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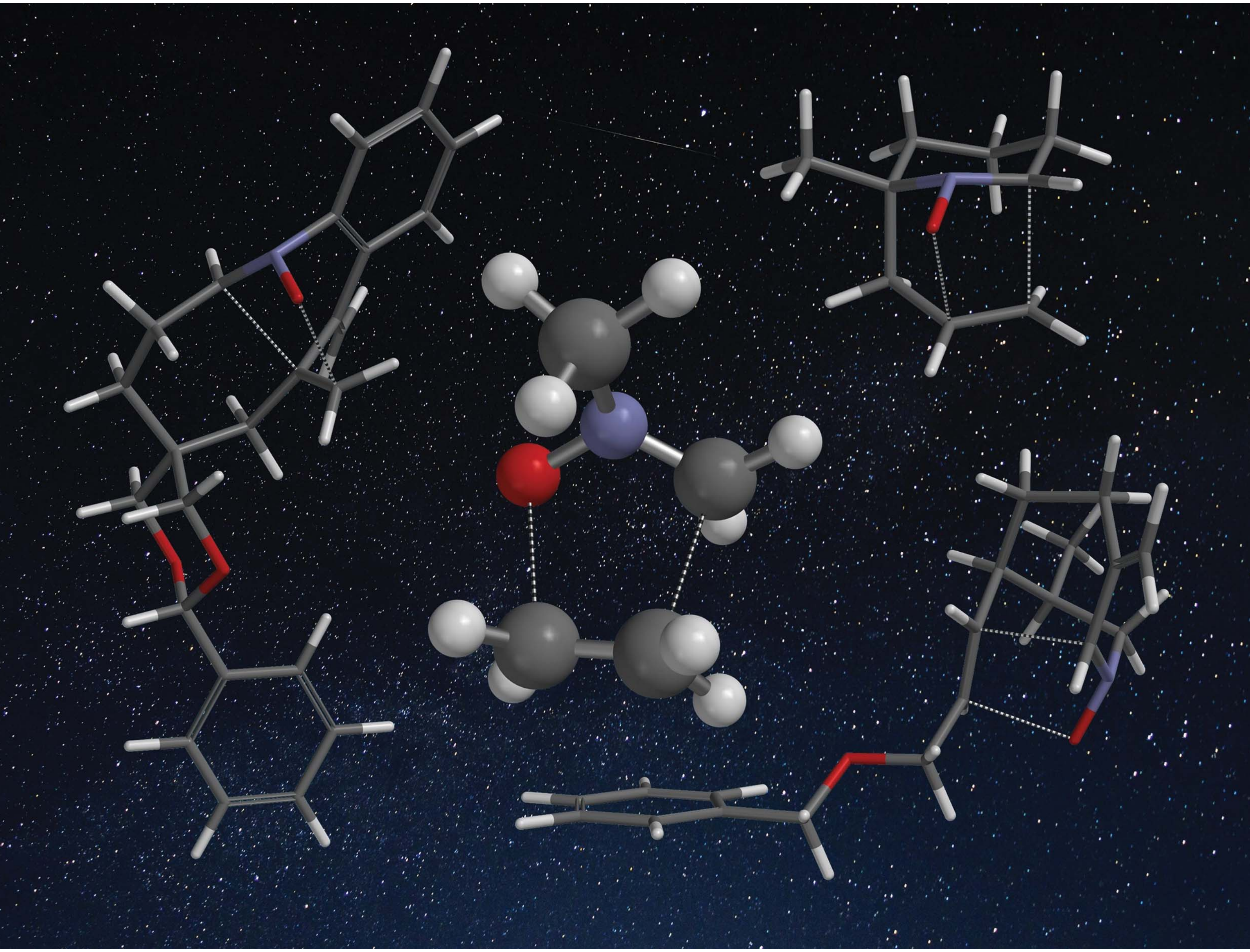

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REVIEW ARTICLE
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REVIEW

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Intramolecular cycloaddition of nitrones in total synthesis of natural products

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Covering 2015 to 2024

Cycloaddition of nitrones with alkenes forms isoxazolidines, which are five-membered heterocycles containing nitrogen and oxygen atoms. This transformation functionalizes alkenes by forming C–C and C–O bonds. The N–O bond in the resultant isoxazolidines is easily cleaved. Additionally, when the cycloaddition is carried out intramolecularly, the regioselectivity of the reaction is influenced by the tether connecting the nitrone and alkene and can differ from the selectivity governed by frontier molecular orbital interaction. These features make the intramolecular cycloaddition of nitrones attractive in the synthesis of complex molecules. In this review, we discuss the intramolecular cycloaddition of nitrones used in the total synthesis of natural products.

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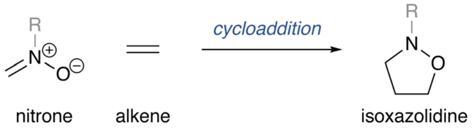
1. Introduction

A nitrone is a 1,3-dipole consisting of carbon, nitrogen, and oxygen atoms arranged in that sequence.[1] It is usually depicted as a structure in which carbon and nitrogen atoms form a double bond, with the oxygen atom negatively charged and the nitrogen atom positively charged (Scheme 1). A nitrone undergoes cycloaddition with an alkene to form an isoxazolidine.[2] In this transformation, the C–C double bond is functionalized to form C–O and C–C bonds. The N–O bond in the isoxazolidine is readily cleaved. These observations show that the cycloaddition of a nitrone is a useful method to introduce oxygen and nitrogen functionalities with concomitant formation of a C–C bond.

In the cycloaddition step, there is an issue of regioselectivity, which can be understood by frontier molecular orbital (FMO) interaction.[1a,h,3] Typical examples of intermolecular



Scheme 1 Cycloaddition of nitrone.

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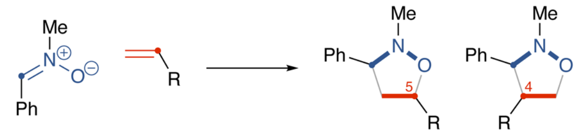
Table 1 Regioselectivity in cycloaddition of nitrones



1 **2** **A** 5-substituted **B** 4-substituted

Entry	R	Yield (%)	A : B	*Cis* : *trans*
1[a]	n-C_6H_{13}	77	100 : 0	1 : 1
2[b]	Ph	79	100 : 0	3 : 1
3[c]	OEt	78	100 : 0	1 : 1
4[d]	CO_2Et	97	82 : 18	1 : 7[f], 2 : 7[g]
5[e]	NO_2	—	0 : 100	2 : 1

[a] Toluene, reflux. [b] Toluene, 100 °C. [c] 80 °C. [d] Benzene, reflux. [e] 60 °C. [f] For regioisomer **A**. [g] For regioisomer **B**.

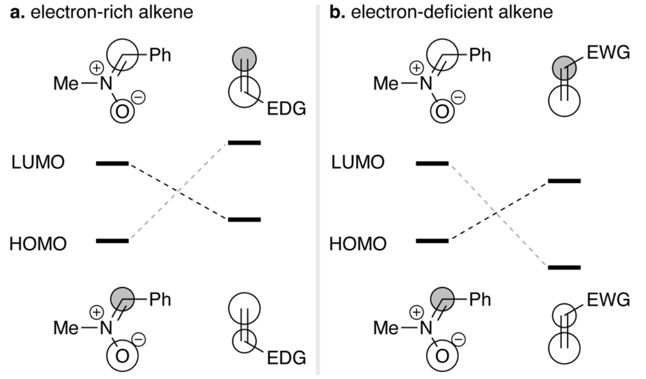


Fig. 1 HOMO–LUMO interaction of cycloaddition of nitrone. (a) Cycloaddition with an electron-rich alkene. (b) Cycloaddition with an electron-deficient alkene.

cycloaddition of a nitrone with various alkenes are summarized in Table 1. Reactions of nitrone **1** with electron rich alkenes produce 5-substituted isoxazolidines **A** (entries 1–3).[4] These can be understood by the matching of the largest coefficients both in the $\mathrm{LUMO}_{\mathrm{nitrone}}$–$\mathrm{HOMO}_{\mathrm{alkene}}$ and $\mathrm{HOMO}_{\mathrm{nitrone}}$–$\mathrm{LUMO}_{\mathrm{alkene}}$ interactions (Fig. 1a). In the reaction of **1** with nitroethylene (entry 5),[5] the $\mathrm{HOMO}_{\mathrm{nitrone}}$–$\mathrm{LUMO}_{\mathrm{alkene}}$ interaction is dominant, selectively producing 4-substituted isoxazolidine **B** (Fig. 1b). In the case of ethyl acrylate (entry 4),[6] which is a less electron-deficient alkene than nitroethylene, the less energetically preferred $\mathrm{LUMO}_{\mathrm{nitrone}}$–$\mathrm{HOMO}_{\mathrm{alkene}}$ also contributes to the regioselectivity in addition to the $\mathrm{HOMO}_{\mathrm{nitrone}}$–$\mathrm{LUMO}_{\mathrm{alkene}}$ interaction, leading to the formation of a mixture of 5- and 4-substituted isoxazolidines.

These regioselectivities are often changed in the case of intramolecular cycloaddition where the nitrone and alkene are connected by a tether. This tether regulates the approach between the nitrone and the alkene, determining the selectivity.[7] In the case of intramolecular cycloaddition, the stereoselectivity, including facial and endo/exo-selectivities, tends to also be controlled by the tether. This feature makes the intramolecular cycloaddition of nitrones attractive for the synthesis of complex molecules, including natural products.

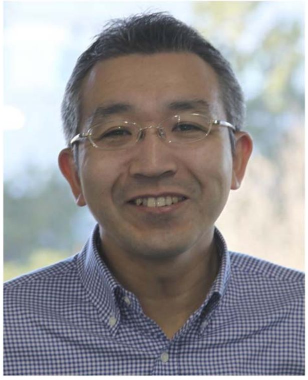
This review summarizes intramolecular cycloaddition reactions of nitrones in natural product syntheses reported between 2015 and 2024.[8–11] The preparation of the nitrones and the transformations after the cycloadditions are also described.

2. Construction of isoxazolidine rings in natural products

Although some natural products contain isoxazolidine rings (Fig. 2), such natural products are rare.[1e] The biosynthetic pathway might involve the generation of a nitrone and its cycloaddition.[12] In this section, three syntheses of natural products containing an isoxazolidine ring are demonstrated.

2.1. Synthesis of alsmaphorazine B

Alsmaphorazine B (**15**) is a hexacyclic indole alkaloid containing an isoxazolidine ring (Scheme 2). Although a biosynthetic



Satoshi Yokoshima

Satoshi Yokoshima received his B.S. in 1997, and his PhD in 2002 from The University of Tokyo under the guidance of Professor Tohru Fukuyama. After working for Mitsubishi Pharma Corporation as a medicinal chemist (2002–2004), he joined Professor Fukuyama's group at The University of Tokyo as an assistant professor. He was promoted to lecturer in 2008 and to associate professor in 2011. In 2012 he moved to Nagoya University as an associate professor and was promoted to professor in 2017. His current research interests focus on the synthesis of natural and unnatural molecules with polycyclic systems.

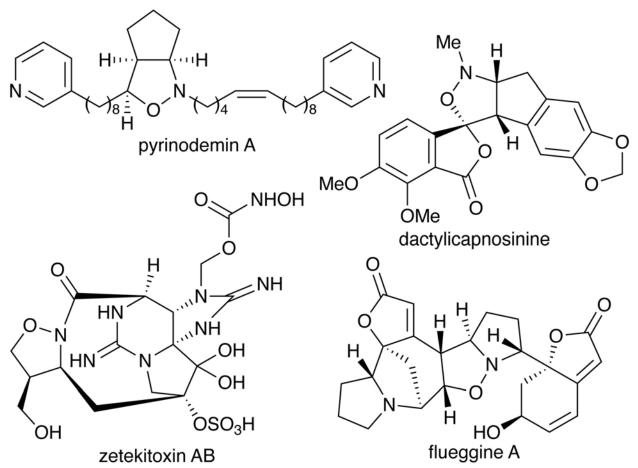


Fig. 2 Selected Natural products containing an isoxazolidine ring.

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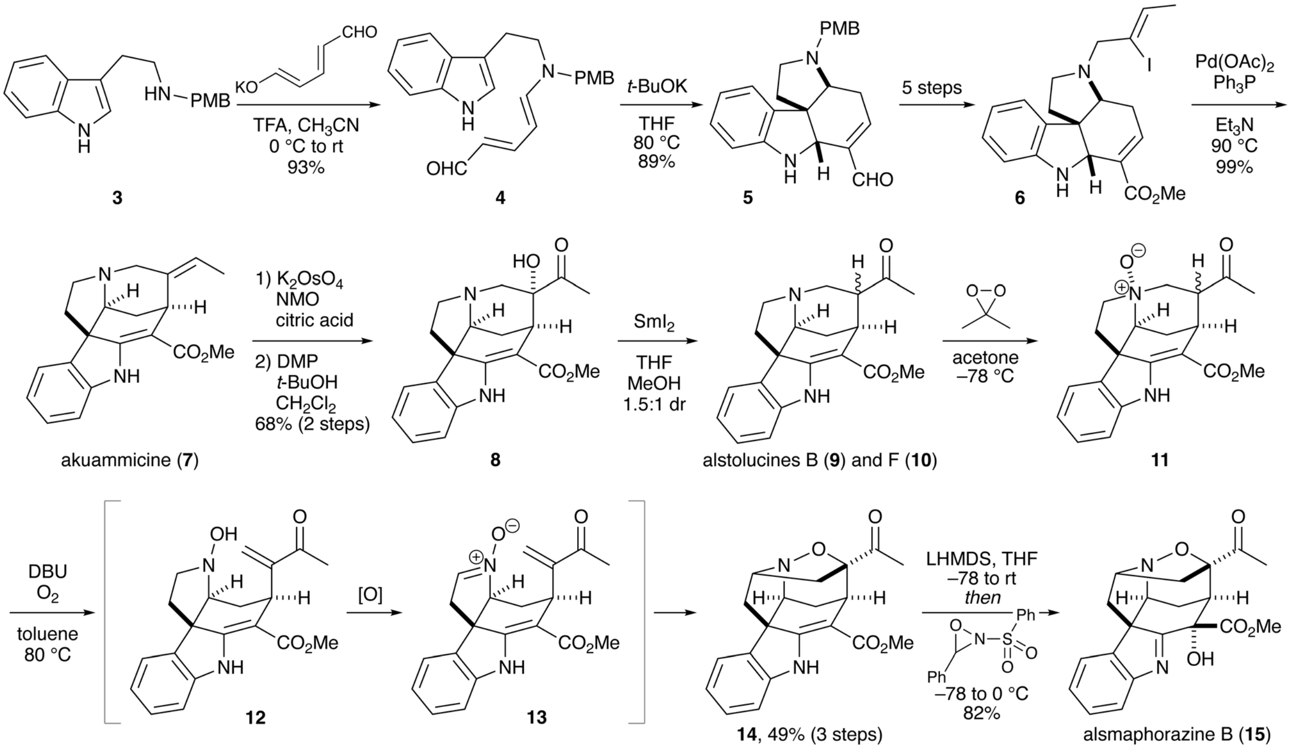


Scheme 2 Synthesis of alsmaphorazine B.

pathway of alsmaphorazine B from an akuammicine-type molecule *via* multiple stepwise oxidation and rearrangements had been proposed in a paper reporting isolation of alsmaphorazine B,[13] Vanderwal and coworkers independently devised an alternative biosynthetic pathway, along which they achieved the synthesis of alsmaphorazine B (racemic, 15 steps).[14]

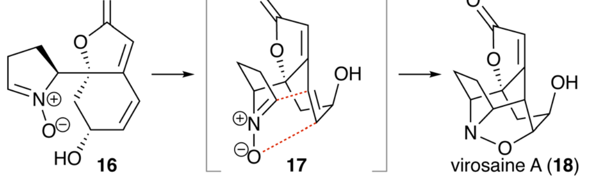
They first prepared akuammicine (**7**) from tryptamine in nine steps. One of the key reactions is base-mediated cycloaddition of Zincke aldehyde **4** to afford tetracyclic compound **5**. After the conversion that included introducing an iodoalkene unit onto the nitrogen atom, the resultant unsaturated ester **6** was subjected to an intramolecular Heck reaction to give akuammicine (**7**).

The next task was to convert the ethylidene into a ketone moiety. After extensive investigations, they established a three-step sequence involving osmium-mediated dihydroxylation, oxidation with Dess–Martin periodinane (DMP) in the presence of *tert*-butanol, and reduction of α-ketol **8** with samarium(II) iodide. The products—a 1.5 : 1 mixture of alstolucines B (**9**) and F (**10**)—were oxidized with dimethyldioxirane (DMDO) to afford *N*-oxide **11**, which was heated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) under an oxygen atmosphere. Under these conditions, base-mediated E1cb elimination or Cope elimination occurred to liberate an enone and a hydroxylamine.[15] Oxidation of the hydroxylamine with gaseous oxygen furnished nitrone **13**, which underwent intramolecular cycloaddition with the enone moiety to give cycloadduct **14** in 49% yield. The structure of **14** was confirmed by X-ray crystallographic analysis. In this transformation, a nitrone isomer was also isolated in 29% yield. Further oxidation of the vinylogous carbamate moiety by treatment with lithium hexamethyldisilazide (LHMDS) and Davis oxaziridine afforded alsmaphorazine B (**15**).

2.2. Synthesis of virosaine A

Virosaine A (**18**) is a pentacyclic natural product containing an isoxazolidine ring (Scheme 3). In the proposed biosynthetic pathway, the isoxazolidine ring is constructed at the end of the biosynthesis *via* intramolecular cycloaddition of a five-membered cyclic nitrone **16**.[16] Hughes and Gleason reported a synthesis of virosaine A (enantioselective, 15 steps),[17,18] in which the formation of the isoxazolidine ring was conducted in an early stage of the synthesis *via* cycloaddition of a five-membered cyclic nitrone.

An asymmetric Diels–Alder reaction of 2-bromoacrolein (**19**) with furan (**20**) catalyzed by oxazaborolidinone **21** yielded bicyclic aldehyde **22**,[19] which was reacted with organolithium reagent **23** to furnish a 2.7 : 1 diastereomeric mixture of alcohols



Scheme 3 A proposed biosynthetic pathway of virosaine A *via* intramolecular cycloaddition of a five-membered cyclic nitrone.

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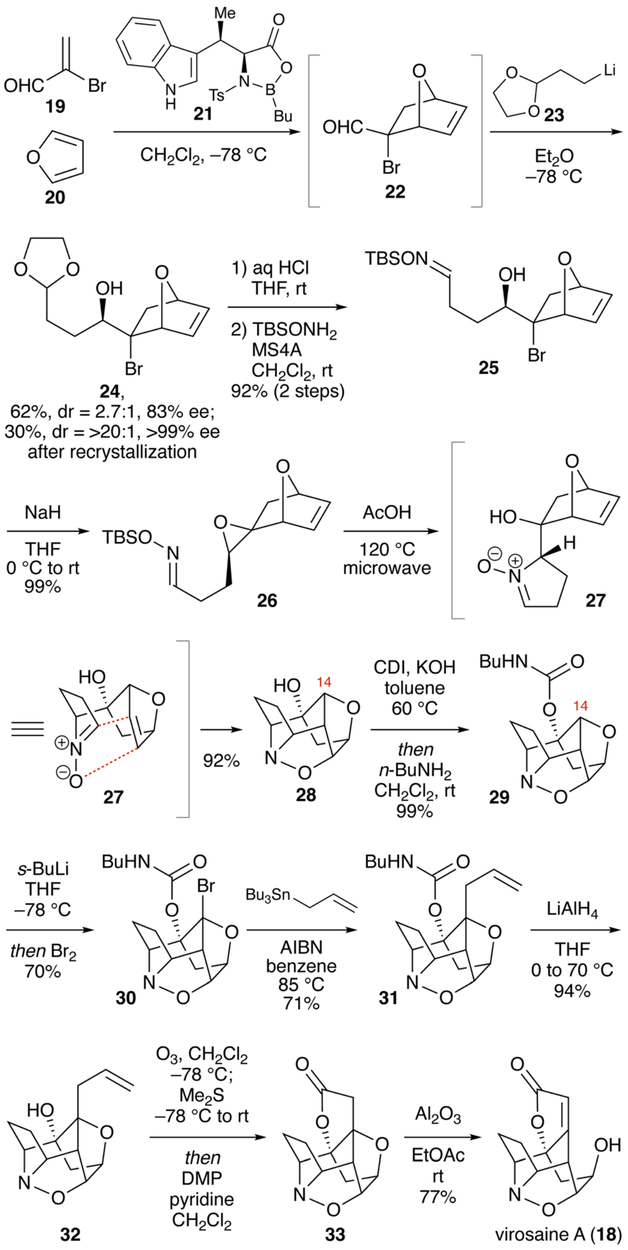
24 (Scheme 4). The diastereomeric ratio and the enantiomeric excess could be improved by recrystallization. Acidic hydrolysis of the acetal moiety, followed by a reaction of the resultant cyclic acetal with *O*-TBS hydroxylamine (TBS = *tert*-butyldimethylsilyl), afforded *O*-silyl oxime **25**. Treatment of **25** with sodium hydride induced epoxide formation to give **26**. When **26** was heated in acetic acid at 120 °C under microwave irradiation, the nitrogen atom intramolecularly attacked the epoxide to form nitrone **27**, which underwent cycloaddition to give pentacyclic compound **28** in 92% yield.

The remaining task for the synthesis of virosaine A was functionalization of C14 for the construction of the butenolide moiety. The first attempts involved the intramolecular C–H insertion of carbene or nitrene at C14, but the desired products were not obtained. The insertion reactions of carbene or nitrene occurred at undesired positions. Finally, the authors found a site-directed deprotonation was effective for the transformation. Thus, reaction of the hydroxy group in **28** with 1,1′-carbonyldiimidazole (CDI) and then with *n*-butylamine afforded carbamate **29**. Selective lithiation at C14 by treatment with *sec*-butyllithium, followed by addition of bromine, yielded bromide **30**. Radical allylation under Keck's conditions introduced an allyl group at the bridgehead position.[20] Reductive cleavage of the carbamate moiety with lithium aluminum hydride liberated alcohol **32**. Ozonolysis of the terminal alkene followed by oxidation of the resultant hemiacetal with DMP furnished lactone **33**, which was exposed to activated neutral Al_2O_3 to afford virosaine A (**18**).

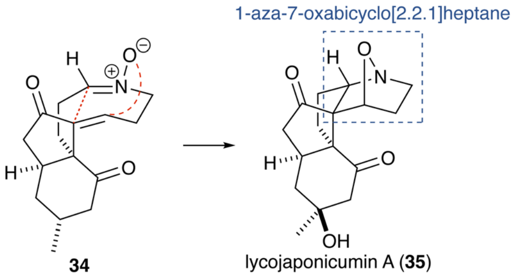


Scheme 4 Synthesis of virosaine A.

2.3. Synthesis of lycojaponicumin A

Lycojaponicumin A (**35**) is an alkaloid containing a bicyclo[2.2.1] system within which an isoxazolidine ring is embedded as a 1-aza-7-oxabicyclo[2.2.1]heptane (Scheme 5).[21] A biosynthetic pathway of lycojaponicumin A has been proposed, in which the bicyclo[2.2.1] system is formed *via* intramolecular cycloaddition of nine-membered cyclic nitrone **34**. Zhang, Tu and coworkers reported a synthesis of lycojaponicumin A (racemic, 23 steps).[22] They constructed the 1-aza-7-oxabicyclo[2.2.1] system *via* cycloaddition of an NH nitrone and subsequent intramolecular alkylation.

A reaction of amide **36** with triflic anhydride formed a keteniminium salt, which underwent intramolecular [2 + 2] cycloaddition with the terminal alkene moiety to give cyclobutanone **37** (Scheme 6). Introduction of a dihydrofuran unit afforded tertiary alcohol **38**. Upon treatment of **38** with $BF_3 \cdot OEt_2$, a ring expansion reaction occurred *via* selective migration of the quaternary carbon to furnish cyclopentanone **39** with a good diastereoselectivity (11 : 1 dr at C4). After a five-step conversion, the tetrahydrofuran ring in **40** was reductively cleaved by treatment with samarium(II) iodide. The resulting enolate was transformed into silyl enol ether **41** *via* addition of TBS triflate and subsequent thermal isomerization. Phenylselenylation of the silyl enol ether **41**, followed by one-pot oxidative elimination afforded *Z*-enone **42**, which was subjected to photoinduced isomerization with an LED lamp (395 nm), giving, after cleavage of the TBS group with TBAF, *E*-enone **43**. A three-step conversion afforded aldehyde **44**, which was reacted with hydroxylamine



Scheme 5 A proposed biosynthetic pathway of lycojaponicumin A *via* intramolecular cycloaddition of a nine-membered cyclic nitrone.

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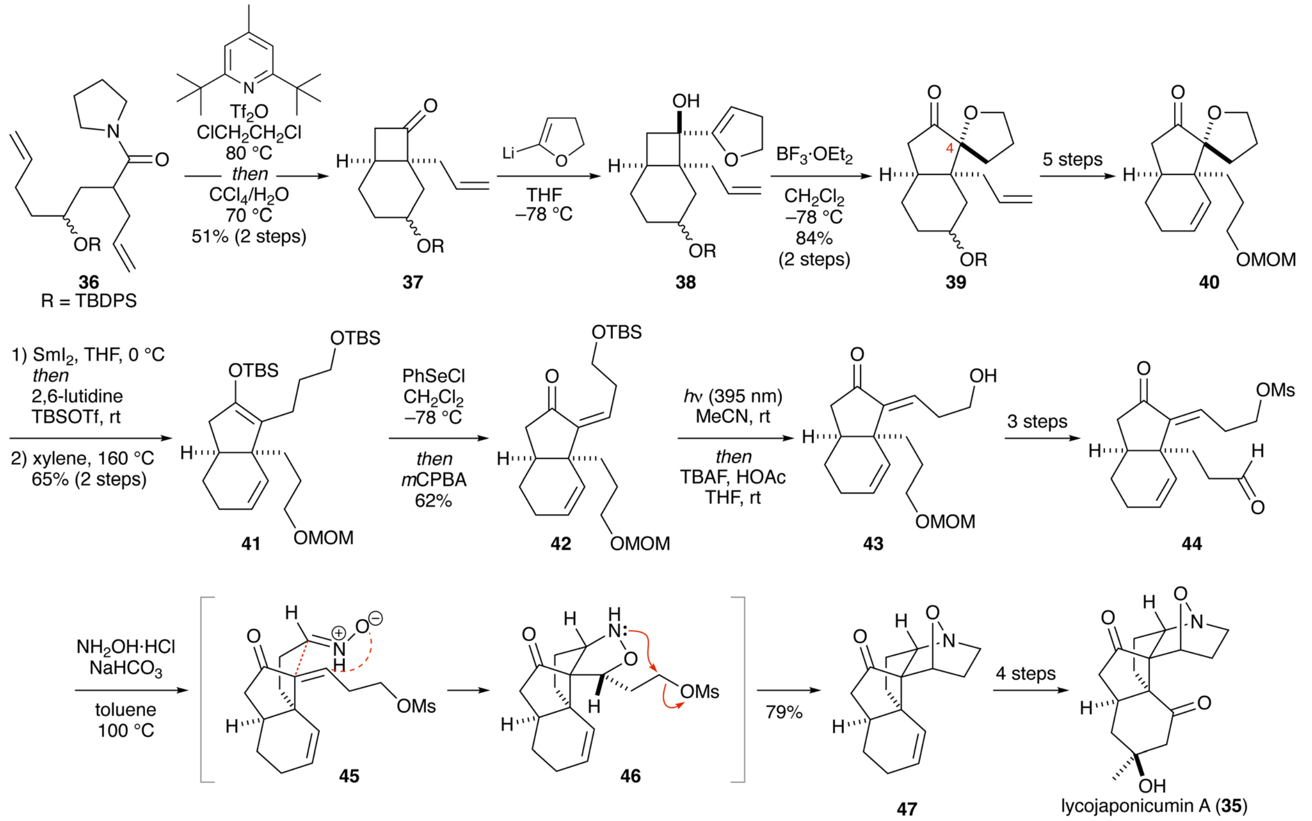
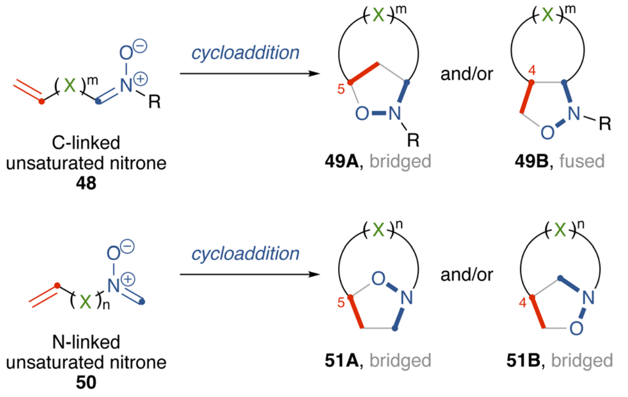


Scheme 6 Synthesis of lycojaponicumin A.

hydrochloride and sodium bicarbonate in toluene at 100 °C. Under these conditions, NH nitrone **45** was formed and underwent intramolecular cycloaddition with the enone moiety.[23] Subsequent intramolecular S_N2 reaction between the nitrogen atom in the resulting isoxazolidine ring and the mesylate moiety furnished pentacyclic compound **47**. Sequential oxidation of the cyclohexene ring in four steps produced lycojaponicumin A (**35**).

3. Synthesis *via* intramolecular cycloaddition of acyclic nitrones

Acyclic nitrones for the intramolecular cycloaddition can be classified into two groups depending on whether the unit containing the alkene moiety is attached to the carbon atom or the nitrogen atom of the nitrone. The former (C-linked unsaturated nitrone, **48**) can be basically prepared from aldehydes bearing an alkene moiety by condensation with a hydroxylamine, and its cycloaddition produces bridged and/or fused isoxazolidines (**49A** and/or **49B**, Scheme 7). The latter (N-linked unsaturated nitrone, **50**) can be derived from hydroxylamines bearing an alkene moiety, leading to bridged isoxazolidines (**51A** and/or **51B**). Isoxazolidines **49A** and **51A** are 5-substituted isoxazolidines similar to isoxazolidine **A** described in Table 1, whereas isoxazolidines **49B** and **51B** are 4-substituted isoxazolidines resembling isoxazolidine **B**. This section presents syntheses *via* intramolecular cycloaddition of acyclic nitrones using C-linked unsaturated nitrones followed by N-linked unsaturated nitrones.



Scheme 7 C-linked and N-linked nitrones.

3.1. Syntheses *via* cycloaddition of C-linked unsaturated nitrones

3.1.1. Synthesis of himalensine A. Gao and coworkers reported a synthesis of himalensine A (racemic, 29 steps; Scheme 8).[24] Heating aldehyde **52** with hydroxylamine **53** yielded a nitrone, which underwent intramolecular cycloaddition *via* a transition state **54** to give *cis*-fused isoxazolidine **55**. Reductive cleavage of the N–O bond with zinc in acetic acid,

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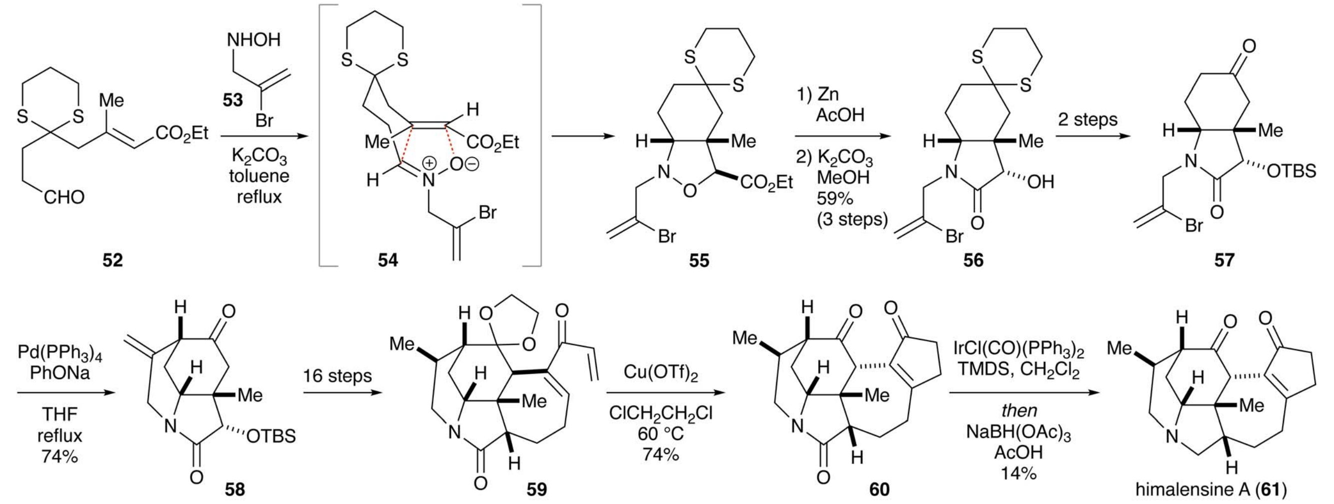
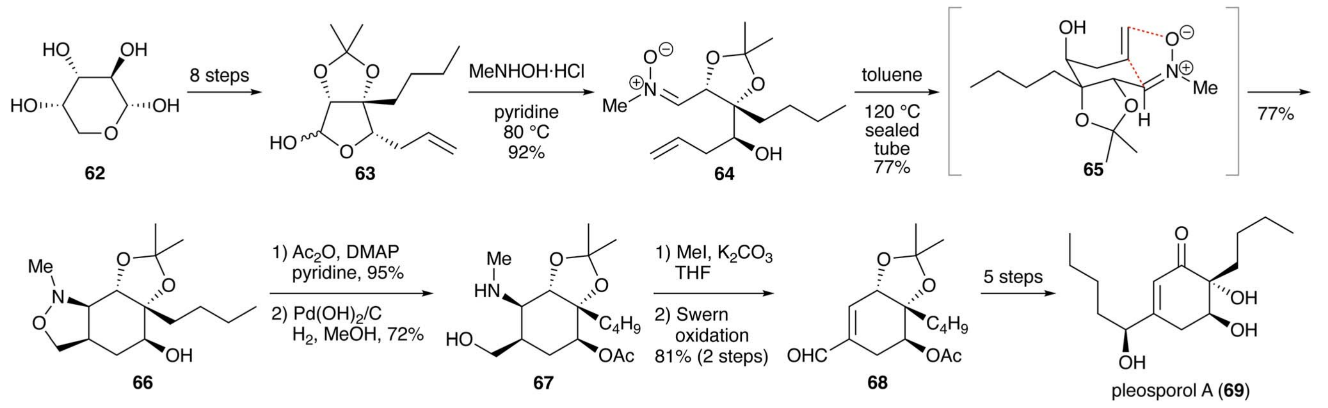


Scheme 8 Synthesis of himalensine A.

followed by basic treatment, produced lactam **56**. A two-step conversion of compound **56** including protection of the secondary alcohol with a TBS group and removal of the 1,3-dithiane group afforded ketone **57**, which underwent Pd-mediated intramolecular vinylation to produce tricyclic compound **58**. Ring-closing metathesis constructed a seven-membered ring, and Nazarov cyclization of **59** led to a cyclopentenone ring. The selective reduction of the lactam in **60** with Vaska's catalyst gave himalensine A (**61**).[25]

3.1.2. Synthesis of pleosporol A. Xu and coworkers reported a synthesis of pleosporol A (19 steps; Scheme 9).[26] Starting from L-arabinose (**62**), compound **63** was prepared. Treatment with *N*-methylhydroxylamine hydrochloride in pyridine at 80 °C opened the lactol moiety to furnish nitrone **64** in 92% yield. Cycloaddition of the nitrone was induced by heating in toluene at 120 °C in a sealed tube to give *cis*-fused isoxazolidine **66** in 77% yield. The transition state **65** explains the stereoselectivity of the cycloaddition. After acetylation of the hydroxy group, the N–O bond was cleaved by hydrogenolysis in the presence of Pearlman's catalyst. Formation of the corresponding quaternary ammonium salt by treatment with iodomethane, followed by Swern oxidation, gave α,β-unsaturated aldehyde **68**, which was converted into pleosporol A (**69**) in five steps.

3.1.3. Synthesis of isolysergol. Wang and coworkers reported a synthesis of an ergot alkaloid, isolysergol (18 steps from (2*R*)-phenyloxirane; Scheme 10).[27] Palladium-catalyzed aminoalkynylation of carbamate **70** with 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX, **71**) proceeded stereoselectively to afford 4,5-*trans*-substituted product **72**,[28] which was converted into aldehyde **73** *via* three steps including *N*-allylation. Treatment of **73** with *N*-methylhydroxylamine led to nitrone formation, and subsequent cycloaddition *via* transition state **74** gave *cis*-fused isoxazolidine **75** in 67% yield. Reductive cleavage of the N–O bond with zinc, followed by reductive amination with formalin, furnished compound **76** with a dimethylamino group. After a two-step conversion including removal of the TIPS group and protection of the primary alcohol with a TBS group, the dimethylamino group was oxidized with *m*-chloroperbenzoic acid (*m*CPBA) to produce the corresponding *N*-oxide, which was heated at 145 °C in neat conditions to induce *syn*-elimination (Cope elimination), giving **78** in 73% yield over two steps. Copper-catalyzed Huisgen



Scheme 9 Synthesis of pleosporol A.

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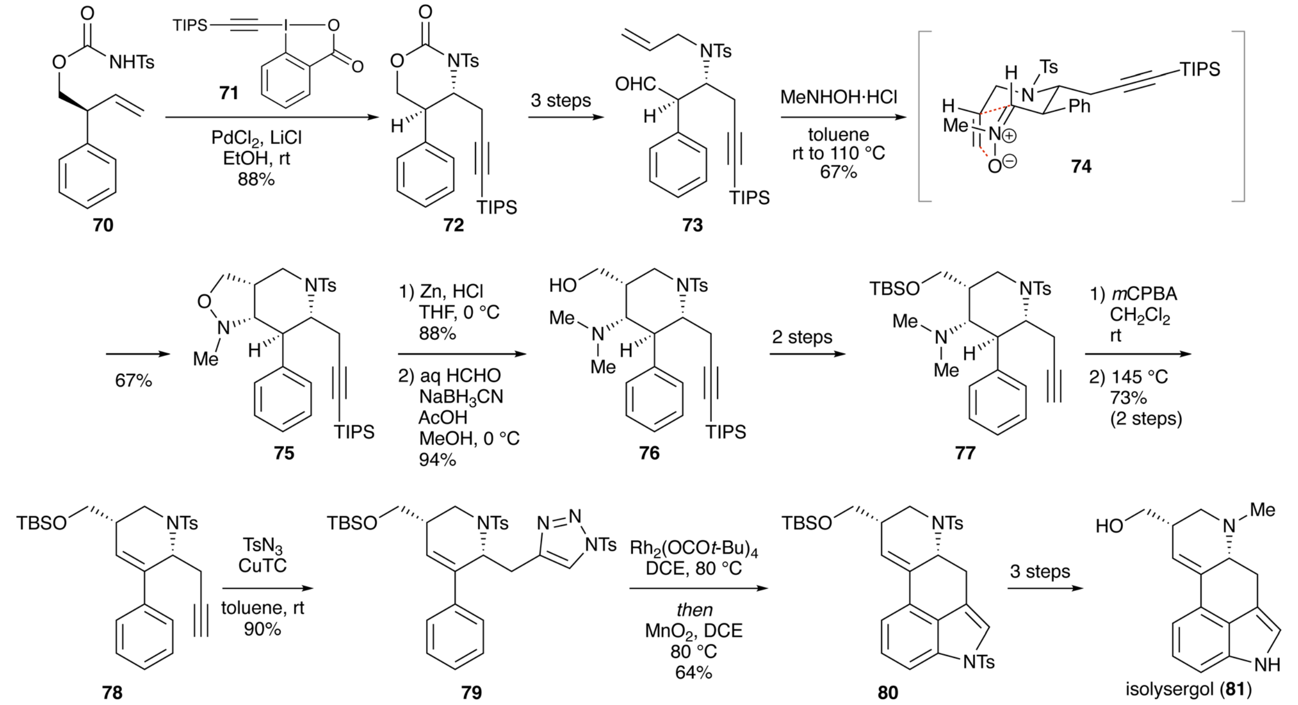

Scheme 10 Synthesis of isolysergol.

cycloaddition with *p*-toluenesulfonyl azide (TsN_3) afforded *N*-tosyl-1,2,3-triazole **79**, which was treated with a rhodium catalyst in 1,2-dichloroethane at 80 °C to give, after oxidation with manganese(IV) oxide, 3,4-fused indole **80**.[29] Deprotection and *N*-methylation afforded isolysergol (**81**).

3.1.4. Synthesis of thebainone A. Metz and coworkers reported a synthesis of thebainone A (racemic, 22 steps; Scheme 11).[30] An intramolecular Heck reaction of **82** afforded spiro lactone **83**. After cleavage of the acetal moieties by treatment with a mild Lewis acid, $Pd(MeCN)_2Cl_2$, the resultant ketoaldehyde **84** was treated with *N*-methylhydroxylamine without purification. The formation of a nitrone and subsequent cycloaddition proceeded at low temperature with high diastereoselectivity *via* a transition sate **85**. Reduction of the ketone and the lactone moieties in **86** with lithium aluminum hydride, followed by reductive cleavage of the N–O bond by treatment with RANEY® nickel under a hydrogen atmosphere, furnished aminotetraol **88**, which could be converted into compound **89** *via* an intramolecular Mitsunobu reaction between the amino group and the primary alcohol moiety. Elaboration of the oxygen functionalities on the cyclohexane ring in eight steps produced thebainone A (**90**).

3.2. Syntheses *via* cycloaddition of N-linked unsaturated nitrones

3.2.1. Synthesis of lasubine II. Sato, Chida and coworkers reported a synthesis of lasubine II (racemic, 7 steps; Scheme 12).[31] 3,4-Dimethoxybenzaldehyde (**91**) was converted into *N*-methoxylamine **92** *via* the formation of an oxime ether and its reduction. Three-component coupling of **92** with aldehyde **93** and allyltributylstannane in the presence of $Gd(OTf)_3$ produced the desired product **94** in 93% yield. Oxidation with *m*CPBA selectively yielded nitrone **95** without forming the other isomer. When nitrone **95** in toluene was heated at 130 °C in a sealed tube, intramolecular cycloaddition occurred to form isoxazolidine **97** in 74% yield, along with two other diastereomers in 10% yield. Reduction with zinc in hydrochloric acid cleaved the N–O bond and the acetal, and cyclization *via* reductive amination also occurred to furnish quinolizidine **98**. Inversion of the secondary alcohol moiety *via* a Mitsunobu reaction, followed by methanolysis, produced lasubine II (**99**).

3.2.2. Synthesis of palhinines A and D. Palhinine A (**111**, Scheme 13) is an alkaloid characterized by a unique skeleton that includes a nitrogen-containing nine-membered ring. Fan and coworkers successfully constructed the nine-membered ring *via* nitrone cycloaddition, thereby completing the synthesis of palhinine A (racemic, 23 steps).[32] Starting from readily available enone **100**, compound **101** was prepared through 6 steps including Hosomi–Sakurai allylation and Nozaki–Hiyama–Kishi coupling.[33] Treatment of **101** with trimethylsilyl triflate and triethylamine produced siloxy-diene **102**, which was heated in *p*-xylene at 180 °C to induce an intramolecular Diels–Alder reaction that gave tricyclic compound **103** in 65% yield. After conversion in six steps including a Wittig olefination, the resultant aldehyde **104** was transformed into hydroxylamine **105** through the formation and reduction of an oxime. Condensation of the hydroxylamine with aqueous formaldehyde in a biphasic system afforded nitrone **106**, which was subjected to the subsequent step without further purification because of its instability. Thus, nitrone **106** was heated in *o*-dichlorobenzene at 150 °C under microwave irradiation. The cycloaddition of nitrone occurred intramolecularly, and

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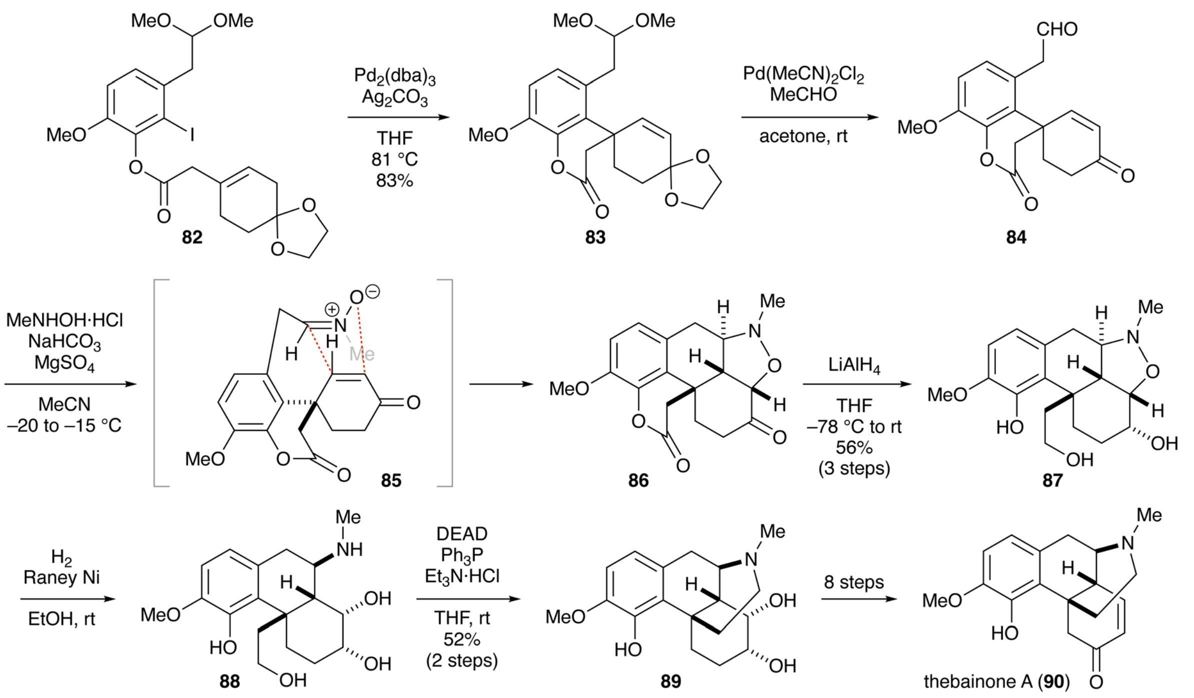
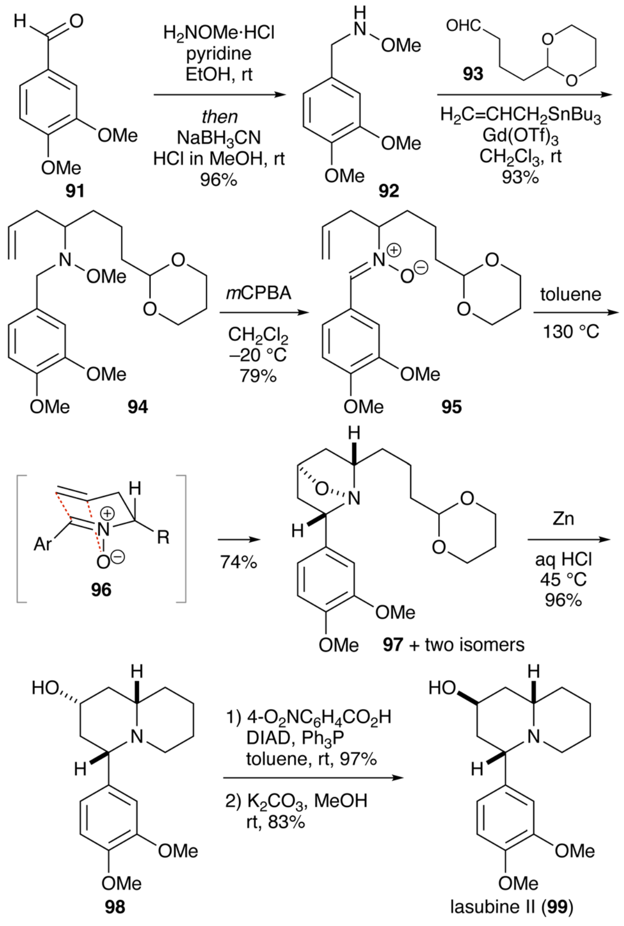


Scheme 11 Synthesis of thebainone A.



Scheme 12 Synthesis of lasubine II.

isoxazolidine **108** was obtained in 52% yield as a sole isomer. Fan and coworkers attributed the high regio- and stereoselectivity to the minimal steric interaction and the favorable dipole–dipole attraction in the transition state (Fig. 3). *N*-Methylation, followed by reductive cleavage of the N–O bond with zinc, yielded aminoalcohol **109**. Inversion of the secondary alcohol in **109** was induced by an oxidation/reduction sequence. Acidic hydrolysis of the cyclic acetal afforded palhinine A (**111**). When *N*-allylation of **108** was carried out instead of *N*-methylation, palhinine D (**117**) was also synthesized according to the same sequence (Scheme 14). The allyl group was removed by treatment with ruthenium(III) chloride in a mixture of acetonitrile and water.

3.2.3. Synthesis of (19*Z*)-taberpsychine, isodihydrokoumine, and isodihydrokoumine *N*$_4$-oxide. Kerkovius and Kerr reported a synthesis of (19*Z*)-taberpsychine (racemic, 11 steps; Scheme 15).[34] Diol **118** was prepared through a sequence including hydrostannylation of an alkyne, Stille coupling, and copper-catalyzed conjugate addition. A Mitsunobu reaction of diol **118** with *N*,*O*-bis(Boc)-hydroxylamine (Boc = *tert*-butoxycarbonyl) occurred selectively at the allylic position to furnish protected hydroxylamine **119** in 83% yield.[35] Cleavage of the Boc groups by treatment with trifluoroacetic acid (TFA), followed by condensation with aldehyde **120** in the presence of triethylamine, afforded nitrone **121**, which was heated in refluxing benzene to give isoxazolidine **123** (2 : 1 ratio about the 2-hydroxyethyl chain, 1 : 1 ratio about the indoline). To understand the reactivity of the hydroxylamine, the reader should note that when the hydroxylamine salt was neutralized with triethylamine in the absence of aldehyde **120**, *N*-hydroxypyrrolidine **129** was produced *via* a Cope-type hydroamination (Scheme 16).[36]

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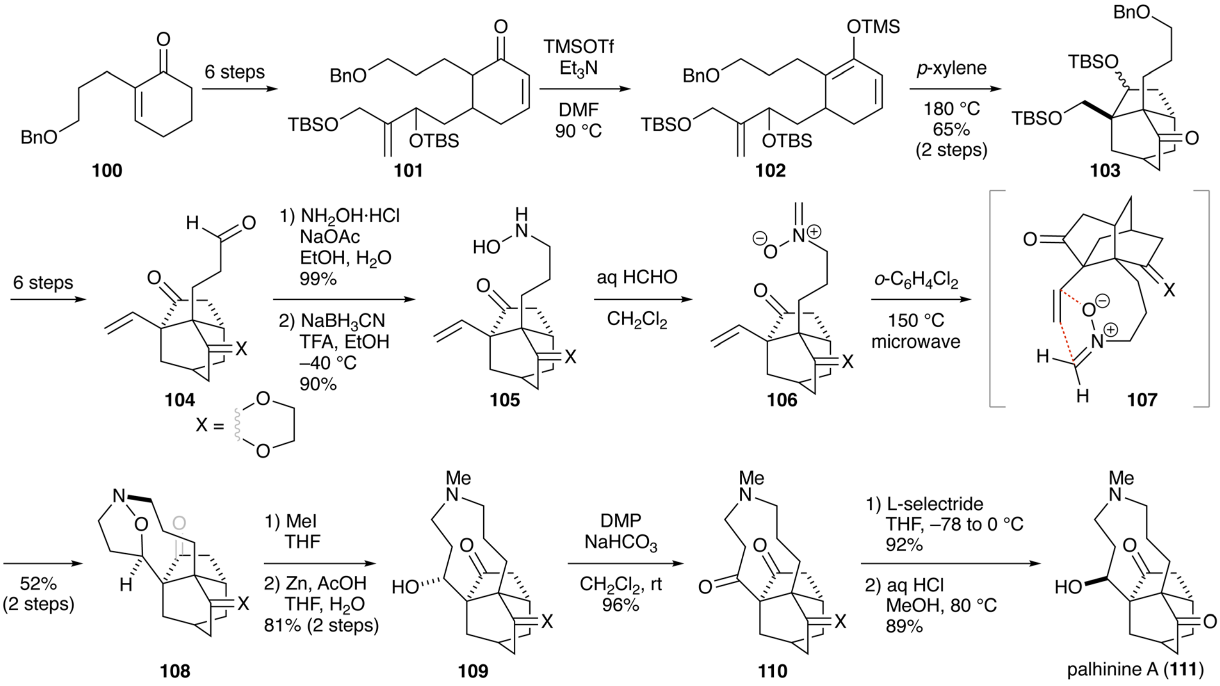


Scheme 13 Synthesis of palhinine A.

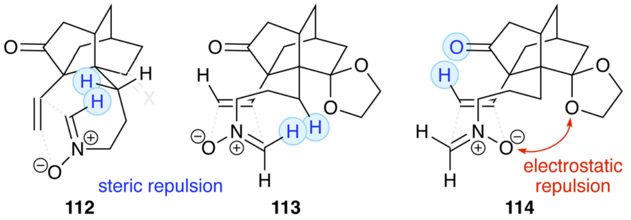
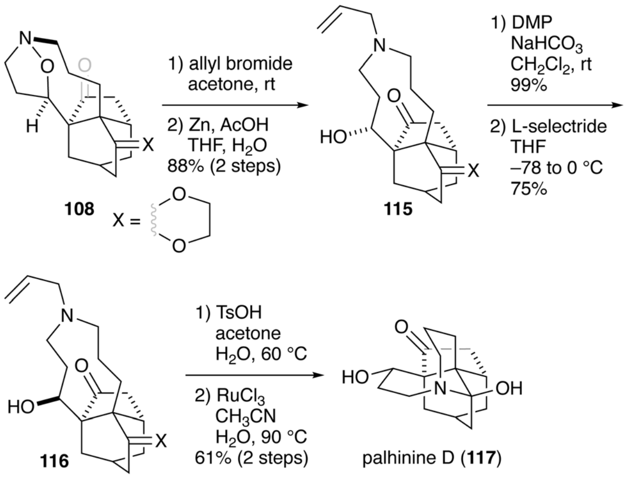


Fig. 3 Discussion on regio- and stereoselectivity.



Scheme 14 Synthesis of palhinine D.

After cleavage of the Ts group, the resultant compound was subjected to Swern oxidation. Under these conditions, simultaneous oxidation of the primary alcohol and the indoline occurred; the aldehyde was then protected as its dimethyl acetal. At this stage, the diastereomers could be separated. The N–O bond was cleaved by a reaction with samarium(II) iodide. Upon treatment with $BF_3 \cdot OEt_2$ in acetonitrile, the dimethyl acetal moiety in **124** was activated and then intramolecularly attacked by the primary alcohol. Subsequent Friedel–Crafts reaction with the indole nucleus gave **125**. Reductive methylation of the secondary amine afforded (19*Z*)-taberpsychine (**126**). Treatment of (19*Z*)-taberpsychine (**126**) with trimethylsilyl iodide led to a Conia-ene-type reaction between the indole and the ethylidene moiety to furnish isodihydrokoumine (**127**). Oxidation with *m*CPBA produced isodihydrokoumine *N*$_4$-oxide (**128**).

4. Synthesis *via* intramolecular cycloaddition of cyclic nitrones

Intramolecular cycloaddition of mono-cyclic nitrones produces tricyclic isoxazolidines, beneficial for the synthesis of complex molecules (Scheme 17). Although preparation of cyclic nitrones has some difficulties, such as introducing multiple functional groups in a molecule, various methods to generate cyclic nitrones have been explored. This section presents syntheses *via* intramolecular cycloaddition of cyclic nitrones.

4.1. Synthesis of 19-hydroxyibogamine

Alkayar and Coldham reported a formal synthesis of 19-hydroxyibogamine (racemic, 16 steps; Scheme 18).[37] Aldehyde **132** was prepared *via* malonic ester synthesis and alkylation of a 1,3-dithiane. Oxime formation, followed by intramolecular alkylation, formed six-membered cyclic nitrone **134**, which

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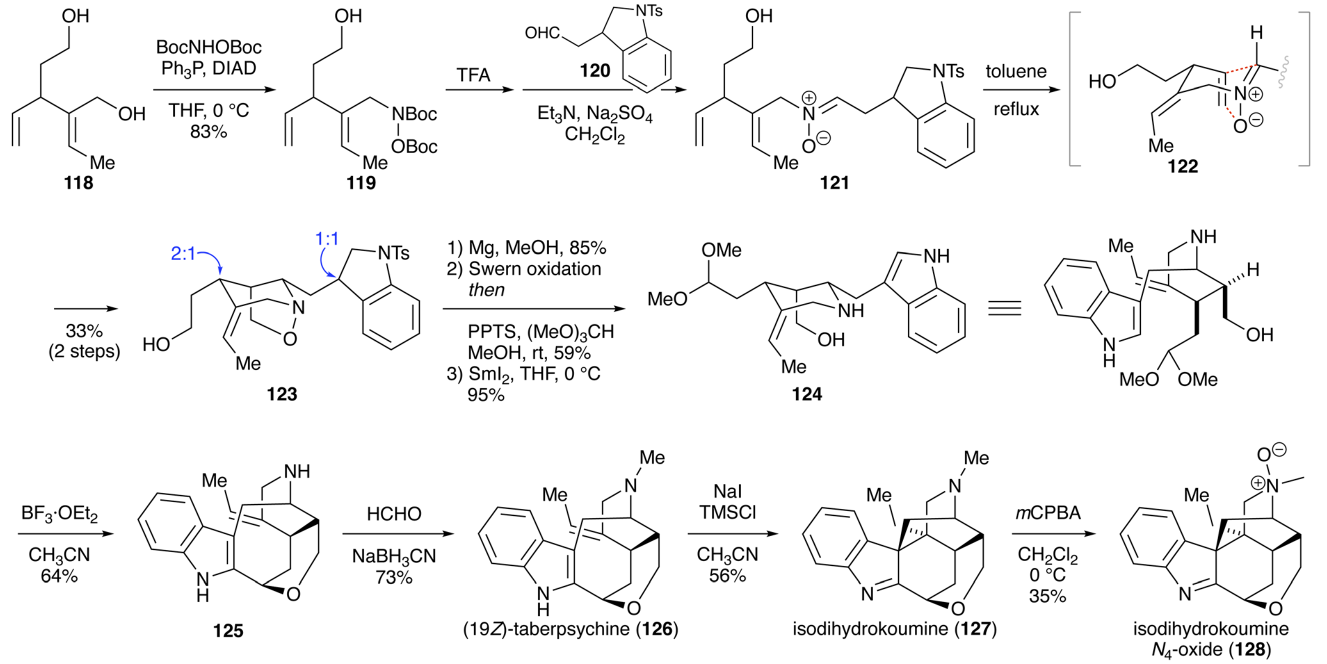
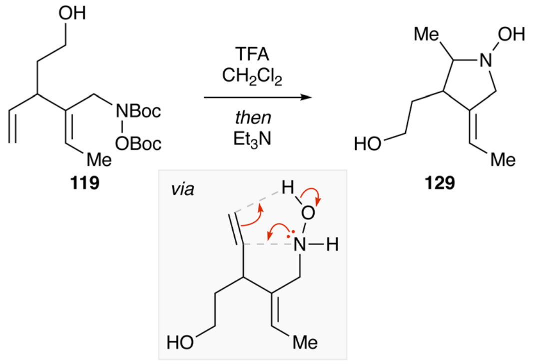
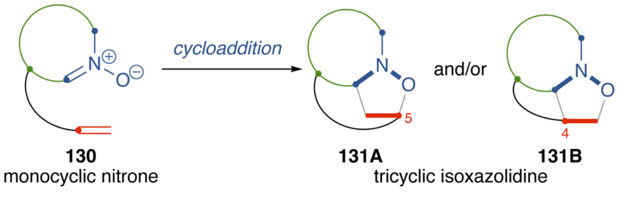


Scheme 15 Synthesis of (19*Z*)-taberpsychine, isodihydrokoumine, and isodihydrokoumine *N*$_4$-oxide.



Scheme 16 Cope-type hydroamination of hydroxylamine.



Scheme 17 Intramolecular cycloaddition of cyclic nitrones.

underwent intramolecular cycloaddition to give isoxazolidine **135**. Hydrolysis of the 1,3-dithiane moiety under oxidative conditions afforded ketone **136**. Reductive cleavage of the N–O bond with zinc and acetic acid afforded aminoalcohol **137**, which was condensed with indoleacetic acid to give **138**. Conversion of the ketone moiety into an acetal, followed by acetylation of the hydroxy group, gave the reported intermediate **139**, which could be converted into 19-hydroxyibogamine (**140**) in three steps.

4.2. Synthesis of *N*-methyl-euphococcine

Kürti and coworkers developed a method for *C*-allylation of unprotected oximes and applied the method to the synthesis of *N*-methyl-euphococcine (racemic, 6 steps; Scheme 19).[38] Oxime **141** was treated with diisopropyl allylboronate in the presence of 3,5-difluorophenylboronic acid as a catalyst to give hydroxylamine **142**. After acidic hydrolysis of the acetal moiety and subsequent basic workup, the resultant six-membered cyclic nitrone was heated in toluene at 110 °C to produce isoxazolidine **144** in 57% yield in two steps. *N*-methylation, followed by reduction with zinc, cleaved the N–O bond, and oxidation of the resultant secondary alcohol **146** with DMP afforded *N*-methyl-euphococcine (**147**).

4.3. Synthesis of cylindricine C

Sato, Chida and coworkers developed a method to synthesize cyclic nitrones from *N*-hydroxylactams, and applied it to the synthesis of cylindricine C (asymmetric, 12 steps; Scheme 20).[39] *O*-Methylation of known lactam **148** with Meerwein's reagent yielded imidate **149**, which was converted into *N*-hydroxylactam **150** *via* oxidation with *m*CPBA, acidic hydrolysis of the resultant oxaziridine, and lactam formation under basic conditions. After the hydroxy group was protected with a 2-(trimethylsilyl)ethoxymethyl (SEM) group, the addition of hexenyllithium and subsequent acidic treatment afforded five-membered cyclic nitrone **152**. When heated in *tert*-butylbenzene, **152** underwent intramolecular cycloaddition to give a 1.3 : 1 mixture of regioisomers **155** and **156**. After separation

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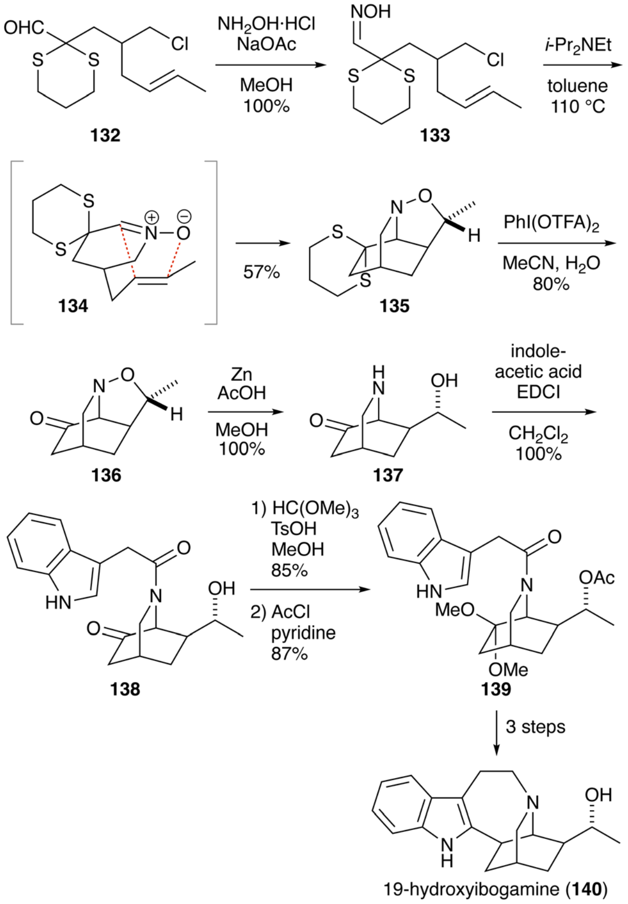
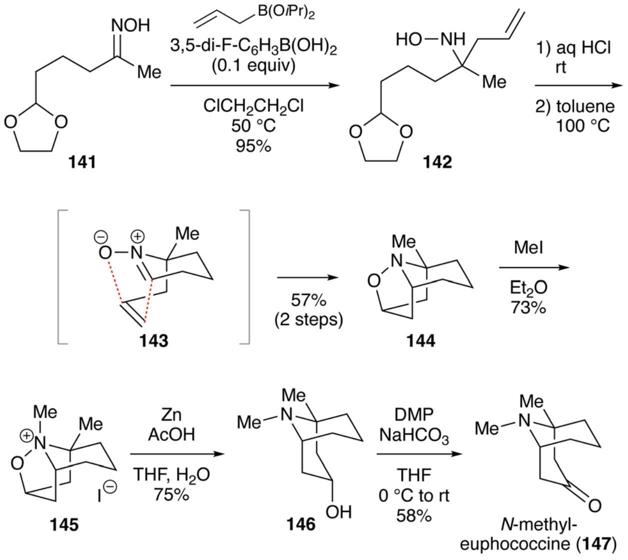
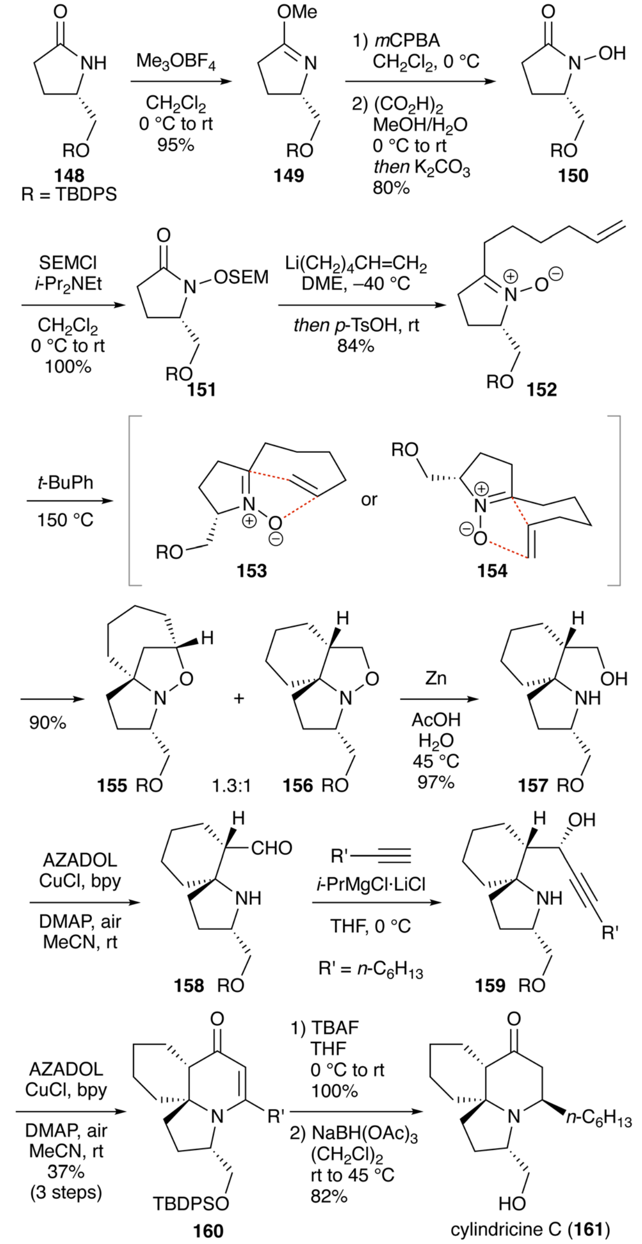


Scheme 18 Synthesis of 19-hydroxyibogamine.



Scheme 19 Synthesis of *N*-methyl-euphococcine.



Scheme 20 Synthesis of cylindricine C.

of the isomers, the N–O bond in **156** was reductively cleaved with zinc in aqueous acetic acid. The resultant alcohol was converted into aldehyde **158** in the presence of the unprotected secondary amine under the conditions developed by Iwabuchi and coworkers.[40] Addition of an acetylide to aldehyde **158** produced **159**, which was oxidized again under Iwabuchi's conditions, where intramolecular Michael addition also proceeded to furnish dihydro-4-pyridone **160.** Removal of the *tert*-butyldiphenylsilyl (TBDPS) group, followed by stereoselective reduction of the enamine moiety directed by the hydroxy group, afforded cylindricine C (**161**).

4.4. Synthesis of sarain A

Yokoshima, Fukuyama and coworkers reported a formal synthesis of sarain A (enantioselective; Scheme 21).[41] Claisen–Ireland rearrangement of **162** selectively constructed the contiguous stereogenic centers to produce **163.** After conversion of **163** into alcohol **164,** a hydroxylamine unit was introduced

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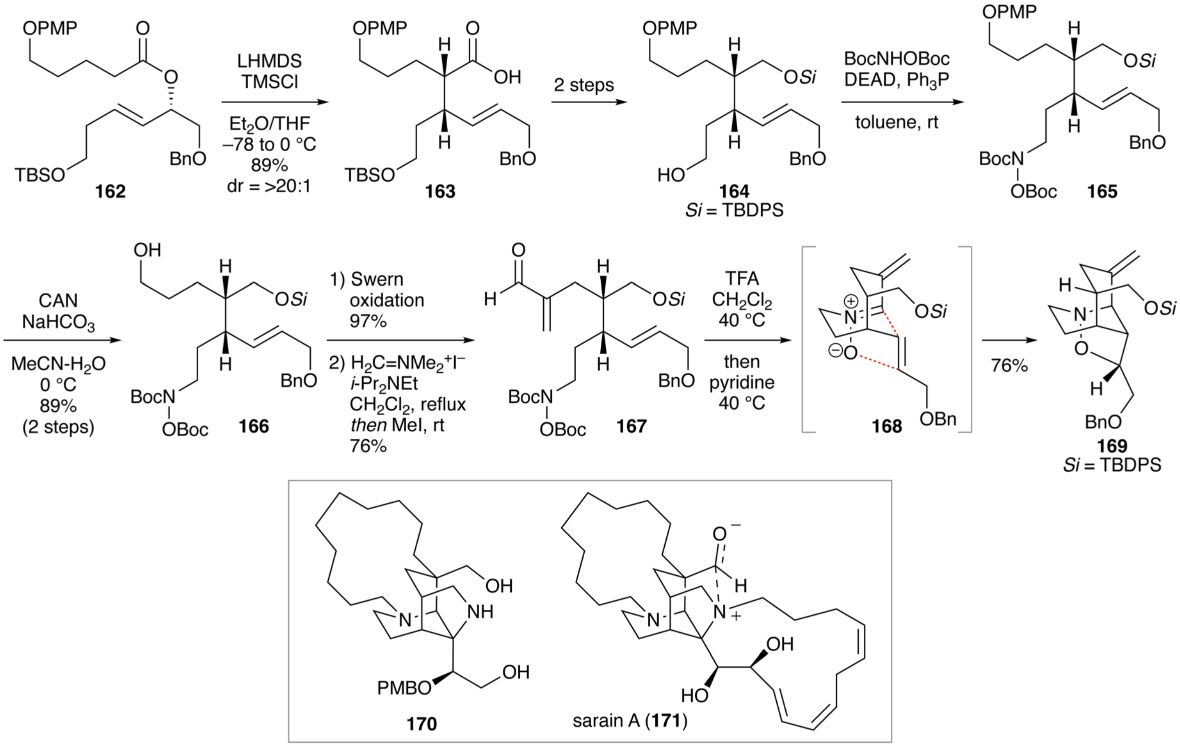

Scheme 21 Synthesis of sarain A.

via a Mitsunobu reaction. The *p*-methoxyphenyl (PMP)-protected alcohol was transformed into α,β-unsaturated aldehyde **167** *via* steps including oxidative cleavage of the PMP group, Swern oxidation, a Mannich reaction, and a methylation-E1cb elimination process. Treatment of **167** with TFA cleaved the two Boc groups to liberate the hydroxylamine moiety. Upon neutralization with pyridine, condensation of the hydroxylamine with the aldehyde moiety proceeded intramolecularly to form 8-membered cyclic nitrone **168**, which underwent intramolecular cycloaddition with the alkene moiety, giving tricyclic compound **169**. This intermediate could be converted into an advanced intermediate (compound **170**) in Overman's synthesis of sarain A.[42]

4.5. Synthesis of kopsone

Yokoshima and coworkers reported a synthesis of kopsone (enantioselective, 19 steps; Scheme 22).[43] Claisen–Ireland rearrangement and subsequent methylation produced compound **173**. Reduction of the ester moiety in **173**, followed by a Mitsunobu reaction with *N*,*O*-bis(Boc)-hydroxylamine, furnished **174**. The TBS-protected alcohol was converted into α,β-unsaturated aldehyde **176** in three steps. Upon treatment of **176** with TFA, the two Boc groups in **176** were cleaved. Neutralization with triethylamine induced the formation of eight-membered cyclic nitrone **177**, which underwent intramolecular cycloaddition to give tricyclic isoxazolidine **178** in 76% yield. The diastereomeric compound **176′**, which was prepared from *Z*-isomer of **172** by an analogous sequence, could also be converted into tricyclic isoxazolidine **178′** in 57% yield. After reductive cleavage of the N–O bond in **178** with zinc and acetic acid, the resultant secondary amine was protected with a Boc group. Hydrogenation of the C–C double bond and hydrogenolysis of the benzyl ether were carried out under a hydrogen atmosphere in the presence of palladium(II) hydroxide. The resultant 1,2-diol was oxidatively cleaved to yield aldehyde **180**, which was converted into ketone **181** by treatment with sodium hydride and oxygen.[44] Cleavage of the Boc group and reductive methylation afforded kopsone (**182**).

4.6. Synthesis of stephadiamine A

Stephadiamine (**196**) is a densely-functionalized pentacyclic natural product (Scheme 23). Zhu and coworkers used nitrone cycloaddition to efficiently construct the skeleton and introduce functional groups.[45] Asymmetric Michael addition of phenol **183** to nitroethylene mediated by Takemoto catalyst **184** produced ketone **185** with a quaternary stereocenter.[46] Oxidative cleavage of the terminal alkene formed an aldehyde, which was reductively condensed with Meldrum's acid in the presence of Hantzsch ester and L-proline. After 1,4-reduction of the enone moiety in **186** with L-selectride, a reaction with Eschenmoser's salt in methanol afforded α,β-unsaturated ester **188**. Upon treatment of **188** with an excess amount of sodium dithionite in a mixed solvent system of methanol and water at 80 °C, a domino sequence involving reduction of the nitro group into a hydroxylamine, nitrone formation, and intramolecular cycloaddition with the unsaturated ester moiety gave isoxazolidine **190** in 63% yield.

Cleavage of the N–O bond with zinc in acetic acid liberated aminoalcohol **191**, which was converted into acyl azide in three steps. When heated in allyl alcohol, **192** underwent Curtius rearrangement to produce compound **193**. Benzylic oxidation was carried out using a photocatalytic method reported by Yoon

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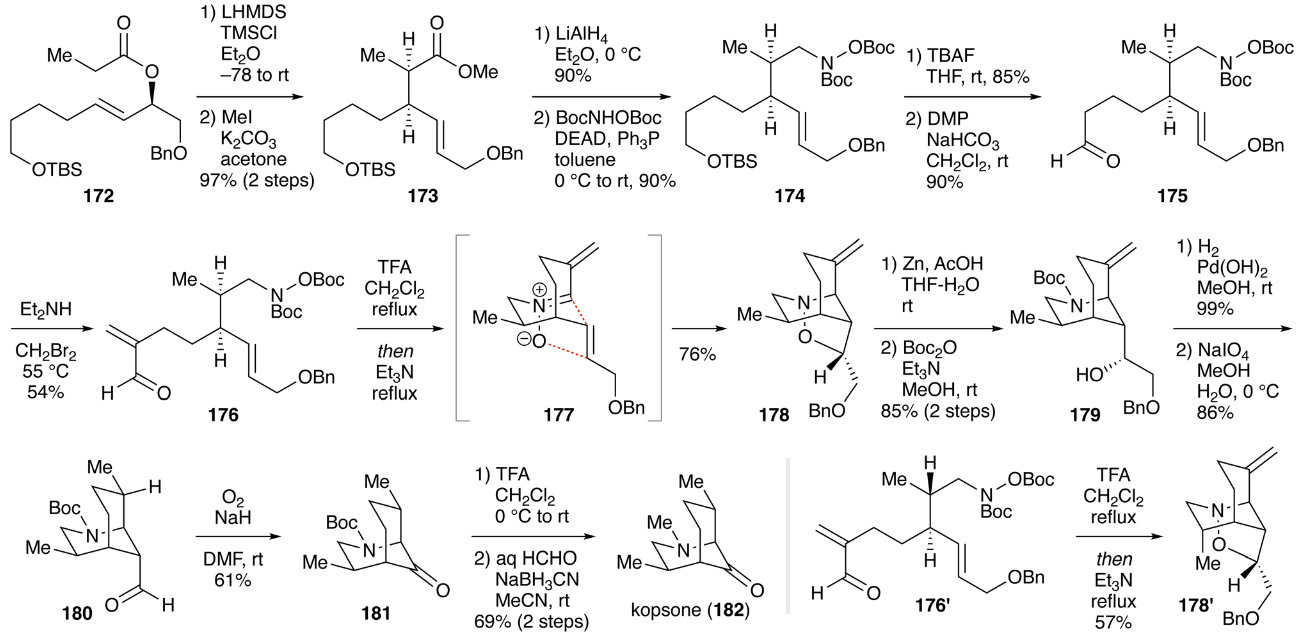
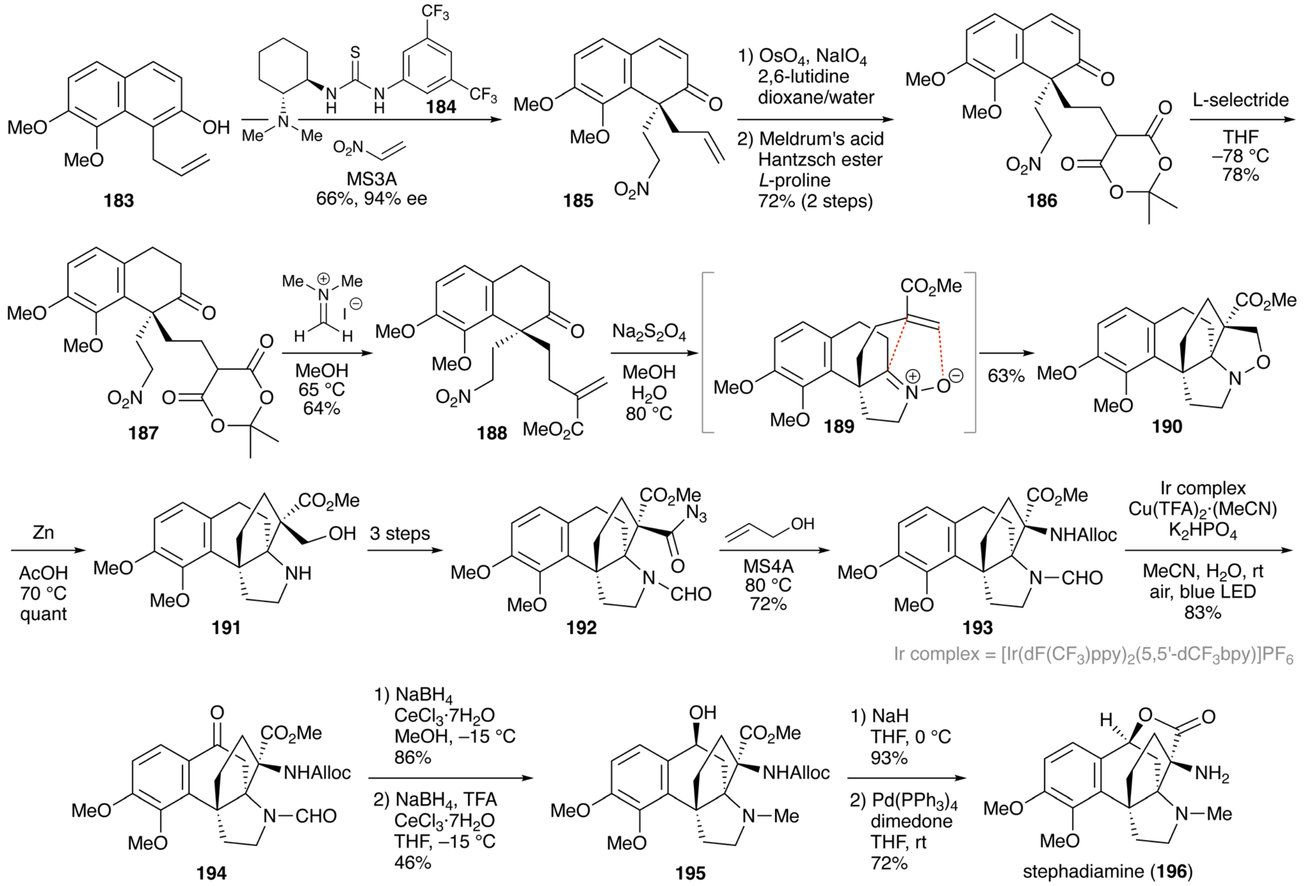


Scheme 22 Synthesis of kopsone.



Scheme 23 Synthesis of stephadiamine.

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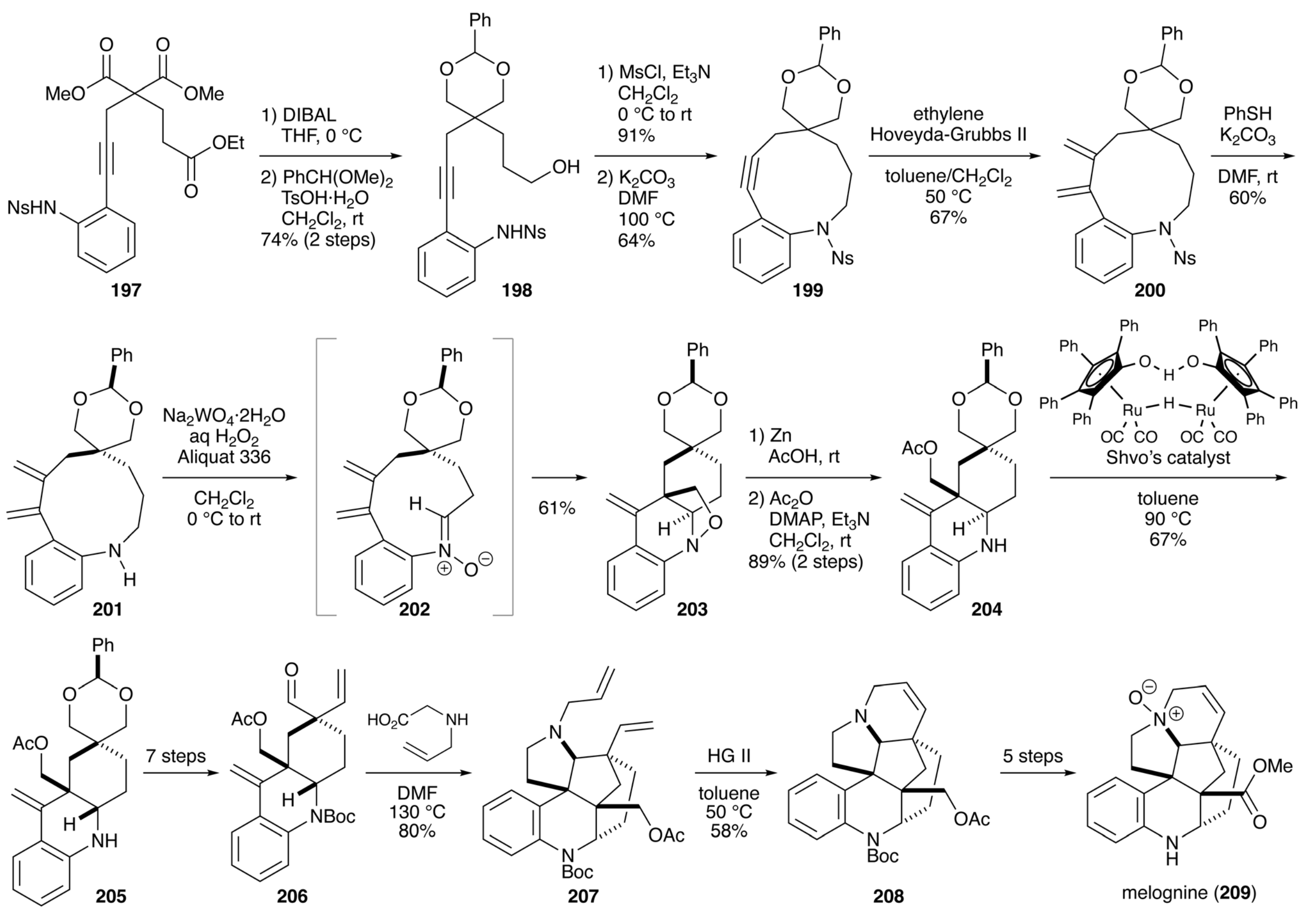
and coworkers,[47] giving ketone **194**, which was stereoselectively reduced under Luche's conditions to afford an alcohol. The formyl group was also reduced with sodium borohydride in THF in the presence of cerium(III) chloride and TFA to yield **195**. Lactone formation under basic conditions, followed by palladium-catalyzed cleavage of the allyloxycarbonyl (Alloc) group, produced stephadiamine (**196**). The synthesis was completed in 18 steps.

4.7. Synthesis of putative melognine

Irie and Yokoshima reported a synthesis of putative melognine (racemic, 29 steps; Scheme 24).[48] Compound **197** was prepared using malonic ester synthesis and Sonogashira coupling. Reduction of the ester moieties with diisobutylaluminum hydride (DIBAL), followed by selective protection of the 1,3-diol as its benzylidene acetal, furnished **198**. After mesylation of the primary alcohol moiety in **198**, the resultant mesylate was heated with potassium carbonate in *N*,*N*-dimethylformamide (DMF) at 100 °C to induce an intramolecular S_N2 reaction, giving ten-membered cyclic alkyne **199**. Enyne metathesis with ethylene in the presence of Hoveyda–Grubbs second-generation catalyst (HG II) yielded 1,3-diene **200**.[49] Cleavage of the Ns group liberated the aniline. In this step, the diastereomers derived from the benzylidene acetal could be separated. Treatment of **201** with hydrogen peroxide in the presence of sodium tungstate formed ten-membered cyclic nitrone **202**,[50] which underwent intramolecular cycloaddition to give isoxazolidine **203** as a sole isomer. Considering the stereochemistry of the product (compound **203**), the nitrone formed *in situ* must be the *Z*-isomer (Scheme 25). The diastereomeric product (compound **210**), which is derived from the *E*-isomer, was not detected. The regioisomeric product (compound **211**) was also not obtained. Interestingly, in the absence of the constraint imposed by the ten-membered ring, the opposite regioselectivity has been observed.[51]

When the oxidation of **201** was carried out in methanol,[52] isoxazolidine **203** and *N*-oxide **213** were obtained in 23% and 39% yields, respectively (Scheme 26). The latter is speculated to have formed *via* a Cope-type hydroamination of hydroxylamine **212**.[36]

Cleavage of the N–O bond in **203** and protection of the resultant hydroxy group with an acetyl group furnished compound **204**, which was heated in the presence of Shvo's catalyst to induce isomerization at the α-position of the nitrogen atom.[53] A seven-step transformation of compound **205** gave aldehyde **206**, which was reacted with *N*-allylglycine in DMF at 130 °C. Under these conditions, the formation of an azomethine ylide and its cycloaddition proceeded to yield pentacyclic compound **207**. Ring-closing metathesis with HG II



Scheme 24 Synthesis of putative melognine.

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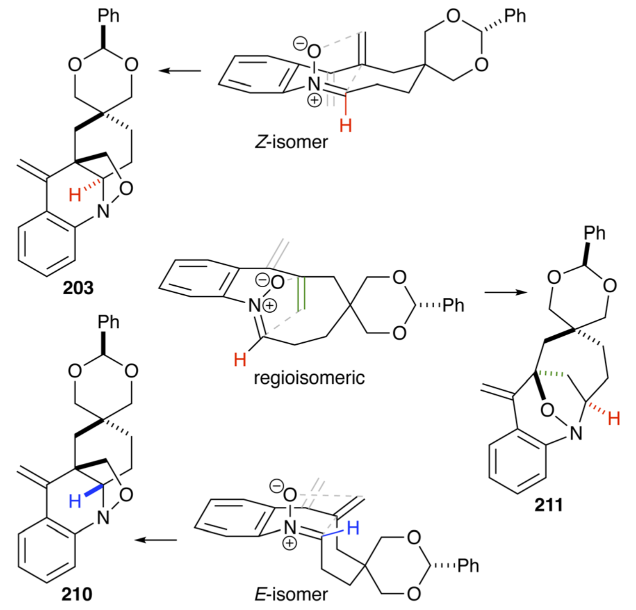
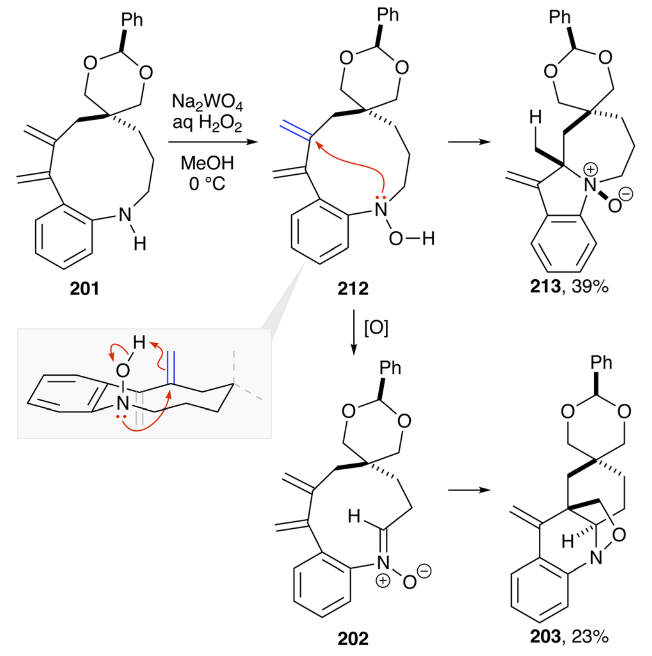


Scheme 25 Stereo- and regioselectivity in the cycloaddition.



Scheme 26 Cope-type hydroamination of hydroxylamine.

constructed a piperidine ring, and further transformation yielded putative melognine (**209**).

5. Discussion on regioselectivity

5.1. Intramolecular cycloaddition of acyclic nitrones

In this review, acyclic nitrones for intramolecular cycloaddition are classified into two groups: C-linked unsaturated nitrones and N-linked unsaturated nitrones. The C-linked unsaturated nitrones discussed in Section 3 (nitrones **54**, **65**, **74**, and **85**) are classified as having a four-carbon tether, with a structure like **214** (Fig. 4), and their cycloaddition produced fused isoxazolidines, represented by **215B** (4-substituted isoxazolidine). There are many examples of producing fused isoxazolidines as shown in this review. However, formation of bridged isoxazolidine **215A** (5-substituted isoxazolidine) has also been reported.[54] The regioselectivity is not primarily determined by the tether length. Instead, it depends on the substituents on the nitrone, alkene, and tether.

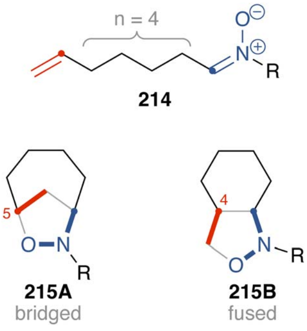


Fig. 4 C-linked unsaturated nitrone.

Cycloaddition of N-linked unsaturated nitrones can produce two types of regio isomers (**51A** *vs.* **51B**, Scheme 7). For a two-carbon tether (**216**, $n = 2$; Fig. 5), **217A** (5-substituted isoxazolidine) is typically the major or sole product,[55] consistent with the results observed in the synthesis of lasubine II (Scheme 12). For a three-carbon tether (**218**, $n = 3$), the regioselectivity varies depending on the substituents.[51,55a,56] In the synthesis of isodihydrokoumine (Scheme 15), a 4-substituted isoxazolidine, corresponding to **219B** (4-substituted isoxazolidine) was obtained. The nitrone used in the synthesis of palhinines (Scheme 13) is formally designated as **220** ($n = 5$), and the product of the cycloaddition was a 5-substituted isoxazolidine, corresponding

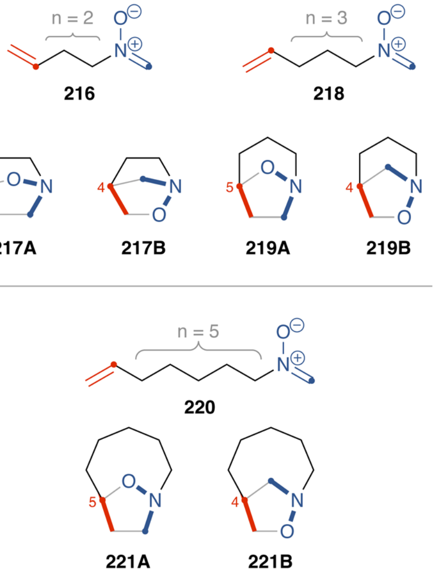


Fig. 5 N-linked unsaturated nitrone.

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to **221A.** Fan and coworkers explain the regioselectivity using steric and electrostatic repulsion (Fig. 3).

5.2. Intramolecular cycloaddition of cyclic nitrones

In contrast to acyclic nitrones, cyclic nitrones have an additional linkage that imposes constraints on the interaction between the nitrone and the alkene during intramolecular cycloaddition (Fig. 6), which can affect regioselectivity.

Nitrones **134**, **168**, **177**, and **202** are considered as both C-linked unsaturated nitrones with a four-carbon tether (**214**) and N-linked unsaturated nitrones with a three-carbon tether (**218**). Although the cycloaddition of acyclic unsaturated nitrones **214** or **218** can yield both regioisomers (**215A**/**B** or **219A**/**B**) depending on substituents, cycloaddition of cyclic nitrones **134**, **168**, **177**, and **202** produced sole regioisomers, corresponding to **223B**, **225B**, and **227B** (4-substituted isoxazolidines, Scheme 27).

Fig. 7 illustrates the transition states involved in the cycloaddition of acyclic C-linked unsaturated nitrone **214**. Nitrone **214** has two alkyl chains attached to the carbon and nitrogen atoms of the nitrone. When the two alkyl chains are positioned on opposite sides, the configuration is referred to as "*trans*", while when they are positioned on the same side, it is referred to as "*cis*". In the transition state **228** from *trans*-nitrone, the nitrone and alkene moieties can smoothly interact to produce bridged isoxazolidine **215A**, whereas in the *cis*-nitrone, interaction between the nitrone and alkene moieties such as to form bridged isoxazolidine **215A** is geometrically restricted. This makes transition state **231** unfavorable. On the other hand, *cis*-nitrone undergoes intramolecular cycloaddition to form fused isoxazoline **215B** through the transition state **232** or **233**.[57] Since cyclic nitrones **222** and **224** are *cis*-nitrones, cycloaddition through a transition state such as **231** to form **223A** or **225A** is unfavorable. However, cycloaddition through a transition state such as **232** is expected to proceed. This discussion explains the selective formation of **223B** or **225B** in the cycloaddition of **222** or **224**. The transition states of these cycloaddition (**222**$^{\mathrm{TS}}$ and **224**$^{\mathrm{TS}}$) can be depicted by adding a linkage to **232** (Fig. 8). The transition state **222**$^{\mathrm{TS}}$ adopts a boat-shaped six-membered conformation.

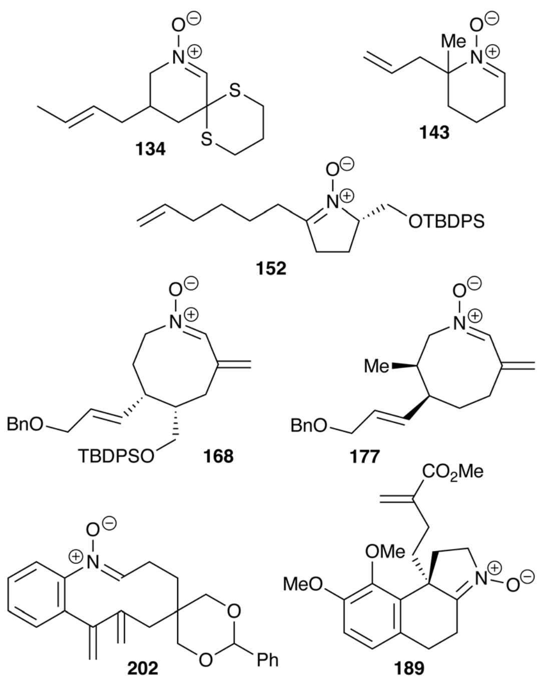
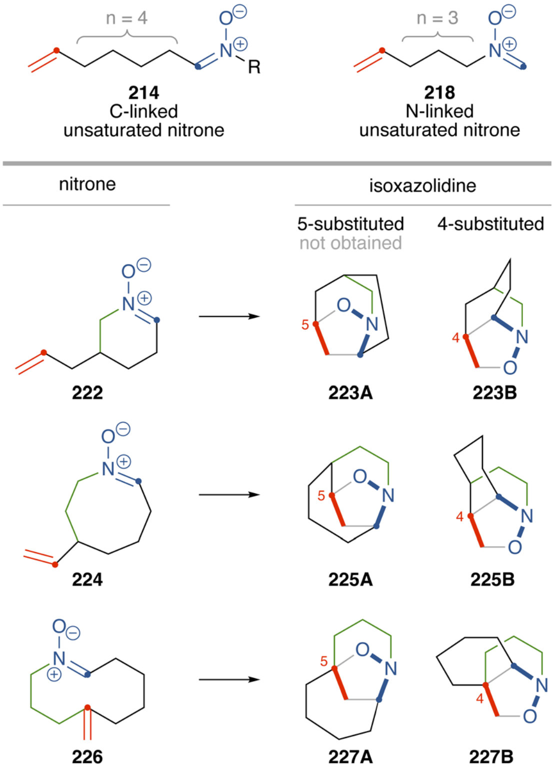


Fig. 6 Cyclic nitrones.



Scheme 27 Cycloaddition of cyclic nitrones.

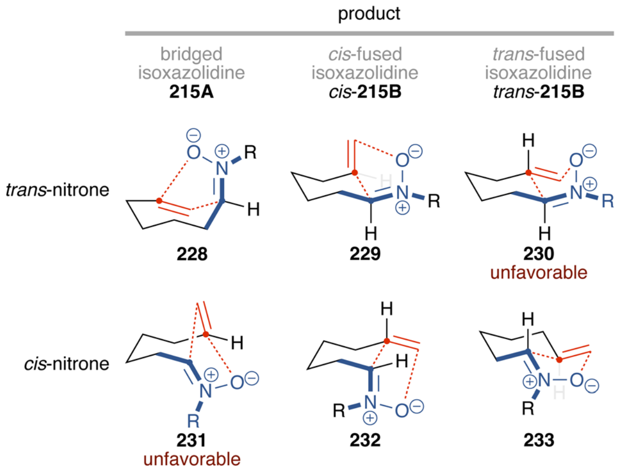


Fig. 7 Transition states in cycloaddition of C-linked unsaturated nitrone **214**.

Cyclic nitrone **226** is a *trans*-nitrone, and therefore the above argument cannot be adopted to explain the selective formation

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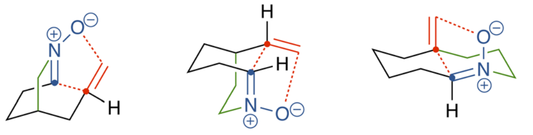


222^{TS} **224^{TS}**
cis-nitrone to form
cis-fused isoxazolidine

226^{TS}
trans-nitrone to form
cis-fused isoxazolidine

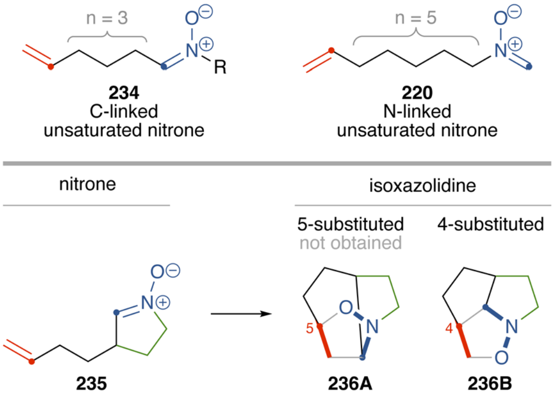
Fig. 8 Transition states in cycloaddition of cyclic nitrones.

of **227B**. In a transition state forming **227B** (**226^{TS}**, Fig. 8), newly formed rings other than the isoxazolidines are six-membered rings, while in the transition state to yield the regioisomers (**227A**), newly formed rings become seven-membered rings, causing strains in the transition state of the cycloaddition.

Nitrone **189** is considered as both C-linked unsaturated nitrones with a three-carbon tether (**234**) and N-linked unsaturated nitrones with a five-carbon tether (**220**), represented by **235** (Scheme 28). In the cycloaddition of acyclic nitrone **234**, the formation of a bridged isoxazolidine from a *cis*-nitrone is unfavorable, as is the transition state **231**, while in the transition state to form a fused isoxazolidine, the nitrone and alkene moieties can sufficiently interact. Since cyclic nitrone **235** is a *cis*-nitrone, this explains why the formation of bridged (5-substituted) isoxazolidine **236A** is unfavorable, leading to the selective formation of **236B** in the cycloaddition of **235**.[58]

Nitrone **152** is a 5-membered cyclic nitrone, and can be considered as a C-linked unsaturated nitrone with a four-carbon tether (**214**, Fig. 4 and Scheme 27). Since the alkenyl chain is attached to the carbon atom of the nitrone, the geometry of the nitrone is necessarily *trans*, allowing for the formation of bridged and fused isoxazolidines (Fig. 7). Indeed, cycloaddition of nitrone **152** produced a mixture of bridged and fused isoxazolidines (**155** and **156** in Scheme 20).[59]

Nitrone **143** is regarded as a N-linked unsaturated nitrone with a two-carbon tether (**216**, Fig. 5). The cycloaddition of **143** regioselectively produces isoxazolidine **144**, a 5-substituted isoxazolidine. This is consistent with the regioselectivity in cycloaddition of **216** to yield **217A** (5-substituted isoxazolidine, Fig. 5) as the major or sole product.[60]



Scheme 28 Cycloaddition of cyclic nitrones.

6. Conclusions

Various ring systems of natural products have been constructed *via* the intramolecular cycloaddition of nitrones. The cycloaddition of nitrones can be carried out under simple conditions, typically heating in a solvent. This reaction enables the functionalization of alkenes through the formation of both C–O and C–C bonds, making it possible to construct even quaternary carbon centers. As discussed in Section 5, regioselectivity of intramolecular cycloaddition is often different from that of intermolecular cycloaddition of nitrones. In particular, intramolecular cycloaddition of cyclic nitrones tends to proceed in a regioselective manner as the additional bond forming the cyclic nitrone may limit the access between the nitrone and the alkene.

The preparation of nitrones is also an important issue in this review. Condensation of hydroxylamines with aldehydes or ketones is a simple method for the preparation of nitrones. In addition, the oxidation of amines (Schemes 2, 12 and 24), the *N*-alkylation of oximes (Schemes 4 and 18), and the transformation of an *N*-hydroxylactam (Scheme 20) are included in this review.[61] For the preparation of hydroxylamines, various methods have been demonstrated, including reduction or *C*-allylation of an oxime (Schemes 12, 13 and 19), introduction of a hydroxylamine unit *via* a Mitsunobu reaction (Schemes 15, 21 and 22), and reduction of a nitro group (Scheme 23). After the cycloaddition, reduction with zinc, samarium(II) iodide, or RANEY® nickel is widely used to cleave the N–O bond in the isoxazolidine, yielding versatile 1,3-amino alcohols. Oxidative cleavage of the N–O bond has also been reported but is not included in this review.[62] Further accumulation of results related to the cycloaddition of nitrones could lead to the synthesis of various molecules with complex structures.

7. Conflicts of interest

There are no conflicts to declare.

8. Acknowledgements

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