Recent Advances in Natural Product Synthesis by Using Intramolecular Diels−Alder Reactions†

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1. Introduction

It is widely recognized that Diels−Alder reactions are the most useful pericyclic reactions for the construction of six-membered functionalized carbocyclic compounds. The potency of Diels−Alder reactions is validated especially in cases of structurally complex natural products synthesis.[1] The usefulness of Diels−Alder reactions is further demonstrated in cases of their intramolecular versions, that is, intramolecular Diels−Alder (IMDA) reactions.[2] In this review, we summarize a number of recently completed total syntheses of natural products achieved by using IMDA reactions as the key steps in the construction of their basic frameworks. We focus on the total synthesis of biologically intriguing and pharmacologically important natural products completed during the past 10 years. Also included are transannular Diels−Alder approaches and Diels−Alder reactions using furan and other heterocyclic substructures as diene parts for the stereoselective construction of the main carbon frames of the targeted natural products. Some prominent total syntheses achieved based on intramolecular hetero-Diels−Alder reactions are also exemplified. In this review, we divide each IMDA reaction-based natural product synthesis according to the generally accepted structural classification of natural products, such as terpenoids, steroids, alkaloids, and polyketide-derived natural products. Multifunctionalized and polycyclic natural products with a number of stereogenic centers were selected for the present survey. The completed total synthesis for each natural product is the exclusive object of this review. At the end of each section, some other total syntheses of related natural products are mentioned, but without a structural drawing. Although we summarize the stereochemical outcome, such as endo- and exo-selectivity, of each mentioned IMDA reaction, the precise account of the transition state of each IMDA reaction is omitted because of space limitations. In addition, we explain the reported IMDA reaction step for each cited natural product synthesis. The preparation of the substrate for the IMDA reaction and further functional group transformation for the total synthesis are omitted or described only briefly.

2. Terpenoids

2.1. Sesquiterpenoids

trans-Dihydroconfertifolin (**5**), a sesquiterpenoid isolated from a marine sponge found in New Zealand, displays antimicrobial activity.[3] Taber and co-workers have used an IMDA reaction in the total synthesis of (±)-**5** (Scheme 1).[4] Heating a solution of triene **1** (*E*/*Z* = 2:1), prepared from γ-hydroxylated acetoacetic acid ester, in benzonitrile under reflux gave cycloadducts **2** and **3** in a 4:1 ratio (66% yield). Pure **2** was obtained from the mixture by chromatographic separation, followed by recrystallization. Assuming that the IMDA reaction proceeded through a chairlike transition state, the desired trans-fused **2** would be formed from the (*E*)-isomer **1***E*. Exposure of **2** to representative Simmons−Smith reaction conditions introduced a cyclopropane ring in **2**, providing **4**

† This paper is dedicated to the memories of the late Professors Kenneth L. Rinehart and Katsumi Kakinuma.

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Ken-ichi Takao, was born in Tokyo, Japan, in 1967. He received his Ph.D. in 1995 from Keio University under the direction of Professor Kin-ichi Tadano. Then he worked at Sagami Chemical Research Center for one year. From 1996 to 1998, he joined Science University of Tokyo (Professor Susumu Kobayashi) as an instructor. In 1998, he moved to Keio University, where he is now an assistant professor. His research interests are focused on total synthesis of biologically and structurally interesting natural products and the development of stereoselective synthetic organic reactions.

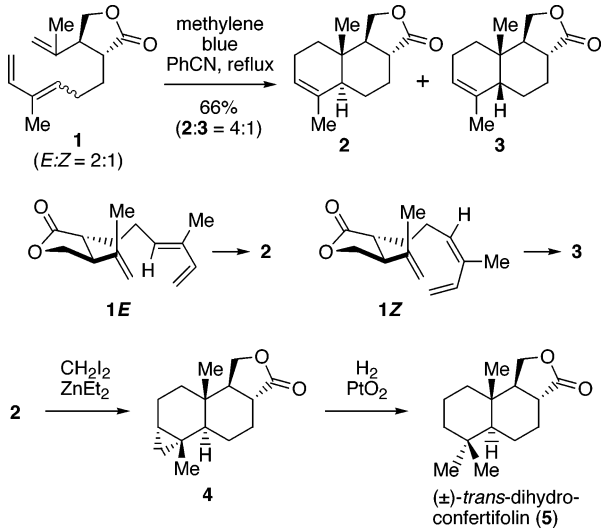
Ryosuke Munakata was born in 1977 in Takamatsu, Japan. He studied chemistry at Keio University and received his Ph.D. degree in 2004 for his research on total synthesis of macquarimicins under the supervision of Professor Kin-ichi Tadano. Since 2004, he has worked as a medicinal chemist for Yamanouchi Pharmaceutical Co., Ltd. (now Astellas Pharma Inc.) at Tsukaba, Japan.

stereoselectively. The strained three-membered ring was regioselectively cleaved to provide (±)-**5**.

The type 2 IMDA reaction is an efficient method for the formation of medium-size rings.[2c] The antifungal ledol (**12**) is characterized by a tricyclic system fused by five-/seven-/three-membered rings.[5] Shea and co-workers have demonstrated the significance of the type 2 IMDA reaction in their total synthesis of (±)-**12** (Scheme 2).[6] 2-Methyl-3-(4-oxo-5-hexenyl)-1,3-butadiene **6** underwent an IMDA reaction in the presence of Lewis acid (Et_2AlCl at room temperature), providing the bridged bicyclic adduct **7** (70% yield). By the treatment of **7** with MeLi, followed by protection, **8** was obtained exclusively. Oxidative cleavage of the bridgehead double bond in **8** provided a cycloheptanone derivative with a 3-butanoyl tether **9**, which was cyclized to a bicyclo[5.3.0]decane skeleton in an intramolecular aldol fashion, providing enone **10**. The catalytic hydrogenation of **10** produced the cis-fused **11** stereoselectively, which was eventually transformed into (±)-**12** by installation of the geminally dimethylated cyclopropane moiety.

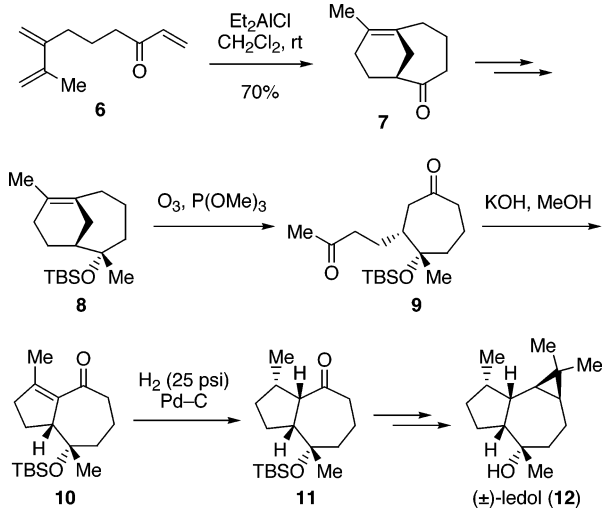
Kin-ichi Tadano was born in Chiba Prefecture, Japan, in 1948. He received his Ph.D. degree from Keio University in 1977 under the supervision of Professor Tetsuo Suami on the synthetic studies of carbocyclic nucleosides. He started his academic career in 1973 as an instructor at Department of Applied Chemistry, Keio University. During 1977–1979, he joined the laboratory lead by Professor Kenneth L. Rinehart of the University of Illinois at Urbana-Champaign as a research associate. Then he returned to Keio University to resume the experience as an academic staff member. He was promoted to Assistant Professor (1982), to Associate Professor (1988), and then to Professor in 1994. His principle scientific concerns are synthetic studies on biologically important and structurally unique natural products and development of asymmetric synthesis using sugars as a chiral environment.

Scheme 1. Total Synthesis of (±)-*trans*-Dihydroconfertifolin by Taber and Co-workers[4]

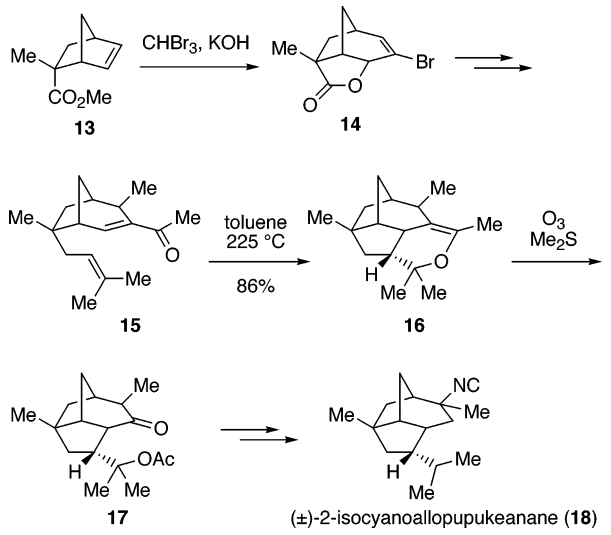


2-Isocyanoallopupukeanane (**18**) is an isocyanopupukeanane, belonging to a class of structurally unique marine sesquiterpenoids.[7] Ho and co-workers have employed an intramolecular hetero-Diels–Alder reaction as a key step in the total synthesis of (±)-**18** (Scheme 3).[8] The addition of dibromocarbene to a 5-norbornene-2-carboxylic acid ester **13** caused a ring expansion to provide tricyclic lactone **14**, which was elaborated to bicyclo[3.2.1]oct-2-ene **15**, possessing an α,β-unsaturated ketone and a 2-methylbutenyl unit as a hetero-diene and a dienophile, respectively. When a toluene solution of **15** (225 °C) was heated, the intramolecular hetero-Diels–Alder reaction proceeded to afford cycloadduct **16** with the tricyclic carbon framework required for the allopupukeanane total synthesis. The dihydropyran moiety in **16** was

Scheme 2. Total Synthesis of (±)-Ledol by Shea and Co-workers[6]



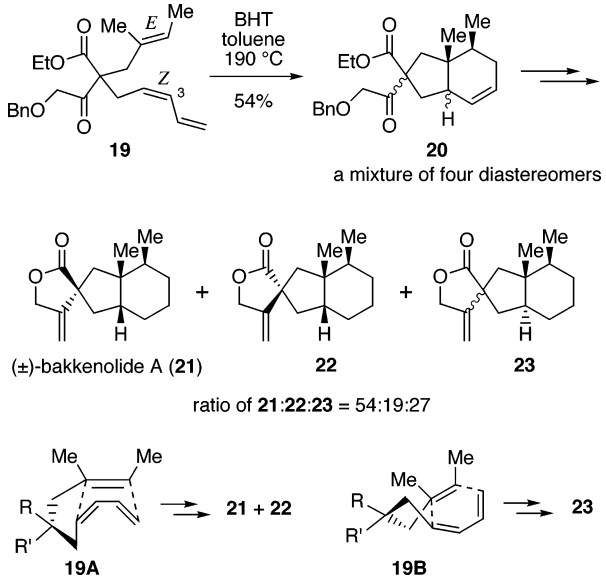
Scheme 3. Total Synthesis of (±)-2-Isocyanoallopupukeanane by Ho and Co-workers[8]



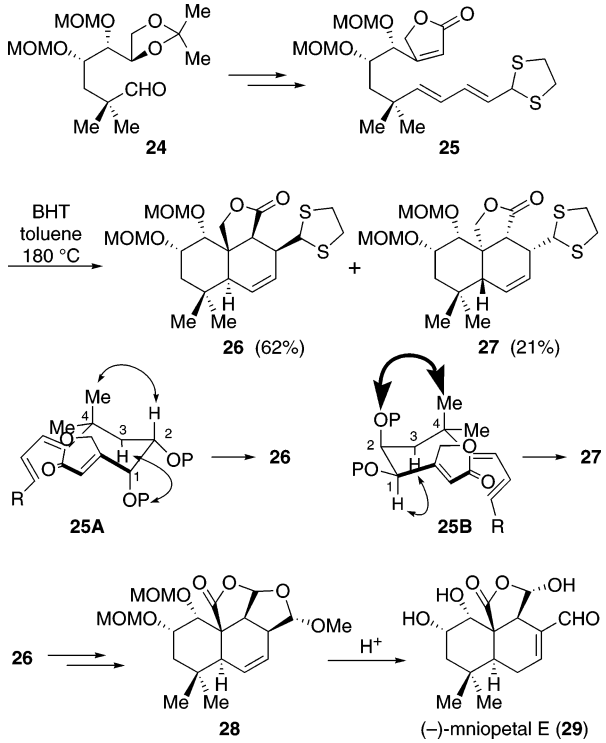
then cleaved by ozonolysis to give **17**. With seven more synthetic operations from **17**, including the introduction of an isocyano group, the total synthesis of (±)-**18** was completed.

The spirocyclic γ-lactone-type sesquiterpenoid bakkenolide A (**21**) displays cytotoxicity against several carcinoma cell lines, as well as insect antifeedant activity.[9] Back and co-workers have reported the total synthesis of (±)-**21** (Scheme 4).[10] An α,α-differentially alkenylated γ-hydroxyacetoacetate derivative **19** with a (2*Z*)-2,4-pentadienyl group has been used in the key IMDA step. The IMDA reaction of the substrate **19** was carried out in toluene (190 °C) to afford cycloadduct **20** as an inseparable mixture of four possible diastereomers (54% combined yield). The mixture **20** was converted into β-methylene spirocyclic lactones **21**−**23**. The ratio of **21**, **22**, and **23** was 54:19:27. In general, the endo-transition state (TS) for (3*Z*)-1,3,8-nonatrienes is more strained than the exo-TS, which causes to the preferential formation of a cis-fused tetrahydroindan skeleton.[11] In the present case, as expected, the cis-fused cy-

Scheme 4. Total Synthesis of (±)-Bakkenolide A by Back and Co-workers[10]



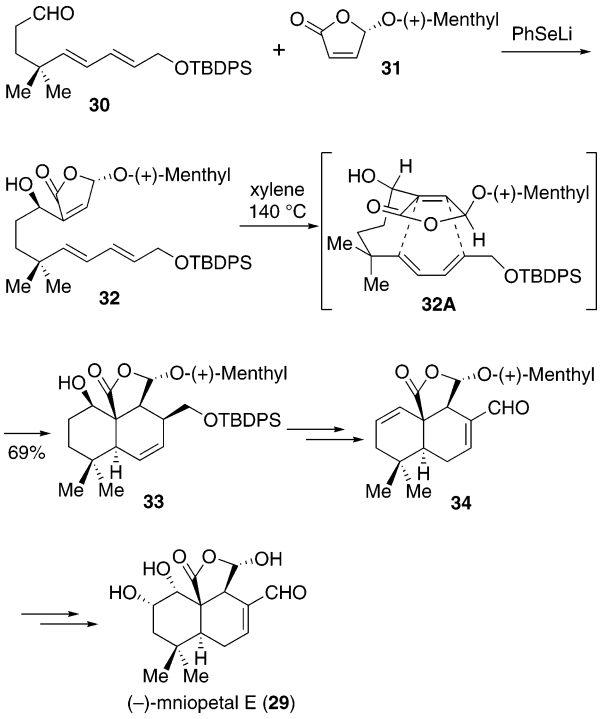
Scheme 5. Total Synthesis of (−)-Mniopetal E by Tadano and Co-workers[13]



cloadducts leading to **21** and **22** were formed predominantly (cis/trans = 73:27) from (*E*,*Z*)-**19**, indicating that transition state **19A** (exo) is favored over **19B** (endo). The mixture of **21**−**23** was efficiently separated by HPLC to provide pure (±)-**21**.

(−)-Mniopetal E (**29**) is a drimane sesquiterpenoid that inhibits the reverse transcriptase of the human immunodeficiency virus, type 1 (HIV-1).[12] Tadano and co-workers have achieved the enantiospecific total synthesis of (−)-**29** by using an IMDA strategy for the construction of the core tricyclic skeleton (Scheme 5).[13] As an advanced synthetic intermediate, an enantiomerically pure highly oxygenated heptanal derivative **24** was prepared from D-mannitol. The

Scheme 6. Total Synthesis of (−)-Mniopetal E by Jauch[15]



introduction of a conjugated diene unit into **24** as the diene part and then the construction of the butenolide moiety as the dienophile part led to the substrate **25**. The IMDA reaction of **25** proceeded under thermal conditions in a high-dilution toluene solution (180 °C) in the presence of a trace amount of 2,6-di-*tert*-butyl-*p*-cresol (BHT), giving two endo-cycloadducts, **26** and **27**, in an approximately 3:1 ratio (62% and 21% yield). Regarding the π-facial selectivity, which affected the ratio of **26** and **27**, the total magnitude of the 1,3-diaxial repulsions in the transition state **25A**, that is, those occurring between the OMOM at C1 and H3 and also between H2 and the axial methyl group at C4, is likely to be smaller than that expected in **25B** between the OMOM at C2 and the axial methyl at C4 and also between H1 and H3. The major product **26** was converted into a tetracyclic γ-lactone **28** through the adjustment of the oxidation states in the γ-lactone moiety in **26**. Acid hydrolysis of **28** resulted in a sequence of deprotection of the two MOM groups, hydrolysis of the methyl acetal, and double-bond migration to provide eventually (−)-**29**. Furthermore, Tadano and co-workers have reported the total synthesis of the closely related natural product (−)-mniopetal F using an analogous IMDA strategy.[14]

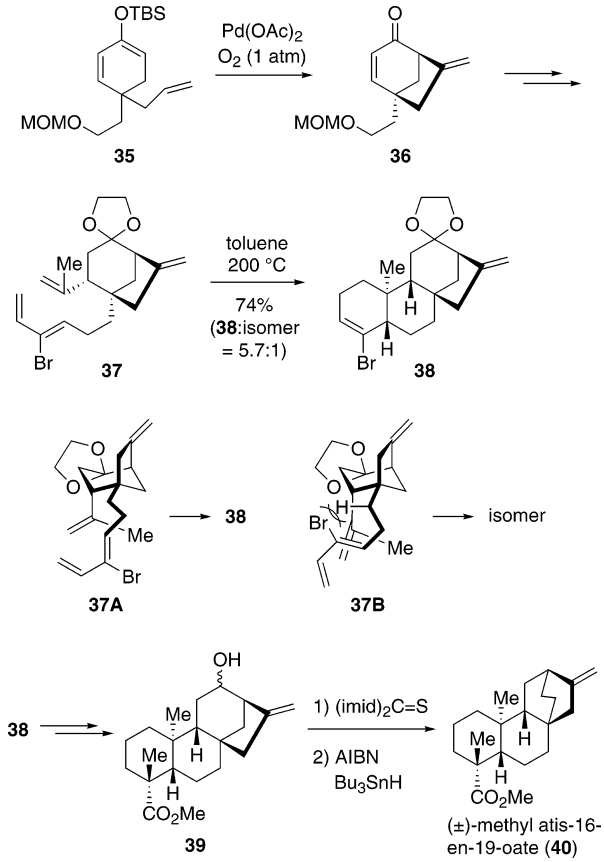
Jauch has also reported the total synthesis of (−)-mniopetal E (**29**) by employing an IMDA reaction strategy (Scheme 6).[15] The substrate **32** for the IMDA reaction was synthesized through the lithium phenylselenide-induced Baylis−Hillman reaction of aldehyde **30**, using a butenolide carrying (+)-menthol **31** as an acceptor of the initial 1,4-addition. The resulting Baylis−Hillman adduct **32** was subjected to a thermal (140 °C) IMDA reaction, which proceeded with remarkable endo- and π-facial selectivities via the transition state **32A**, providing the desired cycloadduct **33** (69% yield). The chiral auxiliary, that is, (+)-menthol, acts as a superior control element to construct the correct absolute configuration of the tricyclic core. Elimination of the hydroxy group in **33**, followed by deprotection and oxidation of the resulting homoallylic alcohol, eventually provided α,β-unsaturated aldehyde **34**. Finally, diastereoselective dihydroxylation of **34** and the subsequent removal of the menthyl residue gave (−)-**29**. From the key intermediate **33**, (−)-mniopetal F has been also synthesized by the same author.[16]

A number of total syntheses targeting other sesquiterpenoids, such as (±)-α-dictyopterol,[17] (±)-*endo*-hirsutene,[18] (±)-pentalenene,[19] (−)-myltaylenol,[20] (±)-cuparene and (±)-herbertene,[21] (+)-3-methyl-α-himachalene,[22] the pheromone gland of a stink bug *Tynacantha marginata*,[23] and (±)-chiloscyphone,[24] have been completed through a variety of IMDA reaction approaches.

2.2. Diterpenoids

Atisane diterpenoids have a unique tetracyclic carbon framework, comprising a number of contiguous stereogenic centers.[25] Toyota, Ihara, and co-workers have employed an IMDA reaction in their total synthesis of (±)-methyl atis-16-en-19-oate (**40**) (Scheme 7).[26] In the initial stage of the synthesis, the palladium(II)-catalyzed cycloalkenylation reaction using a silyloxylated cyclohexadiene **35** gave rise to a functionalized bicyclo[3.2.1]oct-3-en-2-one **36**, which was then converted into bromine-containing IMDA

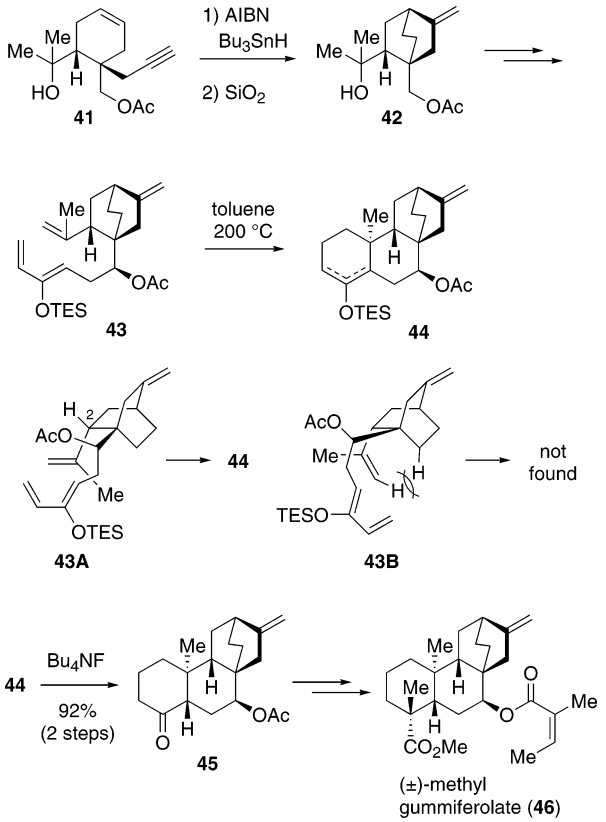
Scheme 7. Total Synthesis of (±)-Methyl Atis-16-en-19-oate by Toyota, Ihara, and Co-workers[26]



substrate **37**. The attempted IMDA reaction of **37** was conducted in toluene under thermal conditions (200 °C), providing a mixture of the desired perhydrophenanthrene derivative **38** and its diastereoisomer in a ratio of 5.7:1 (74%). This observed stereoselectivity for the IMDA reaction may be attributed to the bromine-directing steric effect, previously explored by Roush and co-workers.[27] Thus, the major product **38** arises via conformer **37A**. In the alternative conformer **37B**, the diene unit suffers from unfavorable steric interactions with the allylic hydrogen. In the last stage of the total synthesis, a homoallyl−homoallyl radical rearrangement reaction of the thioimidazolide form of **39**, an advanced intermediate prepared from **38**, efficiently constructed the bicyclo[2.2.2]octane ring system to furnish the atisane diterpenoid (±)-**40** as a single product. Furthermore, the same authors have achieved the enantioselective synthesis of (−)-**40** by applying the asymmetric Michael reaction in the initial stage for prepartion of enantioenriched **37**.[28] The use of a similar synthetic strategy, that is, a combination of palladium-catalyzed cycloalkenylation and an IMDA reaction, has also allowed the formal synthesis of gibberellin diterpenoids.[29]

Toyota, Ihara, and co-workers have also described the total synthesis of (±)-methyl gummiferolate (**46**), in which an IMDA reaction was employed after the construction of the common bicyclo[2.2.2]octane ring system in the atisane skeleton (Scheme 8).[30] Thus, the homoallyl−homoallyl radical rearrangement of **41**, a tri-C-substituted cyclohexene carrying a 2-propynyl group, followed by protodestannylation, afforded the bicyclo[2.2.2]octane intermediate **42**. The

Scheme 8. Total Synthesis of (±)-Methyl Gummiferolate by Toyota, Ihara, and Co-workers[30]



side-chain elongation of **42** provided silyloxylated butadiene **43** equipped with an isopropenyl dienophile. A solution of **43** in toluene was heated (200 °C) to provide a 7.5:1 regioisomeric mixture of the tetracyclic silylated enol ether **44**. The high stereoselectivity observed for the present cycloaddition may be attributed to the fixed conformation of the isopropenyl group, in which 1,3-allylic strain between the olefinic hydrogen and H2 is minimum in conformer **43A**. On the other hand, conformer **43B** suffers from severe interaction between the olefinic hydrogen and the ethano bridge. Treatment of **44** with tetrabutylammonium fluoride gave the A-ring cyclohexanone derivative **45** as a single isomer. As a result, the more thermodynamically stable **45** with a trans-fused A/B ring was obtained predominantly. Through some further transformations, the total synthesis of (±)-**46** was completed.

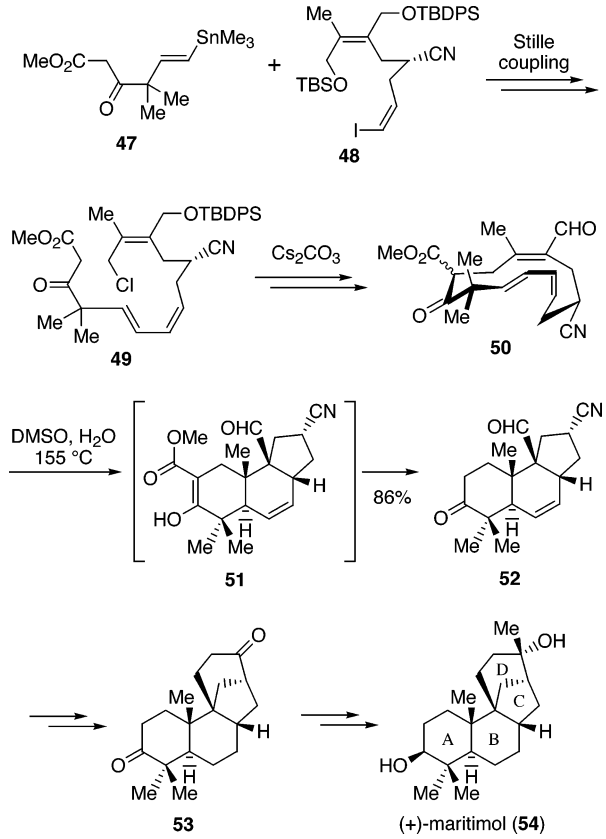
Abad and co-workers have also reported the use of an IMDA reaction in the total syntheses of (−)-atis-16-en-3,14-dione and (+)-3-hydroxy-atis-16-en-2,14-dione.[31]

Deslongchamps and co-workers have investigated extensively the transannular Diels−Alder (TADA) strategy.[2d] The Deslongchamps group has successfully applied the developed TADA strategy to the total synthesis of stemodane diterpenoid (+)-maritimol (**54**),[32] a Caribbean folk medicine for the treatment of venereal diseases.[33] From a synthetic point of view, the TADA reaction applied to a 13-membered trans−cis−cis (TCC) macrocyclic triene such as **50** was expected to produce the trans−syn−cis (TSC) ring system found in **54** (A/B/C ring system) (Scheme 9). The Stille coupling reaction of vinylstannane **47** and vinyl iodide **48**, followed by allylic chlorination, gave a 14-carbon β keto ester with a 1,3,8-triene unit **49**. The intramolecular macroallylation of **49** was achieved using Cs_2CO_3 as a base under high dilution conditions to provide unsaturated aldehyde **50** after oxidation of the allylic alcohol moiety of the resulting 13-membered TCC-macrocyclic triene product. Treatment of this carbocyclic substrate **50** with $MeAlCl_2$ in dichloromethane (23 °C) provided a TSC-fused tricyclic compound **51** (75%) exclusively. Demethoxycarbonylation of **51** under thermal conditions provided **52**. On the other hand, heating **50** under the same conditions directly gave the functionalized tricyclic compound **52** (86% yield). It is notable that both Lewis acid-catalyzed and thermal TADA reactions proceeded with similar stereoselectivities, perhaps induced by a remote nitrile group. Construction of the D-ring of the stemodane skeleton from **52** afforded **53**, which was eventually converted into (+)-**54**. The utility of the TADA strategy was further demonstrated by the Deslongchamps group in their total syntheses of (±)-momilactone A[34] and (+)-chatancin.[35]

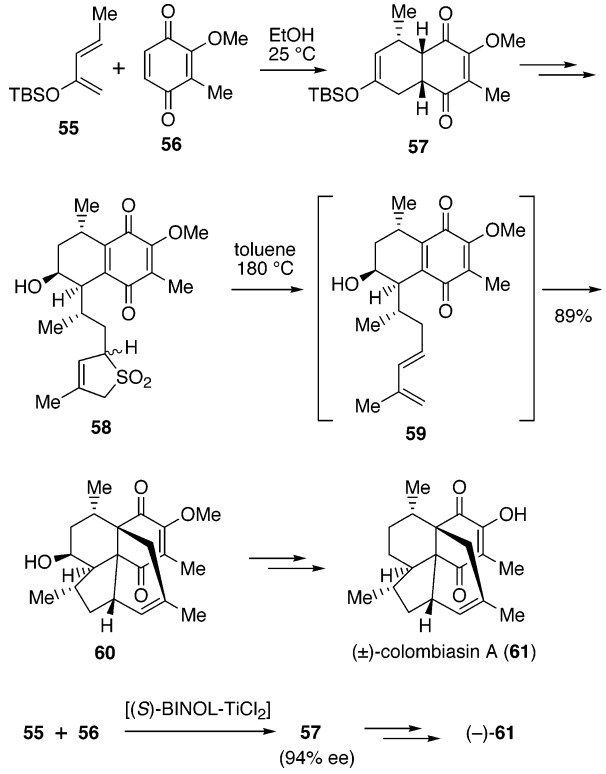
Recently, Toyota, Ihara, and co-workers have used an IMDA reaction strategy in the formal synthesis of (±)-aphidicolin, a stemodane diterpenoid, to form the A/B ring system.[36]

The marine elisabethane diterpenoid (−)-colombiasin A (**61**) was isolated, along with its structurally related isomers (−)-elisapterosin B (**66**) and (+)-

Scheme 9. Total Synthesis of (+)-Maritimol by Deslongchamps and Co-workers[32]

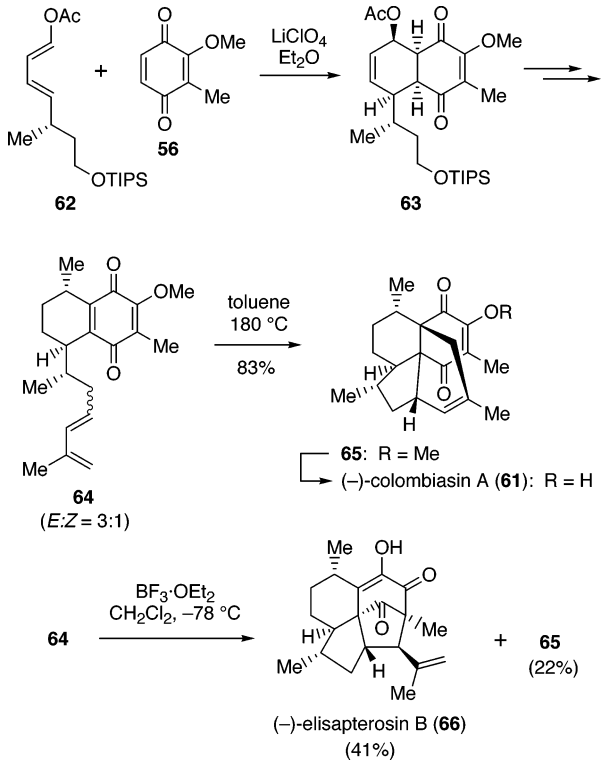


Scheme 10. Total Syntheses of (±)- and (−)-Colombiasin A by Nicolaou and Co-workers[38]



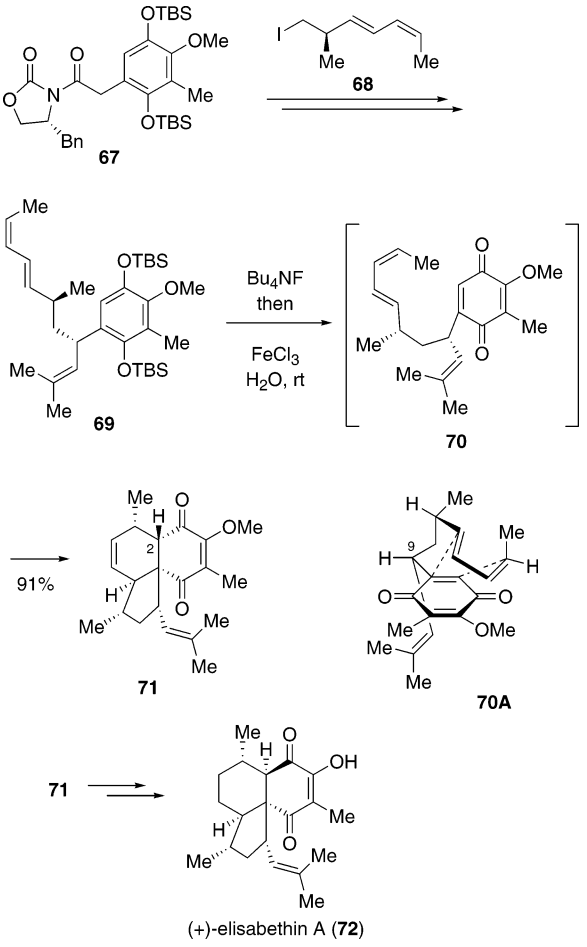
elisabethin A (**72**), from the gorgonian octocoral (Schemes 10−12).[37] The unprecedented cage-like skeletons of **61** and **66** were suggested to be biosynthesized from **72**. These complex molecular architectures and the interesting biological activity of the elisabethane diterpenoids have made them attractive synthetic targets. Nicolaou and co-workers have achieved the total synthesis of (±)- and (−)-colombiasin A (**61**) (Scheme 10).[38] The total synthesis began with the intermolecular Diels−Alder reaction of 2-silyloxy-1,3-pentadiene **55** and 2-methoxy-3-methyl-1,4-quinone **56**, providing the desired endo-cycloadduct **57** as a sole product. The resulting **57** was elaborated to **58**, a bicyclic intermediate carrying a cyclic sulfone tether. Heating **58** in toluene (180 °C) led to a single endo-adduct **60** (89% yield), through the cheletropic extrusion of SO_2, followed by [4 + 2] cycloaddition via **59**, the presumed intermediate possessing a diene−quinone structure. Removal of the extra hydroxyl group in **60**, followed by deprotection of the phenolic methyl ether, provided (±)-**61**. To address the asymmetric synthesis of **61**,[39] the Nicolaou group has devised an initial Diels−Alder reaction of **55** and **56** as an asymmetric version by using a chiral catalyst [(*S*)-BINOL-$TiCl_2$]. The adduct **57** was obtained in 94% ee. The natural enantiomer, (−)-**61**, was synthesized from enantiomerically enriched **57**, thereby establishing the absolute stereochemistry of the natural product.

Scheme 11. Total Syntheses of (−)-Colombiasin A and (−)-Elisapterosin B by Kim and Rychnovsky[40]



Kim and Rychnovsky have used intramolecular [4 + 2] and [5 + 2] cycloadditions in the total syntheses of (−)-colombiasin A (**61**) and (−)-elisapterosin B (**66**) (Scheme 11).[40] Preparation of the substrate **64** for the attempted intramolecular [4 + 2] cycloaddition, that is, bicyclic quinone with a diene tether, was started from the Diels−Alder reaction between the chiral diene **62** and the quinone-type dienophile **56**. Lithium perchlorate in diethyl ether[41] was an effective promoter for this Diels−Alder reaction, which produced the adduct **63** and its diastereomer as a 1.7:1

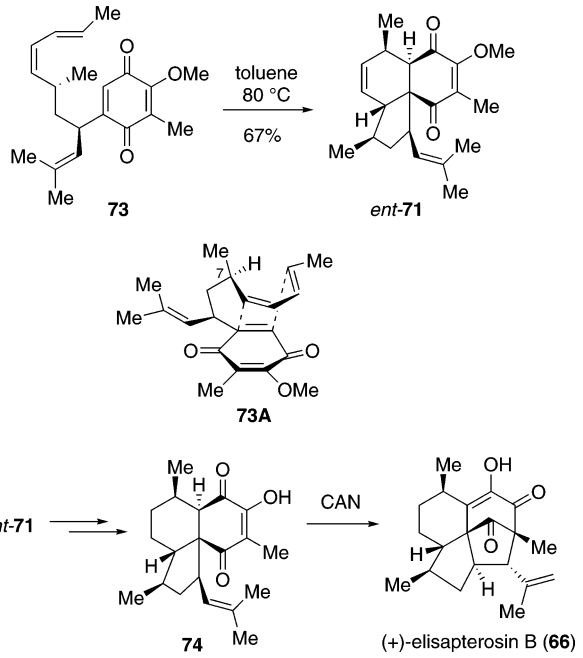
Scheme 12. Total Synthesis of (+)-Elisabethin A by Heckrodt and Mulzer[42]



mixture. When the substrate **64**, derived from **63**, was heated (180 °C) in toluene, the IMDA product **65** was obtained (83% yield). The diene **64** was used as an *E*/*Z* (3:1) mixture, suggesting that *E*/*Z* isomerization was taking place under the reaction conditions and also that the (*E*)-diene cyclized preferentially. Synthesis of **61** was completed by deprotection of the phenolic methyl ether in **65**. On the other hand, treatment of the substrate **64** with a large excess of $BF_3 \cdot OEt_2$ at −78 °C produced the intramolecular [5 + 2] cycloadduct **66** (41% yield), along with **65** (22%). These total syntheses of (−)-**61** and (−)-**66** provide support for the biosynthetic proposal of elisabethane terpenoids.

The total synthesis of (+)-elisabethin A (**72**), the prototype of **61** and **66**, has recently been achieved by Heckrodt and Mulzer (Scheme 12).[42] The IMDA reaction of trisubstituted 1,4-quinone **70** was the key step in the construction of the elisabethane carbon skeleton. The IMDA precursor **69** was synthesized via the alkylation of Evans oxazolidinone derivative **67** with chiral iodide **68**. The di-O-silylated 1,4-hydroquinone **69** was deprotected with Bu_4NF and then oxidized with aqueous $FeCl_3$ to form the 1,4-quinone intermediate **70**, which spontaneously cyclized to produce adduct **71**. The significance of this IMDA reaction lies in the following: (1) the use of a terminal (*Z*)-olefin, (2) the unusually mild and virtually biomimetic conditions (aqueous medium, room temperature), and (3) the high yield and stereoselectivity. The facial selectivity of the diene−quinone attack is controlled by a minimization of allylic strain between the substituents at C9 and the quinoid carbonyl functionality in the endo transition state **70A**. Regioselective hydrogenation of **71**, followed by epimerization at C2 and deprotection, eventually led to (+)-**72**.

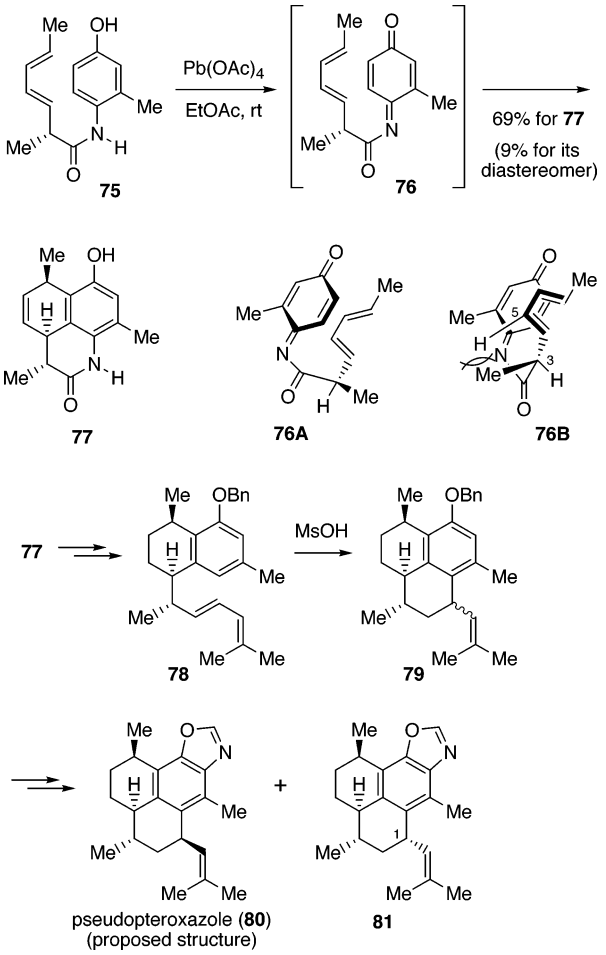
Scheme 13. Total Synthesis of (+)-Elisapterosin B by Rawal and Co-workers[43]



Rawal and co-workers have used a similar IMDA strategy in the synthesis of (+)-elisapterosin B (**66**) (Scheme 13).[43] Upon being heated in toluene, **73**, the enantiomeric and geometric isomer of Mulzer's intermediate **70**, underwent a smooth cycloaddition to afford the expected endo-adduct, *ent*-**71**, as a single diastereomer. The transition state **73A** avoids potentially severe allylic strain between the methyl group at C7 and propenyl unit on the cis-double bond. The crucial step in a later stage was the biosynthesis-inspired oxidative cyclization of **74**, derived from *ent*-**71**. Thus, treatment of **74** with $Ce(NH_4)_2(NO_3)_6$ provided (+)-**66**, an antipode of the natural enantiomer (−)-**66**.

The enantiospecific synthesis of a tetracyclic oxazole-containing compound **80**, previously assigned as the antitubercular marine diterpenoid pseudopteroxazole,[44] has been accomplished by Johnson and Corey (Scheme 14).[45] In their synthetic study, an oxidative IMDA reaction was developed. Treatment of chiral amide **75** with lead tetraacetate in ethyl acetate (room temperature) generated the corresponding quinone monoimide **76**, which spontaneously underwent an internal Diels−Alder addition to afford the endo-adduct **77** (69% yield) along with a small amount (9%) of its diastereomer. The endo-transition state **76A** leading to **77** involves no unfavorable steric factors, whereas **76B** involves a significant repulsion between the methyl substituent on the C3 stereocenter and the olefinic hydrogen at C5. Therefore, the observed high diastereoselectivity was realized. The major adduct **77** was transformed into

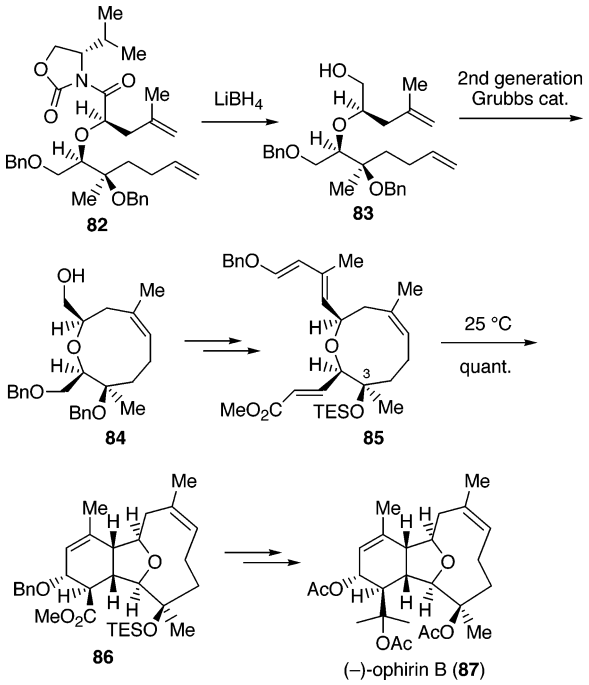
Scheme 14. Total Synthesis of (±)-Pseudopteroxazole (Proposed Structure) by Johnson and Corey[45]



78, which was subjected to a cationic aromatic alkylation to afford a tricyclic product **79** as a mixture of two diastereomers. This mixture **79** was separated. Both of these diastereomers were transformed into the proposed structure of pseudopteroxazole **80** and its (1*S*)-diastereomer **81** by a parallel four-step sequence. Neither **80** nor **81** was identical to natural pseudopteroxazole, indicating the need for a revision of the structure.

(−)-Ophirin B (**87**) is a cladiellane diterpenoid having a unique oxatricyclic ring system with seven stereogenic centers.[46] Quite recently, Crimmins and Brown reported the total synthesis of (−)-**87** using an IMDA strategy (Scheme 15).[47] First, an oxygen-containing nine-membered cyclic intermediate, such as **84**, was constructed via ring-closing metathesis. Thus, the functionalized oxazolidinone imide **82** was reduced to **83**, a long-chain ether possessing both olefin terminals. The intermediate **83** was then exposed to a second-generation Grubbs catalyst at 80 °C, leading to oxonene **84** and a trace amount of the dimer. The oxonene **84** was transformed into the IMDA substrate **85**, which was rapidly (room temperature) and quantitatively converted into the oxatricyclic system **86** as a single diastereomer. The use of the free form or a benzyl ether at the C3 hydroxyl resulted in significantly reduced diastereoselectivity and slower rates of the cycloaddition reaction. The cycloadduct **86** was then transformed to (−)-**87**.

Scheme 15. Total Synthesis of (−)-Ophirin B by Crimmins and Brown[47]

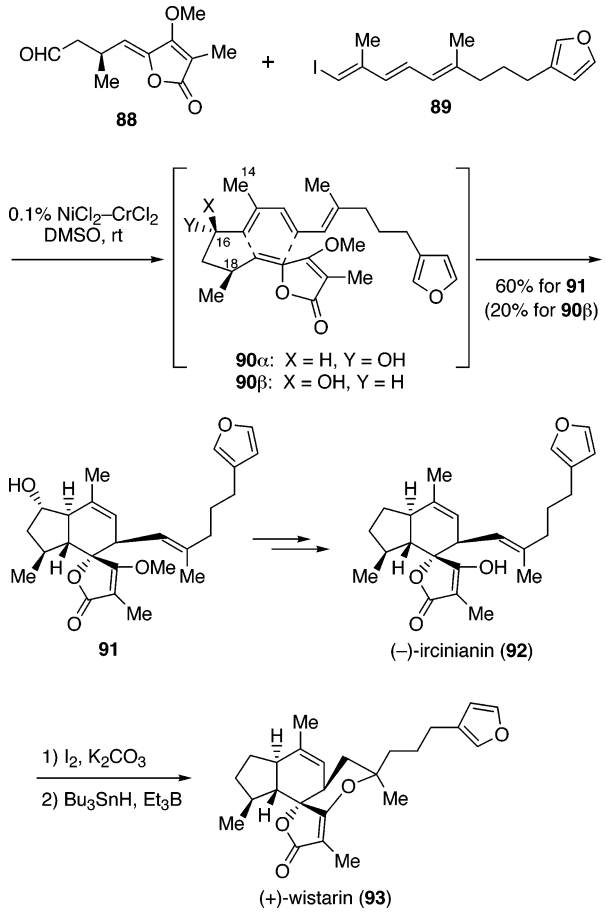


A variety of IMDA reaction approaches have been used in the total syntheses of other diterpenoids, such as (+)-gibberellins A_1 and A_3,[48] (±)-forskolin,[49] (−)-stypodiol,[50] (−)-spongiadiene,[51] (+)-quassin,[52] (+)-kalihinene X,[53] (±)-kalihinol C,[54] and (−)-sordaricin.[55]

2.3. Sesterterpenoids

(−)-Ircinianin (**92**) was isolated from a marine sponge,[56] and later its cyclic ether form (+)-wistarin (**93**) was also isolated.[57] They are both classified by structurally unique bicyclic furanosesterterpene tetronic acids. Uenishi and co-workers have completed total syntheses of (−)-**92** and (+)-**93** (Scheme 16).[58] The key step involves a $NiCl_2$−$CrCl_2$-mediated coupling reaction of **88**, a chiral aldehyde with a γ-methylene−butenolide substructure, and a conjugated triene with an iodo group and a furan at both terminals, that is, **89**. The coupling reaction was carried out in DMSO at room temperature. It is interesting that the targeted IMDA reaction occurred in the coupling reaction medium. Therefore, the coupling reaction proceeded to afford the desired diastereomeric alcohols **90α** and **90*β*** first. One of the two isomers, presumably **90α**, started to undergo smooth cycloaddition at the reaction temperature and eventually gave a single product **91** (60% yield). The other diastereomer **90*β*** did not proceed to the cyclization but remained in the reaction mixture. In comparison of the conformation of **90α** with that of **90*β***, the hydroxyl group at C16 completely eclipses the C14 Me group in **90*β***, but not in **90α**. The matching of 16*R* and 18*S* chiral centers in **90α** may have allowed the observed exo-cyclization, leading to the product **91**. Deoxygenation of the hydroxyl group introduced in **91**, followed by deprotection, provided (−)-**92**. Moreover, intramolecular iodo-etheration of (−)-**92** for the formation of a tetrahydropyran ring and radical-induced removal of the resulting iodide accomplished the total synthesis of (+)-**93**.

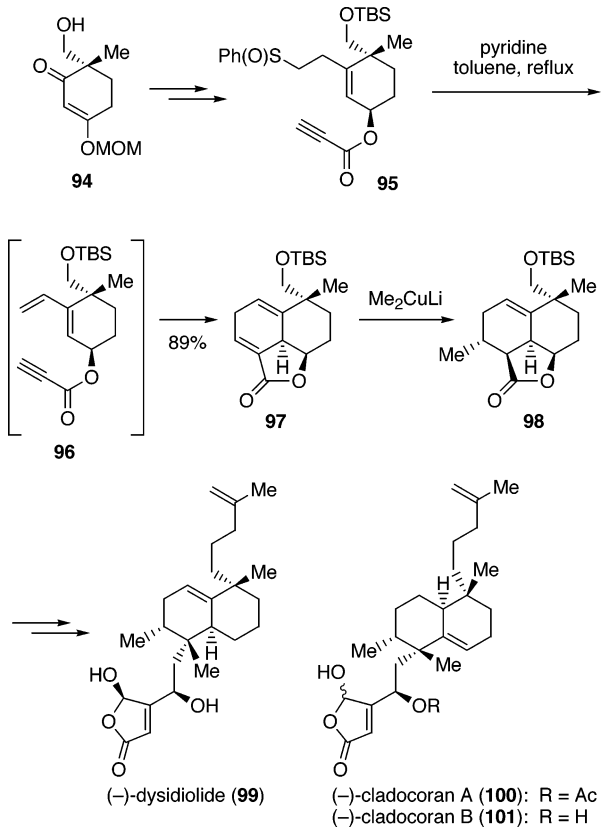
Scheme 16. Total Syntheses of (−)-Ircinianin and (+)-Wistarin by Uenishi and Co-workers[58]



(−)-Dysidiolide (**99**) is the first compound isolated as a natural inhibitor of protein phosphatase cdc25A, which is essential for cell proliferation.[59] (−)-Cladocorans A and B (**100** and **101**) possess structures closely related to that of dysidiolide.[60] Yamada and co-workers have reported the total syntheses of (−)-**99**, (−)-**100**, and (−)-**101** (Scheme 17).[61,62] For the construction of the highly functionalized octahydronaphthalene substructures in **99**−**101**, the core structure of these terpenoids, the Yamada group utilized an IMDA reaction approach. The total synthesis commenced with optically active cyclohexenone **94**, readily obtained by the lipase-catalyzed kinetic resolution of racemic **94**. A solution of ester **95**, derived from **94** after functionalization of the enone moiety, in toluene was refluxed in the presence of pyridine, generating once diene propiolic acid **96** by the elimination of phenyl sulfoxide. The spontaneous IMDA reaction of the resulting **96** provided a hexahydronaphthalene derivative **97** as the sole product (89% yield). The stereoselective 1,4-addition of a methyl group to **97** afforded **98**, which was eventually converted into (−)-**99**, (−)-**100**, and (−)-**101**. These syntheses revised the proposed structures of cladocorans A and B.

Liao and co-workers have developed IMDA reactions of masked *o*-benzoquinones. In the total syntheses of (±)-bilosespenes A and B (**108** and **109**), cytotoxic marine sesterpenic acids,[63] a combination of an IMDA reaction of a masked *o*-benzoquinone and the anionic oxy-Cope rearrangement of a synthetic

Scheme 17. Total Syntheses of (−)-Dysidiolide and (−)-Cladocorans A and B by Yamada and Co-workers[61,62]

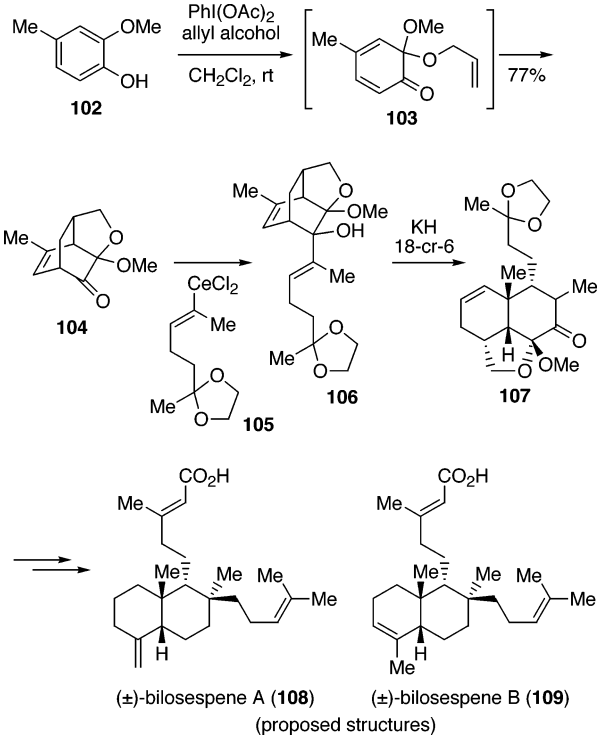


intermediate derived from the IMDA reaction were used for the stereoselective construction of a *cis*-octahydronaphthalene skeleton found in an advanced intermediate **107** (Scheme 18).[64] In the initial stage of the total synthesis, a cage-like tricyclic compound **104** was obtained via the IMDA reaction of masked *o*-benzoquinone with an allyloxy group **103**, which in turn was prepared in situ from 2-methoxy-4-methylphenol (**102**) by oxidation with diacetoxyiodobenzene in the presence of allyl alcohol. Treatment of the resulting IMDA adduct **104** with a vinylcerium reagent **105** provided a single stereoisomeric product **106**. The [3,3] sigmatropic rearrangement of **106** using potassium hydride in the presence of 18-crown-6 provided the desired rearranged product **107** via the expected anionic oxy-Cope rearrangement manner. This cis-fused octahydronaphthalene derivative **107** was transformed into the proposed bilosespenes (±)-**108** and (±)-**109** through some functional group manipulations. As a result, both NMR spectra of **108** and **109** were different from those reported for the natural products. Additionally, Liao and co-workers have reported the total syntheses of terpenoids such as (±)-2-oxo-*cis*-clerodadienoic acid[65] and (±)-pallescensin B[66] using the IMDA reaction of masked *o*-benzoquinones.

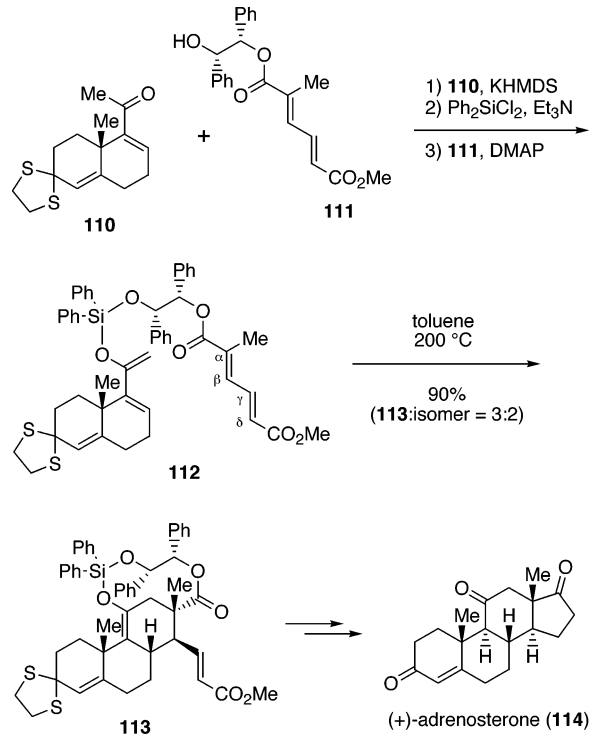
2.4. Steroids

Cortical steroids, some of which are prominent instances of active substances responsible for important biological functions, are secreted by the cortex of the adrenal glands in mammals.[67] Shea and co-

Scheme 18. Total Syntheses of (±)-Bilosespenes A and B (Proposed Structures) by Liao and Co-workers[64]

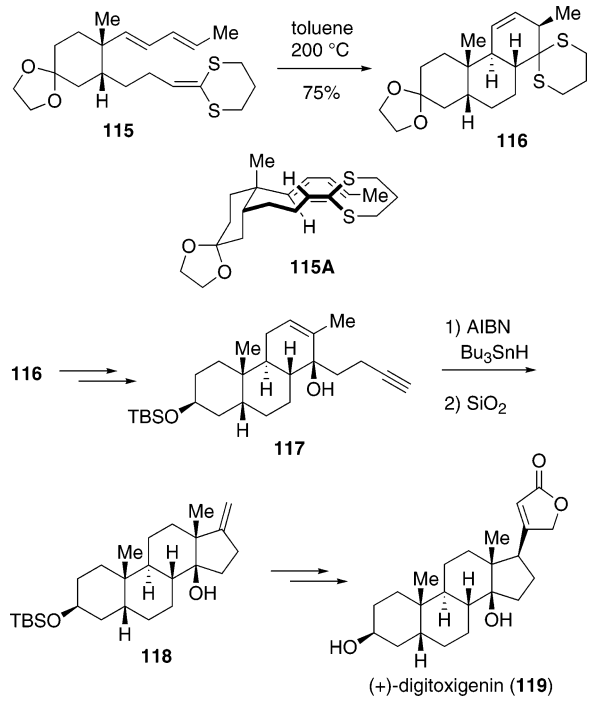


Scheme 19. Total Synthesis of (+)-Adrenosterone by Shea and Co-workers[68]



workers have reported the total synthesis of (+)-adrenosterone (**114**), a useful intermediate for cortical steroid synthesis (Scheme 19).[68] As a key step in the synthesis, they utilized a temporary union of the diene and dienophile parts for the targeted type 2 IMDA reaction to construct the C-ring of the steroid. Thus, the diene precursor **110** was prepared from (+)-Wieland−Miescher ketone. On the other hand, the

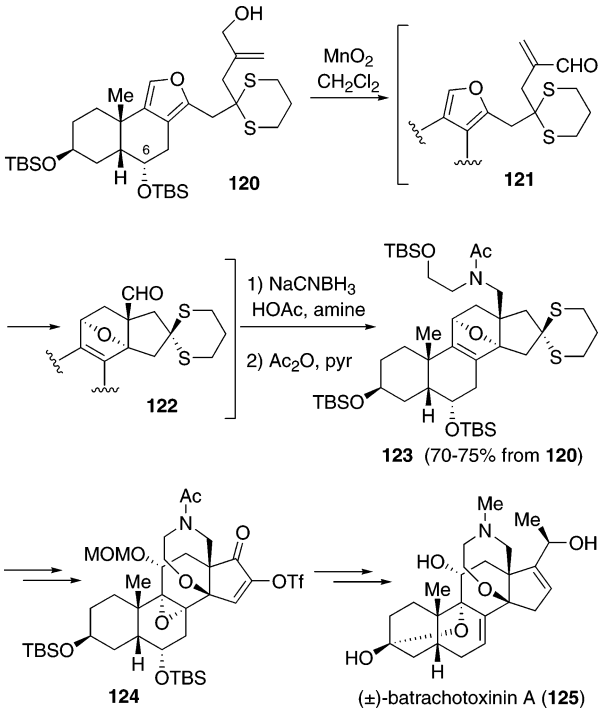
Scheme 20. Total Synthesis of (+)-Digitoxigenin by Stork and Co-workers[69]



dienophile precursor **111**, (*E*,*E*)-1-methyl-1,3-butadiene-1,4-dicarboxylic acid, possessing a (−)-hydrobenzoin auxiliary at one carboxyl terminal, was prepared from methacrylic acid. The diene and dienophile fragments, **110** and **111**, were joined through a temporary silyl acetal form. For this purpose, the diene part **110** was kinetically deprotonated, trapped as the diphenylchlorosilyl enolate, and then quenched with hydrobenzoin ester **111** to provide silyl acetal **112**. The type 2 IMDA reaction of **112** was carried out in toluene (200 °C) to afford a 3:2 mixture of **113** and its diastereomer (90% yield from **110**, based on 45% conversion). The cycloadducts arose through an exclusive endo-attack of the dienophile with complete regiochemical control (the α,β- vs γ,δ-double bond). With use of the achiral ethylene glycol tether instead of the (−)-hydrobenzoin auxiliary, remarkable π-facial selectivity was not realized. The tether in **113** was removed to produce the corresponding ketone, which was eventually converted into (+)-**114**.

Stork and co-workers have used an IMDA reaction strategy for the construction of the B/C ring system of (+)-digitoxigenin (**119**),[69] a biologically active cardenolide[70] (Scheme 20). The functionalized masked cyclohexanone derivative with a conjugated diene and a conjugated dithiane side chain, that is, **115**, was prepared from (+)-Wieland−Miescher ketone. The attempted IMDA reaction of **115** was conducted in toluene (200 °C), which provided exclusively the desired cycloadduct **116** (75% yield). This stereochemical outcome suggested that the endo transition state **115A** is the lowest energy conformation. Conversion of **116** into **117**, followed by radical cyclization with tributylstannane and destannylation, finally provided the entire A/B/C/D structure of **119**, that is, **118**, with the correct stereochemistry. The formation of the remaining butenolide moiety and deprotection completed the total synthesis.

Scheme 21. Total Synthesis of (±)-Batrachotoxinin A by Kishi and Co-workers[73]



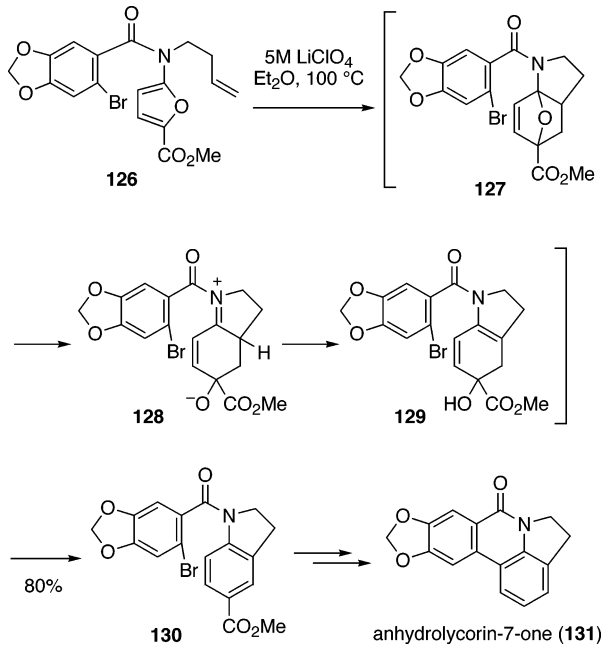
The batrachotoxins are a unique class of steroidal alkaloids, isolated in minute quantities from the skins of poison arrow frogs[71] as well as from the feathers of a New Guinea bird.[72] Kishi and co-workers have achieved the total synthesis of (±)-batrachotoxinin A (**125**) by using an intramolecular furan Diels−Alder reaction (Scheme 21).[73] The synthetic precursor **120** of the substrate **121** for the attempted IMDA reaction was prepared efficiently from (±)-Wieland−Miescher ketone. With MnO_2 the allylic alcohol **120** was oxidized to terminal enal **121**, which smoothly underwent an intramolecular [4 + 2] cycloaddition with the furan moiety. The resulting cycloadduct **122**, obtained highly stereoselectively, was directly subjected to reductive amination and then acetylation, affording a single product **123** (70−75% yield). The stereoselectivity of the IMDA reaction was dramatically influenced by the C6 substituent (OTBS group). In fact, a C6 deoxy analogue provided the corresponding cycloadduct in 3−4:1 diastereoselectivity, while the C6 β-OMPM derivative underwent [4 + 2] cycloaddition with poor (3:2) selectivity. The cycloadduct **123** was then transformed into **124** via an intramolecular oxy-Michael reaction. After further functional group manipulations, (±)-**125** was eventually synthesized.

3. Alkaloids

3.1. Amaryllidaceae Alkaloids

The alkaloids of the Amaryllidaceae family have attracted considerable attention among organic chemists due to their challenging synthetic structures and a wide range of pharmaceutical properties. Anhydrolycorin-7-one (**131**) is a member of the pyrrolophenanthridine class of alkaloids isolated from Amaryllidaceae plants.[74] Padwa and co-workers have investi-

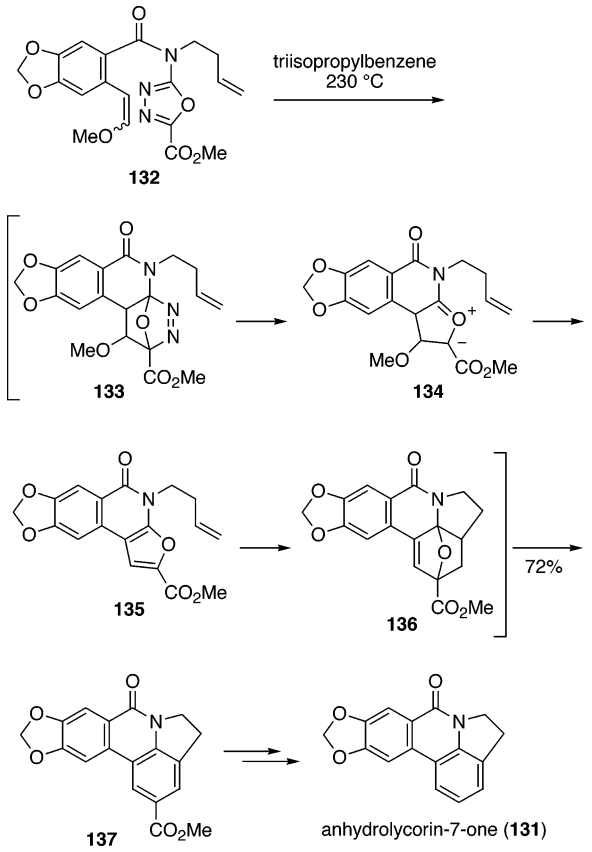
Scheme 22. Total Synthesis of Anhydrolycorinone by Padwa and Co-workers[75]



gated extensively the IMDA reaction of functionalized 2-aminofurans and achieved the total synthesis of **131** using this methodology (Scheme 22).[75] The amino group in the furan brings an alkene unit as a dienophile part. The IMDA reaction of an amidofuran, such as **126**, proceeded either thermally (165 °C) or by using the Grieco conditions[41] (ethereal $LiClO_4$ at 100 °C), providing **130**. The reaction is presumed to involve an initial [4 + 2] cycloaddition, as shown, to provide an oxa-bridged adduct **127**, which readily undergoes a nitrogen-assisted ring opening of the 7-oxabicyclo[2.2.1]heptane substructure, providing an intermediary iminium bicyclic zwitter structure **128**. Subsequent proton exchange, followed by the dehydration of **129**, provided eventually the aromatized product **130** (80% yield). Further functionalization to the target natural product **131** was accomplished by an intramolecular aryl−aryl coupling reaction, followed by decarboxylation. In addition, several synthetic approaches toward Amaryllidaceae alkaloids have been investigated by the Padwa group through the use of similar IMDA reactions of the 2-aminofuran derivatives containing a terminal alkenyl group.[76]

Boger and co-workers reported another total synthesis of anhydrolycorin-7-one (**131**), by applying one-pot 2-fold IMDA reactions of 2-amino-1,3,4-oxadiazoles (Scheme 23).[77] The Boger group developed the IMDA reactions of 2-amino-1,3,4-oxadiazoles, tethering an alkenyl functionality, which serves as a dienophile. This sophisticated strategy was effectively used for the total synthesis of **131**. Therefore, the IMDA reaction was subjected to thermal conditions for the construction of an advanced intermediate **137** in a single step by heating (230 °C) an N-functionalized 2-amino-1,3,4-oxadiazole-5-carboxylate **132**. The initial [4 + 2] cycloaddition afforded heterocycle **133**, which underwent the loss of N_2 to generate a carbonyl ylide **134**. This zwitterionic intermediate then aromatized through elimination of methanol, furnishing a furan intermediate **135**. Consistent with

Scheme 23. Total Synthesis of Anhydrolycorinone by Boger and Co-workers[77]



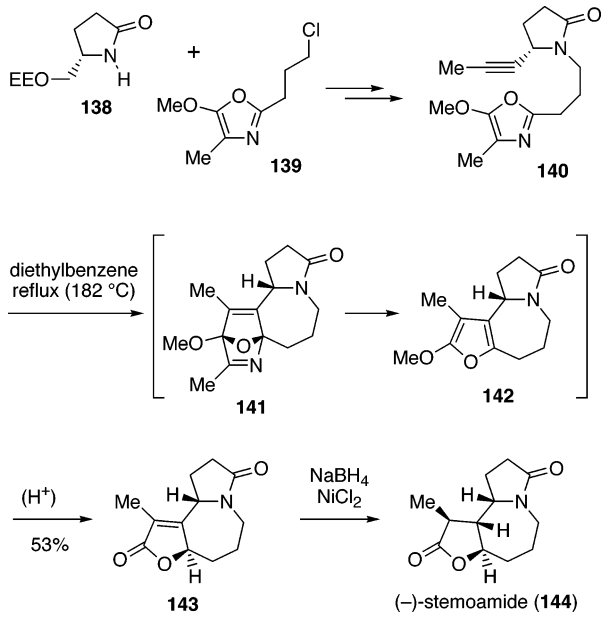
Padwa's precedents, such as the formation of **130** from **126**, the 2-amidofuran **135** proceeded to the similar IMDA reaction followed by aromatization with the removal of water, eventually providing **137**. The conversion of **137** into **131** was achieved by decarboxylation, as mentioned in Padwa's total synthesis. The Boger group employed analogous sequential IMDA reactions of *N*-acyl-6-amino-1,2,4,5-tetrazine in the total syntheses of anhydrolycorin-7-one (**131**) and hippadine.[78]

As another example of the total synthesis of Amaryllidaceae alkaloids, Hoshino and co-workers completed the total synthesis of (±)-lycorine using an IMDA strategy.[79]

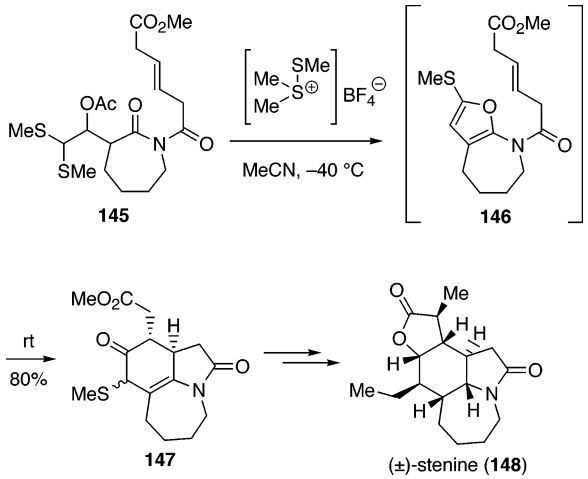
3.2. *Stemona* Alkaloids

Extracts of the *Stemona* species have been used in Chinese traditional medicines for many years. (−)-Stemoamide (**144**) is a member of the stemona class of alkaloids, which was isolated from *Stemona tuberosa*.[80] Jacobi and Lee used an IMDA−retro-Diels−Alder reaction sequence using the substrate **140**, consisting of a functionalized oxazole tethering an alkyne unit, to built up the tricyclic skeleton of (−)-**144** (Scheme 24).[81] The substrate for the IMDA reaction **140** was prepared by the N-alkylation of the L-pyroglutamic acid-derived γ-alkylated γ-lactam **138** and a highly functionalized oxazole **139**. When a solution of **140** in diethylbenzene was refluxed (182 °C), a single cycloadduct **143** was predominantly obtained (53% yield) after acid treatment. Initially,

Scheme 24. Total Synthesis of (−)-Stemoamide by Jacobi and Lee[81]



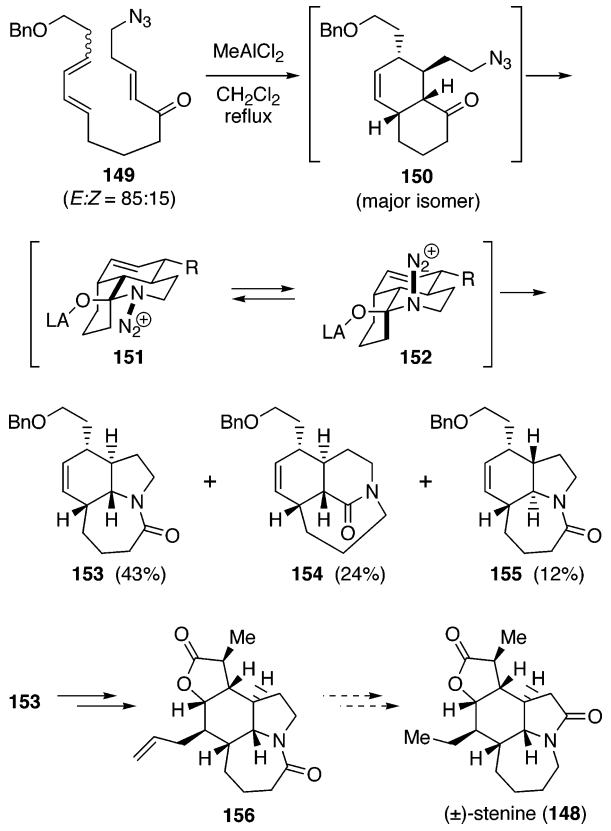
Scheme 25. Total Synthesis of (±)-Stenine by Ginn and Padwa[83]



this [4 + 2] cycloaddition of **140** formed a transient adduct **141** diastereoselectively, which suffered a rapid loss of acetonitrile, providing **142**, an N-bridged-head-heterocyclic compound with a fused 2-methoxyfuran. The mild acid hydrolysis of **142** provided a 5/7/5 tricyclic compound **143**, an advanced precursor of **144**. The remaining two stereocenters in (−)-**144** were introduced by a highly stereoselective 1,4-hydride addition to the unsaturated carbon−carbon bond in **143** using a $NaBH_4/NiCl_2$ system, followed by equilibration to the thermodynamically favored natural configuration.

(−)-Stenine (**148**) consists of a multifunctionalized perhydroindole core skeleton containing seven contiguous stereocenters.[82] The IMDA reaction of a 2-methylthio-5-amidofuran derivative such as **146** has been used by Ginn and Padwa to create the azepinoindole skeleton in (±)-**148** (Scheme 25).[83] The azepine ring was incorporated at an early stage of the synthetic sequence. Thus, methylsulfenylation of the bis(methylthio) group in azepine derivative **145** with dimethyl(methylthio)sulfonium tetrafluorobo-

Scheme 26. Formal Synthesis of (±)-Stenine by Golden and Aubé[84]



rate accelerated thionium-induced cyclization, and the resulting dihydrofuran rapidly lost acetic acid to furnish the bicyclic furan **146** as the IMDA substrate. The 2-methylthio-5-amidofuran **146** was not isolated under these conditions, but it rapidly cyclized and then rearranged to afford azepinoindole **147** (80% yield as a 1:1 mixture of diastereomers). This rearranged cycloadduct **147** was converted into (±)-**148** through a synthetic sequence, for example, (1) removal of the methylthio group, (2) stereoselective reduction of the carbonyl group, and (3) lactonization.

A combination of an IMDA reaction and an intramolecular Schmidt reaction was applied by Golden and Aubé for the formal synthesis of (±)-stenine (**148**) (Scheme 26).[84] The Lewis acid-mediated IMDA reaction of terminally carbon-elongated (*E*,*E*,*E*)-1,7,9-decatrien-3-one **149**, containing the (9*Z*)-isomer (*E*/*Z* = 85:15 mixture), with $MeAlCl_2$ in refluxing dichloromethane provided three tricyclic lactams **153**, **154**, and **155** (43%, 24%, and 12% yields, respectively). It has been proposed that both **153** and **154** form from the IMDA endo-cycloadduct **150** by a Lewis acid-mediated Schmidt reaction. Assuming the *antiperiplanar* bond migration, the intermediate **151** containing an equatorial diazonium ion would produce the major product **153**, whereas an axially oriented leaving group would give the bridged compound **154**. The minor product **155**, a diastereomer of **153**, was derived from an exo-cycloadduct of the initial IMDA reaction. The formal synthesis was completed by conversion of the major product **153** into the Hart intermediate **156**.[85]

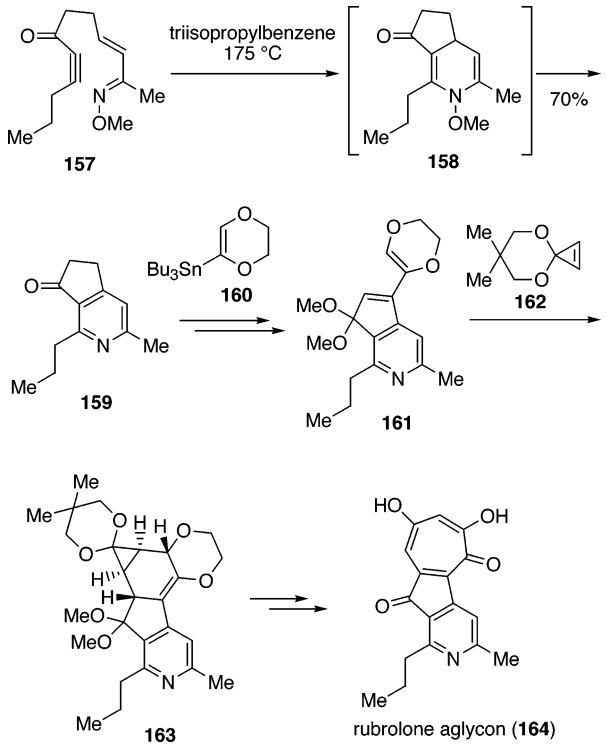
The Hart and Morimoto groups have independently utilized an IMDA reaction as the key step in the total synthesis of (±)- and (−)-stenine (**148**).[85,86]

3.3. Tropolone Alkaloids

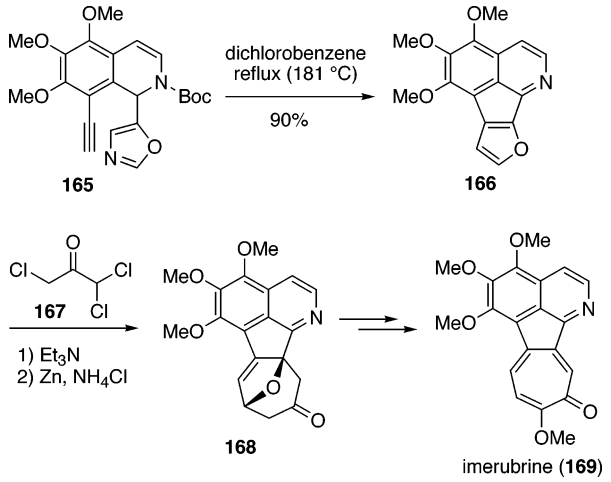
Rubrolone is a red tropolone alkaloid that possesses the unique azuleno[2,3-*c*]pyridine-2,5,13-trione aglycon **164**.[87] Boger and co-workers have developed the IMDA reaction of O-alkylated α,β-unsaturated oximes carrying an activated alkyne part, such as **157**, for the construction of 2,3,4,6-tetrasubstituted pyridines. Using this valuable methodology, the Boger group has accomplished the total synthesis of the rubrolone aglycon **164** (Scheme 27).[88] The hetero-IMDA reaction of the oxime **157** proceeded under thermal conditions (170−200 °C). The O-alkylated α,β-unsaturated oxime part serves as an effective 4π-component of the Diels−Alder reaction. The elimination of methanol from the [4 + 2] cycloadduct **158** occurred under the reaction conditions to provide an indanone-like pyridine analogue **159** directly (70% yield). By a method featuring the Stille coupling with a 1,4-dioxene **160** carrying a tributylstannyl group, **159** was converted into a more functionalized pyridine **161**. For the construction of the tropolone skeleton of **164**, the Diels−Alder reaction of **161** with the highly reactive cyclopropenone ketal **162** was conducted, providing a single cycloadduct **163** (even at room temperature). This cycloadduct **163** was eventually converted into **164** through an electrocyclic rearrangement accompanied by the cleavage of the cyclopropane ring.

Lee and Cha have used the IMDA reaction of an acetylene-containing isoquinoline-derived oxazole **165** in their total synthesis of imerubrine (**169**) (Scheme 28),[89] a tropoloisoquinoline alkaloid.[90] The pivotal IMDA reaction of the substrate **165**, which follows a

Scheme 27. Total Synthesis of Rubrolone Aglycon by Boger and Co-workers[88]



Scheme 28. Total Synthesis of Imerubrine by Lee and Cha[89]



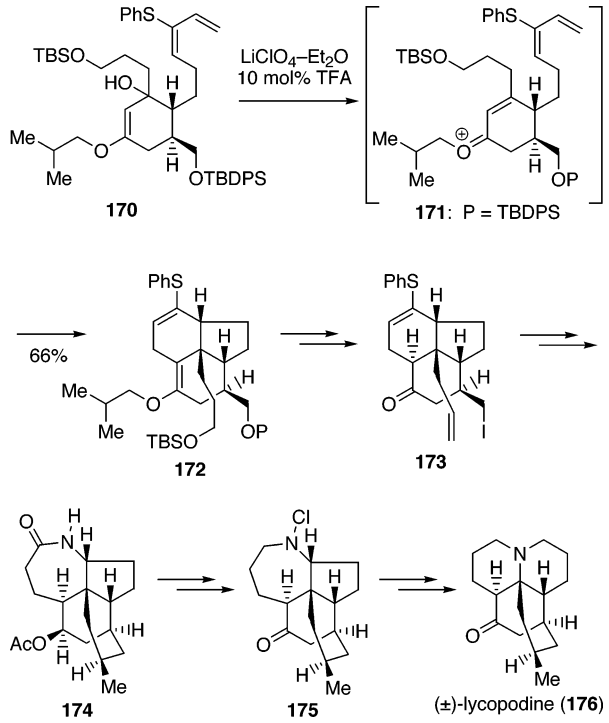
retro-Diels–Alder reaction with the elimination of hydrogen cyanide, almost as in Jacobi's work,[81] provided a tetracyclic compound **166** after the simultaneous removal of the Boc group. Remarkably this cyclization elimination event occurred smoothly in a one-pot operation under thermal conditions (*o*-dichlorobenzene, reflux, 90%). Through further synthetically notable reactions including the oxyallyl [4 + 3] cycloaddition reaction of **166** with α,α,α′-trichlorinated acetone **167**, the IMDA reaction product **166** was converted into the target compound **169** via the [4 + 3] cycloadduct **168**. The same group has also reported the total synthesis of (−)-colchicine, a related tropolone alkaloid, using a similar strategy.[91]

3.4. Quinolizidine Alkaloids

Grieco and co-workers have developed a synthetic methodology for the stereoselective construction of highly functionalized tricyclic carbon frameworks via the IMDA reactions of in situ-generated heteroatom-stabilized cationic species in polar media.[92] Grieco and Dai have extended this methodology to achieve the total synthesis of (±)-lycopodine (**176**) (Scheme 29),[93] one of the *Lycopodium* alkaloids.[94] Exposure of **170** to 10 mol % trifluoroacetic acid in 2 M $LiClO_4$–Et_2O provided tricyclic enol ether **172** (66% yield). This cycloaddition proceeds through in situ-generated allylic oxonium-stabilized species **171** in an exclusive exo-cyclization mode. As a result, the asymmetric quaternary carbon center in **176** was constructed stereoselectively. Further functional group elaboration from **172** features (1) the stereoselective radical cyclization between vinyl carbon and an iodomethyl group in an advanced intermediate **173**, (2) a Beckmann rearrangement leading to the formation of a seven-membered lactam **174**, and (3) the classic Stieglitz rearrangement[95] of an *N*-chloro cyclic amine **175** to introduce the bridgehead nitrogen in the final product (±)-lycopodine (**176**).

(+)-Aloperine (**184**) has been isolated from plants that have long been used in traditional Chinese medicine for the treatment of inflammation.[96] Overman and co-workers have reported the enantiospecific total synthesis of (+)-**184** (Scheme 30).[97] The central element of the synthetic strategy is an IMDA

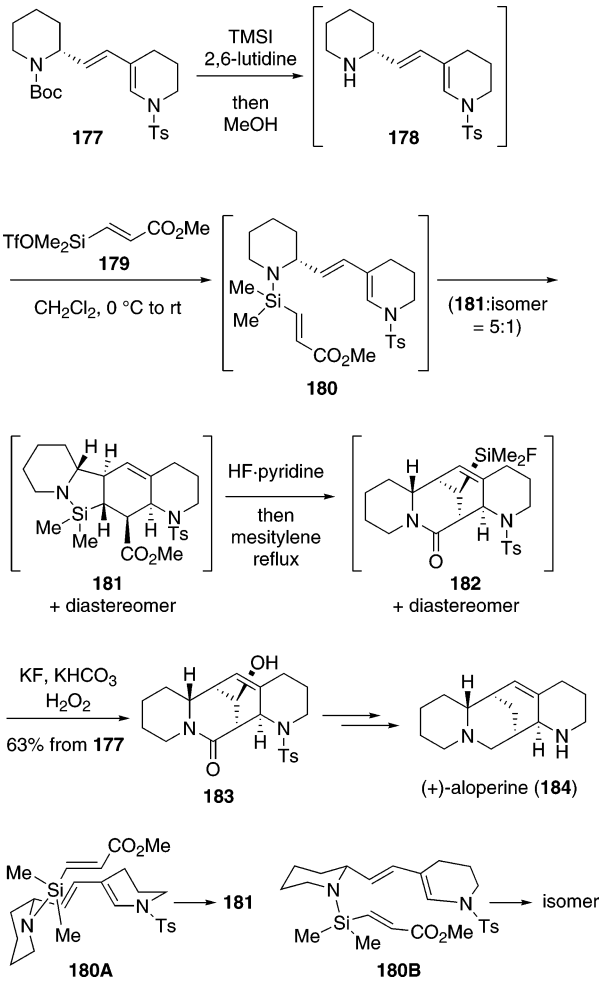
Scheme 29. Total Synthesis of (±)-Lycopodine by Grieco and Dai[93]



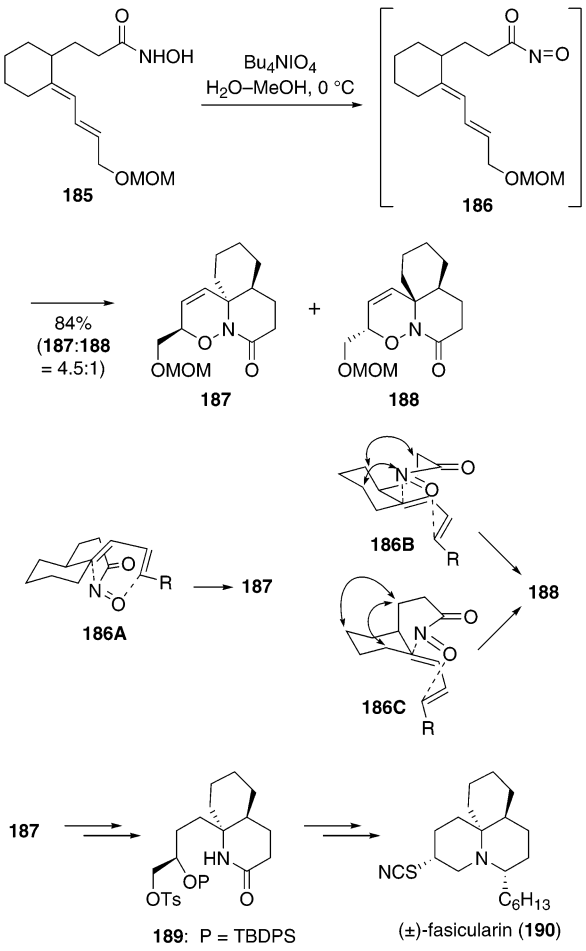
reaction, in which the cycloadducts are linked through an *N*-silylamine linkage. In their (+)-aloperine total synthesis, the starting sulfonamide **177** carrying a diene structure was prepared via the union of (*R*)-pipecolinic acid and 3-hydroxypiperidine hydrochloride. Removal of the Boc group in **177**, followed by coupling of the resulting piperidine free base **178** with *β*-silylated acrylic acid ester **179**, resulted in the formation of a 5:1 mixture of tetracyclic Diels–Alder adduct **181** and its diastereomer via a trialkylsilylamide **180**, the substrate for the expected IMDA reaction. The dimethylsilyl-tethered cycloaddition promoted preferential formation of **181** via **180A**, with the minor cycloadduct arising from the conformer **180B**. Treatment of this mixture of cycloadducts with anhydrous HF·pyridine cleaved the N–Si bond and placed a fluorine atom on the silicon. After the solvent changed to mesitylene, the mixture was heated (165 °C) to induce intramolecular *δ*-lactamization. The resulting tetracyclic compound **182**, equipped with the aloperine skeleton with correct stereochemistry, was subjected to typical Tamao–Fleming oxidation conditions. After chromatographic purification, homogeneous **183** was obtained efficiently (63% overall yield from **177**). For the total synthesis of (+)-**184**, three additional steps were required.

The tricyclic marine quinolizidine-type alkaloid fasicularin (**190**) shows selective activity against a DNA repair-deficient organism.[98] The acylnitroso group-mediated Diels–Alder strategy, extensively explored by Kibayashi and co-workers, was employed by them for the synthesis of some alkaloids, culminating in the total synthesis of (±)-**190** (Scheme 31).[99] Upon oxidation of cyclohexane carrying a conjugate diene and a three-carbon hydroxamic acid, that is, **185**, with Bu_4NIO_4 in aqueous MeOH (0 °C), the in

Scheme 30. Total Synthesis of (+)-Aloperine by Overman and Co-workers[97]



Scheme 31. Total Synthesis of (±)-Fasicularin by Kibayashi and Co-workers[99]

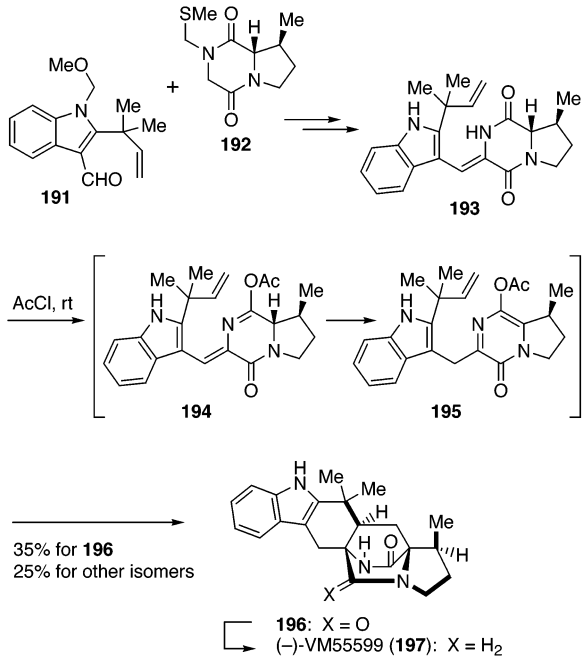


situ-generated acylnitroso compound **186** cyclized facilely, providing a mixture of trans- and cis-fused δ-lactams, **187** and **188**. On the other hand, the conventional nonaqueous conditions using $CHCl_3$ for this cyclization showed low diastereoselection (2.1:1) and low yield (58%). The use of an aqueous medium significantly enhanced the desired trans-selectivity (4.5:1) as well as yield (84%). The anti-facial preference observed in the cycloaddition of **186** can be rationalized in terms of endo transition states **186A**−**C**. The syn-facial transition state conformer **186B** or **186C** leading to the cis-fused adduct **188** would produce repulsive interactions as depicted. Thus, avoidance of these unfavorable steric interactions should lead to the most favored anti-facial conformer **186A**, affording the trans-fused adduct **187**. These isomers **187** and **188** were separated chromatographically. The major trans-fused adduct **187** was then manipulated toward the final product (±)-**190** via a N−O bond-cleaved intermediary tosylate **189**. From the common intermediate **187**, the synthesis of (±)-lepadiformine was also completed. Furthermore, the use of an acylnitroso Diels−Alder reaction has been employed for access to other alkaloids such as (−)-lepadins,[100] (+)-azimine, and (+)-carpaine[101] by the Kibayashi group.

3.5. Indole Alkaloids

(−)-VM55599 (**197**) is a member of the paraherquamide family, which shares the diketopiperadine-based 2,5-diazabicyclo[2.2.2]octane ring system as a common substructure that has been proposed to arise through a [4 + 2] cycloaddition involving an isomerized isoprene moiety attached at the α-carbons of the indole nucleus.[102] The total synthesis of (−)-**197** has been achieved by Williams and co-workers, featuring the IMDA reaction of an advanced intermediate such as **195** (Scheme 32).[103] In the initial stage of the total synthesis, a chiral bicyclic diketopiperazine **192** was prepared from L-isoleucine. The aldol-like condensation of **192** with indolic aldehyde carrying an isomerized isoprene substituent, that is, **191**, provided **193** after deprotection. When compound **193** was treated with acetyl chloride, a [4 + 2] cycloadduct bearing a 2,5-diazabicyclo[2.2.2]octane substructure **196** (35% yield) and its two diastereomers (25%) were obtained. It is reasonable to explain the mechanism of this cycloaddition as follows: (1) the acetylation of **193** to yield the O-acylated six-membered lactim **194**, (2) tautomerization of **194** to azadiene **195**, which suffers a hetero-Diels−Alder reaction, and (3) the loss of an acetyl group from the cycloadduct. This cyclization process is most likely due to the biosynthetic construction of the natural product. Finally, regioselective reduction of one of the amido carbonyls in **196**

Scheme 32. Total Synthesis of (−)-VM55599 by Williams and Co-workers[103]

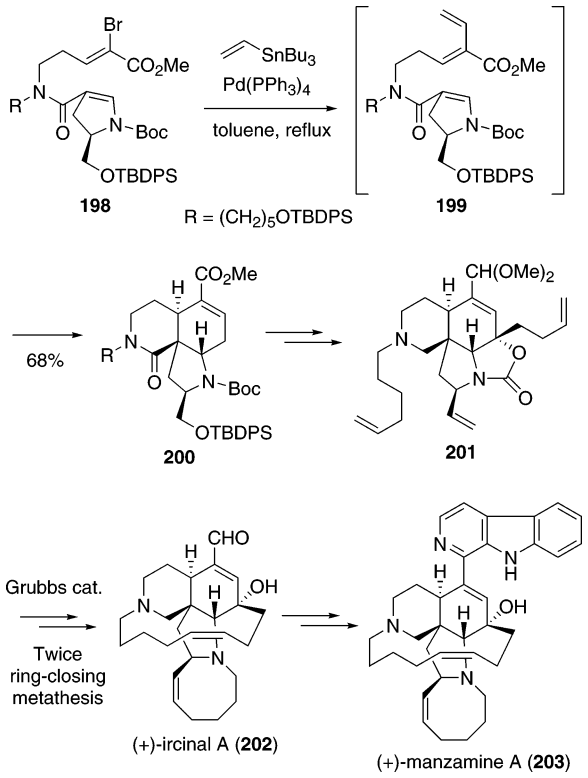


provided (−)-**197**, which concluded the absolute stereochemistry of the natural product.

The manzamines constitute a growing family of structurally complex indole alkaloids that have been isolated from marine sponges found in the Okinawa Islands, Japan. (+)-Manzamine A (**203**) exhibits potent antitumor activity in a number of assay systems.[104] A marine natural product (+)-ircinal A (**202**), a possible biosynthetic precursor of (+)-manzamine (**203**), has been isolated.[105] Martin and co-workers have demonstrated the potency of the IMDA reaction for facile entry to the 6/6/5 tricyclic core of **202** and **203** (Scheme 33).[106] In the initial stage of their total synthesis, a functionalized chiral dehydropyrrolidine **198** was prepared from commercially available (5*S*)-5-(hydroxymethyl)-2-pyrrolidinone. Reaction of **198** with vinyl tributylstannane in the presence of a Pd(0) catalyst produced the intermediary Stille coupling product **199**, which spontaneously gave rise to an IMDA reaction, providing the cycloadduct **200** as a single product (68% yield). In this sequential Stille/Diels−Alder reaction, the single stereocenter existing in the substrate **198** defined the absolute and relative stereochemistry of the three newly introduced stereogenic centers in **200**. From the tricyclic compound **200**, ring-closing metathesis reactions were employed twice to form the 13- and 8-membered rings in **202** via **201**, eventually leading to the natural product (+)-**202**. Furthermore, the total synthesis of (+)-manzamine A (**203**) itself was completed from (+)-**202**, as followed by the synthetic strategy reported by the Kobayashi group.[105]

In addition to the above-mentioned examples of the total synthesis of the indole alkaloids, the potential of an IMDA reaction has been strengthened through the total synthesis of other indole alkaloids such as (+)-*cis*-trikentrin B,[107] (±)-eburnamonine,[108] (±)-albifloranine,[109] (−)-vindoline,[110] (±)-alloyohimbane,[111]

Scheme 33. Total Syntheses of (+)-Ircinal A and (+)-Manzamine A by Martin and Co-workers[106]

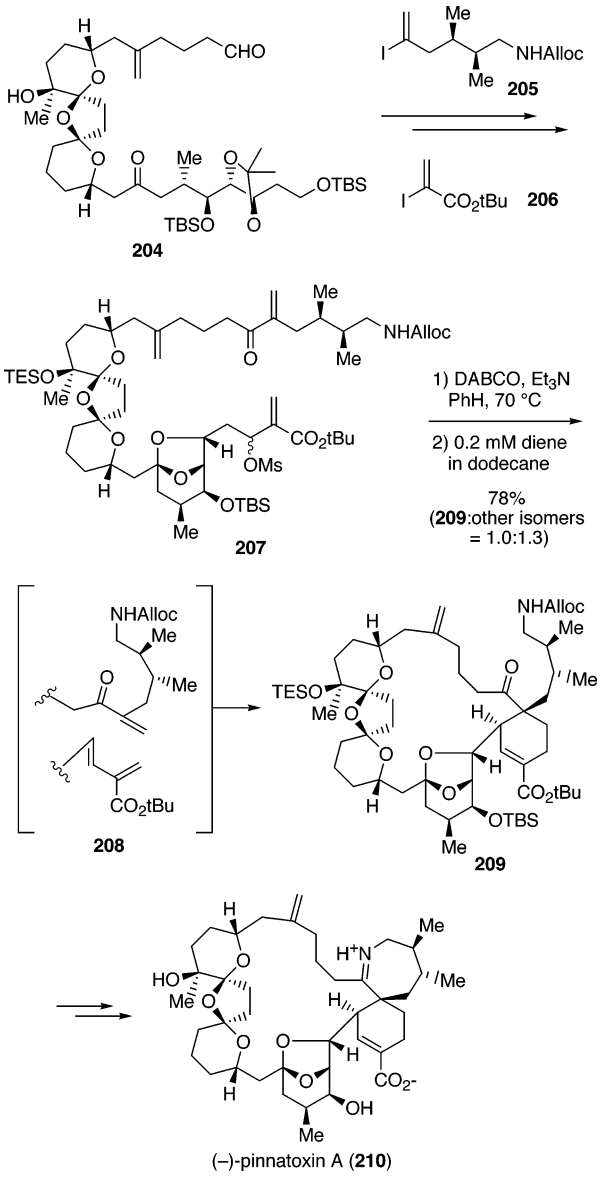


(−)-normalidine,[112] (−)-coronaridine,[113] (−)-suaveoline,[114] and natural minovine.[115]

3.6. Other Alkaloids

Uemura and co-workers have isolated (+)-pinnatoxin A (**210**), which is one of the major toxins responsible for outbreaks of *Pinna* shellfish intoxication in China and Japan.[116] The total synthesis of (−)-**210** has been accomplished by Kishi and co-workers, who relied on Uemura's biosynthetic proposal, which entails an IMDA reaction to construct the macrocyclic part of the natural product (Scheme 34).[117] The highly functionalized diene precursor **207**, which already contains most requisite skeletal carbons and the characteristic contiguous spirocyclic polyketal portions, was prepared from a highly functionalized bis-spiroketal **204** by using sequential Ni(II)/Cr(II)-mediated couplings with vinyl iodides **205** and then **206** at both side chain terminals. The diene part was introduced via the S_N2' displacement of the allylic mesylate in **207** with DABCO, followed by the removal of a proton by treatment with triethylamine. Upon concentration, the resulting labile IMDA substrate **208** readily underwent complete dimerization. However, heating a 0.2 mM solution of **208** in a variety of solvents led to the desired IMDA reaction. Using dodecane as a solvent, the ratio of the desired exo-product **209**, one undesired exo-product, and one endo-product was 1.0:0.9:0.4 (78% combined yield). In a later stage of the total synthesis, an intramolecular cyclic imine formation for the construction of the 6/7-spiro-ring system was subjected to the IMDA product **209**. With remarkable success, the cycloadduct **209** was eventually converted into (−)-**210**. This outstanding total synthesis established the absolute

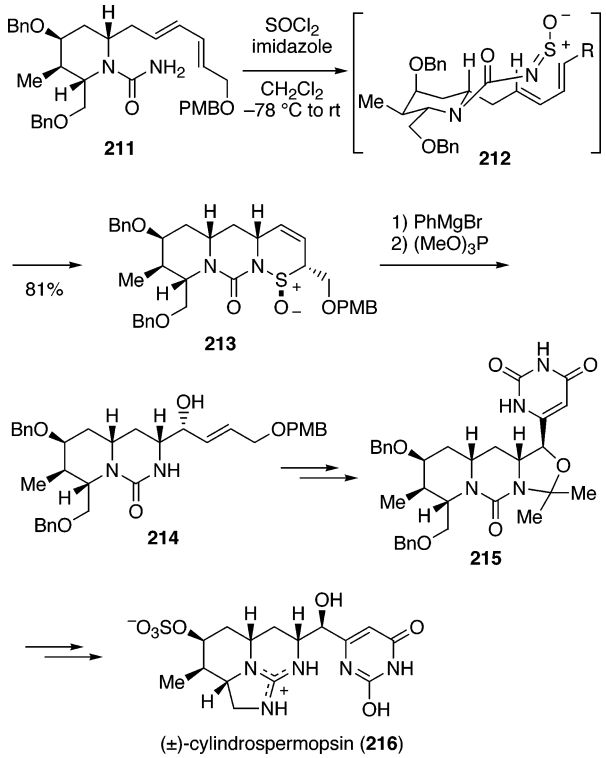
Scheme 34. Total Synthesis of (−)-Pinnatoxin A by Kishi and Co-workers[117]



stereochemistry of natural pinnatoxin A as the antipode of the structure (−)-**210**.

A freshwater blue-green alga (cyanobacterium) has long been known to produce a toxic substance causing symptoms of hepatotoxicity. The toxin, cylindrospermopsin (**216**), consists of an unprecedented guanidinium-containing polycyclic structure.[118] Utilizing the IMDA reaction of an *N*-sulfinylureido-containing piperidine such as **212**, Weinreb and co-workers have achieved the total synthesis of (±)-**216** (Scheme 35).[119] Treatment of **211**, a chiral piperidine derivative carrying a urea moiety, with thionyl chloride/imidazole resulted in the formation of a single cycloadduct **213** (81% yield). It is apparent that this tricyclic dihydrothiazine oxide **213** was formed through the IMDA reaction of the transient *N*-sulfinylurea **212** with a high level of diastereoselectivity. This result can be rationalized by assuming that cycloaddition of a (*Z*)-*N*-sulfinyl urea occurs via the conformation shown in **212**. The cycloadduct **213** underwent a ring-opening, stereospecific [2,3]-sigmatropic rearrangement to produce a bicyclic compound **214**.

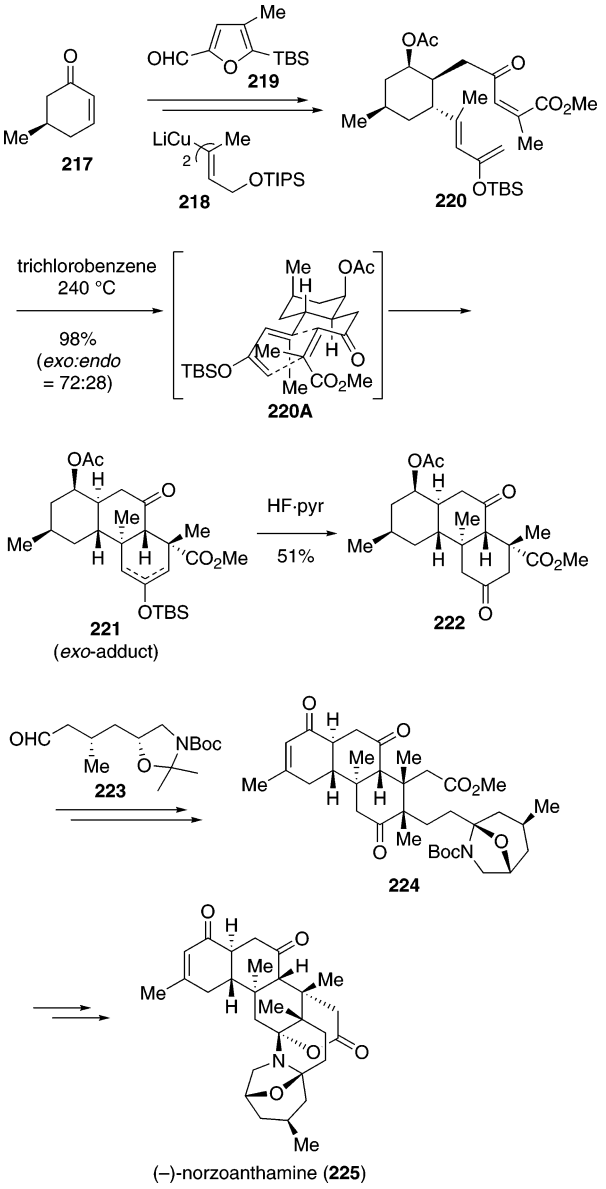
Scheme 35. Total Synthesis of (±)-Cylindrospermopsin by Weinreb and Co-workers[119]



The installation of a uracil nucleus to **214** providing an advanced intermediate **215** and finally the construction of the guanidine moiety completed the total synthesis of (±)-**216**.

(−)-Norzoanthamine (**225**), a heptacyclic aminal-containing alkaloid isolated from the marine colonial zoanthids, suppresses the loss of bone weight and strength in ovariectomized mice.[120] In addition to this physiological effect, norzoanthamine derivatives strongly inhibit the growth of P388 murine leukemia cell lines and human platelet aggregation. The total synthesis of (−)-**225** has been completed by Miyashita and co-workers through a formidable IMDA reaction for the construction of the tricyclic system with two quaternary asymmetric carbon centers (Scheme 36).[121] In an early stage of the total synthesis, the substrate **220** for the targeted IMDA reaction was synthesized starting from a chiral cyclohexanone **217**, featuring a three-component coupling reaction. Therefore, the conjugate addition of a vinylcupurate **218** to **217** followed the aldol reaction with a functionalized furaldehyde **219**. After some conventional functional group transformations, the substrate **220** was synthesized from the resulting highly functionalized cyclohexane derivative. The thermal (240 °C) IMDA reaction of **220** proceeded with high yield by the dropwise addition of a solution of **220** in 1,2,4-trichlorobenzene into the same solvent, which gave rise to a 72:28 mixture of the exo-adduct **221** and the endo-adduct (98% combined yield). Thus, the IMDA reaction of **220** occurred stereoselectively through the exo transition state **220A**. When this mixture was treated with hydrogen fluoride−pyridine, the trans−anti−trans-fused tricyclic compound **222** was obtained (51% yield). After some transformations from

Scheme 36. Total Synthesis of (−)-Norzoanthamine by Miyashita and Co-workers[121]



the cycloadduct **222**, a six-carbon aldehyde unit **223**, which possesses a protected vicinal amino alcohol part, was introduced eventually producing **224** after further functional group transformations. The final aminoacetalization of **224** culminated in the total synthesis of (−)-**225**.

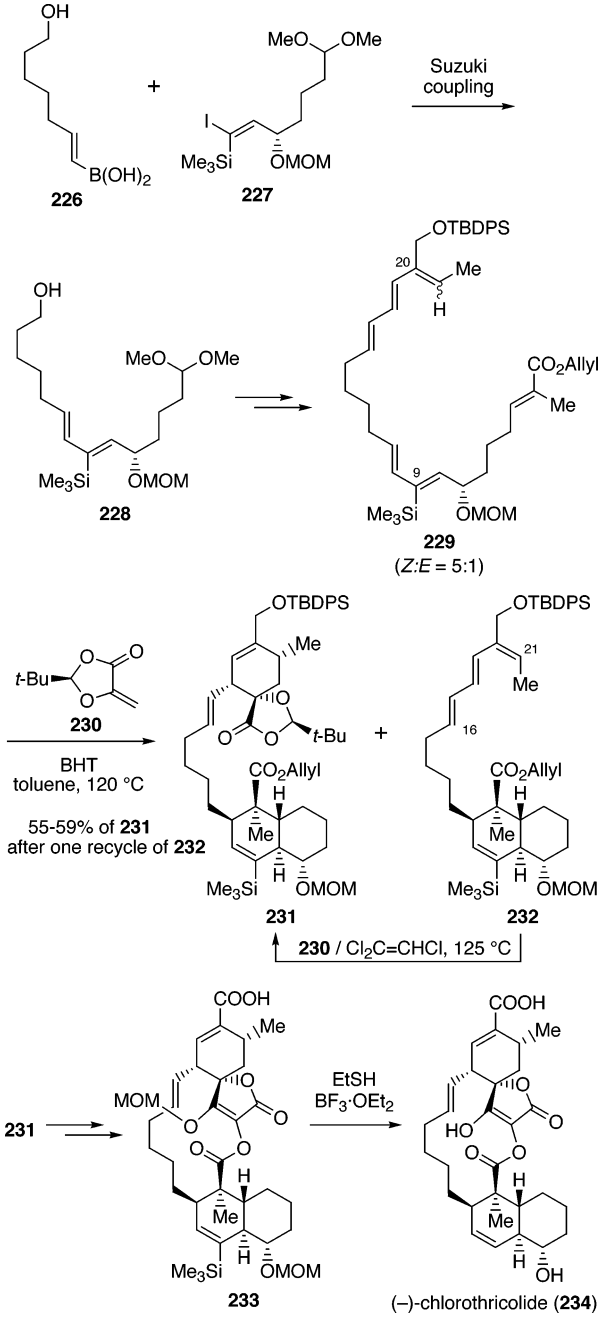
Total syntheses of other structurally interesting alkaloids such as (+)-himbacine and (+)-himbeline,[122−124] (+)-himandravine,[125] (±)-keramaphidin B,[126] cerpegin,[127] and luotonin A[128] using various kinds of IMDA reactions have been reported.

4. Polyketides

4.1. Chlorothricolide and Tetronolide

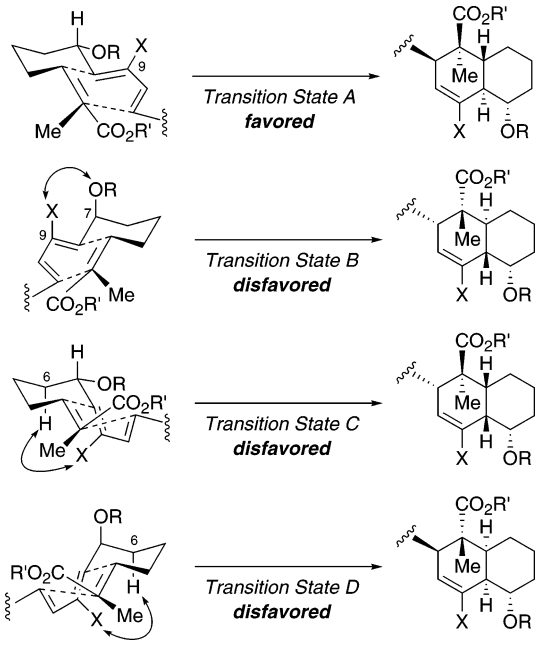
(−)-Chlorothricolide (**234**) is the aglycon of chlorothricin, which was isolated from *Streptomyces antibioticus*.[129] Chlorothricin is an inhibitor of pyruvate carboxylase and is also active against Gram-positive

Scheme 37. Total Synthesis of (−)-Chlorothricolide by Roush and Sciotti[130]



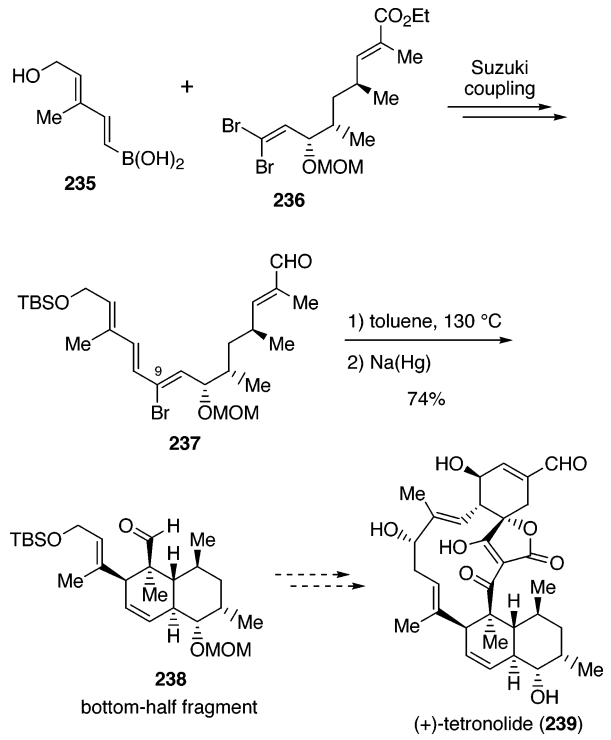
bacteria. The enantioselective total synthesis of (−)-**234** has been completed by Roush and Sciotti via a route involving the simultaneous inter- and intramolecular Diels−Alder reactions of a 21-carbon linear substrate with six carbon−carbon double bonds, that is, **229**, and an enolate-protected form of pyruvate **230** as a dienophile (Scheme 37).[130] The substrate **229** was synthesized by the Suzuki coupling of (*E*)-vinylboronic acid with a 5-hydroxypentyl substituent, that is, **226**, and a functionalized vinyl iodide with a trimethylsilyl group at the vinyl carbon, that is, **227**. This coupling reaction constructed a silicon-containing conjugate diene structure, providing **228**. This diene **228** was further elaborated to the IMDA substrate **229** (20*Z*/20*E* = 5:1) for the targeted IMDA reaction through sequential Horner−Emmons-type olefinations. The crucial simultaneous inter- and

Scheme 38. Steric Directing Group Strategy[27]



intramolecular Diels–Alder reactions were performed by heating a mixture of **229** and **230** in toluene (120 °C). As a result, the expected doubly cyclized product **231** was obtained (40–45% yield), along with other cycloadduct isomers (19%) and the IMDA adduct **232** possessing the (*E*,*E*,*E*)-C16–C21 triene part (25–30%). Notably, the intermolecular [4 + 2] cycloaddition of **229** occurred with strict regioselectivity regarding the upper conjugate triene part. The last IMDA product **232** was independently subjected to the intermolecular Diels–Alder reaction with **230** (125 °C), providing an additional **231**. After one recycle, the desired octahydronaphthalene derivative **231** was obtained practically (total 55–59%). This intermolecular Diels–Alder reaction shows high diastereofacial and exo-selectivity of the chiral dienophile **230**, which enables the introduction of the desired relative and absolute stereochemistry for the three stereocenters in the top half fragment. Also, the steric effect of the C9-trimethylsilyl group in **229** plays a key role, serving as the stereochemical controlling element for the IMDA reaction. The IMDA reactions of a series of C7-alkoxy-substituted (2*E*,8*Z*,-10*E*)-undecatrienoates containing C9-bromo or C9-trimethylsilyl substituents were previously studied by Roush (Scheme 38).[27] Cis-fused transition states C and D suffer from serious interactions between C9-X and the axial H6, while trans-fused transition state B is destabilized by a 1,3-eclipsing interaction with the C7-alkoxy group. Only trans-fused transition state A suffers from no serious interactions involving the C9 steric directing group. Therefore, the IMDA reaction of **229** led to the bottom half octahydronaphthalene unit of **234** with the desired stereoinduction. Elaboration of **231** to the protected form of (−)-chlorothricolide (**234**), that is, **233**, was accomplished by a conventional reaction sequence, including the construction of the spiro-tetronate subunit and macrolactonization of the seco acid. Finally, removal of the MOM ethers and cleavage of the trimethylsilyl substituent were carried out simultaneously by treatment of **233** with EtSH and $BF_3{\cdot}OEt_2$ to provide (−)-**234**.

Scheme 39. Formal Synthesis of (+)-Tetronolide by Roush and Co-workers[131]

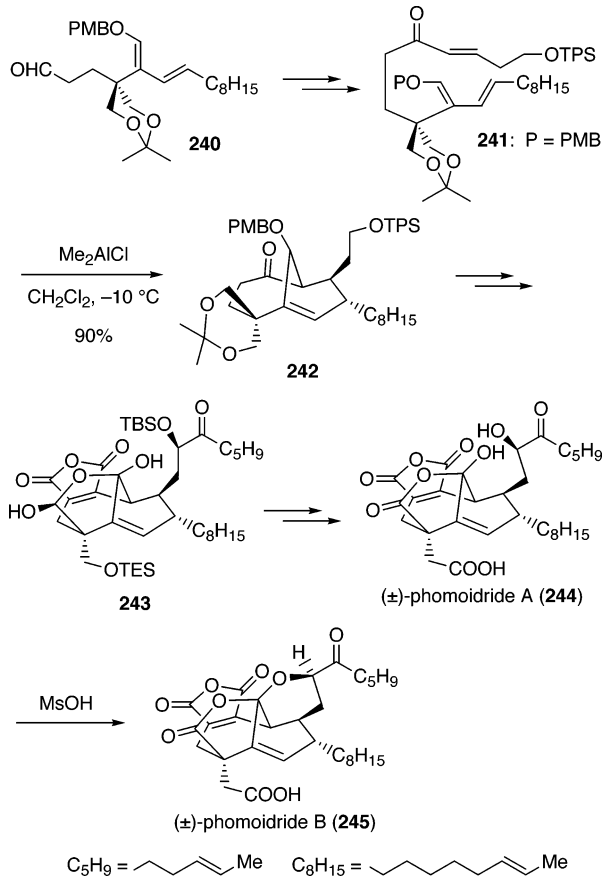


Roush and co-workers have also applied the steric-directing group effect on the IMDA reaction[27] to realize the highly stereoselective synthesis of the bottom half fragment of (+)-tetronolide (**239**) (Scheme 39),[131] the aglycon of the tetrocarcins.[132] Therefore, unsaturated ester with an α,α-dibromoolefin terminal **236** underwent cross-coupling with vinylboronic acid **235** under modified Suzuki coupling conditions to provide the C9-bromo-substituted tetraenoate, which was then converted into unsaturated aldehyde **237**, the substrate for the targeted IMDA reaction. A toluene solution of **237** was heated (130 °C), providing the desired cycloadduct as a single diastereomer. Subsequent reductive removal of the C9-bromo steric-directing group by using 5% Na(Hg) provided the tetronolide bottom half fragment **238** (74% yield from **237**). The compound **238** served as a key synthetic intermediate in Yoshii's total synthesis of (+)-**239**.[133]

4.2. Phomoidrides

Phomoidrides A and B (**244** and **245**) were isolated from the culture broth of an unidentified fungus and were shown to inhibit squalene synthase, as well as Ras farnesyl transferase.[134] In addition to these intriguing biological activities, phomoidrides exemplify architectures of unprecedented molecular connectivity and complexity. Nicolaou and co-workers have used a type 2 IMDA reaction for the construction of the central bicyclic core of the phomoidrides and achieved the total syntheses of (±)-**244** and (±)-**245** (Scheme 40).[135] As a key substrate for the IMDA reaction, the prochiral conjugate diene **241**, carrying an (*E*)-unsaturated ketone moiety as a dienophile, was prepared from dimethyl malonate via 2-alkylated

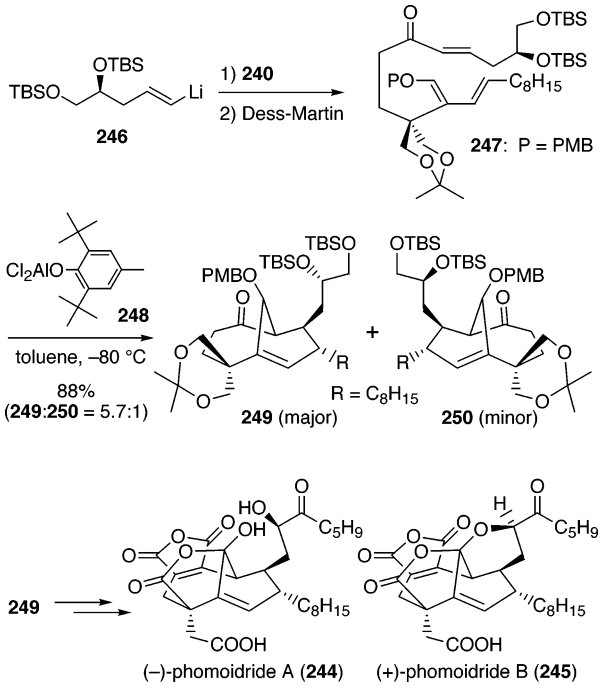
Scheme 40. Total Syntheses of (±)-Phomoidrides A and B by Nicolaou and Co-workers[135]



1,3-butadiene **240**, installing an aldehyde terminal. The IMDA reaction of **241** was remarkably facilitated (−10 °C) by a catalytic amount of Me_2AlCl, affording exclusively the expected cycloadduct **242** (90% yield). The Diels−Alder product **242** was elegantly converted into an advanced intermediate **243** through the elongation of the "upper" side chain, installation of the maleic anhydride moiety, and construction of the characteristic γ-hydroxy lactol functionality. A one-carbon homologation of the "lower" side chain for the carboxylic acid construction succeeded eventually in furnishing (±)-**244**. Furthermore, direct treatment of **244** with methanesulfonic acid resulted in quantitative conversion into another natural product (±)-**245**.

Nicolaou and co-workers have approached asymmetric total syntheses of phomoidrides for the establishment of their absolute configurations (Scheme 41).[136] The Nicolaou group has employed a similar IMDA strategy to achieve the substrate-directed diastereoselectivity observed in the aforementioned racemic version. The enantiopure substrate **247** for the IMDA reaction was prepared by the coupling of chiral vinyllithium with a vicinal diol system, that is, **246**, which was derived from (*R*)-glycidol, with the aldehyde **240**, followed by oxidation of the resulting carbinol. The bulky dienophile terminal in **247** was envisaged to influence the π-facial selectivity of the IMDA reaction. The Lewis acid-promoted IMDA reaction of **247**, however, resulted in a low diastereomeric excess. After some trials, a bulky Lewis acid catalyst **248** was found to effect a satisfactory result.

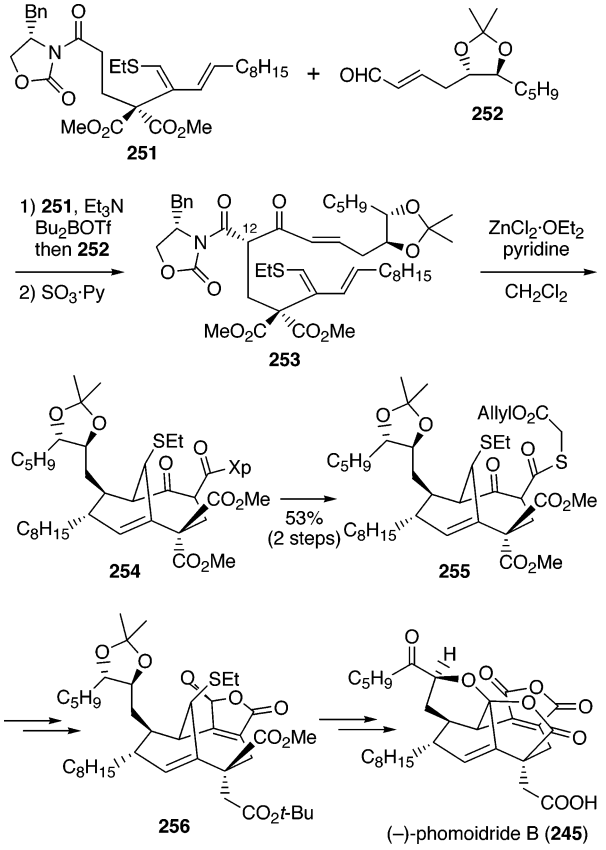
Scheme 41. Total Syntheses of (−)-Phomoidride A and (+)-Phomoidride B by Nicolaou and Co-workers[136]



Thus, in the presence of **248** (20 mol %, −80 °C), the cycloaddition proceeded to produce a 5.7:1 mixture of **249** and **250** (88% combined yield). By using the established route for the racemic version, the major adduct **249** was efficiently converted to (−)-**244** and then (+)-**245**, both antipodes of natural products.

Fukuyama and co-workers have reported the total synthesis of natural (−)-phomoidride B (**245**), in which a type 2 IMDA reaction has been utilized for the preparation of strained bicyclic carbocyclic intermediate **254** (Scheme 42).[137] A 2-functionalized 1,3-butadiene with an ethylthio group at the diene terminal, that is, **251**, was prepared from *N*-acryloyl-(*S*)-4-benzyloxazolidinone. A boron-mediated diastereoselective aldol reaction of **251** with chiral dihydroxylated unsaturated aldehyde **252**, which was in turn prepared from (*S*)-epichlorohydrin, provided the aldol-adduct as a single diastereomer. The resulting carbinol was then oxidized to furnish **253**, the substrate for the type 2 IMDA reaction. Upon treatment with a zinc chloride−ether complex in the presence of a small amount of pyridine, **253** underwent a smooth IMDA reaction, producing the desired bicyclic compound **254** predominantly. This high stereoselectivity seems to be dictated by the existence of the C12 chiral side chain. With the removal of the chiral auxiliary, the cycloadduct **254** was converted into thiol ester **255** (53% yield from **253**). Construction of the maleic anhydride moiety in **255** was performed via a thiomaleic anhydride. The oxidation of the sulfide in **256**, followed by Pummerer rearrangement to introduce a ketone functionality and acidic hydrolysis, provided γ-lactone-acetal, which was eventually converted into natural enantiomer (−)-**245**.

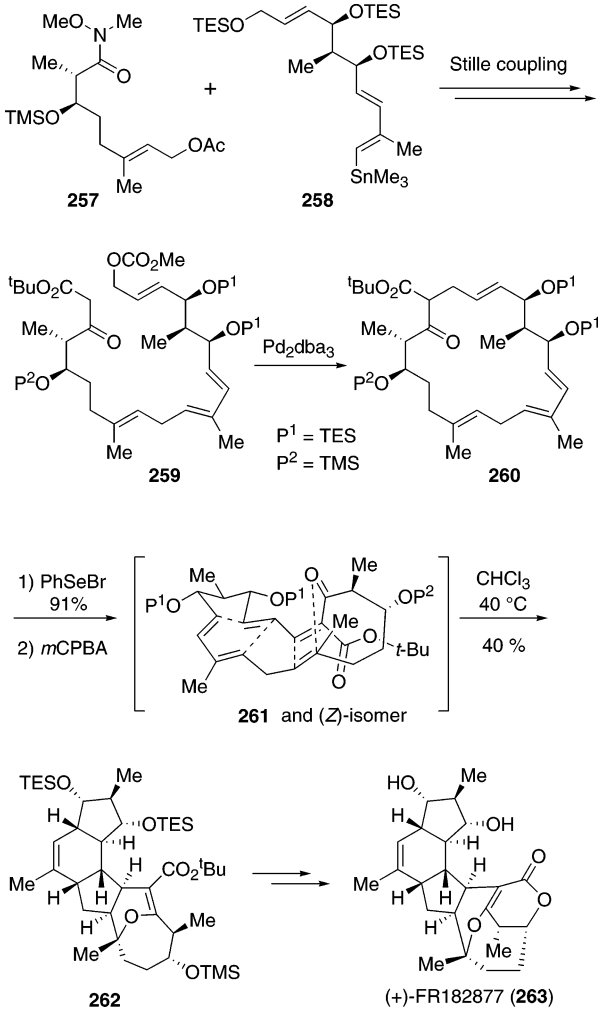
Scheme 42. Total Synthesis of (−)-Phomoidride B by Fukuyama and Co-workers[137]



4.3. FR182877

FR182877 (**263**) exhibits remarkable microtubule stabilizing activity similar to the mode of action studied for paclitaxel, and it shows potent cytotoxicity toward multiple tumor cell lines.[138] The highly carbon- and oxygen-functionalized hexacyclic core structure of **263** comprises 12 stereogenic centers and a strained double bond through the bridgehead position. Sorensen and co-workers have proposed that the structure of **263** might arise from a polyunsaturated linear biosynthetic intermediate by a cascade of intramolecular Diels−Alder reactions.[139] Furthermore, they have succeeded in the total synthesis of (+)-**263**, the proposed structure for FR182877, based on this concept (Scheme 43).[140] Thus, a long-chain polyketide-like intermediate with a conjugate diene part, that is, **259**, was synthesized via the efficient Stille coupling of two components, a Weinreb amide carrying an allyl acetate part **257** and (*E*,*E*)-dienylstannane **258**. Then the allylic alkylative 19-membered ring formation was conducted for **259** by exposure to a catalytic amount of Pd_2dba_3, which provided a macrocyclic compound **260** via the π-allyl palladium(II) species. Next, the introduction of a double bond at the α-carbon of the β-keto ester moiety in **260** was carried out. The reaction of **260** with phenylselenenyl bromide provided a 3:1 mixture of the selenides, which was oxidized with *m*CPBA, affording the (*E*)-α,β,γ,δ-unsaturated ester **261** and its (*Z*)-isomer. When a solution of this geometrical mixture was warmed (40 °C), a 2-fold IMDA reaction occurred to produce a pentacyclic cycloadduct **262**

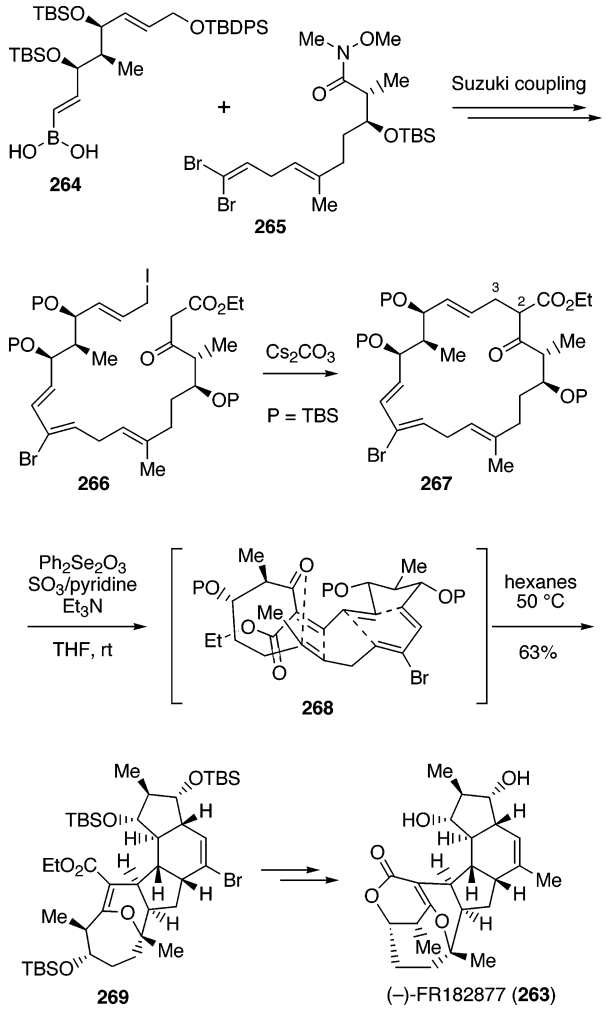
Scheme 43. Total Synthesis of (+)-FR182877 by Sorensen and Co-workers[140]



stereoselectively (40% yield) via the sequential transannular Diels−Alder (TADA) and hetero-Diels−Alder reactions as shown. In one operation, these two TADA reactions transformed the substrate **261** into a pentacyclic structure with seven newly introduced stereogenic centers. It should be emphasized that this process was highly diastereoselective, producing the pentacyclic intermediate incorporating the correct stereochemical relationship found in (+)-**263**. The intermediate **262** was converted into (+)-**263**, the antipode of the natural product, by the final δ-lactonization. Soon after, the Sorensen group disclosed the synthesis of the natural enantiomer (−)-**263**.[141]

At almost the same time that the Sorensen group reported the total synthesis of (+)-FR182877 (**263**), Evans and Starr completed the total synthesis of natural (−)-FR182877 (**263**) (Scheme 44).[142] In their total synthesis, tandem TADA reactions similar to those in the Sorensen's synthetic plan were applied to construct a pentacyclic structure such as **269**. For this event, the Suzuki coupling of an (*E*)-vinylboronic acid **264** and vinyl dibromide **265**, followed by two-carbon homologation and allylic iodination, was conducted to provide an acyclic polyketide-like intermediate **266** resembling **259**. This allyl iodide **266** was submitted to a Cs_2CO_3-mediated macrocyclization to produce **267** as a 1:1 diastereomeric mixture.

Scheme 44. Total Synthesis of (−)-FR182877 by Evans and Starr[142]

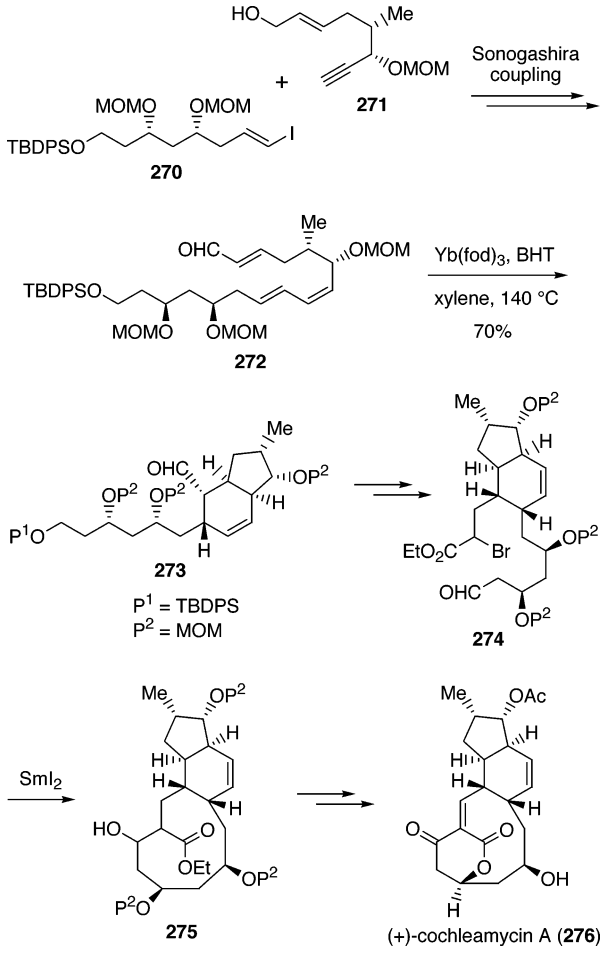


The introduction of the C2−C3 double bond into **267** initiated a sequence of transannular cycloadditions, culminating in the formation of **269** as a single isolable diastereomer (63% yield) via the α,β,γ,δ-unsaturated macrocyclic compound **268**. Semiempirical calculations of this transannular Diels−Alder cycloaddition cascade were executed to determine the origins of asymmetric induction.[143] The cycloadduct **269** was subsequently transformed to (−)-**263**.

4.4. Cochleamycin A and Macquarimicins

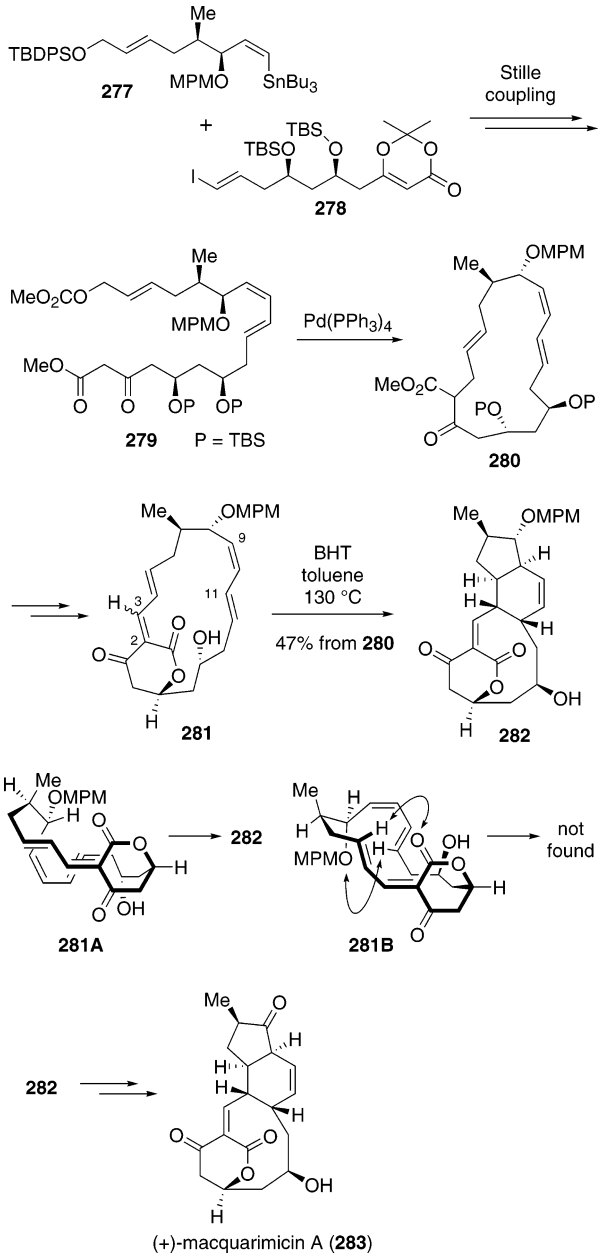
(+)-Cochleamycin A (**276**) exhibits antimicrobial activities and cytotoxicity against P388 leukemia cells.[144] The structure of **276** is characterized by a 5/6/10/6-membered tetracyclic framework. A closely related natural product is (+)-macquarimicin A[145] (**283** in Scheme 46), a selective inhibitor of membrane-bound neutral sphingomyelinase (N-SMase) which exhibits antiinflammatory activity in vivo.[146] It is hypothesized that these natural products share a biogenetic component that may involve the IMDA reaction of a polyketide-derived intermediate.[147] Tatsuta and co-workers have reported the total synthesis of (+)-**276** using an IMDA reaction strategy (Scheme 45).[148] In an early stage of their total synthesis, the assembly of functionalized (*E*)-vinyl iodide **270** and terminal acetylene **271** under Sonogashira conditions, followed by hemi-hydrogenation of the acetylenic moiety, produced a long-chain (*E*,*Z*,*E*)-trienal with a skipped diol moiety, that is, **272**. A solution of **272** in xylene was heated (140 °C) in the presence of a lanthanide Yb(fod)$_3$, providing the desired IMDA adduct **273** as a single product (70% yield). This stereochemical outcome demonstrates that the IMDA reaction of (*E*,*Z*,*E*)-triene such as **272** is a promising way to access the cis−anti−cis-fused multisubstituted tetrahydroindan skeleton.[149] The lower-half 10-membered carbocyclic moiety, sharing a δ-lactone structure, was then constructed by an SmI_2-mediated intramolecular Reformatsky-like reaction using an α-bromo-aldehyde intermediate **274**, derived from **273**. This intramolecular carbon−carbon bond-forming reaction provided a tricyclic product **275**, from which the natural (+)-cochleamycin A (**276**) was produced eventually by δ-lactonization, introduction of the double bond, and other synthetic steps.

Scheme 45. Total Synthesis of (+)-Cochleamycin A by Tatsuta and Co-workers[148]



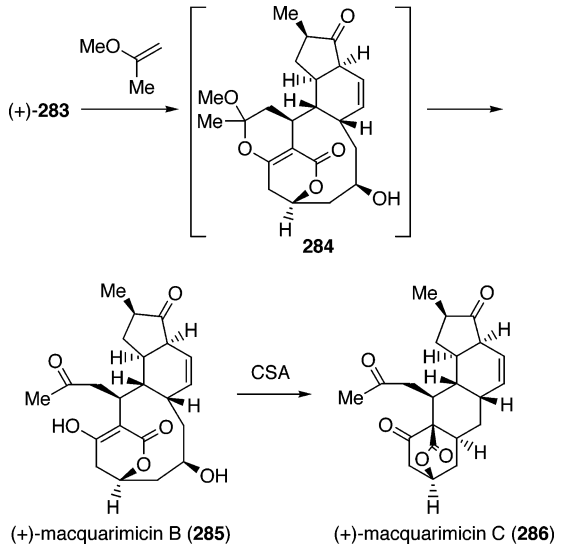
Tadano and co-workers have achieved the total synthesis of (+)-macquarimicin A (**283**) using a transannular Diels−Alder (TADA) approach inspired by a biosynthetic pathway (Scheme 46).[150] An acyclic intermediate **279**, equipped with an (*E*,*Z*)-diene part and a dienophilic (*E*)-olefin part, was prepared via the Stille coupling of (*Z*)-stannylalkene **277** and (*E*)-iodoalkene **278**. The intramolecular Trost−Tsuji reaction of **279** was conducted to produce a 17-membered macrocycle **280** as a 3:2 diastereomeric

Scheme 46. Total Synthesis of (+)-Macquarimicin A by Tadano and Co-workers[150]



mixture without event. By the formation of the β-keto-δ-lactone ring, followed by a double-bond introduction, **280** was converted into **281** as a mixture of C2−C3 geometrical isomers. Under thermal conditions (130 °C), the TADA reaction of **281** produced the diastereomer **282** as a sole cycloadduct. In this reaction, the (9*Z*,11*E*)-geometry of the reacting diene in **281** is the origin of endo-selectivity.[149] Comparing the two endo transition states of the (2*Z*)-isomer, **281A** seems to be substantially favorable, considering that two severe steric interactions are present in **281B**. The (2*E*)-**281** might isomerize to its (2*Z*)-isomer rather easily or might decompose under the reaction conditions. The cycloadduct **282** was converted into (+)-**283** through a few more steps. Furthermore, the total synthesis of (+)-macquarimicin B (**285**) was accomplished by the intermolecular hetero-Diels−Alder reaction of (+)-**283** with 2-methoxypropene, followed by spontaneous hydrolysis of

Scheme 47. Total Syntheses of (+)-Macquarimicins B and C by Tadano and Co-workers[151]



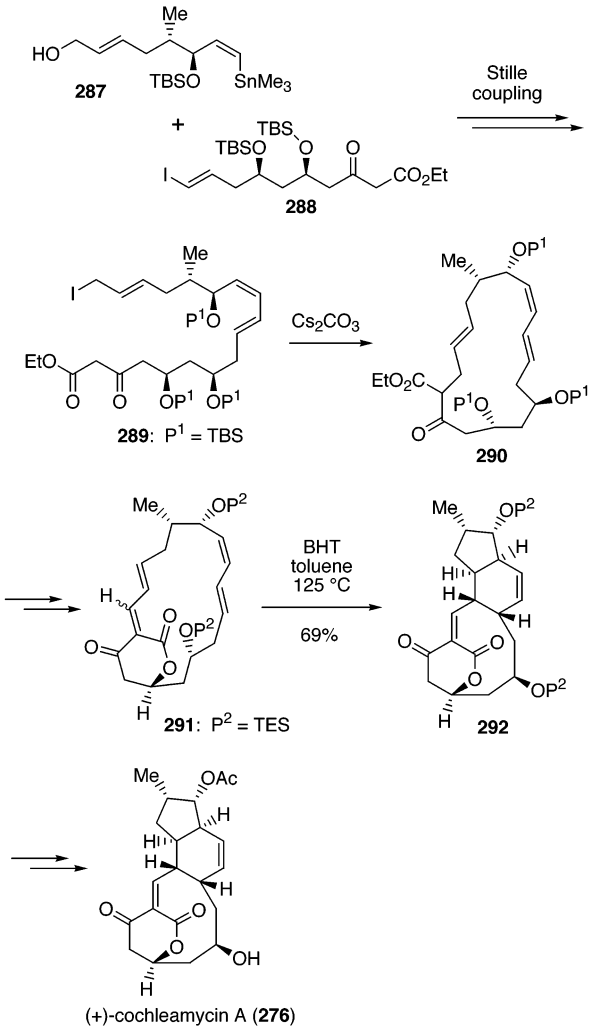
the transient cycloadduct **284**. Also, treatment of (+)-**285** with CSA produced (+)-macquarimicin C (**286**) through intramolecular dehydrative alkylation, the probable biosynthetic pathway (Scheme 47).[151]

Dineen and Roush have also completed the total synthesis of (+)-cochleamycin A (**276**) (Scheme 48).[152] As one of the key steps in their total synthesis, (*Z*)-vinylstannane **287** and (*E*)-vinyl iodide **288** were joined via a Stille coupling protocol for access to the substrate for macroallylation, providing allyl iodide **289**. By use of Cs_2CO_3-mediated intramolecular allylation, a 17-membered carbocyclic compound **290** was obtained. The TADA substrate **291** was derived from **290** through δ-lactonization and the introduction of a double bond. Heating (125 °C) a mixture of the geometrical isomers **291** in toluene resulted in the formation of the sole IMDA adduct **292** (69%). These stereochemical outcomes in endo/exo- and π-facial selectivity are closely similar to those observed for the TADA reaction in Tadano's total synthesis of (+)-macquarimicin A (**283**). Deprotection of **292** and selective acetylation eventually led to (+)-**276**.

4.5. Spinosyn A

The tetracyclic macrolide (−)-spinosyn A (**299**) possesses extraordinary insecticidal activity.[153] The spinosyn structure is comprised of a 12-membered lactone fused to a 5,6,5-cis−anti−trans carbocyclic ring system. Total syntheses of **299** have been reported by Evans and Black,[154] using a chiral auxiliary-controlled IMDA reaction, and Paquette and co-workers.[155] A convergent, highly stereoselective total synthesis of **299** has been recently achieved by Roush and co-workers via a TADA reaction of the functionalized macrocyclic pentaene **296** (Scheme 49).[156] L-Rhamnopyranosyl (Rham) aldehyde **293** and β-ketophosphonate **294** were coupled by a Horner−Wadsworth−Emmons reaction, which provided aldehyde-phosphonate **295** after some functional group transformations. The treatment of **295** with *i*-Pr_2NEt and LiCl in MeCN directly afforded Diels−Alder

Scheme 48. Total Synthesis of (+)-Cochleamycin A by Dineen and Roush[152]

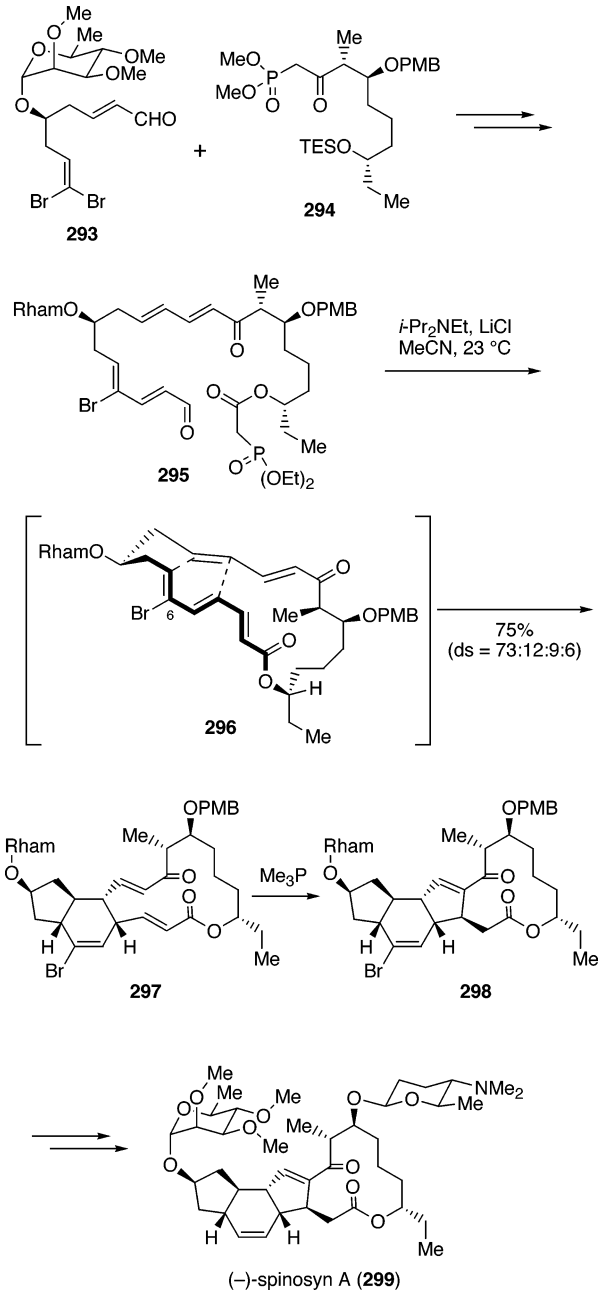


cycloadducts **297** and diastereomers in 75% yield as a 73:12:9:6 mixture. Cycloadducts presumably arise from a tandem macrocyclization and TADA reaction sequence. It seems that conformational preferences of the C6-brominated macrocycle **296** play a role in determining the stereoselectivity of the TADA reaction. The spinosyn tetracyclic structure was constructed by the vinylogous Morita−Baylis−Hillman cyclization of the cycloadduct **297**, providing the desired product **298**. The installation of the forosamine unit proceeded with a high selectivitiy for the formation of the required β-glycoside and completed the total synthesis of (−)-**299**.

4.6. Tubelactomicin A

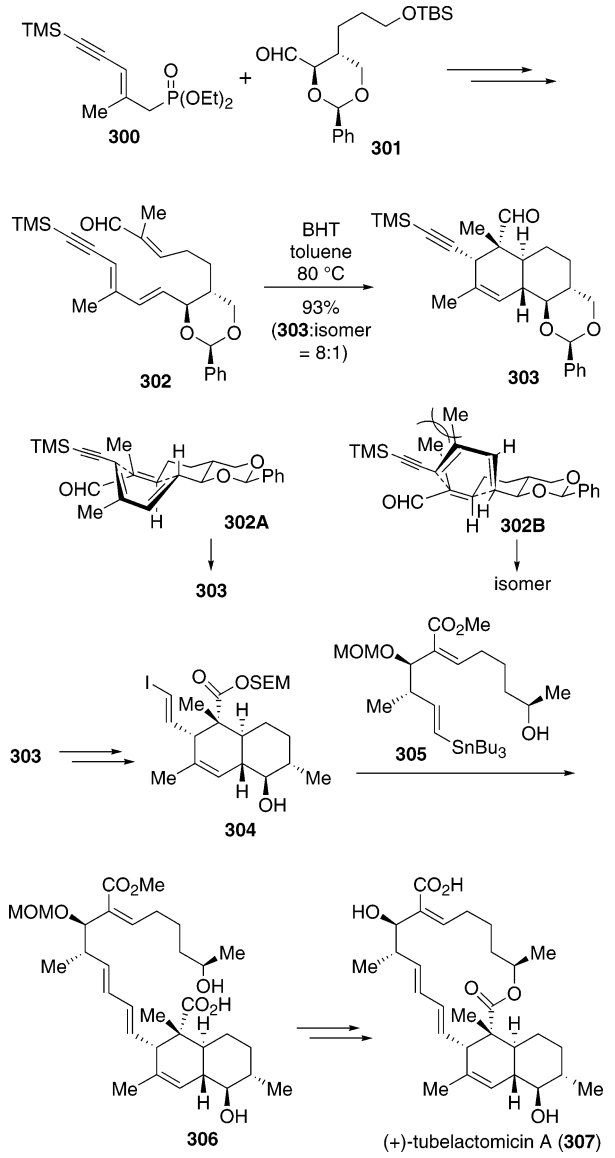
(+)-Tubelactomicin A (**307**), a 16-membered macrolide antibiotic, showed potent antimicrobial activity against acid-fast bacteria, including drug-resistant strains.[157] Tadano and co-workers have used an IMDA reaction for the stereoselective synthesis of the lower-half segment **304** and completed the total synthesis of natural (+)-**307** (Scheme 50).[158] A β-substituted (*E*)-methacrolein derivative **302**, possessing a 10-carbon tether incorporating an (*E*,*E*)-dienyne terminal, was prepared through the *E*-selective Horner−Emmons olefination of an aldehyde **301** with

Scheme 49. Total Synthesis of (−)-Spinosyn A by Roush and Co-workers[156]



phosphonate **300**. The thermal IMDA reaction of **302** in toluene at 80 °C proceeded stereoselectively to provide the desired trans-fused cycloadduct **303** with an 8:1 endo/exo ratio in a combined yield of 93%. As shown, two chairlike transition states, **302A** and **302B**, were conformationally locked by the presence of the trans-oriented benzylidene acetal. As a result, the IMDA reaction of **302** proceeded with complete π-facial selectivity. In the two transition states, a severe nonbonded interaction occurred between the methyl substituent in the diene part and the dienophile terminal, apparently making the exo-transition state **302B** unfavorable. Therefore, the IMDA reaction proceeds through the endo-transition state **302A**. The cycloadduct **303** was converted into the lower-half segment **304**. On the other hand, the upper-half segment **305** was synthesized from methyl (*R*)-lactate. These two segments were connected by

Scheme 50. Total Synthesis of (+)-Tubelactomicin A by Tadano and Co-workers[158]

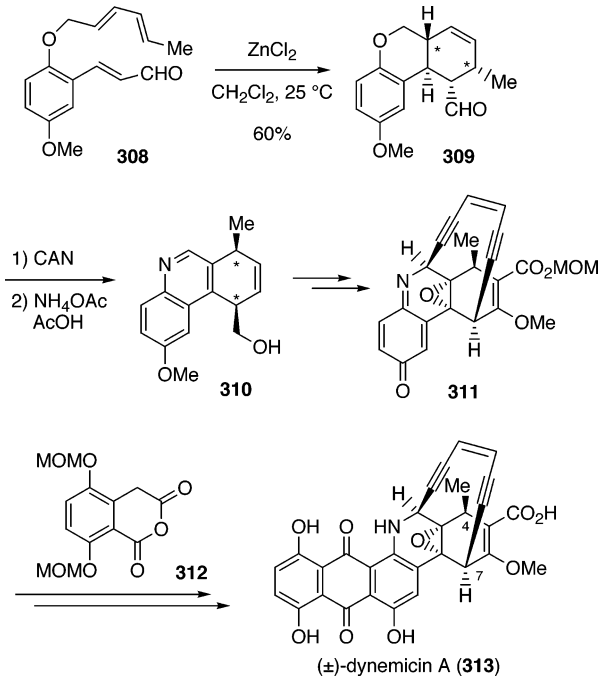


sequentially by Stille coupling and then by macrolactonization of the resulting seco-acid **306** under Mukaiyama conditions to provide (+)-**307**.

4.7. Quinone-Based Natural Products

Dynemicin A (**313**) is a member of the enediyne family of antibiotics.[159] This metabolite shows high levels of in vitro antitumor activity and effects single- and double-stranded DNA cleavage. Schreiber and co-workers have disclosed the synthesis of various methylated versions of **313** using a TADA reaction as a key step.[160] Complete success in the total synthesis of **313** has been realized by Myers and co-workers, using an intermolecular Diels−Alder reaction.[161] Danishefsky and co-workers have reported the total synthesis of (±)-**313**, featuring an IMDA reaction strategy as follows (Scheme 51).[162] Upon exposure of a *p*-dihydroxybenzene derivative with a diene/dienophile system, that is, **308**, to $ZnCl_2$, cycloadduct **309** was provided in an exclusive endo-selective IMDA mode (60% yield). On the other hand, low endo-selectivity (endo/exo = 3:1) was observed

Scheme 51. Total Synthesis of (±)-Dynemicin A by Danishefsky and Co-workers[162]

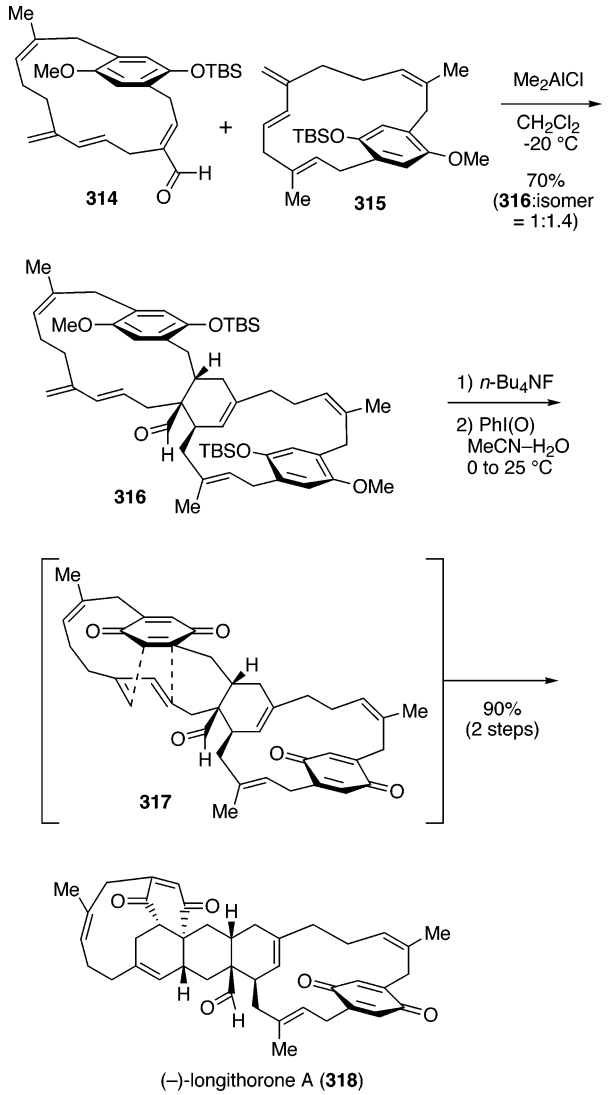


under thermal (uncatalyzed) conditions. This cycloaddition provided the required syn-relationship between C4 and C7 (starred carbons). Treatment of the endo-adduct **309** with ceric ammonium nitrate (CAN) gave rise to a quinone, which was exposed to ammonium acetate to afford a functionalized tricyclic product with a quinoline substructure **310**. Installation of the enediyne unit into **310** was accomplished on a dihydroquinoline derivative by use of a bis-iodoalkyne/distannylethylene interpolative coupling transformation. In the final stage of the total synthesis, iminoquinone ketal **311** was condensed with homophthalic anhydride **312**. Deprotection of the resulting condensation product eventually yielded (±)-**313**.

(−)-Longithorone A (**318**) is a cytotoxic marine natural product with an unusual heptacyclic structure.[163] The proposed biosynthesis of **318** involves a consecutive intermolecular Diels−Alder reaction between two [12]-paracyclophanes and a TADA reaction. Shair and co-workers have completed the biomimetic total synthesis of (−)-**318** (Scheme 52).[164] Two functionalized paracyclophanes **314** and **315** were enantioselectively synthesized via macrocyclization reactions that relied on eneyne metathesis for the construction of the respective 1,3-disubstituted diene parts. The intermolecular Diels−Alder reaction between **314** and **315** was achieved in the presence of Lewis acid Me_2AlCl (−20 °C), producing pseudo-symmetrical macrocyclic compound **316** and a diastereomer as a 1:1.4 ratio disfavoring **316** (70% yield). Removal of both silyl-protecting groups in **316**, followed by oxidation with iodosylbenzene, provided a bisquinone **317**. This intermediary **317** spontaneously underwent a TADA cycloaddition (room temperature) to provide (−)-**318** (90% yield) directly.

Pinnatal (**324**) and sterekunthal A (**325**) show effective antiplasmodial activity, representing inter-

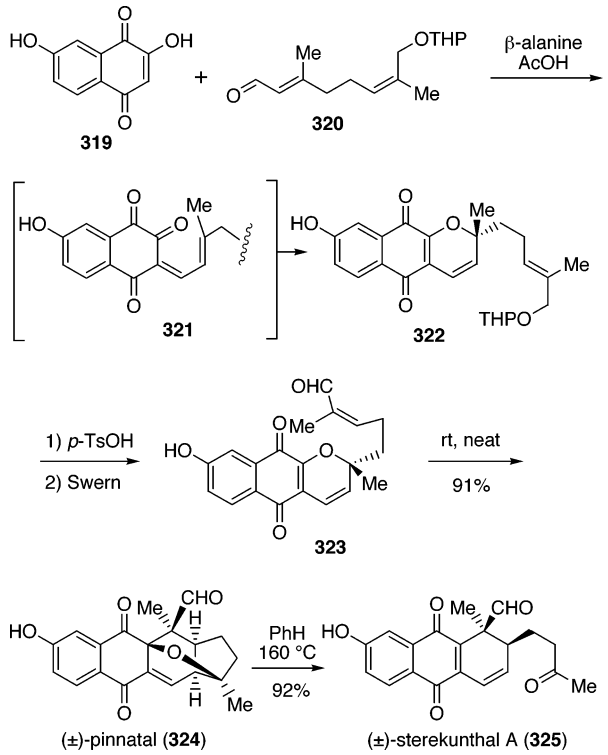
Scheme 52. Total Synthesis of (−)-Longithorone A by Shair and Co-workers[164]



esting lead compounds as drugs against malaria.[165] These natural products hypothetically share biosynthetic processes involving some pericyclic reactions. Malerich and Trauner have reported total syntheses of racemic **324** and **325**, featuring the proposed biosynthetic reactions as key steps (Scheme 53).[166] The Knoevenagel condensation of a geraniol-derived aldehyde **320** with an oxygenated hydroxynaphthoquinone **319** provided an intermediary naphthoquinone **321**, which immediately underwent a 6π-electrocyclization reaction to produce a pyran ring, that is, **322**. Several functional group transformations at the side-chain terminal produced **323**, the hypothetical biosynthetic precursor for the IMDA reaction. Upon standing (neat, room temperature), this substrate underwent a spontaneous IMDA reaction to provide (±)-pinnatal (**324**). This cyclization is considered to be catalyzed by the phenolic hydroxy group in **323**. On the other hand, the *O*-methyl phenol version of **323** failed to undergo the cycloaddition at room temperature. Furthermore, heating (±)-**324** in benzene resulted in retro hetero-Diels−Alder reaction to provide (±)-sterekunthal A (**325**).

During the past decade, a variety of IMDA or TADA reactions have been applied for the total

Scheme 53. Total Syntheses of (±)-Pinnatal and (±)-Sterekunthal A by Malerich and Trauner[166]



syntheses of decalin-type polyketides such as (−)-oblongolide,[167] (−)-PI-201,[168] (+)-calbistrin A,[169] (−)-equisetin,[170,171] and (+)-phomopsidin,[172] for quinone polyketides such as (±)-xestoquinone,[173] (±)-fredericamycin A,[174] and (±)-halenaquinone,[175] and for other polyketides such as (−)-isopulo'upone,[176] (±)-endianodric acid A,[177] (−)-cytochalasin D,[178] (−)-hamigerans A and B,[179] and (±)-forbesione.[180]

5. Conclusions

In the progress of modern organic synthesis, especially in the field of natural product synthesis, the role of Diels−Alder reactions for the construction of cyclic carbon framework is tremendous. As evidenced by a huge amount of literature, the incorporation of Diels−Alder reactions in the synthetic scheme frequently makes synthetic manipulation facile and concise. In many cases, compared to an intermolecular Diels−Alder reaction, an intramolecular variant (IMDA reaction) is not necessarily manageable and predictable enough to control the selectivities of cycloaddition such as regio-, endo/exo-, or π-facial selectivity. Nevertheless, the literature contains well-designed IMDA reaction approaches for the stereoselective construction of the formidable core skeletons found in a variety of natural products. Such impressive and elegant precedents of natural product synthesis will continue to stimulate the interest of synthetic chemists. Sophisticated natural product synthesis shows the potency of organic synthesis and frequently offers conceptual innovation for current organic chemistry.

In this review, we have summarized a number of recent publications concerning IMDA-based natural products synthesis. Special attention has been put

on structurally complex natural products, that is, terpenoids, alkaloids, and polyketide-derived natural products. Although many of the cited natural product syntheses have been the focus of activity for several research groups and a variety of the synthetic approaches have also appeared in the literature, we have introduced in this review completed total synthesis alone. Most of the total syntheses cited in this review are milestones of current natural product synthesis. Furthermore, some total syntheses are considered to be mimics to the biogenetic or biosynthetic pathway proposed for the target natural product. The synthetic approaches, guided by the biosynthetic consideration for the target natural product, will enhance the importance and effectiveness of IMDA reactions. We conclude confidently that the IMDA and TADA approaches toward natural product synthesis will further embody their inestimable value in the future.

6. Acknowledgments

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