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# Marine Toxins with Spiroimine Rings: Total Synthesis of Pinnatoxin A

**Stéphane Beaumont**[a], **Elizabeth A. Ilardi**[a], **Nicholas D. C. Tappin**[a], and **Armen Zakarian***,[a]

[a]Department of Chemistry and Biochemistry, University of California at Santa Barbara, Santa Barbara, CA 93106, USA

## Abstract

This microreview provides a compilation of synthetic approaches and total syntheses of pinnatoxin A in a survey of the literature up to early 2010. Pinnatoxin A is the first discovered and representative member of a fascinating group of potent marine toxins that share a spiroimine subunit as a unifying structural element.

### Keywords

Natural products; Total synthesis; Marine toxins; Spiroimine natural products; Pinnatoxin; Spiro compounds

## 1. Introduction

Pinnatoxin A is an early member of the growing family of nonproteinaceous macrocyclic marine toxins, currently consisting of pinnatoxins (Figure 1), pteriatoxins (Figure 2), spirolides and gymnodimines (Figure 3), and spiro-prorocentrimine.[1] Numerous shellfish poisoning instances have been attributed to these bioactive alkaloids, which have established themselves as appealing synthetic targets. The producing organism responsible for the biogenesis of pinnatoxins is presently unknown, and continuing efforts are being devoted towards the synthesis of these compounds to provide viable access to the materials for biological testing.[1,7]

Among anisomyarian clams, the bivalve family Pinnidea has received increased attention over the last two decades, being the culprit responsible for an outbreak of shellfish poisoning in China and Japan.[4] Subsequent investigation of the frequently consumed adductor muscle of the shellfish led to the isolation from *Pinna attenuata* of a bioactive extract described as pinnatoxin A, which is reported to be a $Ca^{2+}$ channel activator.[4]

*Pinna* has a worldwide distribution, inhabiting shallow and warm tropical seas, although certain species are restricted to the Indo-Pacific region.[5] One of these species is *Pinna muricata*, viscera of which (45 kg) were collected in Okinawa, Japan, eventually leading to the isolation of pinnatoxins A (3.5 mg), B and C (1.2 mg as a mixture), and D (2.0 mg), along with the structural characterization of pinnatoxin A by detailed NMR and positive ion ESI MS/MS analysis.[6] The biological activities of the spiroimines, including pinnatoxins, have been briefly documented:[7] for pinnatoxins, in vitro toxicity to isolated cells was


zakarian@chem.ucsb.edu.

found to be low, whereas acute intraperitoneal toxicity in mice was found to be notable for a 1:1 mixture (as isolated) of pinnatoxins B and C ($LD_{99}$ = 22 μgkg$^{-1}$).[8] Similarly, natural (+)-pinnatoxin A is a rapidly acting toxin characterized by the rapid onset of symptoms closely followed by death ($LD_{99}$ = 180 μgkg$^{-1}$),[9] whereas (−)-pinnatoxin A was inactive in mouse assays in doses of up to 100 μg[28] (5000 μgkg$^{-1}$ bodyweight).[7] Pinnatoxin D showed the weakest acute toxicity ($LD_{99}$ = 400 μgkg$^{-1}$), but the strongest cytotoxicity against the murine leukemia cell line P388 ($IC_{50}$ = 2.5 μgmL$^{-1}$).[1b]

Harmful algal blooms (HABs) may give rise to catastrophic fish deaths due to the toxic metabolites produced from phytoplankton;[10] of particular note are dinoflagellates of the genus *Alexandrium*, which have caused several cases of paralytic shellfish poisoning in humans.[11] Filter-feeding bivalves accumulate lethal doses of algal toxins after feeding on the toxic phytoplankton, and it is probable that pinnatoxin A found in *Pinna muricata* has its origin in a similar mechanism, although evidence for this is circumstantial.[12] It has been shown that the dinoflagellate *Alexandrium ostenfeldii*, collected from field samples of aquaculture sites in south-eastern Nova Scotia, Canada, is the producing organism for spirolides.[13] Spirolides, containing the macrocycle-nested spiroimine moiety, are close analogues of the pinnatoxins, and after studies of the hydrolytically labile spirolides A and B it has been suggested that the spiroimine subunit is the pharmacophore of the toxins.[14,15]

Continuing efforts focusing on the identification of toxins responsible for diarrhetic, paralytic, and neurotoxic shellfish poisoning (DSP, PSP, and NSP, respectively) have led to the characterization of other spiroimine marine toxins. In 1994, after unprecedented NSP coinciding with HABs of the dinoflagellate *Gymnodinium* cf. *mikimotoi*, gymnodimine was isolated from oysters (*Tiostrea chilensis*, 3 kg) collected at Foveaux Strait, South Island, New Zealand. Gymnodimine was also isolated from cultured *G*. cf. *mikimotoi* (60 L), thereby assigning its origin as a metabolite from the dinoflagellate that is likely to be in the oysters' food chain.[16] Again, gymnodimine exhibited high toxicity by intraperitoneal injection in mice ($LD_{50}$ = 96 μgkg$^{-1}$).[17] More gymodimine analogues have been found subsequently, albeit in much smaller quantities.[18] In 2001, another spiroimine, spiro-prorocentrimine ($LD_{99}$ = 2500 μgkg$^{-1}$),[19] was isolated from a benthic *Prorocentrum* species from Taiwan. Spiro-prorocentrimine is closely related to the other nitrogenous polyether macrocycles prorocentrolide[20] and prorocentrolide B.[21] Although these polar, lipid-soluble metabolites have not been linked to human poisoning, benthic marine dinoflagellates in the genus *Prorocentrum* sp. algae are well known for the biogenesis of toxins such as okadaic acid and derivatives leading to cases of DSP.[22] In the same year, the extremely potent pteriatoxins, with macrocyclic cores identical to those of the pinnatoxins, were isolated from 75% aqueous ethanol extracts of viscera (82 kg) of another oyster: the Okinawan bivalve *Pteria penguin*.[23] Three isomers – pteriatoxin A ($LD_{99}$ = 100 μgkg$^{-1}$) and pteriatoxins B and C as a 1:1 mixture ($LD_{99}$ = 8 μgkg$^{-1}$) – were identified and their stereochemistry was designated after their synthesis.[24]

Pinnatoxins possess a common 27-membered carbocyclic backbone composed of a unique 6,7-azaspiro-linked imine fragment (AG ring), a bridged 5,6-bicycloketal (EF ring), and a 6,5,6-dispiroketal (BCD ring),[25] as well as varying functional group substitution at C21, C22, C28, and C33. Along with its isolation and structural characterization, Uemura proposed a biosynthetic pathway to pinnatoxin A through a Diels–Alder cycloaddition to install the G ring together with formation of the macrocycle. The polycyclic ether could thus arise from a linear polyketide. Feeding studies on *Alexandrium ostenfeldii* demonstrated that most of the carbons in the macrocycle of 13-desmethyl spirolide C are polyketide-derived and that a glycine unit is incorporated intact in the imine.[26]

This microreview documents the synthetic studies and total syntheses of pinnatoxin A, covering the literature up to early 2010. The account of the strategies employed to construct the characteristic spiroimine macrocycles begins with the first total synthesis of (−)-pinnatoxin A, the unnatural enantiomer, accomplished by Kishi's group and continues in chronological order, describing contributions from the Murai, Inoue–Hirama, Zakarian, and Nakamura–Hashimoto groups.

## 2. Early Studies of Pinnatoxins

### 2.1 Kishi's Synthesis of (−)-Pinnatoxin A (1998)

The biosynthetic pathway to pinnatoxin A proposed by Uemura served as the basis for the first total synthesis of the unnatural enantiomer of the toxin (*ent*-**1**), which established the absolute stereochemistry of **1**.[28] The toxicity of the unnatural enantiomer was shown to be low to none. An extension of this synthesis has recently provided a complete stereochemical assignment for pinnatoxins B and C[27] and for the related pteriatoxins A–C.[24] The total synthesis of the unnatural enantiomer of pinnatoxin A by Kishi and coworkers set a precedent both for the power and for the limitations of the Diels–Alder approach to the cyclohexene ring of the macrocycle. Inspired by Uemura's proposal, Kishi's group envisioned a synthesis plan in which the AG-spiroimine ring system would be assembled through an intramolecular Diels–Alder reaction followed by imine formation (Scheme 1). It was intended that a dithiane-based coupling would form the C24–C25 and C25–C26 bonds and that the Nozaki–Hiyama–Kishi reaction would be employed twice to incorporate the fragments **4** and **5**.

To begin the synthesis, the diketone **7** was efficiently prepared from pent-4-yn-1-ol in 12 steps (Scheme 2). Removal of the *tert*-butyldimethylsilyl (TBS) and acetonide groups in **7** with the aid of camphorsulfonic acid (CSA) yielded the desired tricyclic spiroacetal **8-b** and its C19-epimer **8-a** in 51% and 30% yields, respectively. As suggested previously by Murai and co-workers,[32] the formation of the C19-epimer was primarily due to hydrogen bonding between the tertiary hydroxy group and the D ring oxygen. Murai determined that acid-catalyzed spiroketalization of the elaborated C10–C24 fragment favored the undesired diastereomer at C19. Molecular mechanics calculations based on the AMBER force field indicate that the unnatural diastereomer, with the free hydroxy group positioned at C15, is 3.2 $kcalmol^{-1}$ more stable than the natural isomer. This energy difference is minimized to 1.8 $kcalmol^{-1}$ if the C15 hydroxy group is protected as its TBS ether. It has been demonstrated that the **8-a**/**8-b** ratio is controlled by acid, solvent, and addition of metal ion effects. With this in mind, the epimers were consequently subjected to acidic equilibration conditions. Silylation of the tertiary hydroxy in the mixture of **8-a** and **8-b** with *tert*-butyldimethylsilyl triflate (TBSOTf) afforded the configurationally more stable **9** in 95% yield.

Conversion of the double bond in **9** to form the aldehyde, followed by four-carbon chain elongation and a Wittig olefination, delivered **11**. The dithiane was installed in four steps to give **12** in 80% overall yield (Scheme 3). Fragment coupling was accomplished by alkylation of the lithiated dithiane **12** with the iodide **3**, followed by two oxidative deprotection steps to deliver **13** in 49% yield over the three steps. After oxidation of the primary hydroxy group in **13** to the aldehyde, the termini of the bisketal fragment were modified by two successive Nozaki–Hiyama–Kishi reactions, first involving iodide **5** to forge the C5–C6 bond, and then iodide **3**, to form the C32–C33 bond. Hydrolysis of the acetonide led to the formation of the EF-bridged ketal (**16**) and a C19-epimer. Fortunately, this position could be re-epimerized to the original configuration upon silylation with triethylsilyl trifluoromethanesulfonate (TESOTf).

$S_N2'$ displacement of the C32 allylic mesylate and removal of the C31 proton afforded the key diene for the intramolecular Diels–Alder reaction (Scheme 4). The results of optimization experiments concluded that the *exo*/*endo* ratio could be enhanced by adjustment of the solvent and temperature. The regioselective reaction thus proceeded at a temperature of 70 °C in dodecane (0.2 $m_M$) to afford a 1.0:0.9:0.4 ratio of Diels–Alder adducts with an overall 5:1 *exo*/*endo* ratio.

Perhaps the most intriguing discovery of this total synthesis is that the final imine ring closure of the amino ketone required a strong thermal activation (200 °C, 1 h, 70% yield, Scheme 4). This observation, in conjunction with the hydrolytic stability of pinnatoxin A, implies that there is a large energy barrier for the interconversion of the cyclic imine to the amino ketone. In the final step, acidic treatment of the *tert*-butyl ester formed synthetic (−)-pinnatoxin A in 70% yield, establishing the absolute stereochemistry of natural (+)-pinnatoxin A (**1**).

### 2.2 Synthetic Studies on Pinnatoxins by Murai's Group (1997–2002)

Murai and co-workers developed a convergent approach to the BCDEF ring polyether fragment (Scheme 5). The C25–C26 bond was to be constructed through a Julia coupling reaction joining fragments **22** and **23**, with most of the chiral centers installed through Sharpless asymmetric epoxidation (AE).[29a] In an optimized approach, a one-step formation of a pentacyclic system related to **19** from the triketone **24** was later developed.[29b] Subsequently, enantioselective Diels–Alder cyclization chemistry between the α-methylene caprolactam **20** and the functionalized diene **21** was investigated as an approach to the spiroimine ring system.[29d]

In initial studies, the sulfone **23** could be accessed in a straightforward 17-step sequence from propargyl alcohol (Scheme 6).[29b] Two consecutive Sharpless AE reactions, followed by regioselective reductive opening of the epoxides, efficiently installed the hydroxylated stereogenic centers. The bis-ketal **22** was prepared by conversion of (*R*)-2-[2-(benzyloxy)ethyl]oxirane into the triketone **25** by a nine-step process. Removal of silyl ethers with 46% aqueous HF in acetonitrile resulted in a stereoselective ketalization, giving **26** as a major product in 76% yield along with a number of isomeric and partially cyclized byproducts that could be recycled. Addition of methyllithium was also selective, and the aldehyde **22** was accessed in two additional steps. Julia coupling followed by a two-step reductive desulfonation gave **29**. Upon ketalization to the EF ketal, complete C19 epimerization was observed during desilylation with HF in MeCN/THF; however, the stereochemistry could be corrected under acidic conditions after the installation of TBS ethers at the tertiary and secondary hydroxy groups, completing the synthesis of the BCDEF-pentacyclic triketal **19**.

Because both ketal fragments (BCD- and EF-) could be procured under similar conditions, a more convenient method for the formation of two intramolecular acetals was elucidated in 2001.[29c] The BCD-tricyclic spiroketal and the EF-bicyclic ketal were constructed simultaneously from the tetraketo precursor. As shown in Scheme 7, a Julia coupling between the sulfone **31** and the aldehyde **32**, followed by desulfonation and oxidation, generated the ketone **33**, which was in turn coupled with the sulfone **23** in a similar fashion. A perruthenate-mediated oxidation of the alkyne yielded the tetraketo precursor **24**. Upon exposure to HF·pyridine in MeCN, the desired pentacyclic system was produced as a single isomer in 71% yield (83% after recycling of partially cyclized byproducts). With THF as a solvent, however, a 1:2:1 (**31-a**/**31-b**/**31-c**) mixture of the isomers was produced. The authors interpreted the substantial difference in reactivity by invoking kinetic control in THF, whereas thermodynamic control was observed with the reaction in acetonitrile.[30]

In 2002, Murai described an approach to the simplified spiroimine ring system of pinnatoxins.[29d] As illustrated in Scheme 8, the fragment could be generated by an asymmetric *exo*-selective Diels–Alder reaction between the α-methylene caprolactam **20** and the diene **21** in the presence of a chiral complex of $Cu^{II}$ as a Lewis acid. Under optimized conditions, the spirocyclic adduct was generated in 82% yield with very high enantioselectively and *exo*-selectivity, which also makes it applicable to the syntheses of other marine spiroimine toxins.

## 3. Recent Total Syntheses of Pinnatoxin A

### 3.1 Formal Synthesis of Pinnatoxin A by the Inoue–Hirama Group (2004)

In 2004, the Inoue–Hirama group reported a formal total synthesis of (+)-pinnatoxin A (**1**) based on a convergent route.[31] As shown in Scheme 9, it was envisioned that two complex fragments (**36** and **37**) would be joined together through a dithiane alkylation reaction at C25. Intramolecular cyclization of an epoxy nitrile in **37** would set the stereochemistry of the C5 quaternary center. Finally, the 27-membered carbocycle would be formed by a ring-closing olefin metathesis reaction.

Construction of the BCD-bis-spiroketal **36** in an enantioselective fashion began with a Sharpless AE reaction of the allylic alcohol **38** in the presence of (+)-diethyl tartrate and proceeding through a Parikh–Doering oxidation to yield the ketone **39** in 41% overall yield after seven standard transformations (Scheme 10). The acetonide in the bis-spiroketalization precursor **39** was initially removed with CSA in methanol at room temperature. Subsequently, substitution of the solvent with the less polar toluene preferentially afforded the desired bis-ketal diastereomer (out of four possible stereoisomers) in 84% yield. Intramolecular hydrogen bonding between the terminal hydroxy groups at C10 and C24 was suggested as a rationale for the observed stereoselectivity in the ketalization (**40-a**).[32] Protection of the OH-10 and OH-15 groups with TESOTf, conversion of the OH-15 into the iodide, and installation of the dithiane ring furnished the BCD-fragment **36** in a direct five-step sequence (stereochemistry confirmed by NOE).

The approach to fragment **52** commenced with 4,6-*O*-benzylidene-D-glucose,[33] which was advanced to the MOM ether **42** in five routine steps (Scheme 11). The alcohol **44** was accessed after chemoselective hydroboration/oxidation of the terminal olefin in **42**, followed by Grignard addition of **43**. Subsequent mesylation, substitution, and a series of protecting group manipulations afforded the epoxy-nitrile **46**.

The G ring was assembled stereoselectively upon exposure to an excess of $KN(SiMe_3)_2$, to afford **47** exclusively in 72% yield. This notable transformation proceeds through the transition state **46a**, in which the large branched carbon chain at C5 adopts an equatorial orientation, furnishing the C5 quaternary and C31 tertiary centers selectively with the desired configuration.[34] The diol **47** was elaborated to the alcohol **48** in preparation for the stereoselective installation of the C36 methyl group (Scheme 11). After Parikh–Doering oxidation of the alcohol, methyl Grignard addition, and further oxidation, the resulting ketone was treated with Tebbe reagent to generate the *exo*-olefin **49** in 82% overall yield. Regio- and stereoselective hydroboration of the diene, followed by pivaloyl ester formation and regioselective desilylation, smoothly afforded **50** with the correct stereochemistry at C25. Selective oxidation of the diol at the primary OH group with PDC and subsequent installation of the TMS ether yielded **51**. After addition of allylmagnesium bromide to the C6 aldehyde and protecting group transformations, the free alcohol at C26 was converted into the iodide in anticipation of the coupling of fragments **36** and **52**.

The unification of the two complex fragments was initiated by lithiation of the dithiane **36**, followed by the addition of a pre-cooled solution of the iodide **52**, delivering the coupled product in 41% isolated yield along with recovered **36** (44%, Scheme 12). It was experimentally determined that the silyl protecting groups in **53** were detrimental for the ring-closing metathesis reaction, presumable due to steric hindrance. After selective cleavage of the TES and two TMS groups with TBAF, the RCM reaction was achieved in the presence of the second-generation Grubbs catalyst, favoring formation of the *E* olefin. The dithiane was then converted into the dimethyl acetal with use of the Stork reagent. En route to the EF ring system, the macrocycle **54** was subjected to acidic conditions, accomplishing protecting group cleavage and EF-ketalization while leaving the trioxadispiroacetal intact. Regioselective oxidation of the allylic alcohol with DDQ generated the α,β-unsaturated ketone, which underwent a 1,4 reduction of the C8=C9 bond with the Stryker reagent. A Wittig reaction installed the *exo*-methylene group at C10 to provide **56**. Protecting group transformations and replacement of the primary hydroxy group gave rise to the azide **57**. Hydrolytic removal of the methoxymethyl ether and subsequent oxidation to the carboxylic acid at C34 provided **58**. Attempts to utilize the Staudinger reduction/aza-Wittig cyclization to convert the azide intermediate directly into **1** were unsuccessful, but the azide was alternatively reduced to an amino group in two steps to provide Kishi's intermediate, thus completing the formal synthesis of (+)-pinnatoxin A.

### 3.2 Total Synthesis of Pinnatoxin A by the Nakamura–Hashimoto Group (2008)

The Nakamura–Hashimoto group reported the synthesis of (+)-pinnatoxin A (**1**) in 2008[35] as the culmination of dedicated studies.[36,37] The synthesis strategy, outlined in Scheme 13, exploits the Diels–Alder reaction, mirroring that of Uemura's biosynthetic proposal. Late stages of the synthesis were to include an *exo*-selective Diels–Alder reaction utilizing the α-methylene lactone **60** as a dienophile for the construction of the G ring, as well as a Ru-catalyzed cycloisomerization to construct the 27-membered carbocyclic ring, culminating with the formation of the seven-membered cyclic imine by self-catalyzed dehydration of an advanced ketoamino acid.

Nakamura and Hashimoto envisaged an approach to the 6,5,6-dispiroketal (BCD ring) system involving a stereoselective tandem double hemiketal formation/intramolecular hetero-Michael addition process. This strategy should have the advantage of generating a chiral center from an enone in the conjugate addition step under thermodynamic control. After the desired dispiroketalization, the synthesis of the entire C10–C31 pentacyclic ketal fragment (BCDEF ring) should also be achievable.

The aldehyde **62** and the methyl ketone **63** were each prepared by a series of conventional transformations and coupled in an aldol condensation with the aid of LiHMDS and $ZnCl_2$ in THF (Scheme 14).[36] After an additional seven steps, the C10–C23 aldehyde fragment **64** was ultimately accessed. The construction of the C23–C24 linkage was based on a fragment assembly by another aldol reaction. The lithium enolate derived from the ketone **65** [prepared in six steps from a known starting material involving a conjugate *anti*-addition of MeCu(CN)Li in the presence of $BF_3{\cdot}OEt_2$ to establish the C27 stereogenic center] reacted with the aldehyde to give a mixture of diastereomeric aldol adducts **66** in 88% yield. Five standard steps subsequently yielded the target triketone **61** in 60% yield. With the key substrate to hand, dispiroketalization through a tandem double hemiketal formation/hetero-Michael addition process was attempted by an established protocol. Treatment of the triketone with aqueous HCl (1 N) selectively liberated the C12 hydroxy group, yielding an equilibrium mixture of hydroxy triketones and hemiketals. Upon treatment with lithium methoxide in THF/MeOH (10:1) at room temperature, the desired dispiroketal was formed in 77% yield, accompanied by a 14% yield of other diastereomers. Removal of the acetonide group in **67** with CSA in dichloromethane and simultaneous ketalization afforded the C10–

C31 fragment **68**, containing the BCDEF pentacyclic ring system, as a single isomer in 55% yield after silylation steps.

Protecting group exchange was necessary because the C15-TBS ether could not be cleaved during the later stages of the synthesis.[35] Selective removal of the C31-TBS ether with TBAF at 0 °C, followed by immediate oxidation with Dess–Martin periodinane buffered with pyridine, yielded the desired aldehyde **70**. Homologation by a Horner–Wadsworth–Emmons reaction with β-ketophosphonate **70-r** under Masamune conditions yielded the diene **69** in 72% yield over four steps to set the stage for the critical Diels–Alder reaction. Regioselective cycloaddition with the α-methylene lactone **60** in *p*-xylene at 160 °C in a sealed tube yielded a separable mixture of stereoisomers in a 45:27:18:10 ratio.[35] The selectivity observed was *exo* (72:28), however, with poor diastereofacial selection (63:37), again underscoring the stereochemical challenges associated with the Diels–Alder approach. The desired adduct **71** was isolated in 35% yield.

Selective removal of the benzyl group at C10, followed by Dess–Martin oxidation and treatment with the Ohira–Bestmann reagent in the presence of $K_2CO_3$ in MeOH, afforded the alkyne **72** in 63% over three steps (Scheme 15). The lactone moiety was reduced with $LiAlH_4$ to the diol, which was first monosilylated at the C1 hydroxy group and then oxidized with the Dess–Martin reagent, and the resulting aldehyde was treated with allylmagnesium bromide to afford **73**. The cycloisomerization precursor was furnished after silylation of the secondary neopentylic hydroxy group with 1-(trimethylsilyl)imidazole. The cyclization product **74** was obtained upon exposure of **73** to $[CpRu\text{-}(MeCN)_3]PF_6$ (10 mol-%, acetone, 50 °C), in 79% yield, with complete regioselectivity, and with no dimerization. The ketone **75** was furnished after the selective removal of silyl protecting groups at C1 and C6 with pyridinium *p*-toluenesulfonate in EtOH, tosylation of the primary alcohol, oxidation of the allylic alcohol at C6, and a final conjugate reduction with the Stryker reagent in wet benzene, in 76% yield over four steps. Displacement of the tosylate with azide, followed by selective removal of the C34-TBDPS ether with TBAF, two consecutive oxidations (Dess–Martin, Pinnick), and hydrogenation with the Lindlar catalyst, efficiently provided the ketoamino acid **76**. One of the most important original contributions of this synthesis is the development of a direct cyclization of the ketamino acid **76** to the cyclic imine under thermolysis conditions (chlorobenzene, 120 °C, 18 h, 74% yield, 84% yield based on recovered starting material). The silyl groups were removed with HF in aqueous MeCN to complete the synthesis of pinnatoxin A.

### 3.3 Total Synthesis of Pinnatoxin A by Zakarian's Group (2008)

Zakarian's group described a series of synthetic studies culminating in the total synthesis of the natural enantiomer of pinnatoxin A in 2008.[38] The synthesis plan is based on a convergent strategy calling for the preparation of the two large fragments **77** and **78** (Scheme 16). It was anticipated that the joining of the fragments by alkyllithium addition to the C6 aldehyde of **78** would be followed by 27-membered macrocycle formation upon ring-closing metathesis with subsequent elaboration of the EF ketal. The acyclic Ireland–Claisen rearrangement of the complex ester **79** is a dominant feature of this synthesis plan, illustrating a departure from the Diels–Alder approach with the goal of improving stereocontrol for the introduction of the adjacent quaternary and tertiary stereogenic centers at C5 and C31.

Scheme 16 represents an early approach to the synthesis of the spirocyclic imine fragment characteristic of pinnatoxins and pteriatoxins. This route employed a cascade sigma-tropic process that utilizes the Claisen and Mislow–Evans rearrangements to construct the quaternary chiral center at the core of the AG-spiroimine.[39,40] It was envisioned that a

tandem sigmatropic rearrangement of the vinylic sulfoxide **80** (Scheme 17), derived from **82** and **83**, would deliver the desired fragment.

The synthesis of **81** began with the addition of pent-4-enylmagnesium bromide to the ketone **84**, readily available from ascorbic acid in four steps (Scheme 18). The lactone **83** was obtained by cleavage of the double bond and oxidation of the lactol. Alkylation of the zincate enolate generated from **83** with the iodide **82**, prepared from (2*R*,3*R*)-dimethylsuccinic acid,[45] afforded the expected product as a 5:1 mixture of diastereomers. Formation of the triflate followed by Negishi coupling yielded the dihydropyran **84**, which was advanced to the sulfoxide **81** by standard transformations.

As illustrated in Scheme 19, upon heating of the starting material in the presence of triethyl phosphite and *s*-collidine as a buffer in a high-boiling alcohol at 150 °C, the rearrangement results in smooth formation of the quaternary C5 chiral center and a stereoselective installation of a tertiary allylic alcohol, presumably proceeding through transition state **87**. Both diastereomers at the sulfoxide stereogenic center proved to be suitable substrates for the tandem sigmatropic rearrangement. The incorporation of imine ring closure into the reaction cascade through an aza-Wittig reaction was not productive. However, the imine **80** could be obtained in a separate event after a series of transformations culminating in a Staudinger reduction of the azide and an aza-Wittig cyclization ($PMe_3$, PhMe, 110 °C).

This key reaction cascade can also be performed in a microwave-assisted version, with significantly reduced reaction times.[40] The formation of the spiroimine **80** presented an opportunity to explore the stability of the spiroimine moiety outside the macrocyclic pinnatoxin framework, in which it displays uncharacteristic stability towards hydrolysis. It was found that **80** is readily hydrolyzed upon exposure to moisture,[40] suggesting that the entire macrocyclic structure of pinnatoxin A is necessary to ensure stability of the spiroimine.

Although this tandem sigmatropic reaction sequence was found to be potentially suitable for the synthesis of (+)-pinnatoxin A (**1**), it was limited in scope, preventing its application in syntheses of the spirolides or of gymnodimine.[46] Another serious obstacle was encountered during attempts to introduce the requisite C31 side chain. After significant experimentation, it was found that cuprate substitution held promise. When the pentafluorobenzoate **90** (Scheme 20), generated from **88** in high yield, was treated with dilithium bis(4-methylbut-3-enyl)cyanocuprate, a single regio- and stereoisomeric product (**91**) was isolated in good yield. It was initially assumed, on the basis of multiple precedent and preliminary NOE data, that **91** had the correct configuration at C31. However, after an extensive eight-step elaboration to a polycyclic advanced intermediate, it was conclusively established by extensive NOE correlations that the C31 stereochemistry introduced during the cuprate substitution was incorrect.[41]

Scheme 21 outlines the second-generation strategy for spiroimine assembly. As in the original approach, introduction of the C5 and C31 stereogenic centers early in the synthesis was anticipated, in order to alleviate some imminent challenges associated with the formation of these chiral centers. In this case, however, the Ireland–Claisen rearrangement was selected as a central transformation for the new strategy. In order to accommodate the key sigmatropic process, the cyclohexene ring (ring G) had to be deconstructed into an acyclic fragment. In a forward sense, an aldol cyclocondensation was deemed an optimal reaction to build the six-membered ring. Subsequent analysis was based on straightforward transformations to reach the Ireland–Claisen chemistry via **78-b** (see Schemes 16 and 21).

An apparent deficiency of the new plan is the key step itself: from prior knowledge one would expect a mixture of diastereomers at C5 from the Ireland–Claisen rearrangement of

the ester **79**. This shortcoming created an opportunity to explore and to develop methodology for diastereoselective Ireland–Claisen rearrangements of complex α-branched acyclic esters (Figure 4).[42] It is well-established that diastereocontrol in the Ireland–Claisen rearrangement is predictably correlated to the geometric selectivity of enolate formation, so the enoliation step became the focus of the method development. Ireland and co-workers proposed a simple model for enolization of carbonyl compounds with lithium amides based on chair-like transition structures (**F** and **G**, Figure 4).[43] If this model is applied to stereodefined esters, it can be hypothesized that the two diastereomeric transition structures would lead to different geometric isomers upon proton transfer (**F**→**Z**, **G**→**E**). Traditional achiral bases would be unlikely to exert a preference for the formation of the six-membered chair-like structures, but the process might be effectively controllable by application of chiral bases. The ready availability of a selection of chiral amines gives this approach further appeal.

In practice, it has been demonstrated that chiral bases as shown in Figure 4 enable highly stereoselective generation of α,α-disubstituted enolates. The examples in Scheme 22 serve to illustrate the stereochemical course of the enolization process, providing a empirical model with which to predict the geometries of enolates based on chirality matching between the substrate and the chiral base. Application of the enolization technique in the Ireland–Claisen rearrangement has been described.[42]

The new enolization method having been developed, its application in the intricate venue of the total synthesis of pinnatoxin A was pursued. The dithioacetal **92** (Scheme 23), derived from D-ribose in one step, was modified by protecting group chemistry to unmask the aldehyde group in preparation for the Horner–Emmons olefination. Reduction of the ester to the allylic alcohol and subsequent Swern oxidation furnished the α,β-unsaturated aldehyde **96**, which was converted into the target allylic alcohol **97** by enantioselective addition of diethylzinc catalyzed by (*S*)-1,1,2-triphenyl-2-(piperidin-1-yl)ethanol.

Esterification of the alcohol **97** with the carboxylic acid **98** [11 steps from (*S*)-citronellic acid] under the Yamaguchi conditions provided the ester **79** in 85% yield (Scheme 24). In the key event, enolization of **79** in the presence of the chiral Koga-type base **100** proved to be highly stereoselective, forming the Z enolate, which underwent a smooth [3,3]-sigmatropic rearrangement to the acid **92** at room temperature after trapping as a silyl ketene acetal. The chiral base could be recovered in almost quantitative yield by extraction with acid.

The product of the Ireland–Claisen rearrangement, containing the requisite C5 and C31 stereogenic centers formed in a single step, was advanced to the diol **99** in five steps (69% yield). Double oxidation of the two primary hydroxy groups under Swern reaction conditions provided the dialdehyde **78-b**, which underwent a completely regioselective aldol cyclocondensation to compound **101** upon treatment with dibenzylammonium trifluoroacetate at slightly elevated temperatures. Above 50 °C, epimerization at C31 became notable, but no epimerization was observed at lower temperatures. Reduction of the aldehyde and protection as a methoxymethyl ether provided **78-a**, which was advanced by deprotection (TIPS), oxidation, olefination to **102**, and finally by reductive debenzoylation and oxidation to the C5 aldehyde **78**.

The central transformation in the synthesis of the BCD-dispiroketal was the thermodynamically controlled ketalization of the diketo diol precursor **110** (Scheme 25).[44] The influence of solvent polarity on the selectivity of the process in favor of the thermodynamically preferred product became the focus of the study. Solvent effects on the extents, and occasionally even the positions, of anomeric equilibria in simple systems have

been known for a long time.[47] It has been demonstrated that the anomeric effect is reinforced in solvents of low polarity. To explore this phenomenon in the context of the BCD-spiroketal synthesis, a racemic mixture of the allylic alcohols **103** was resolved by enzymatic acetylation with immobilized Amano lipase PS-D. The resulting products could easily be separated by chromatography. The alcohol **104** was advanced to the borane **106** (used in situ), whereas the acetate **105** was converted into the iodoalkene **107** (11 steps, 44% yield). These intermediates were reunited in a palladium-catalyzed cross-coupling, delivering **108** in high yield. A three-step sequence involving dihydroxylation, silyl ether removal, and oxidation furnished the diketone **109**; methanolysis of this under acidic conditions set the stage for the study of dispiroketalization. In line with expectations, increasingly higher yields of the fully stabilized diastereomer **111** were isolated with decreasing solvent polarity. The reactions were allowed to continue for 2 d to ensure that the thermodynamic equilibrium has been reached. Under optimal conditions, a 10:1 ratio of **111** and **112** was achieved in cyclohexane (Table 1).

The synthesis of the BCD-dispiroketal fragment was completed in eight additional steps as shown in Scheme 26. The ester **111** was produced in 88% yield after a single recycling step. Protection of the free hydroxy groups as silyl ethers and reduction of the ester with *i*$Bu_2$AlH gave the aldehyde **113** in 82% yield. Chain-extension, oxidation, olefination, oxidative debenzylation, and iododehydroxylation completed the synthesis of the BCD-bisketal fragment **77**.

In one of the major events in the synthesis, the two advanced building blocks were combined by direct addition of a complex lithium reagent generated from **77** to the aldehyde **78** (Scheme 27). Lithium/iodine exchange (**77**, *t*BuLi, $Et_2O$, 1 h, −78 °C) followed by addition of **78** resulted in a high-yielding reaction delivering **115** as an inconsequential mixture of diastereomers (2:1) in 75% yield. After oxidation at C6, three additional steps were needed to reach the ring-closing metathesis (RCM) substrate **116**. Extensive experimentation revealed that under virtually all conditions attempted a 3:1 ratio of the regioisomeric products **118** and **117** was obtained after oxidation with DMP. The isomer **117** clearly arises from the RCM at the C10 double bond. Nevertheless, **118** could be isolated in a practical 57% yield. Cuprate addition, followed by a challenging multiple deprotection/EF ketal formation, provided **120**. Additional functional group manipulations were aimed at the introduction of nitrogen at C1 and the adjustment of the oxidation state at C34. Achieving this goal required seven steps to arrive at the intermediate **122**. In the concluding three-step sequence, reduction of the azide with trimethylphosphane, imine formation under mild conditions developed by Kishi and coworkers,[24a] and a crucial ester hydrolysis delivered the natural enantiomer of pinnatoxin A.

## 4. Conclusion

As is evident from this microreview, pinnatoxin A, as a prototypical member of the expanding family of spiroimine natural products, has inspired a wealth of synthetic strategies and innovative methods applied in the synthesis of this complex compound. Examples include new insights into the chemistry of aliphatic cyclic imines, Diels–Alder cycloadditions, a variety of ketalization processes, new variants of the Ireland–Claisen rearrangement and other [3,3]-sigma-tropic transpositions, and a number of other transformations with complex, multifunctionalized intermediates.

It is particularly notable that chemical synthesis is currently the only realistic source of the important bioactive natural product, in view of the fact that a producing organism remains elusive. Intriguingly, essentially every report citing the biological activity of pinnatoxin A refers to the marine toxin as a calcium-channel activator, even though the evidence for the

mode of action is based on limited phenotypic data provided by the group that reported its isolation.[4] More thorough and convincing studies to elucidate the biological activity of pinnatoxin A are clearly needed, and it is total synthesis that is the most likely source of material for these studies.

## Biographies

Stéphane Beaumont was born in Normandy in 1981. After studying at the IUP of Chemistry and Biology in Nantes and at the University of Paris XI, he received his PhD under the direction of Dr. Robert H. Dodd and Dr. Philippe Dauban at the Institut de Chimie des Substances Naturelles, Gif-sur-Yvette. After postdoctoral studies with Professor Armen Zakarian at the University of California Santa Barbara, he joined GALAPAGOS as a medicinal chemistry scientist in 2010.

Elizabeth A. Ilardi received her B.S. in Chemistry from The College of William and Mary in Virginia in 2006. She is currently working on her Ph.D. in organic chemistry under the supervision of Dr. Armen Zakarian at the University of California Santa Barbara. The focus of her studies includes the development of new methodologies to be applied towards the total syntheses of natural products.

Nicholas D. C. Tappin was born in Manchester in the UK. He attended Queens' College, University of Cambridge, where he obtained a B.A. and an M.Sc. after studies with flow chemistry in the ITC of the Steven Ley Group. In 2009 he made the leap across the Atlantic to UC Santa Barbara, where he is currently working on the synthesis of natural products.

Armen Zakarian was born in Moscow and completed his undergraduate studies at Moscow State University in 1994. His Diploma research was carried out at the Zelinsky Institute of Organic Chemistry with Dr. Vladimir Borodkin. He received his Ph.D. under the direction of Professor Robert A. Holton at Florida State University in 2001, and then spent two years (2002–2004) in the laboratories of Professor Larry E. Overman (University of California, Irvine) as a postdoctoral research associate. He began his independent academic appointment in August 2004, and he is currently a faculty member at the Department of Chemistry and Biochemistry, University of California Santa Barbara. His research interests include synthetic organic chemistry spanning the total synthesis of natural products, bioorganic chemistry, and the development of synthetic methodology.

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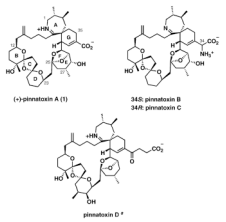



**Figure 1.**

Spiroimine marine toxins: pinnatoxins A–D. [a] The structure of pinnatoxin D given in the literature is inconsistent. Shown above is a structure based on the original proposal presented by Uemura[2] and confirmed by follow-up work from Kitching.[3]

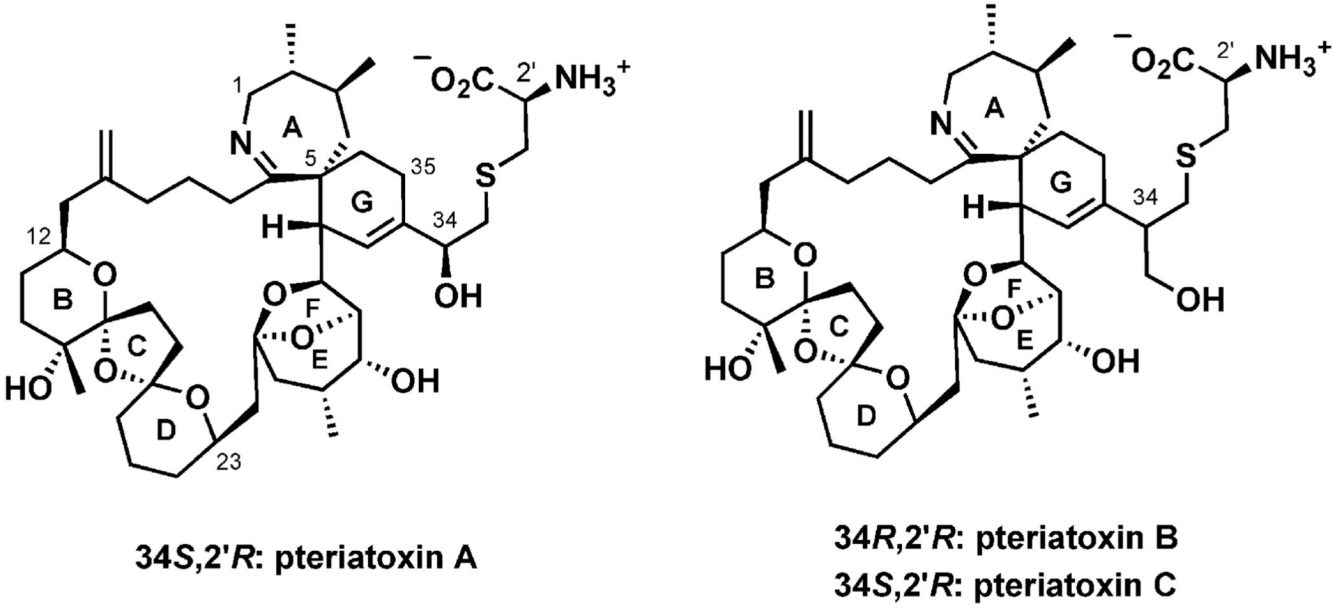



**Figure 2.**
Spiroimine marine toxins: pteriatoxins A–C.

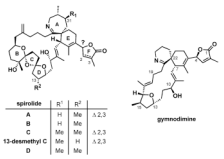



**Figure 3.**
Spiroimine marine toxins: spirolides A–D and gymnodimine.

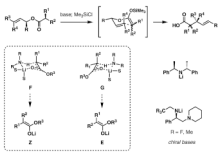
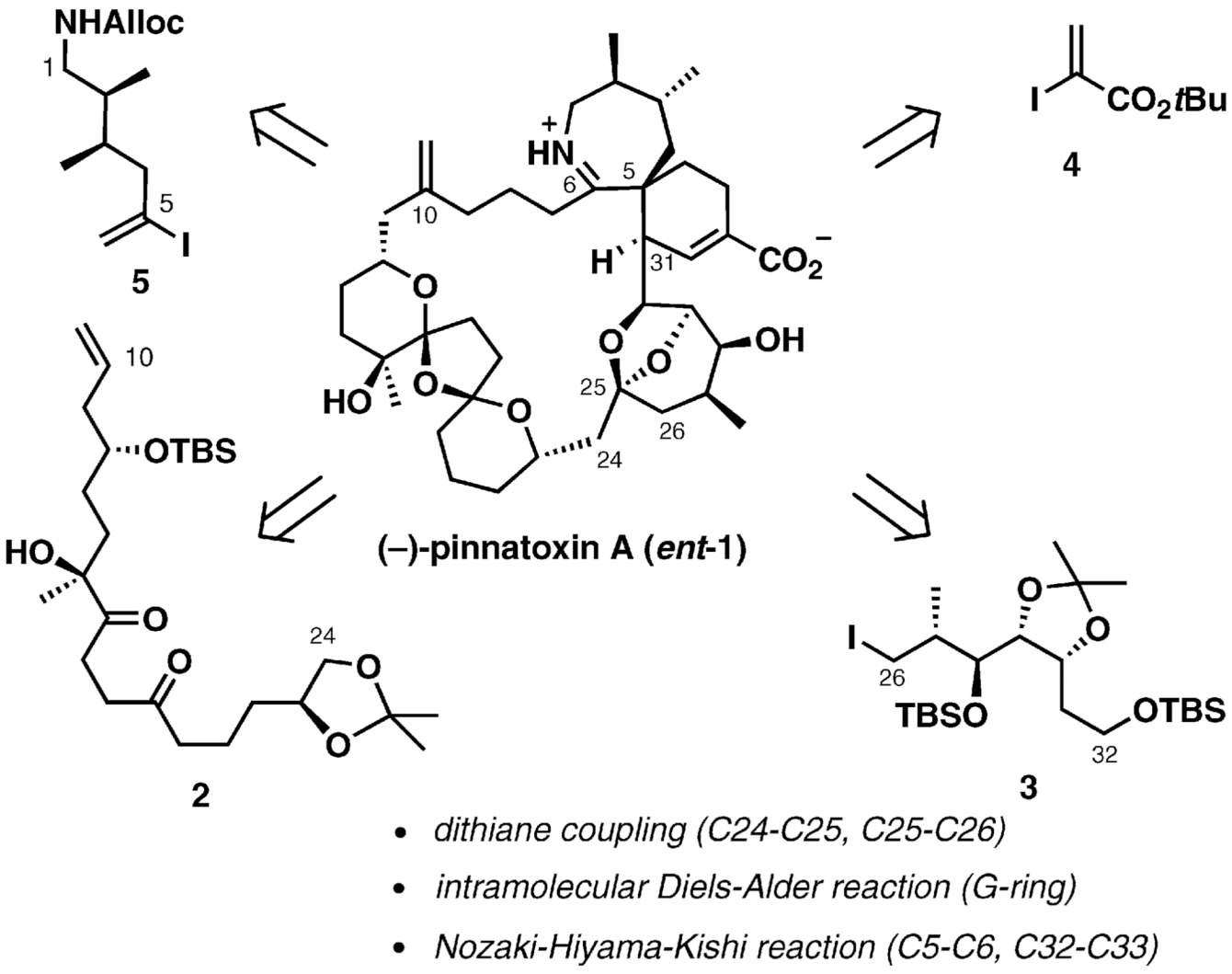
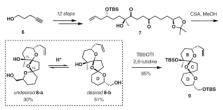


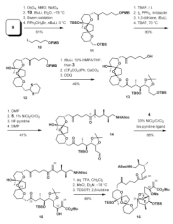
**Figure 4.**
Transition structures of the Ireland–Claisen rearrangement.



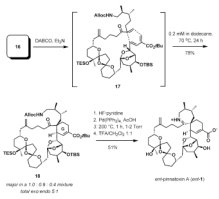

**Scheme 1.**
Synthesis plan for (−)-pinnatoxin A.



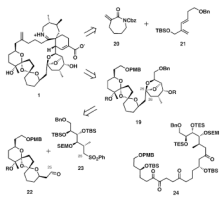
**Scheme 2.**
Synthesis of the BCD-spiroketal.



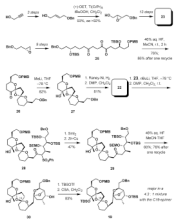
**Scheme 3.**
Synthesis of the substrate for the intramolecular Diels–Alder reaction.



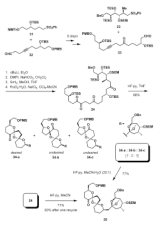
**Scheme 4.**
Endgame.



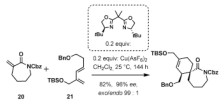
**Scheme 5.**
Target fragments of pinnatoxins.



**Scheme 6.**
Spiroketalization.

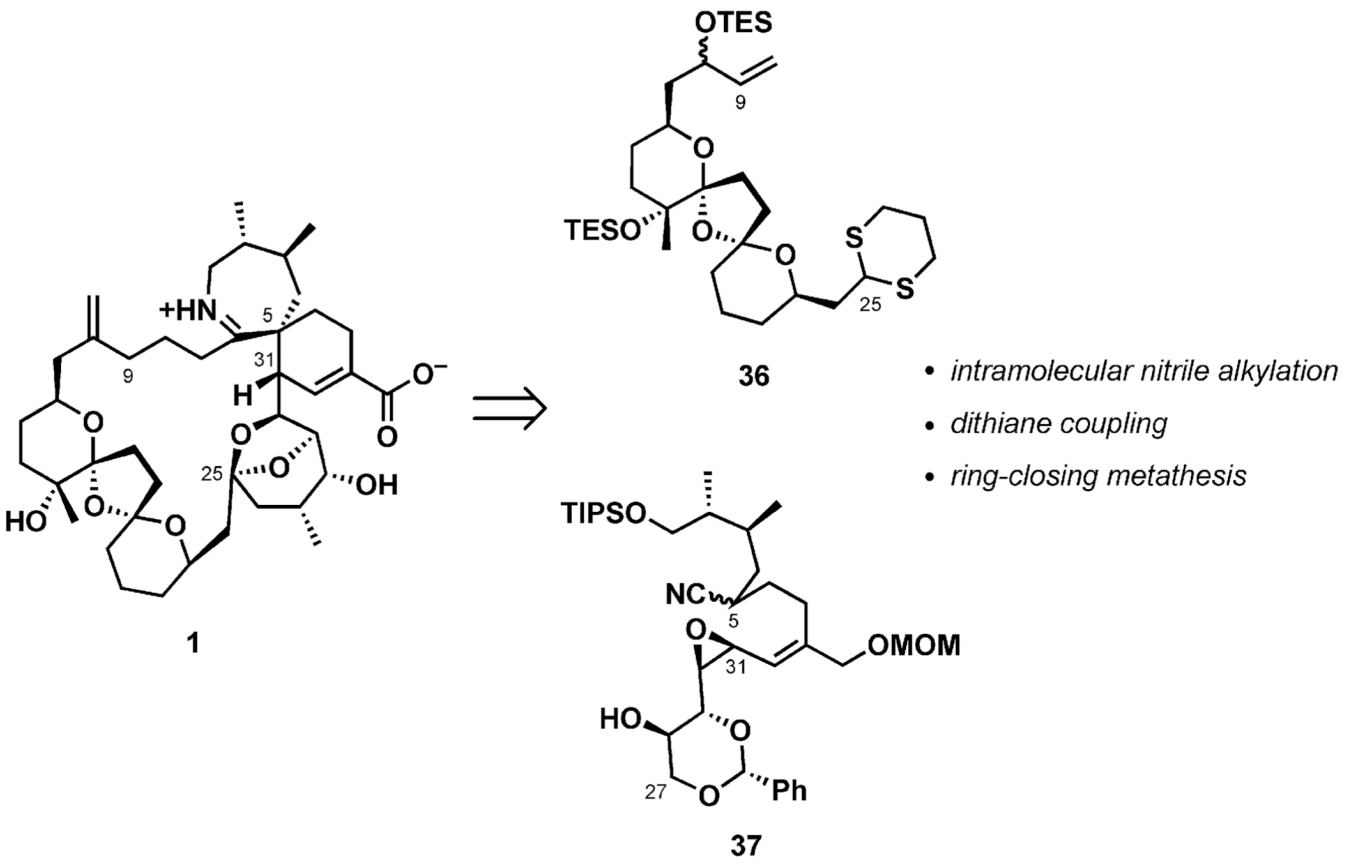


**Scheme 7.**
Synthesis of the BCDEF ring.

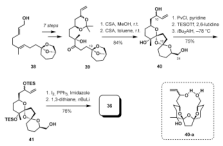


**Scheme 8.**

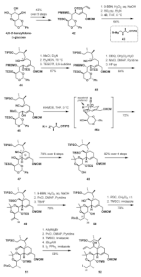
Diastereoselective formation of the spiroimine ring through a copper-bisoxazoline-catalyzed Diels–Alder reaction.



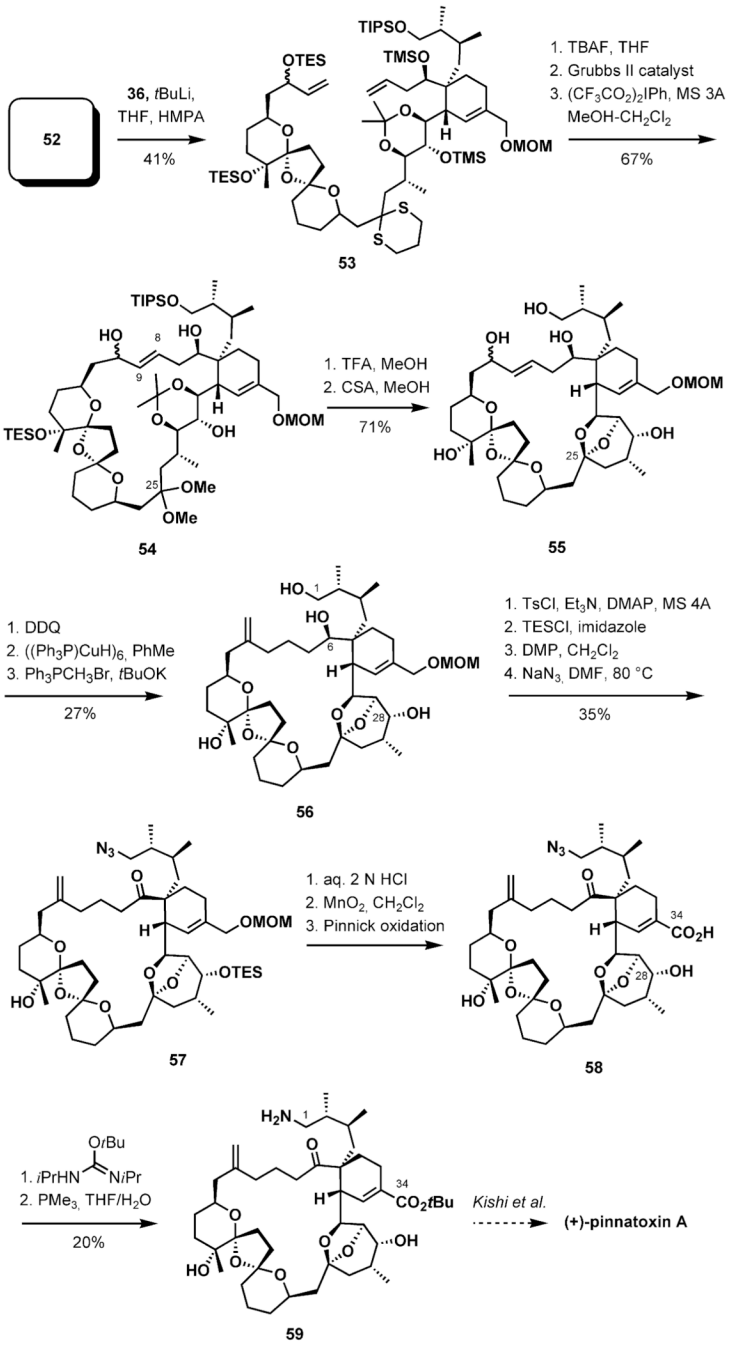

**Scheme 9.**
Synthetic strategy for (+)-pinnatoxin A (**1**).



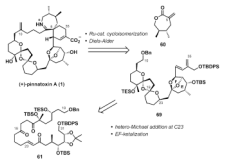
**Scheme 10.**
Preparation of the BCD ring.



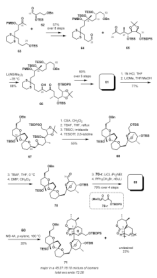
**Scheme 11.**
Synthesis of fragment **52**.



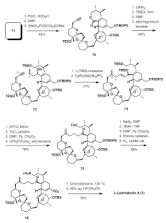

**Scheme 12.**
Endgame.



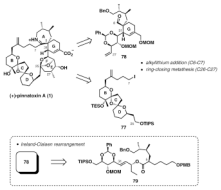
**Scheme 13.**
Synthesis plan.



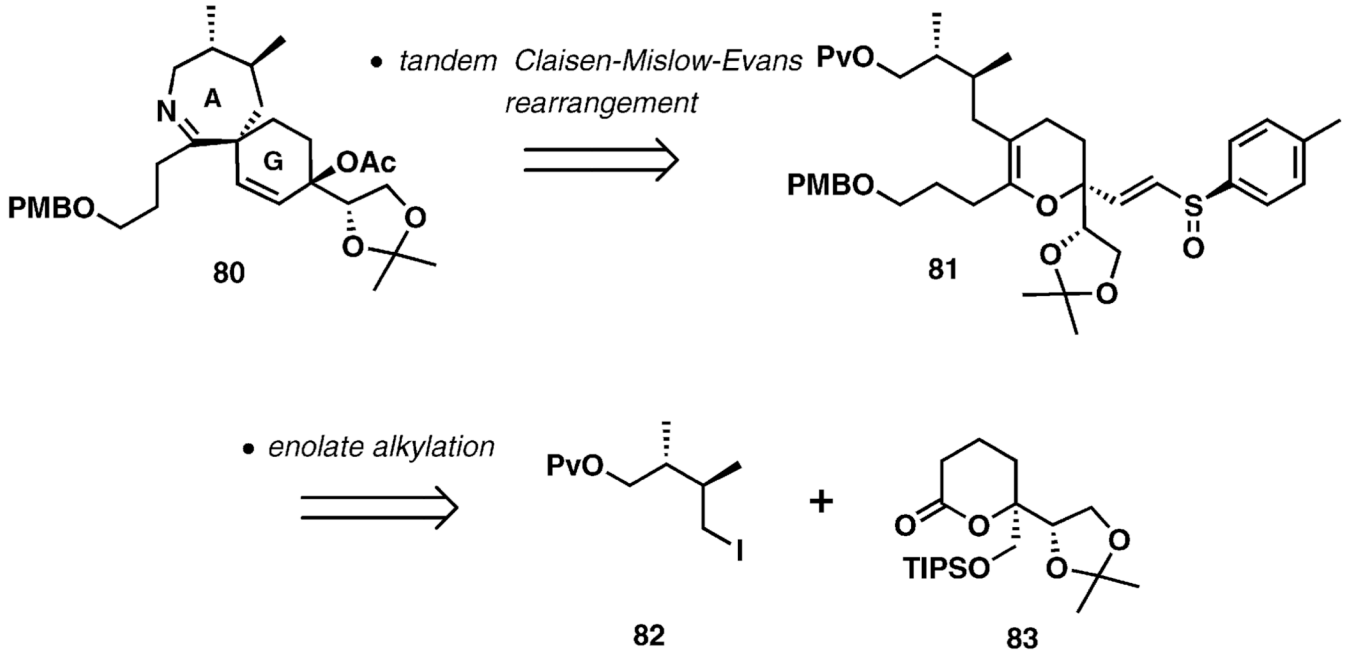
**Scheme 14.**
Synthesis of the Diels–Alder adduct.



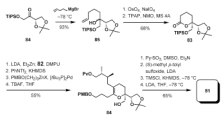
**Scheme 15.**
Endgame.



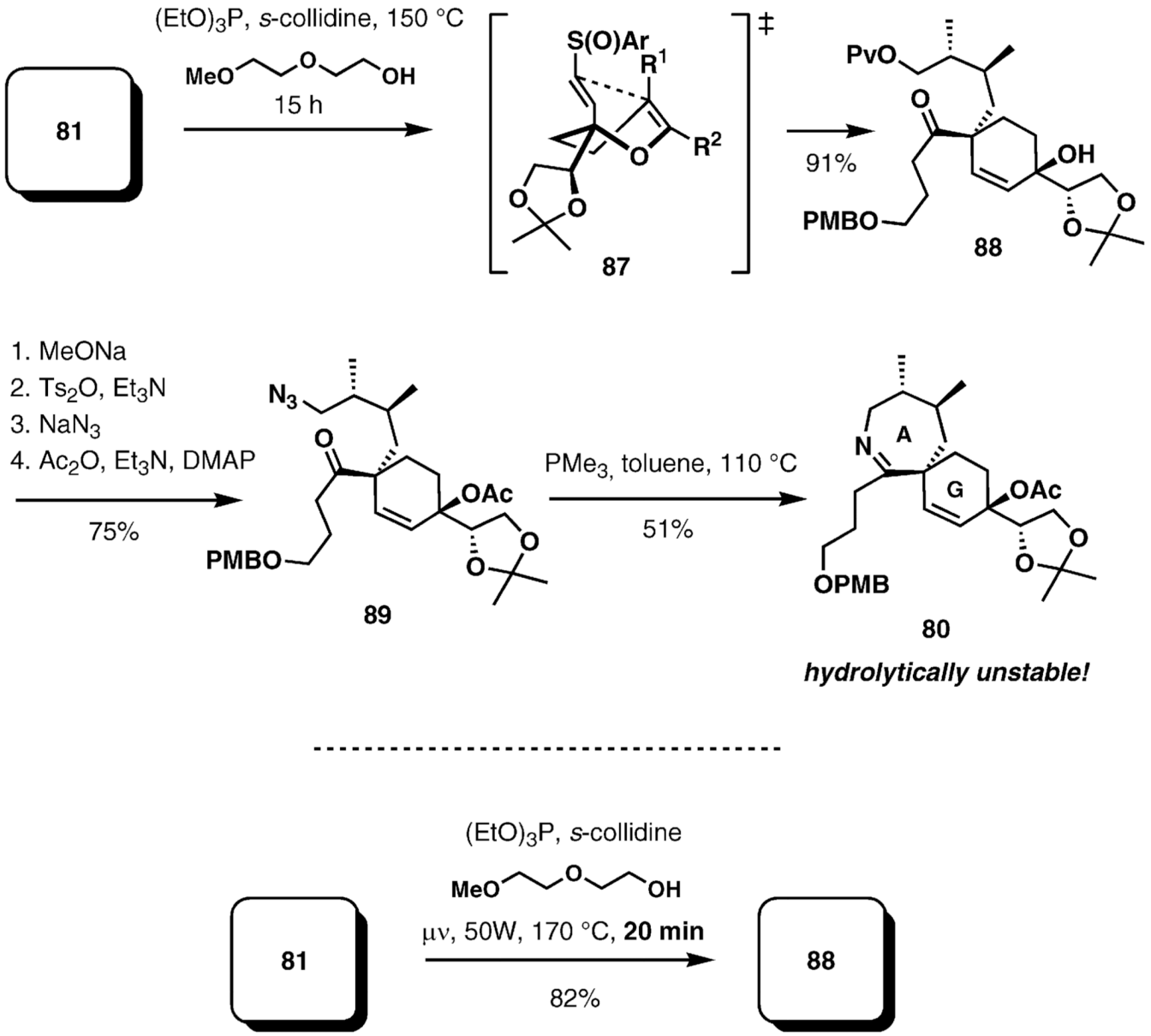
**Scheme 16.**
General synthesis plan.




**Scheme 17.**
Initial approach to the AG-spiroamine ring.



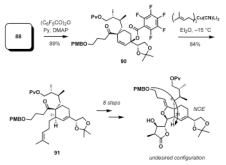
**Scheme 18.**
Synthesis of the vinyl sulfoxide **81**.



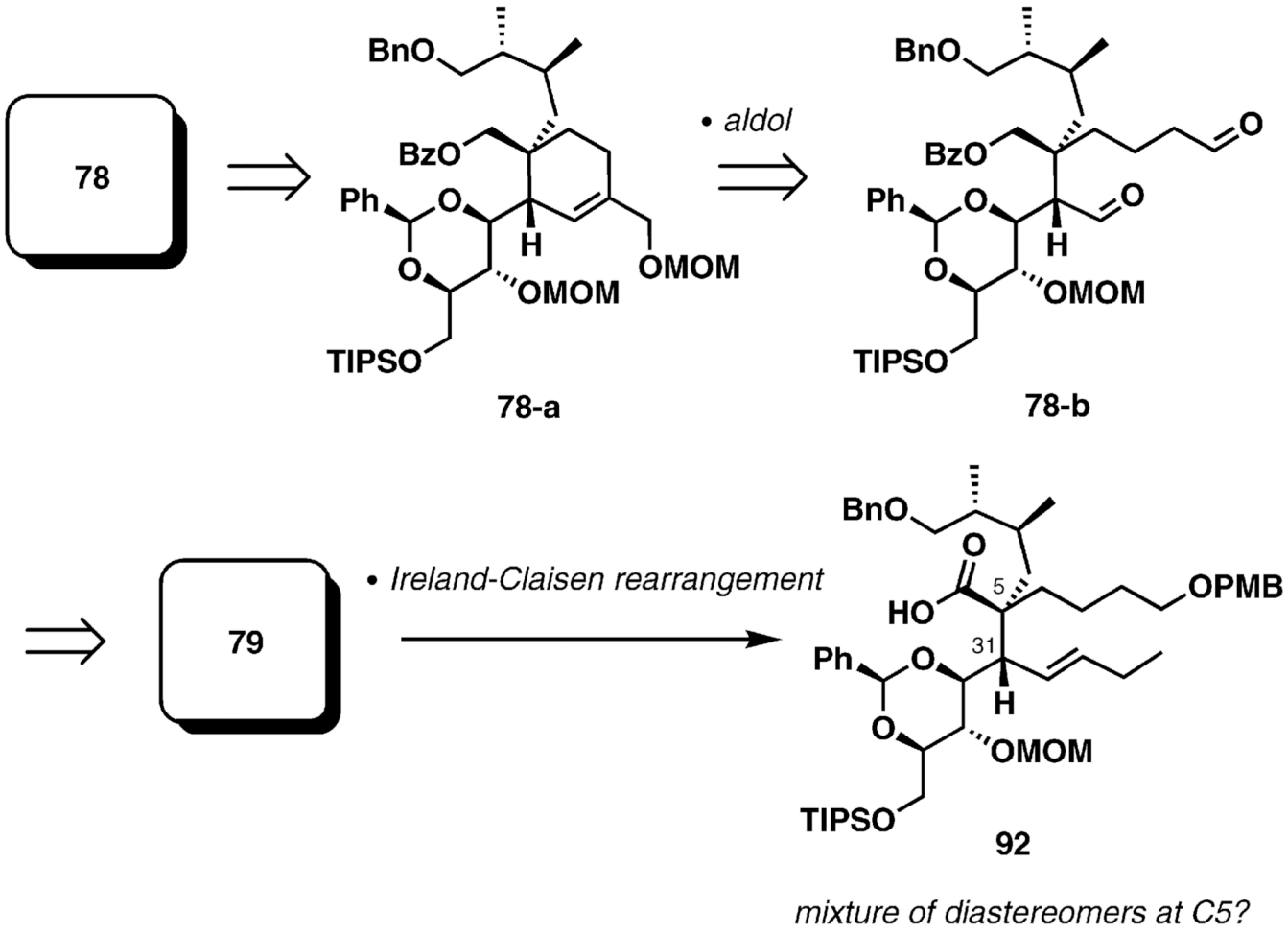




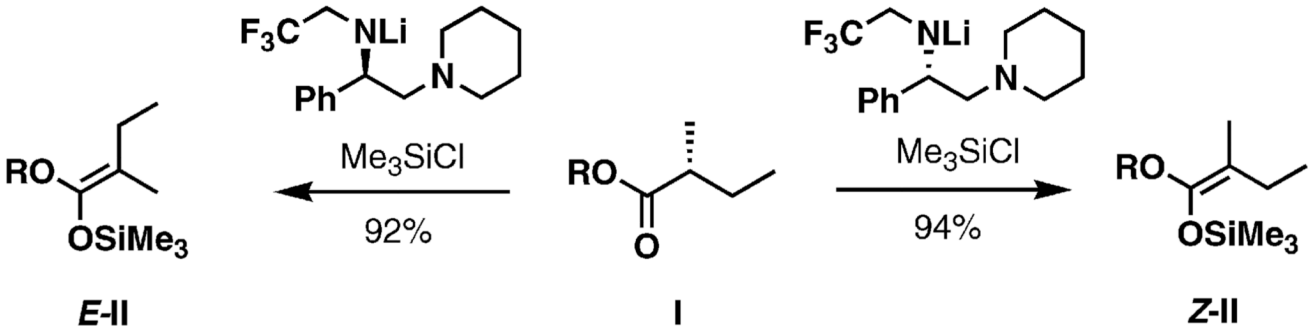
**Scheme 19.**
Cascade Claisen–Mislow–Evans rearrangement.



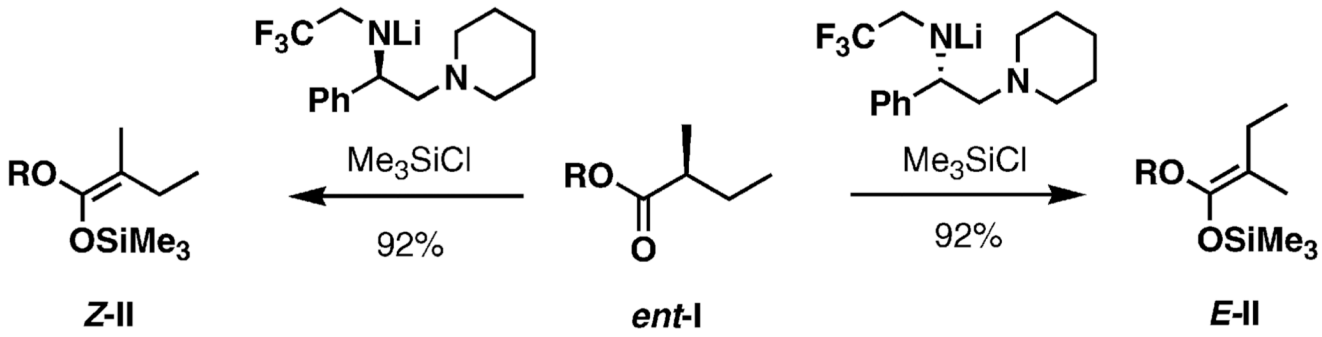
**Scheme 20.**
Lithium cuprate addition.



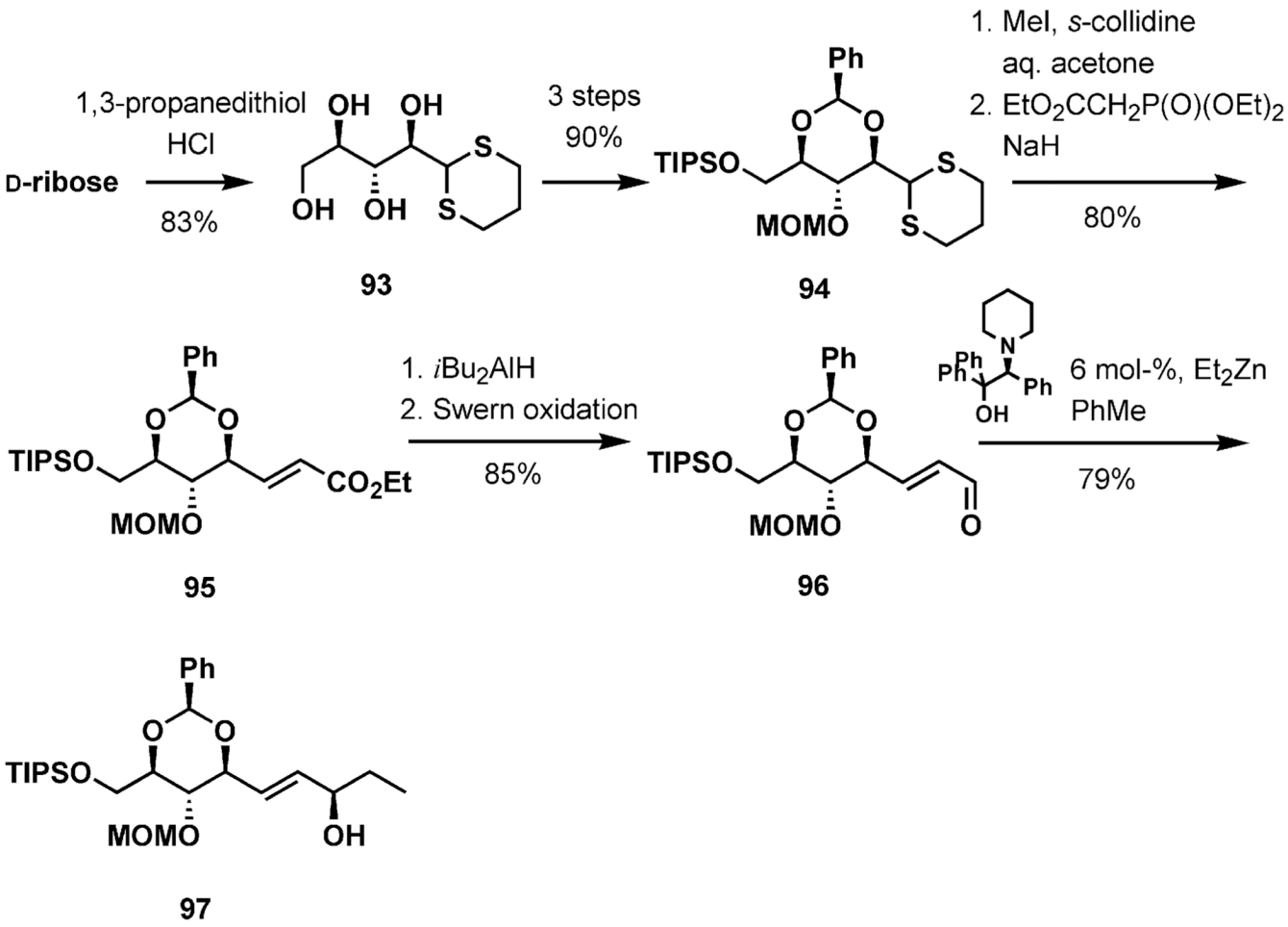

**Scheme 21.**
New strategy for spiroamine formation.



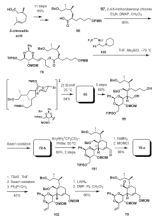

*complementary selectivity:*



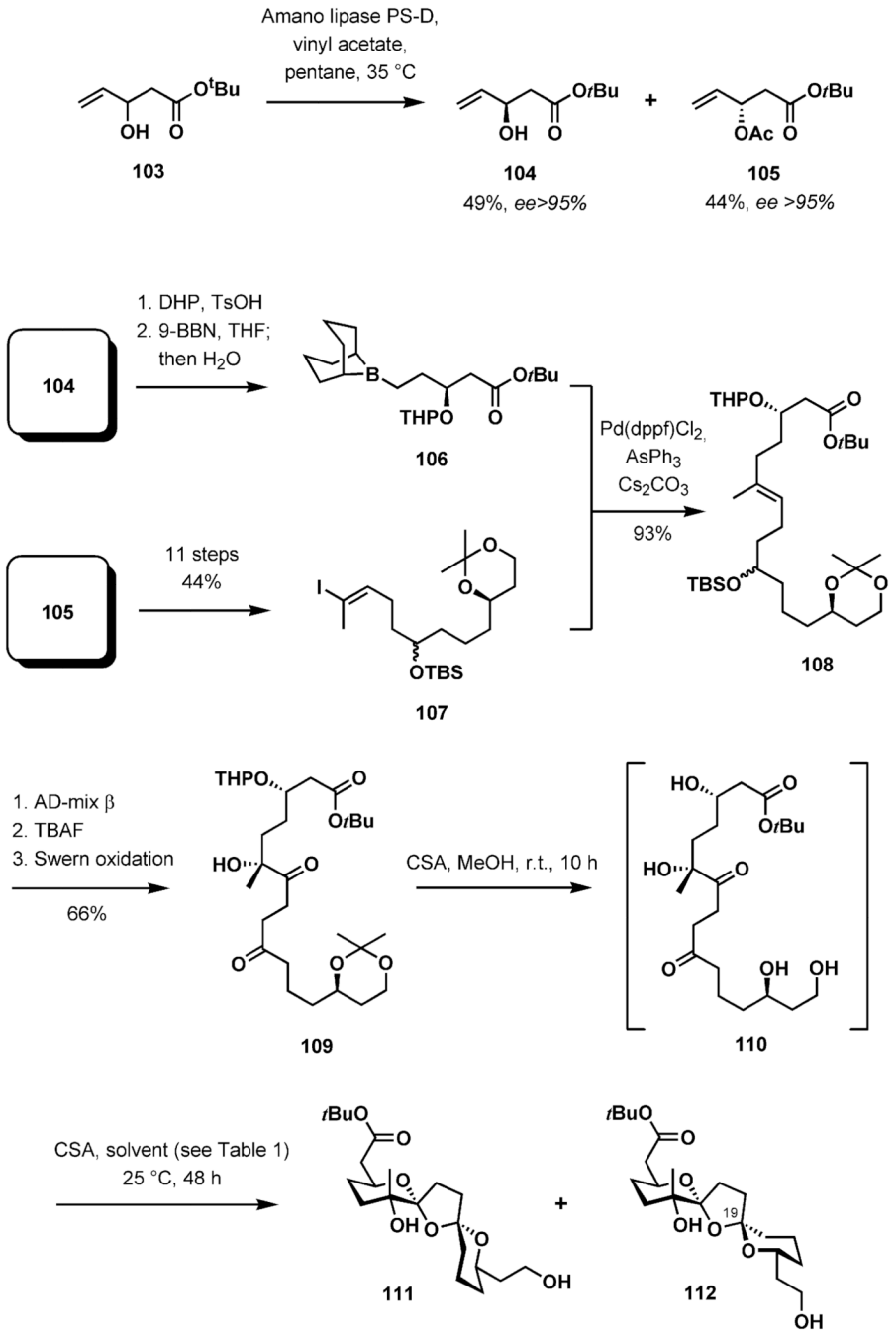

**Scheme 22.**
Chirality of the base dictates stereoselectivity.



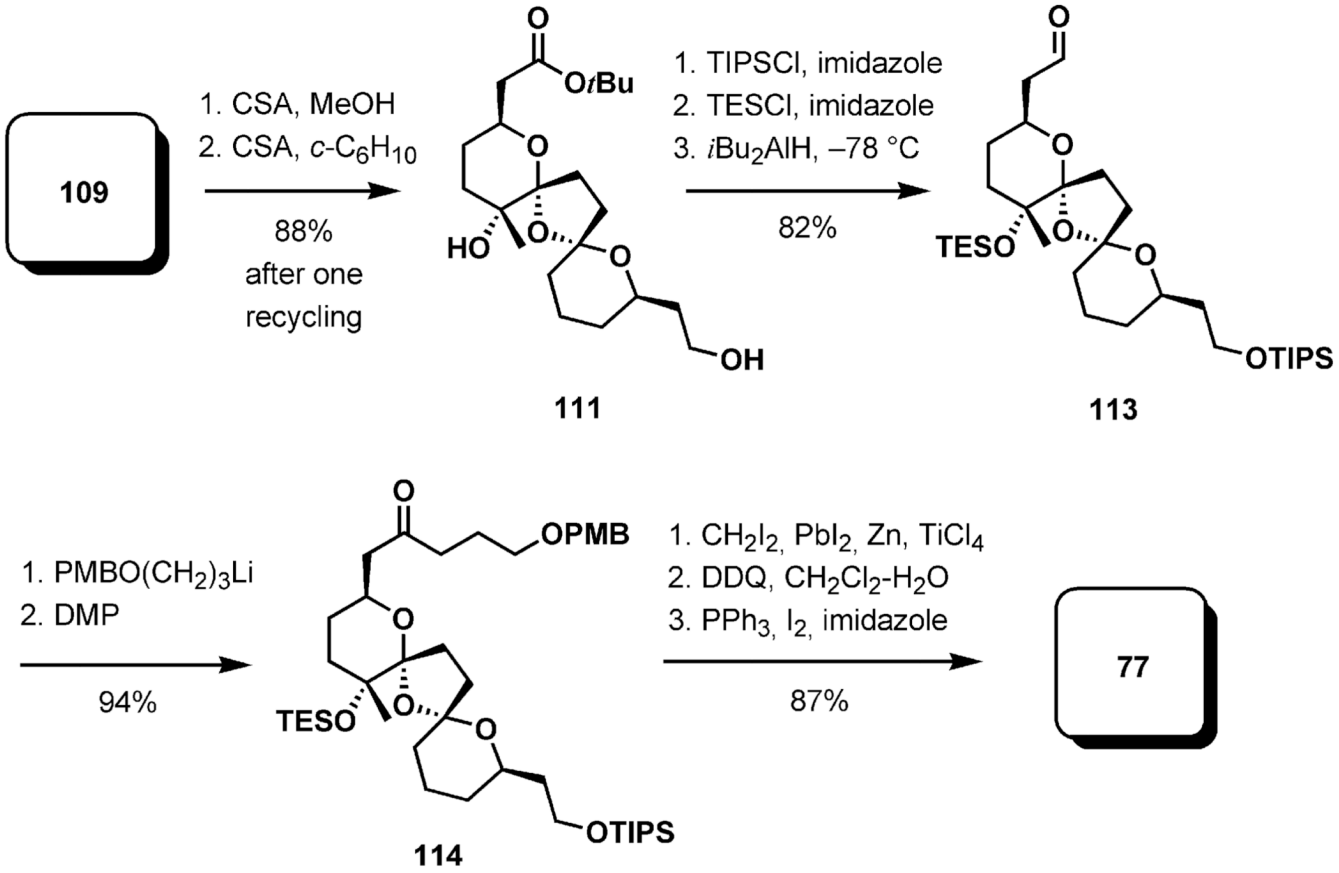

**Scheme 23.**
Preparation of the allylic alcohol **97**.



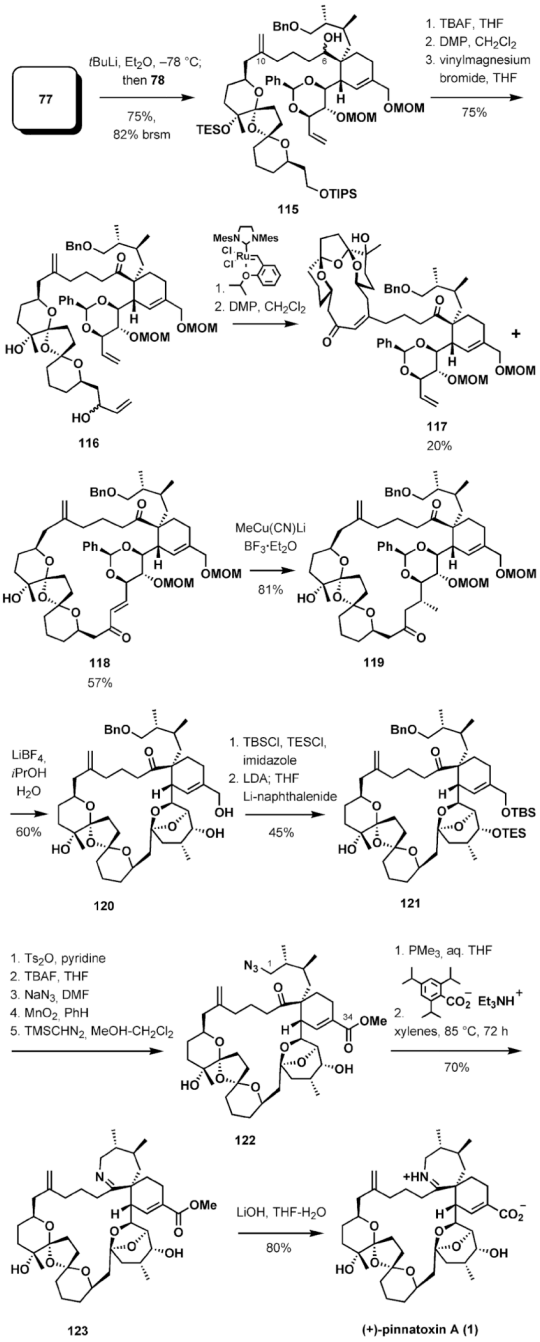
**Scheme 24.**
Application of the [3,3] sigmatropic shift.




**Scheme 25.**
Preparation of the BCD-spiroketal precursor.




**Scheme 26.**
Completion of fragment **77**.




**Scheme 27.**
Completion of the synthesis.

**Table 1**

Solvent effects on spiroketalization.

| Entry | Solvent | 111 (% yield) | 112 (% yield) |
|---|---|---|---|
| 1 | methanol | 49 | 22 |
| 2 | dichloromethane | 62 | 23 |
| 3 | toluene | 63 | 13 |
| **4** | **cyclohexane** | **78** | **8** |