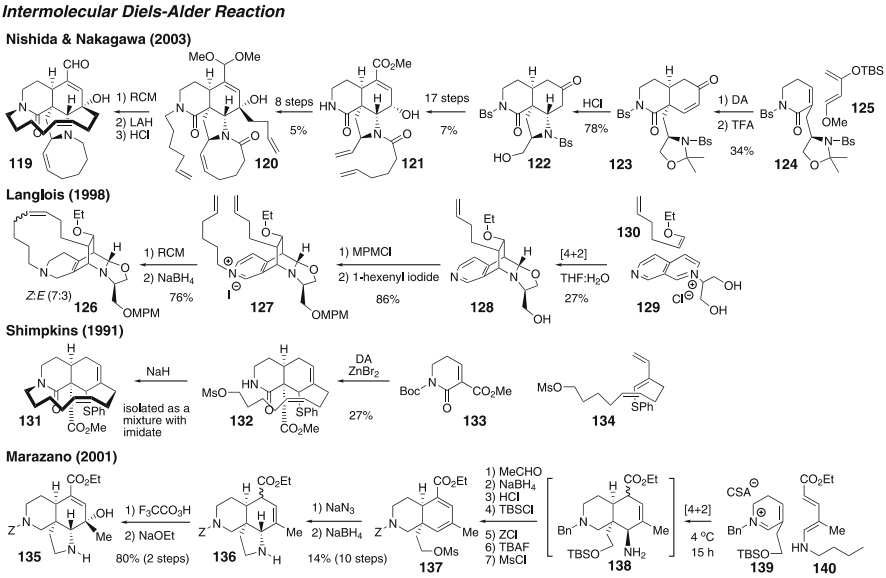
Nishida and Nakagawa [80–82], Langlois [83, 84], Simpkins [85] and Marazano [86, 87] have used the intermolecular Diels–Alder reaction to synthesize the central core of manzamine A (Scheme 12). We have also demonstrated that an efficient Diels–Alder reaction using Danishefsky-type siloxydiene (**125**) followed by acid treatment resulted in a Michael reaction to give the chiral ABC ring intermediate (**122**) of manzamine A (Scheme 12). This intermediate was converted to 36-oxo-ircinal A (**119**) using sequential RCM to prepare the D- and E-rings.

3.6.2 Intramolecular Diels–Alder Reaction

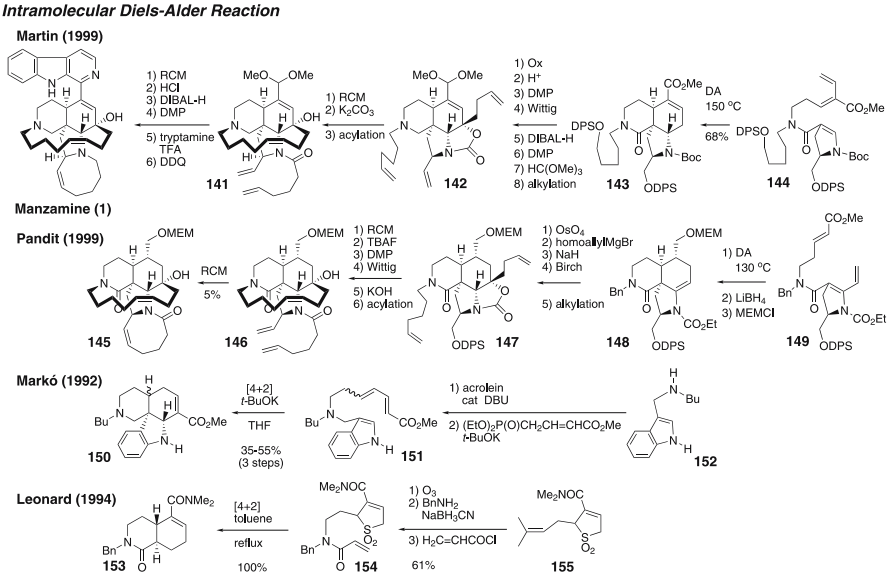
Martin [26, 27], Pandit [77–79], Markó [88, 89], and Leonard [90] have described intramolecular Diels–Alder reactions for constructing the central 6/6 or 6/6/5 core of manzamine A.

Particularly, Martin and coworkers have demonstrated a sequential Stille/intramolecular Diels–Alder reaction, which was a facile entry to the chiral ABC tricyclic core of manzamine A (Scheme 13). This synthesis was highly efficient and gave the desired product in 46% overall yield in only five steps starting from commercially available pyroglutaminol. The core (**143**) was then fully functionalized by an allylic oxidation/alkylation procedure. Furthermore, RCM reactions were used to synthesize 13- and eight-membered rings (Scheme 13). Finally, they completed the total synthesis of manzamine A (**1**) using Kobayashi's strategy to introduce a β-carboline unit [91].

Pandit and coworkers also prepared a functionalized tricyclic core (**148**) by a different version of the intramolecular Diels–Alder reaction (Scheme 13). For further introduction of an alkenyl group, the trisubstituted alkene in **148** was subjected to osmium dihydroxylation followed by dehydration under



Scheme 12 Strategies for the synthesis of manzamine A (part 1)



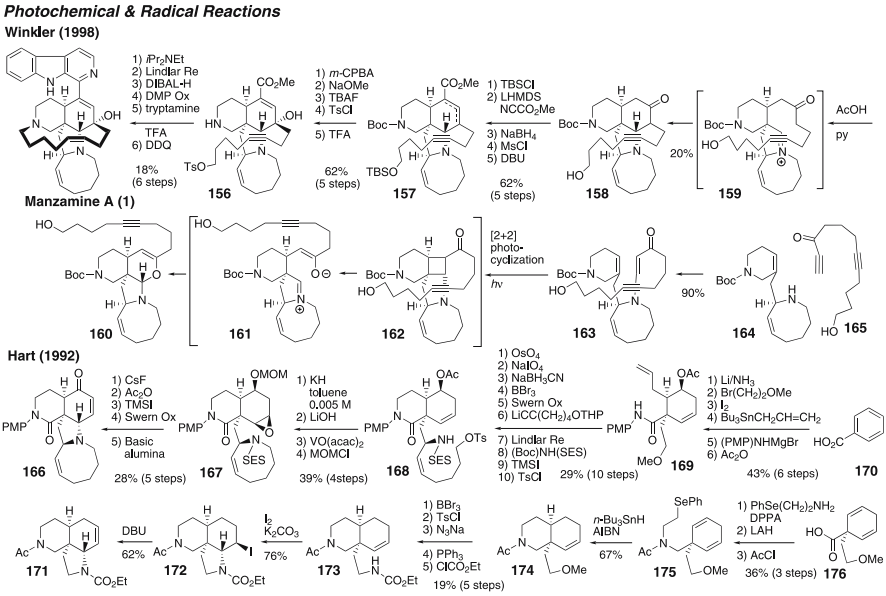
Scheme 13 Strategies for the synthesis of manzamine A (part 2)

acidic conditions. The resulting carbonyl group was alkylated by Grignard reagent. The intermediate was then converted to a diene system (**147**) and stepwise RCM gave a pentacyclic intermediate (**145**).

3.6.3
Photochemical and Radical Reaction

Winkler and Axten [18, 19] reported the first total synthesis of manzamine A in which an intramolecular [2 + 2] photoaddition/fragmentation/Mannich closure sequence starting from a vinylogous amide (**163**) (Scheme 14). A chiral (dehydropiperidinyl)methylazocine (**164**), prepared by asymmetric alkylation of glycine derivative with bromomethyldehydropiperidine using Myers' method [92] followed by azocine formation, was added to ethynyl ketone (**165**) with an alkynyl side chain to synthesize a 13-membered ring. Photoaddition and retro-Mannich fragmentation of β-hexahydroazocino-α,β-unsaturated ketone (**163**) led to an *O*-closure intermediate (**160**), which was isomerized to the desired ABCD tetracyclic intermediate (**158**). A 13-membered ring was then constructed by intramolecular alkylation of the acetylenic side chain under high-dilution conditions with Hünig's base. The triple bond was reduced to (*Z*)-olefin with Lindlar catalyst to give an ABCDE ring system.

Hart and coworkers used 6-*exo* radical cyclization of **175** in the synthesis of a hydroisoquinoline skeleton (**174**) [93, 94] (Scheme 14). However, they used reductive amination in the synthesis of an advanced AB ring intermediate (**168**). The ABCD tetracyclic intermediate (**166**) was constructed using intramolecular nucleophilic epoxide-opening by nitrogen in the azocine ring.



Scheme 14 Strategies for the synthesis of manzamine A (part 3)

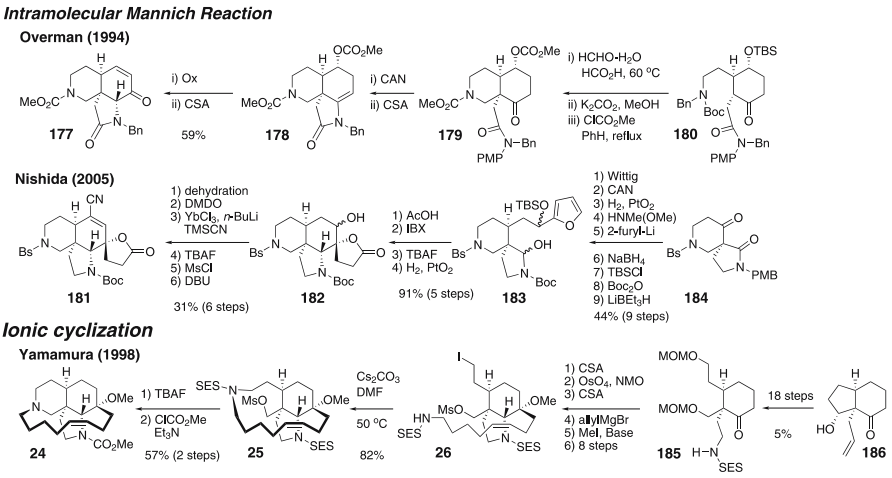
3.6.4
Intramolecular Ionic Cyclization

Overman and coworkers synthesized the ABC core (**177**) by a stereoselective intramolecular Mannich reaction from *trans*-2,3-dialkylated cyclohexanone (**180**), which was prepared from D-(–)-quinic acid [95] (Scheme 15). The ABC ring system was constructed by ene-amide formation. The ene-amide (**178**) was converted to **177** by successive epoxidation, acid-rearrangement, and elimination.

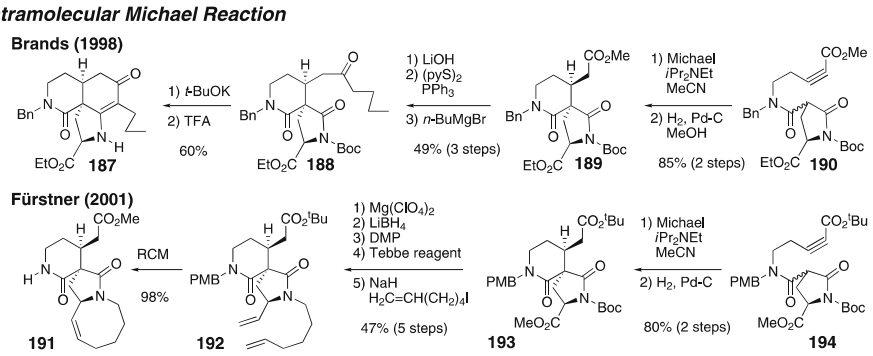
Nishida and coworkers recently demonstrated a stereoselective cyclization of acyliminium cation and furan, which was tethered to a spiro-ring system (**184**). The reaction provided an ABC tricyclic intermediate (**181**) [96].

Yamamura reported a synthesis of the ABCE tetracyclic intermediate (**24**) [17]. In this synthesis, 15-membered azacycle (**25**) was efficiently prepared by cyclization of SES-amide and alkyl iodide in the presence of cesium carbonate in 82% yield. Further cyclization of secondary amine and mesylate gave **24**.

Brands and DiMichele reported the intramolecular Michael cyclization of a 1,3-dicarbonyl system (**190**) to alkynyl ester. The resulting double bond was hydrogenated stereoselectively to give an AC ring system (**189**) [97] (Scheme 16). Subsequent intramolecular aldol-type cyclization of **188** furnished a suitably substituted ABC tricyclic intermediate (**187**). Using the same strategy, Fürstner and coworkers synthesized an ACD tricyclic intermediate (**191**) [98].



Scheme 15 Strategies for the synthesis of manzamine A (part 4)



Scheme 16 Strategies for the synthesis of manzamine A (part 5)

3.6.5
[3 + 2] Cyclization, Pauson–Khand Reaction, and Eneyne Metathesis

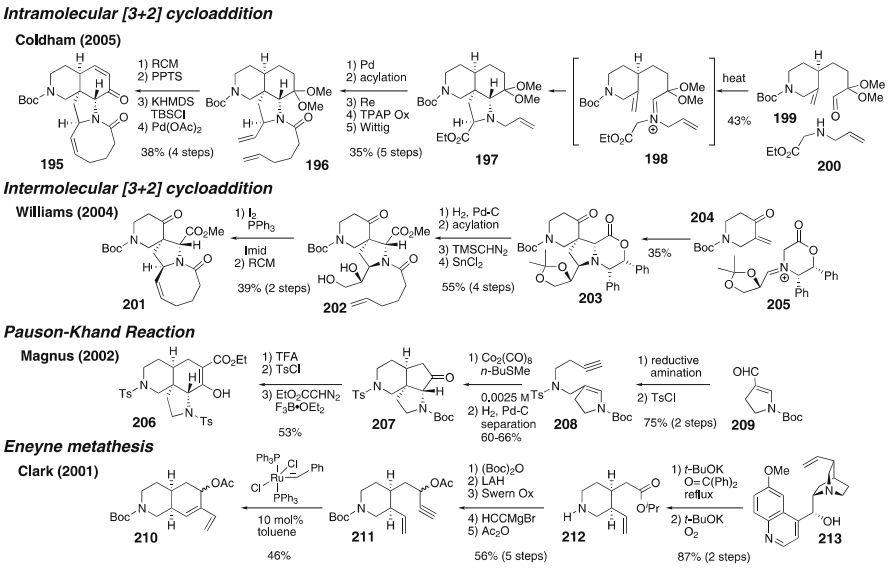
Coldham and coworkers developed a new method, which included an intramolecular [3 + 2] cycloaddition of azomethine ylide (**198**), to construct an ABC tricyclic intermediate (**197**) [99] (Scheme 17). The product (**197**) was further converted to an advanced ABCD tetracyclic intermediate (**195**). An intermolecular version of this cycloaddition was reported by Williams and Ahrendt who used a chiral azomethine ylide (**205**). A chiral AC spiro-cyclic intermediate (**203**) was converted to an ACD tricyclic intermediate (**201**) using RCM [100].

The Pauson–Khand reaction was used for the synthesis of a 6/5/5 tricyclic ring system (**207**), a possible intermediate for nakadomarin A, as shown later, by Magnus and coworkers [101] (Scheme 17). This product (**207**) was further converted to an ABC tricyclic ring system (**206**) by ring expansion.

Eneyne ring-closing metathesis was used for the synthesis of an AB ring system (**210**) by Clark and coworkers [102] (Scheme 15). The chiral *cis*-substituted piperidine precursor (**212**) was prepared by decomposition of (–)-quinine (**213**). The transformation using a substrate with a substituent next to the vinyl group should be challenging.

3.7
Manzamine B

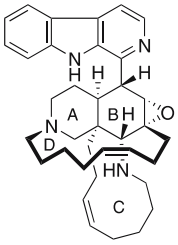
Manzamine B (**2**) (Fig. 7) was isolated by Higa and coworkers from the Okinawan marine sponge *Haliclona* sp. in 1987 [103] and was thought to be a biogenetic precursor of manzamine A (Scheme 5). Its structure is characterized by an 11-membered unsaturated azacycle and six consecutive stereocenters in ring B. Due to these difficulties, no synthetic approach has been reported for manzamine B until now.



Scheme 17 Strategies for the synthesis of manzamine A (part 6)

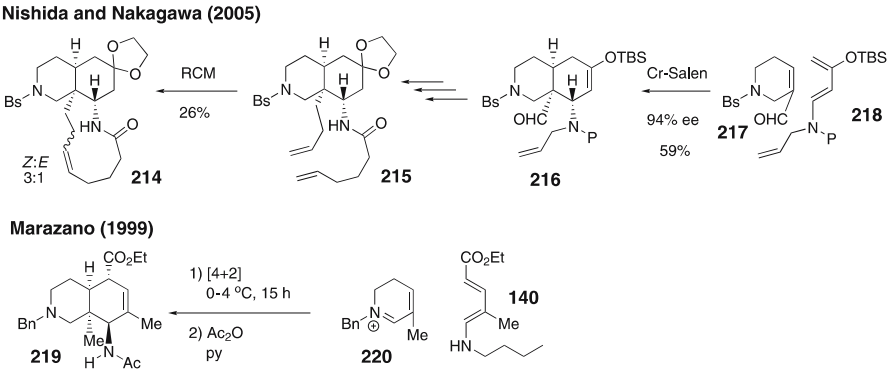
We have attempted to synthesize the 6/6/11 tricyclic core (**214**) of manzamine B (Scheme 18)(Matsumura et al. unpublished results). Asymmetric intermolecular Diels–Alder reaction of a formyl-dehydropiperidine derivative (**217**) and siloxy-aminodiene (**218**) promoted by a chiral Cr-salen complex [104] gave a cycloadduct (**216**) with high enantio- and diastereoselectivity to establish an all-*cis* stereochemistry. The 11-membered ring was constructed by RCM with modest selectivity.

The cyclization developed by Marazano discussed above might be useful for the synthesis of manzamine B if an all-*cis* stereochemistry can be controlled [86, 87].



Manzamine B (2)

Fig. 7 Manzamine B

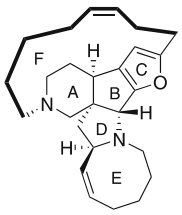


Scheme 18 Strategies for the synthesis of manzamine B

3.8 Nakadomarin A

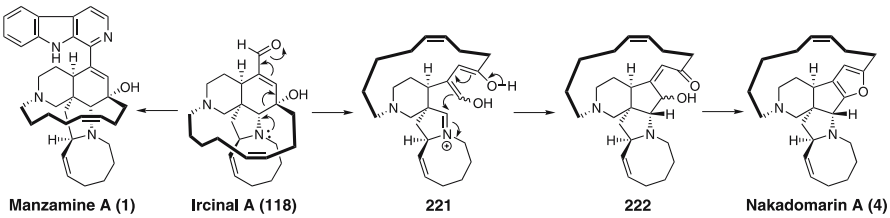
Nakadomarin A (**4**) (Fig. 8) was first isolated from the Okinawan marine sponge *Amphimedon* sp. (SS-264) by Kobayashi and coworkers in 1997 [105, 106]. Nakadomarin A is considered to be a novel manzamine-related alkaloid which contains a unique 6/5/5/5/8/15 ring system involving a furan ring. The biological transformation of ircinal A to nakadomarin A was proposed (Scheme 19) [106].

Attempts to synthesize nakadomarin A have focused on the stereoselective construction of the strained ABCD central core, which involves a reactive furan ring before accessing the EF rings (Scheme 20). We first investigated the synthesis of this strained 6/5/5/5 tetracyclic core of nakadomarin A by two biomimetic pathways. We reported the first synthesis of the ABCD core of nakadomarin A in 2001, in which a novel intramolecular Mannich-type cyclization between a furan ring and an iminium cation was a key reaction [107]. Using this method, we completed the first total syntheses of racemic and antipode of nakadomarin A in 2003 [30]. Starting from piperidine **228**, dia-

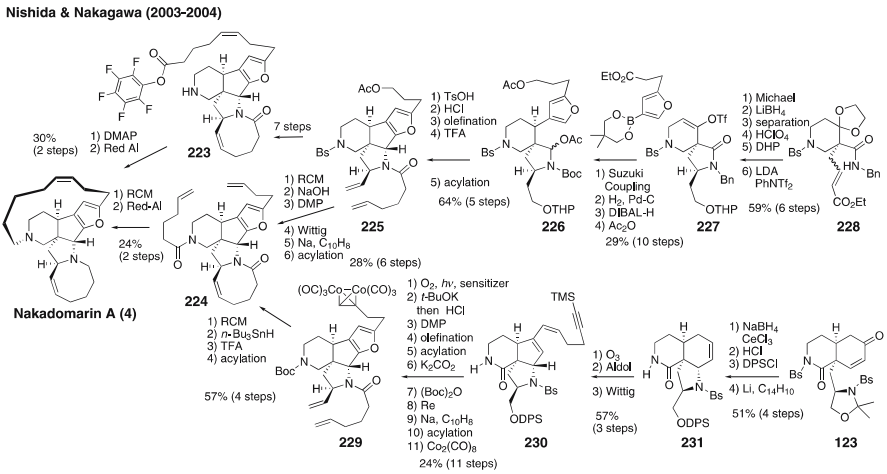


Nakadomarin A (4)

Fig. 8 Nakadomarin A



Scheme 19 Biosynthesis of nakadomarin A



Scheme 20 Strategies for the synthesis of nakadomarin A (part 1)

stereoselective intramolecular Michael reaction, followed by the introduction of a 3-furyl group by Suzuki–Miyaura coupling, and reduction of a lactam carbonyl gave cyclization precursor **226**. Treatment of **226** under mildly acidic conditions resulted in the formation of an ABCD tetracyclic intermediate in high yield, which was converted to diene **225**. Sequential RCM via **224** completed the total synthesis. However, the stereoselectivity of RCM for the formation of a 15-membered ring was poor.

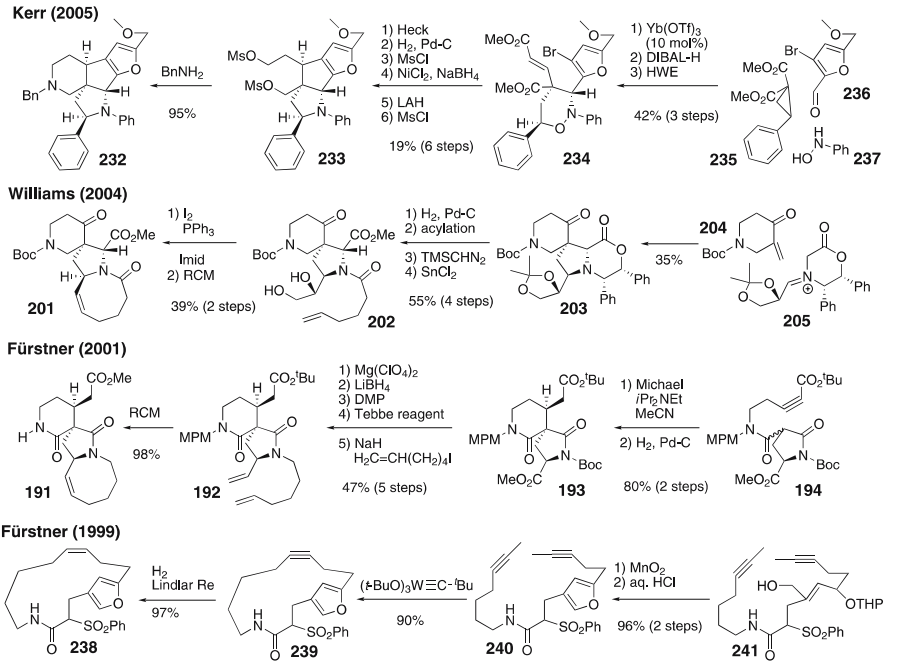
In 2004, we achieved the synthesis of a natural enantiomer of nakadomarin A using the Diels–Alder adduct **123**, which was a key intermediate in our synthesis of 36-oxo-ircinal A, as described in Scheme 12. The adduct **123** was converted to an ABC tricyclic intermediate **231** by S'_N cyclization of benzenesulfonyl amide. The cyclohexene ring in **231** was then transformed to formylcyclopentene by ozonolysis followed by an aldol reaction. After Wittig reaction, 1,3-diene (**232**) was trapped by singlet oxygen to give endoperoxide which was converted to the fused furan by Kondo's method [108]. After construction of the chiral core structure, two RCM reactions were used to synthesize 15- and eight-membered rings to complete the asymmetric

total synthesis of natural nakadomarin A [31]. The formation of an eight-membered ring by RCM in the presence of a terminal alkyne which was protected as a cobalt-carbonyl complex is noteworthy [109]. Conventional Yamaguchi macro-lactamization [8, 9] of 223 was found to provide a more efficient access to this 15-membered ring [110].

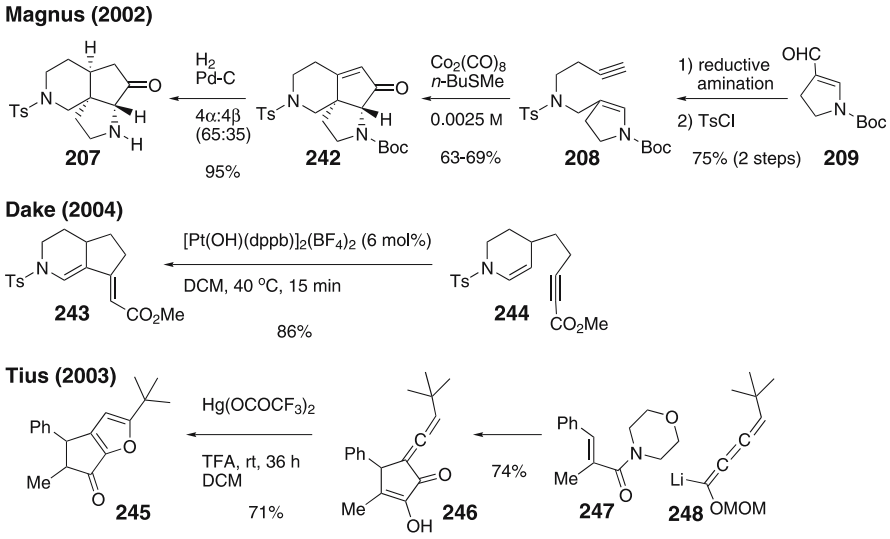
Recently, Kerr and coworkers reported model studies for a racemic ABCD tetracyclic core (232) [111] (Scheme 21). A homo [3 + 2] dipolar cycloaddition with the three-component coupling of phenylhydroxylamine (**237**), furfural (**236**) and cyclopropane (**235**) was demonstrated to be a useful reaction for preparing a 1,2-tetrahydrooxazine derivative. Selective reduction of an ester group and subsequent HWE reaction gave **234**. Intramolecular Heck reaction followed by cleavage of an N – O bond and recyclization gave a BCD ring in **233**. Finally, A ring was synthesized by the double alkylation of benzylamine to give **232**.

Williams and Ahrendt reported an asymmetric ADE-ring system (201), which was shown to include a 1,3 dipolar cycloaddition as a key reaction [100] (Scheme 21).

Fürstner and coworkers described the synthesis of 15-membered unsaturated lactam **238** using an intramolecular alkyne metathesis followed by Lindlar reduction [112] (Scheme 21). They also synthesized a chiral ADE ring



Scheme 21 Strategies for the synthesis of nakadomarin A (part 2)



Scheme 22 Strategies for the synthesis of nakadomarin A (part 3)

system (**191**) [98] for the application of an intramolecular Michael reaction, which was developed by Brands at Merck [97].

Magnus and coworkers reported the synthesis of an ABD ring system (**207**) with the Pauson–Khand reaction as a key step [101] (Scheme 22). Dake reported a model study for an AB ring (**243**) using an intramolecular eneyne metathesis [113]. Tius reported a BC-ring model (**245**) using a Nazarov reaction [114].

4 Summary

We have summarized strategies for the synthesis of manzamine and related alkaloids. As suggested by Baldwin in a stimulating proposal regarding a biogenetic pathway for manzamine A, Diels–Alder-type reactions are powerful methods for constructing the central core, a substituted hydroquinoline. Medium and large azacycles were prepared by Wittig reaction or Yamaguchi macrolactamization. However, due to their poor efficiency, these synthetic studies were limited in model synthesis. After a stable ruthenium carbene catalyst was developed by Grubbs, RCM became the reaction of choice for preparing azamacrocycles, although this reaction is still limited with regard to chemo- and stereoselectivity. As seen in this example, the development of a new reaction or a new catalyst can change the strategy for synthesis and can lead to new possibilities in organic synthesis. However, a new group for protecting nitrogen functionalities and an efficient method for constructing

nitrogen-containing skeletons are still required to achieve the synthesis of complex and interesting molecules.

References

1. Sakai R, Higa T, Jefford CW, Bernardinelli G (1986) J Am Chem Soc 108:6404–6405
2. Magnier E, Langlois Y (1998) Tetrahedron 54:6201–6258
3. Urban S, Hickford SJH, Blunt JW, Munro MHG (2000) Curr Org Chem 4:765–807
4. Hu J-F, Hamann MT, Hill R, Kelly M (2003) In: Codell GA (ed) The alkaloids: chemistry and biology. Academic, New York, p 207–285
5. Stocking EM, Williams RM (2003) Angew Chem Int Ed 42:3078–3115
6. Ang KKH, Holmes MJ, Higa T, Hamann MT, Kara UAK (2000) Antimicrob Agents Chemother 44:1645–1649
7. Matzanke N, Gregg RJ, Weinreb SM (1998) Org Prep Proceed Int 30:1–51
8. Inanaga J, Hirata K, Saeki H, Katsuki T, Yamaguchi Y (1979) Bull Chem Soc Jpn 52:1989–1993
9. Shiina I, Kubota M, Ibuka R (2002) Tetrahedron Lett 43:7535–7539
10. Grubbs RH, Miller S, Fu G (1995) Acc Res 28:446–452
11. Scholl M, Ding S, Lee CW, Grubbs RH (1999) Org Lett 1:953–956
12. Fürstner A (2000) Angew Chem Int Ed 39:3012–3043
13. Deiters A, Martin SF (2004) Chem Rev 104:2199–2238
14. Humphrey JM, Liao Y, Ali A, Rein T, Wong Y-L, Chen H-J, Courtney AK, Martin SF (2002) J Am Chem Soc 124:8584–8592
15. Baldwin JE, Claridge TDW, Culshaw AJ, Heupel FA, Lee V, Spring DR, Whitehead RC (1999) Chem Eur J 5:3154–3161
16. Baldwin JE, Claridge TDW, Culshaw AJ, Heupel FA, Lee V, Spring DR, Whitehead RC, Boughtflower RJ, Mutton IM, Upton RJ (1998) Angew Chem Int Ed 37:2661–2663
17. Li S, Yamamura S (1998) Tetrahedron 54:8691–8710
18. Winkler DJ, Bowen CM, Liotta F (1995) Chem Rev 95:2003–2020
19. Winkler DJ, Axten JM (1998) J Am Chem Soc 120:6425–6426
20. Douglas CJ, Hiebert S, Overman LE (2005) Org Lett 7:933–936
21. Sung MJ, Lee HI, Lee HB, Cha JK (2003) J Org Chem 68:2205–2208
22. Nicolaou KC, Snyder SA, Montagnon T, Vassilikogiannakis G (2002) Angew Chem Int Ed 41:1668–1698
23. Takao K, Munakata R, Tadano K (2005) Chem Rev 105:4779–4807
24. Cardona F, Goti A (2005) Angew Chem Int Ed 44:7832–7835
25. Coldham I, Hufton R (2005) Chem Rev 105:2765–2810
26. Martin SF, Humphrey JM, Liao Y, Ali A, Hillier MC (1999) J Am Chem Soc 121:866–867
27. Humphrey JM, Liao Y, Ali A, Rein T, Wong Y-L, Chen H-J, Courtney AK, Martin SF (2002) J Am Chem Soc 124:8584–8592
28. Barrett AGM, Boys ML, Boehm TL (1996) J Org Chem 61:685–699
29. McDermott TS, Mortlock AA, Heathcock CH (1996) J Org Chem 61:700–709
30. Nagata T, Nishida A, Nakagawa M (2003) J Am Chem Soc 125:7484–7485
31. Ono K, Nakagawa M, Nishida A (2004) Angew Chem Int Ed 43:2020–2023
32. Torisawa Y, Hashimoto A, Nakagawa M, Hino T (1989) Tetrahedron Lett 30:6549–6550

33. Torisawa Y, Hashimoto A, Nakagawa M, Seki H, Hara R, Hino T (1991) Tetrahedron 47:8067–8078
34. Torisawa Y, Hashimoto A, Okouchi M, Iimori T, Nagasawa M, Hino T, Nakagawa M (1996) Bioorg Med Chem Lett 6:2565–2570
35. Nowak N, Gerlach H (1993) Liebigs Ann Chem 153–159
36. MaGee DI, Beck EJ (2000) Can J Chem 78:1060–1066
37. Morimoto Y, Yokoe C, Kurihara H, Kinoshita T (1998) Tetrahedron 54:12197–12214
38. Morimoto Y, Yokoe C, Kurihara H, Kinoshita T (1997) Tetrahedron Lett 38:8981–8984
39. Morimoto Y, Kurihara H, Yokoe C, Kinoshita T (1998) Chem Lett 38:829–830
40. Michelliza S, Mourabit AA, Olesker AG, Marazano C (2002) J Org Chem 67:6474–6478
41. Kong F, Andersen R, Allen TM (1994) J Am Chem Soc 116:6007–6008
42. Kong F, Graziani EI, Andersen R (1998) J Nat Prod 61:267–271
43. Matzanke N, Gregg RJ, Weinreb SM, Parvez M (1997) J Org Chem 62:1920–1921
44. Vila X, Quirante J, Paloma L, Bonjoch J (2004) Tetrahedron Lett 45:4661–4664
45. Amat M, Pérez M, Minaglia AT, Casamitjana N, Bosch J (2005) Org Lett 7:3653–3656
46. Yamazaki N, Kusanagi T, Kibayashi C (2004) Tetrahedron Lett 45:6509–6512
47. Tong HM, Martin M-T, Chiaroni A, Bénéchie M, Marazano C (2005) Org Lett 7:2437–2440
48. Solé D, Peidró E, Bonjoch J (2000) Org Lett 2:2225–2228
49. Baldwin JE, Whitehead RC (1992) Tetrahedron Lett 33:2059–2062
50. Kobayashi J, Tsuda M, Kawasaki N, Matsumoto K, Adachi T (1994) Tetrahedron Lett 35:4383–4386
51. Tsuda M, Inaba K, Kawazaki N, Honma K, Kobayashi J (1996) Tetrahedron 52:2319–2324
52. Kobayashi J, Tsuda M (1997) J Synth Org Chem Jpn 55:1114–1123
53. Gil L, Baucherel X, Martin M-T, Marazano C, Das BC (1995) Tetrahedron Lett 36:6231–6234
54. Rodríguez J, Peters BM, Kurz L, Schatzman RC, McCarley D, Lou L, Crews P (1993) J Am Chem Soc 115:10436–10437
55. Rodríguez J, Crews P (1994) Tetrahedron Lett 35:4719–4722
56. Gagnon A, Danishefsky SJ (2002) Angew Chem Int Ed 41:1581–1584
57. Cimino G, Mattia CA, Trivellone E (1989) Tetrahedron 45:3863–3872
58. Douglas CJ, Hiebert S, Overman LE (2005) Org Lett 7:933–936
59. Downham R, Ng FW, Overman LE (1998) J Org Chem 63:8096–8097
60. Sung MJ, Lee HI, Lee HB, Cha JK (2003) J Org Chem 68:2205–2208
61. Irie O, Samizu K, Henry JR, Weinreb SM (1999) J Org Chem 64:587–595
62. Denhart DJ, Griffith DA, Heathcock CH (1998) J Org Chem 63:9616–9617
63. Hourcade S, Ferdenzi A, Retailleau P, Mons S, Marazano C (2005) Eur J Org Chem 1302–1310
64. Kwak Y-S, Winkler JD (2001) J Am Chem Soc 123:7429–7430
65. Baker BJ, Scheuer PJ, Shoolery JN (1988) J Am Chem Soc 110:965–966
66. Fahy E, Molinski TF, Harper MK, Sullivan BW, Faulkner DJ, Parkanyi L, Clardy J (1988) Tetrahedron Lett 29:3427–3428
67. Braekman JC, Dalòze D, Macedo PA, Piccinni-Leopardi C, Germain G, Meerssche MV (1982) Tetrahedron Lett 23:4277–4280
68. Braekman JC, Dalòze D, Cimino G, Trivellone E (1988) Bull Soc Chim Belg 97:519–524

69. Kobayashi M, Kawazoe K, Kitagawa I (1989) Tetrahedron Lett 30:4149–4152
70. Scott RW, Epperson JR, Heathcock CH (1994) J Am Chem Soc 116:8853–8854
71. Nakagawa M, Endo M, Tanaka N, Gen-Pei L (1984) Tetrahedron Lett 25:3227–3230
72. Kobayashi M, Kawazoe K, Kitagawa I (1989) Chem Pharm Bull 37:1676–1678
73. Hoye TR, North JT, Yao LJ (1994) J Org Chem 59:6904–6910
74. Hoye TR, North JT, Yao LJ (1995) J Org Chem 60:4958
75. Hoye TR, North JT, Yao LJ (1994) J Am Chem Soc 116:2617–2618
76. Hoye TR, Ye Z, Yao LJ, North JT (1996) J Am Chem Soc 118:12074–12081
77. Brands KMJ, Meekel AAP, Pandit UK (1991) Tetrahedron 47:2005–2026
78. Borer BC, Deerenberg S, Bieräugel H, Pandit UK (1994) Tetrahedron Lett 35:3191–3194
79. Pandit UK, Overkleeft HS, Borer BC, Bieräugel H (1999) Eur J Org Chem 959–968
80. Uchida H, Nishida A, Nakagawa M (1999) Tetrahedron Lett 40:113–116
81. Nakagawa M, Torisawa Y, Uchida H, Nishida A (1999) J Synth Org Chem Jpn 57:1004–1015
82. Uchida H (2002) PhD thesis, University of Chiba
83. Urban D, Duval E, Langlois Y (2000) Tetrahedron Lett 41:9251–9256
84. Magnier E, Langlois Y (1998) Tetrahedron Lett 39:837–840
85. Imbroisi DO, Simpkins NS (1991) J Chem Soc Perkin Trans 1, 1815–1823
86. Jakubowicz K, Abdeljelil B, Herdemann M, Martin M-T, Gateau-Olesker A, Mourabit AA, Marazano C, Das BC (1999) J Org Chem 64:7381–7387
87. Herdemann M, Al-Mourabit A, Martin M-T, Marazano C (2002) J Org Chem 67:1890–1897
88. Markó IE, Southern JM, Adams H (1992) Tetrahedron Lett 33:4657–4660
89. Turet L, Markó IE, Tinant B, Declercq J-P, Touillaux R (2002) Tetrahedron Lett 43:6591–6595
90. Leonard J, Fearnley SP, Finlay MR, Knight JA, Wong G (1994) J Chem Soc Perkin Trans 1, 2359–2361
91. Kondo K, Shigemori H, Kikuchi Y, Ishibashi M, Sasaki T, Kobayashi J (1992) J Org Chem Soc 57:2480–2483
92. Myers A, Gleason J, Yoon T (1995) J Am Chem Soc 117:8488–8489
93. Hart DJ, McKinney JA (1989) Tetrahedron Lett 30:2611–2614
94. Campbell JA, Hart DJ (1992) Tetrahedron Lett 33:6247–6250
95. Kamenecka TM, Overman LE (1994) Tetrahedron Lett 35:4279–4282
96. Tokumaru K, Arai S, Nishida A (2006) Org Lett 8:27–30
97. Brands KMJ, DiMichele LM (1998) Tetradedron Lett 39:1677–1680
98. Fürstner A, Guth O, Düffels A, Siedel G, Liebl M, Gabor B, Richard M (2001) Chem Eur J 7:4811–4820
99. Coldham I, Pih SM, Rabot R (2005) Synlett 1743–1745
100. Ahrendt KA, Williams RM (2004) Org Lett 6:4539–4541
101. Magnus P, Fielding MR, Wells C, Lynch V (2002) Tetrahedron Lett 43:947–950
102. Clark JS, Townsend RJ, Blake AJ, Teat SJ, Johns A (2001) Tetrahedron Lett 42:3235–3238
103. Sakai R, Kohmoto S, Higa T (1987) Tetrahedron Lett 28:5493–5496
104. Huang Y, Iwama T, Rawal VH (2000) J Am Chem Soc 122:7843–7844
105. Kobayashi J, Watanabe D, Kawasaki N, Tsuda M (1997) J Org Chem 62:9236–9239
106. Kobayashi J, Tsuda M, Ishibashi M (1999) Pure Appl Chem 71:1123–1126
107. Nagata T, Nishida A, Nakagawa M (2001) Tetrahedron Lett 42:8345–8349
108. Kondo K, Matsumoto M (1976) Tetrahedron Lett 17:4363–4366

109. Ono K, Nagata T, Nishida A (2002) Synlett 1207–1209
110. Nakagawa M, Nagata T, Ono K, Nishida A (2005) J Synth Org Chem Jpn 63:200–210
111. Young IS, Williams JL, Kerr MA (2005) Org Lett 7:953–955
112. Fürstner A, Guth O, Rumbo A, Seidel G (1999) J Am Chem Soc 121:11108–11113
113. Harrison TJ, Dake GR (2004) Org Lett 6:5023–5026
114. Leclerc E, Tius MA (2003) Org Lett 5:1171–1174