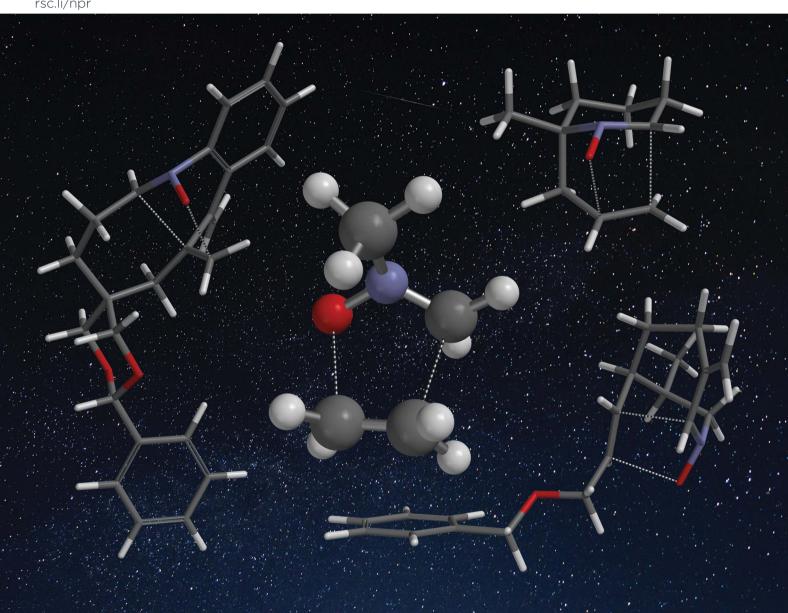
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Intramolecular cycloaddition of nitrones in total synthesis of natural products

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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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- Introduction
- Construction of isoxazolidine rings in natural products 2.
- 2.2. Synthesis of virosaine A
- nitrones
- Syntheses via cycloaddition of C-linked unsaturated 3.1.
- 3.1.1. Synthesis of himalensine A
- 3.1.2. Synthesis of pleosporol A
- Synthesis of isolysergol 3.1.3.
- 3.1.4.
- Syntheses via cycloaddition of N-linked unsaturated 3.2. nitrones
- 3.2.1. Synthesis of lasubine II
- 3.2.2. Synthesis of palhinines A and D
- 3.2.3. and isodihydrokoumine N_4 -oxide
- nitrones
- Synthesis of 19-hydroxyibogamine 4.1.
- Synthesis of N-methyl-euphococcine 4.2.
- Synthesis of cylindricine C 4.3.
- 4.4. Synthesis of sarain A

- 1.
- Synthesis of alsmaphorazine B 2.1.
- 2.3. Synthesis of lycojaponicumin A
- 3. Synthesis via intramolecular cycloaddition of acyclic
- Synthesis of thebainone A
- Synthesis of (19Z)-taberpsychine, isodihydrokoumine,
- 4. Synthesis via intramolecular cycloaddition of cyclic
- 4.5. Synthesis of kopsone
- 4.6. Synthesis of stephadiamine A
- 4.7. Synthesis of putative melognine
- Discussion on regioselectivity 5.

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- Intramolecular cycloaddition of acyclic nitrones 5.1.
- 5.2. Intramolecular cycloaddition of cyclic nitrones
- Conclusions 6.
- 7. Conflicts of interest
- 8. Acknowledgements
- 9. Notes and references

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.

Table 1 Regioselectivity in cycloaddition of nitrones

Entry	R	Yield (%)	A:B	Cis : trans
1^a 2^b 3^c 4^d 5^e	n -C $_6$ H $_{13}$ Ph OEt CO $_2$ Et NO $_2$	77 79 78 97 —	100:0 100:0 100:0 82:18 0:100	1:1 3:1 1:1 1: 7^f , 2: 7^g 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**.

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). These can be understood by the matching of the largest coefficients both in the LUMO_{nitrone}–HOMO_{alkene} and HOMO_{nitrone}–LUMO_{alkene} interactions (Fig. 1a). In the reaction of 1 with nitroethylene (entry 5), the HOMO_{nitrone}–LUMO_{alkene} interaction is dominant, selectively producing 4-substituted isoxazolidine B (Fig. 1b). In the case of ethyl acrylate (entry 4), which is a less electron-deficient alkene than nitroethylene, the less energetically preferred LUMO_{nitrone}–HOMO_{alkene} also contributes to the regioselectivity in addition to the HOMO_{nitrone}–LUMO_{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



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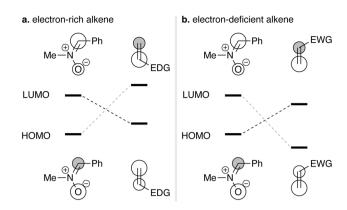


Fig. 1 HOMO-LUMO interaction of cycloaddition of nitrone. (a) Cycloaddition with an electron-rich alkene. (b) Cycloaddition with an electron-deficient alkene.

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. The biosynthetic pathway might involve the generation of a nitrone and its cycloaddition. 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

Fig. 2 Selected Natural products containing an isoxazolidine ring.

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 threestep 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 fivemembered 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 fivemembered 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.

Natural Product Reports Review

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

CH₂Cl₂, -78 °C Et₂O Вr -78 °C 22 1) aq HCl THF. rt 2) TBSONH₂ MS4A Ėι 25 CH₂Cl₂, rt 92% (2 steps) 62%, dr = 2.7:1, 83% ee; 30%, dr = >20:1, >99% ee after recrystallization Nah **AcOH** HO **TBSO** THF 120 °C 0 °C to rt 99% 26 BuHN CDI, KOH toluene 60°C then 92% n-BuNH₂ CH₂Cl₂, rt 28 29 BuHN s-BuLi THF –78 °C LiAIH₄ AIBN then Br₂ THF benzene 0 to 70 °C 94% O₃, CH₂Cl₂ Me₂S Al_2O_3 -78 °Č to rt FtOAc then **DMP** rt 77% pyridine CH₂Cl₂

33

virosaine A (18)

Scheme 4 Synthesis of virosaine A.

32

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. Peductive 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 Al₂O₃ to afford virosaine A (18).

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 BF₃·OEt₂, 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 silvl 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.

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).

Synthesis via intramolecular cycloaddition of acyclic nitrones

Scheme 6 Synthesis of lycojaponicumin A.

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

Scheme 7 C-linked and N-linked nitrones.

using C-linked unsaturated nitrones followed by N-linked unsaturated 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,

Synthesis of himalensine A. Scheme 8

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 1,3dithiane group afforded ketone 57, which underwent Pdmediated intramolecular vinylation to produce tricyclic compound 58. Ring-closing metathesis constructed a sevenmembered 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 Nmethylhydroxylamine 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 (2R)-phenyloxirane; Scheme 10).27 Palladium-catalyzed aminoalkynylation of carbamate 70 with 1-[(triisopropylsilyl) ethynyl]-1,2-benziodoxol-3(1H)-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 (mCPBA) 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

Synthesis of pleosporol A. Scheme 9

Scheme 10

cycloaddition with p-toluenesulfonyl azide (TsN₃) afforded Ntosyl-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 Nmethylation afforded isolysergol (81).

Synthesis of isolysergol.

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)2Cl2, 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 mCPBA 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 odichlorobenzene at 150 °C under microwave irradiation. The cycloaddition of nitrone occurred intramolecularly, and

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 (19Z)-taberpsychine, of isodihydrokoumine, and isodihydrokoumine N4-oxide. Kerkovius and Kerr reported a synthesis of (19Z)-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_0 -bis(Boc)-hydroxylamine (Boc = tert-butoxyearbonyl) 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 2hydroxyethyl 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

Scheme 13 Synthesis of palhinine A

Discussion on regio- and stereoselectivity.

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 BF₃·OEt₂ 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 (19Z)-taberpsychine (126). Treatment of (19Z)-taberpsychine (126) with trimethylsilyl iodide led to a Conia-ene-type reaction between the and the ethylidene moiety to furnish isodihydrokoumine (127). Oxidation with mCPBA produced isodihydrokoumine N_4 -oxide (128).

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 19hydroxyibogamine (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

isodihydrokoumine

 N_4 -oxide (**128**)

Scheme 15 Synthesis of (19Z)-taberpsychine, isodihydrokoumine, and isodihydrokoumine N_4 -oxide.

(19Z)-taberpsychine (126)

125

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

isodihydrokoumine (127)

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*-methyleuphococcine (**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 fivemembered 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

Scheme 18 Synthesis of 19-hydroxyibogamine

Scheme 19 Synthesis of N-methyl-euphococcine.

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

Scheme 20 Synthesis of cylindricine C.

160

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 tertbutyldiphenylsilyl (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

cylindricine C (161)

Scheme 21 Synthesis of sarain A.

 \emph{via} a Mitsunobu reaction. The \emph{p} -methoxyphenyl (PMP)-protected alcohol was transformed into α , β -unsaturated aldehyde **167** \emph{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_i 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

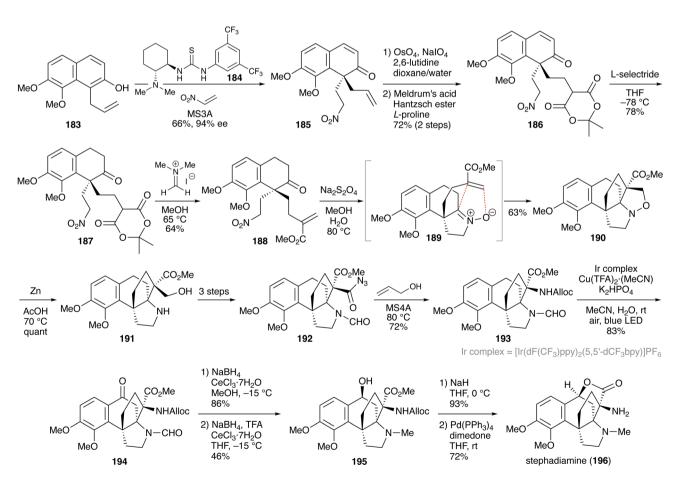
amine was protected with a Boc group. Hydrogenation of the C–C double bond and hydrogenolysis of the benzyl ether were carried out under a hydrogen atmosphere in the presence of palladium(II) hydroxide. The resultant 1,2-diol was oxidatively cleaved to yield aldehyde 180, which was converted into ketone 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

Scheme 22 Synthesis of kopsone



Scheme 23 Synthesis of stephadiamine.

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.

Scheme 25 Stereo- and regioselectivity in the cycloaddition.

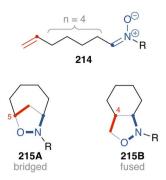
Scheme 26 Cope-type hydroamination of hydroxylamine.

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

5. Discussion on regioselectivity

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



C-linked unsaturated nitrone

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.

Cycloaddition of N-linked unsaturated nitrones can produce two types of regio isomers (51A vs. 51B, Scheme 7). For a twocarbon 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 regionelectivity 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

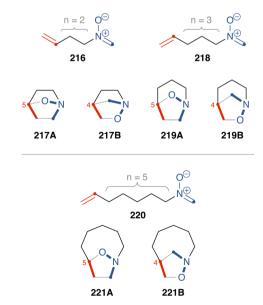


Fig. 5 N-linked unsaturated nitrone.

Natural Product Reports Review

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, cisnitrone 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

Fig. 6 Cyclic nitrones

Scheme 27 Cycloaddition of cyclic nitrones

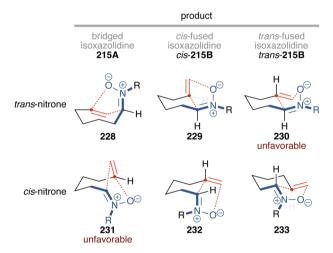


Fig. 7 Transition states in cycloaddition of C-linked unsaturated nitrone 214.

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^{TS} and 224^{TS}) can be depicted by adding a linkage to 232 (Fig. 8). The transition state 222^{TS} adopts a boat-shaped six-membered conformation.

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

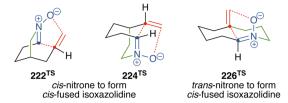


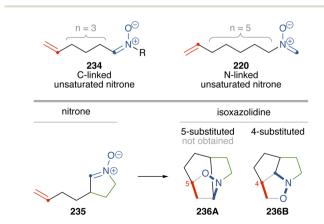
Fig. 8 Transition states in cycloaddition of cyclic nitrones.

of 227B. In a transition state forming 227B (226TS, 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 (5substituted) 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 fourcarbon 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

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 Nalkylation 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 Callylation 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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