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Intramolecular 1,3-dipolar cycloaddition reactions in targeted syntheses

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1. Introduction

Historically, the synthesis of diazoacetic acid ester by Curtius in 1883[1] and its reaction with unsaturated carboxylic esters reported by his younger colleague, Buchner, in 1888 may constitute the embryonic events in the discovery of 1,3-dipolar cycloadditions.[2] Important contributions in subsequent years by Buchner,[2] Beckmann,[3] Werner, Buss,[4] and others for the generation of 1,3-dipoles are also noteworthy. This field, however, lay dormant until 1963, when Huisgen, recognizing the generality of these reactions, created the conceptual framework for the 1,3-dipolar cycloadditions (Huisgen reaction) and provided the much-needed mechanistic rationalization for the process.[5] He invoked the intermediacy of dipoles in some well-known reactions. Later, Sustmann classified the dipolar cycloaddition reactions into three types based on the orbital interactions.[6] With a better understanding of the mechanistic events and the large body of experimental results provided by Huisgen, the area of 1,3-dipolar cycloadditions witnessed enormous progress. The impact was felt mostly in the realm of heterocyclic synthesis. In due course, dipolar cycloaddition reactions became a trusted tool in targeted synthesis, especially in those involving the construction of heterocyclic systems.[7]

Keywords: Intramolecular 1,3-dipolar cycloaddition; Huisgen reaction; 1,3-Dipole; Azomethine ylide; Azomethine imine; Carbonyl ylide; Nitrile oxide; Azide; Nitrone; Mesionic compound; Betaine; Natural product synthesis; Alkaloid.

Abbreviations: Ac, acetyl; aq, aqueous; Boc, tertiary butoxy carbonyl; CAL-B, *Candida antarctica* lipase fraction B; DABCO, 1,4-diazabicyclo-[2.2.2]octane; DMAP, 4-dimethylaminopyridine; DIBALH, diisobutylaluminum hydride; DMF, dimethyl formamide; DMSO, dimethyl sulfoxide; Et, ethyl; IAC, intramolecular azide cycloaddition; IDC, intramolecular dipolar cycloaddition; INC, intramolecular nitrone cycloaddition; INOC, intramolecular nitrile oxide cycloaddition; LDA, lithium diisopropylamide; LSD, lysergic acid diethylamide; *m*-CPBA, *meta*-chloroperoxybenzoic acid; MEM, methoxyethoxymethyl; MVK, methyl vinyl ketone; Ms, mesyl; nAChR, nicotinic acetylcholine receptor; NCS, *N*-chlorosuccinimide; pfb, perfluorobutyrate; RCM, ring-closing metathesis; TBAF, tetrabutylammonium fluoride; TBAT, tetrabutylammonium triphenyldifluorosilicate; TBS, tertiary-butyldimethylsilyl; ^{t}Bu, tertiary butyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; Ts, tosyl.

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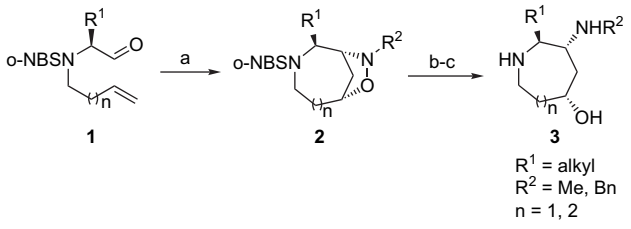
1.1. Dipolar cycloaddition as a synthetic strategy

The impact of dipolar cycloaddition reactions in the area of heterocyclic synthesis is in many ways comparable to that of Diels–Alder reactions on carbocyclic synthesis. In fact, the availability of various classes of dipoles and dipolarophiles has allowed a greater degree of versatility. The discovery of new dipolar species was followed by applications of their reactions in targeted syntheses. Even though all dipolar cycloaddition reactions are, in principle, closely related processes, their applications are seldom discussed together in the chemical literature. The main reason for this anomaly is the vast variety of heterocyclic systems produced in such reactions. Discussions on heterocyclic synthesis generally follow a product-class-based approach. Although convenient, such an approach fails to address the underlying similarities of the various processes involved. There has been no concerted attempt to categorize various dipolar cycloadditions used in the synthesis of natural products, apart from an excellent book edited by Padwa.[8] A discussion on dipolar cycloadditions by Wade published in 1991 is also worth mentioning, although its emphasis is on the general aspects of dipolar cycloadditions.[9] This article will focus on the use of dipolar cycloaddition reactions in the total synthesis of natural products or analogues. The discussion is limited to the literature published after 1991 and instances in which the dipolar cycloaddition serves as a key step of the synthesis and is not intended to be comprehensive. For convenience, the examples are classified on the basis of the dipole involved.

2. Nitrones

1,3-Dipolar cycloaddition reactions of nitrones with alkenes leading to isooxazolidines are a long-known and a well-studied area.[10] Nitrones are usually generated by the condensation of an aldehyde and an *N*-substituted hydroxylamine[11] or the oxidation of a hydroxylamine.[12] Reductive ring opening of isoxazolidines by hydrogenation with Pd or Raney nickel provides access to γ-amino alcohols.[13]

Synthesis of bridged, medium-sized rings has been accomplished by the intramolecular nitrone cycloaddition (INC) reaction of alkenyl nitrones derived from amino acids. This protocol has been applied to the synthesis of 3-amino-5-hydroxyazepines and other *N*-heterocycles (Scheme 1).[14]



Scheme 1. (a) $R^2NHOH\cdot HCl$, $NaHCO_3$, $CaCl_2$, rt, 1–4 h, 15–76%; (b) PhSH, K_2CO_3, DMF, rt; (c) Zn, AcOH, 60 °C, 1.5 h.

Cyclic ether moieties are common motifs in many important marine natural products like brevetoxin B and ciguatoxin. Shing and Zhong employed the INC reaction effectively to construct oxepanes and tetrahydropyrans from sugar derivatives. Nitrone **5** derived from 3-*O*-allyl-D-glucose **4** (and 3-*O*-allyl-D-altrose) underwent an INC reaction to afford the oxepane, which was isolated as tetraacetate **6**. On the other hand, 3-*O*-allyl-D-allose **7** (and 3-*O*-allyl-D-mannose) afforded the tetrahydropyran derivatives **9** and **10** under similar reaction conditions (Scheme 2). The formation of oxepanes from glucose and altrose derivatives may be rationalized by invoking the unfavorable 1,3-diaxial interactions present in the transition states leading to the formation of the tetrahydropyran products.[15]

In a very recent paper, Shing and co-workers reported that the nitrones derived from hept-6-enoses possessing a *trans* acetonide group in the chain exclusively afforded the bridged isoxazolidines after INC reactions. These results are in accordance with the computational models, which suggest that the transition state leading to the *endo* product (i.e., the bridged bicyclo[4,2,1]isoxazolidine) is more stabilized than that leading to the *exo* product. The cycloadducts were further transformed into the calystegine analogues **14** and **15**, tropane **16**, and a hydroxylated aminocycloheptane derivative **17** in a few steps (Scheme 3).[16]

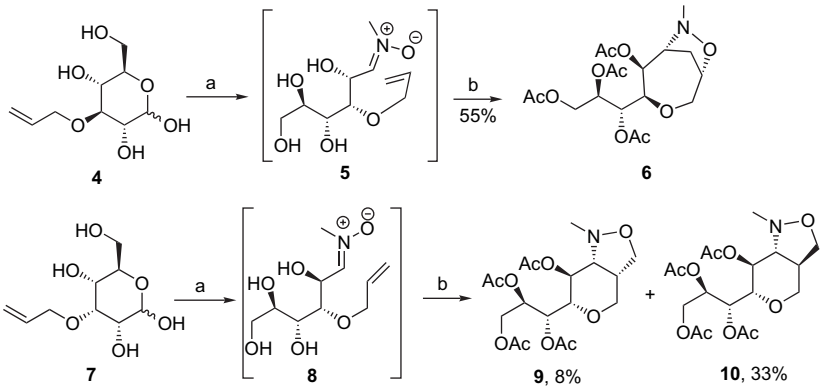
Chiral polyhydroxylated amino five-, six-, or seven-membered carbocycles have been synthesized via an INC reaction of aldehyde **19** derived from 1,2,5,6-di-*O*-isopropylidine-α-D-*ribo*-hexafurano-3-ulose **18**, which is readily prepared from D-glucose (Scheme 4). The cycloadducts **20** and **21** are useful intermediates in the synthesis of various bioactive compounds such as enzyme inhibitors, antibiotics, and bioactive nucleosides.[17]

INC reactions in which the nitrone or olefin partners are part of cyclic systems can lead to tricyclic frameworks. For example, 3-oxa- or 3-aza-nitrones spontaneously afforded tricyclic derivatives, which could serve as intermediates in alkaloid synthesis (Scheme 5).[18]

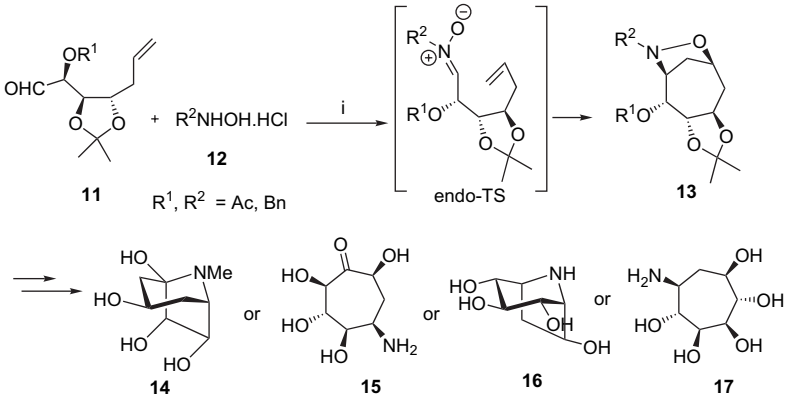
The use of INC reactions of 5-alkenyl- or 5-homoalkenyl proline for the synthesis of azabicyclo[*x*.3.0]alkane amino acids with heteroatom-substituted side chains has been reported (Scheme 6). These compounds are particularly attractive constrained dipeptide mimics, due to their ability to serve as conformationally fixed surrogates of peptide-turn secondary structures.[19]

INC reactions of silicon-tethered 4-hydroxy-2-isoxazolidine-2-oxides afforded a new class of silicon heterocycles **29**, which possess a complex framework of hydroxylated amino acids with an ethoxycarbonyl group, a nitroacetal bicyclic system, and a cyclic silyl ether. The product on Tamao oxidation and subsequent reduction afforded the non-natural amino acid derivative **30** (Scheme 7).[20]

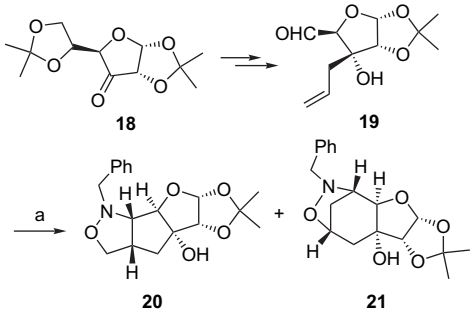
A synthesis of stereodefined aminopolyols was achieved by the INC reaction of nitrones with a silicon tether derived from α- or β-hydroxy carbonyl compounds. The fused bicyclic transition state involved in the concerted cycloaddition renders the reaction highly stereoselective. Tamao oxidation of the silicon heterocycle and the usual hydrogenolysis of the cycloadduct isoxazolidine revealed the additional hydroxyl groups of the target molecule, which is usually isolated as the acetate **34** (Scheme 8).[21]



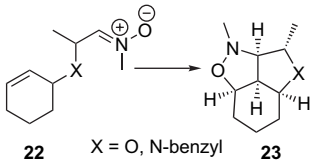
Scheme 2. (a) MeNHOH·HCl, $NaHCO_3$, 80% EtOH, reflux, 48 h; (b) Ac_2O, DMAP, Py, CH_2Cl_2, rt.



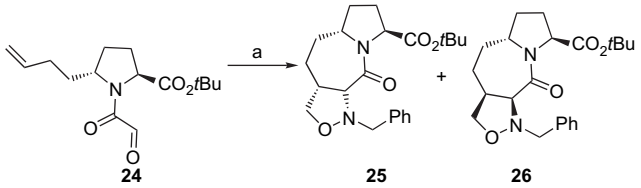
Scheme 3. (i) $NaHCO_3$, MeCN, rt.



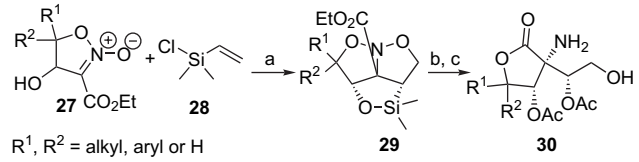
Scheme 4. (a) BnNHOH, EtOH, rt, 20 h, 82%, 4:1.



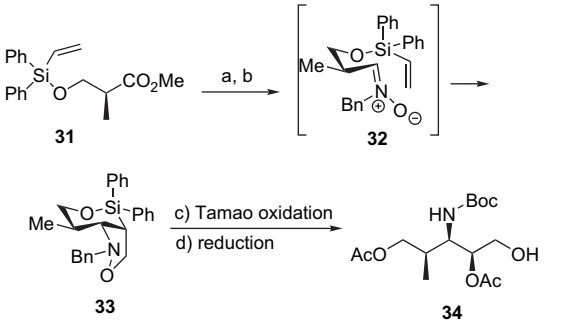
Scheme 5.



Scheme 6. (a) BnNHOH·HCl, $NaHCO_3$, EtOH, H_2O, 71%, 9:1.



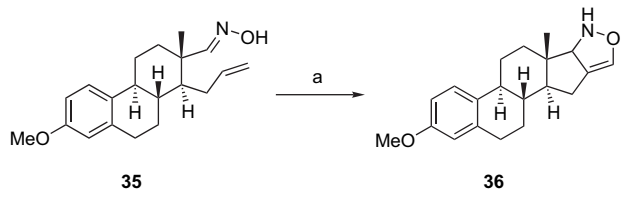
Scheme 7. (a) ImH, CH_3CN; (b) Tamao oxidation; (c) reduction.



Scheme 8. (a) DIBALH, −78 °C, 30 min; (b) BnNHOH, −78 °C to rt, 79%.

A Lewis acid-mediated INC reaction of the tricyclic oxime **35** directly produced the isoxazolidine derivative of estrone **36** (Scheme 9).[22]

Kang and co-workers reported a route to cephalosporin derivatives with cyclic substituents at the 3-position. 3-Alkylidene-4-carboxylic acid derivative **37** was treated with methylhydroxylamine hydrochloride in the presence of a base.



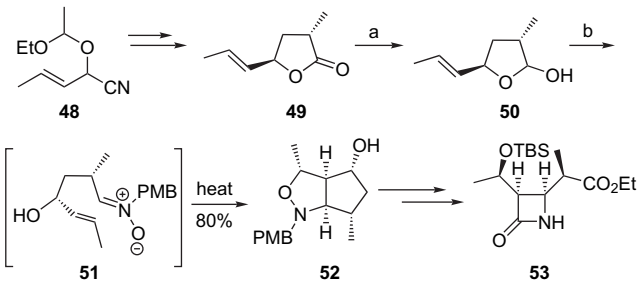
35 36

Scheme 9. (a) $BF_3 \cdot OEt_2$.

The nitrone produced was refluxed in benzene to effect the cycloaddition with the exocyclic olefin to afford a single adduct **38**. Similarly, a nitrile oxide cycloaddition was also carried out to furnish the derivative **40** (Scheme 10).[23]

Haouamine A is a cytotoxic polycyclic alkaloid of marine origin, with a unique 3-aza-[7]-paracyclophane moiety in the structural framework. It exhibits selective activity against a human colon carcinoma cell line HT-29. Haouamine A has been synthesized earlier from the pentacyclic intermediate **47** using a microwave-assisted intramolecular Diels–Alder reaction. Weinreb utilized an INC reaction for the synthesis of the indene ring of the pentacyclic indenotetrahydropyridine derivative **47**. Aldehyde **43** on treatment with *N*-benzylhydroxylamine produced the transient nitrone **44**, which was heated without isolation to afford the cycloadduct **46**. Formation of the kinetically favored cycloadduct **45** was also observed, but this could be converted into the more stable isomer **46** by prolonged heating in toluene. The conversion of **45** into **46** presumably involves a thermal cycloreversion and a subsequent cycloaddition. The cycloadduct was later converted into the desired pentacyclic compound **47** (Scheme 11).[24]

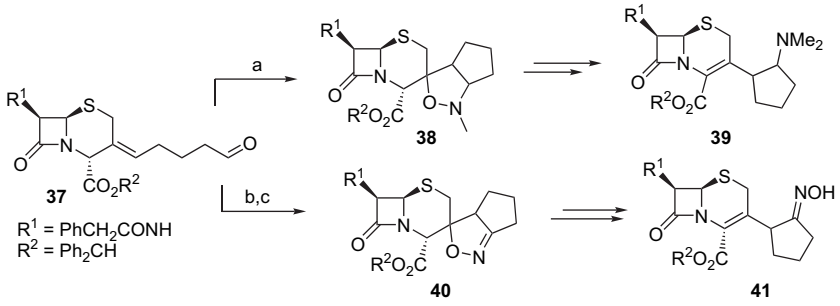
Sung and Hee reported an enantioselective synthesis of the azetedinone fragment of the antibiotic, 1β-methyl carbapenem. Lactone **49** was prepared from ethoxyethyl ether **48** in three steps. Reduction of **49** afforded the corresponding lactol, which was heated with *p*-methoxybenzylhydroxylamine and base to generate the nitrone **51**. The desired cycloadduct **52** was formed in 80% overall yield from **49** as a single isomer. Further synthetic operations were carried out on **52** to arrive at β-lactam **53** (Scheme 12). It is noteworthy that the four contiguous stereocenters in **53** were fixed during the cycloaddition reaction.[25]



48 49 50 51 52 53

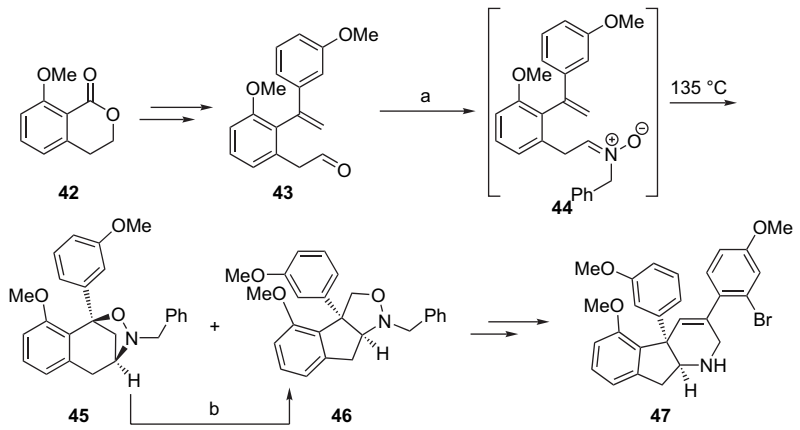
Scheme 12. (a) DIBALH, CH_2Cl_2, −78 °C to rt; (b) *p*-MeO–$C_6H_4CH_2$-NHOH, Et_3N, hydroquinone, benzene, reflux.

Erythroidene **58** and spirojatamol **59** are two sesquiterpenes with an intriguing spirobicyclo[5.4]decane framework. Fukumoto reported a short synthesis of both sesquiterpenes in their racemic form by employing an INC reaction as the pivotal step. Ene-nitrone **55** was prepared from 4-isopropylcyclohexenone **54**. Nitrone **55** on heating afforded two diastereomeric cycloadducts **56** and **57**, of which the major



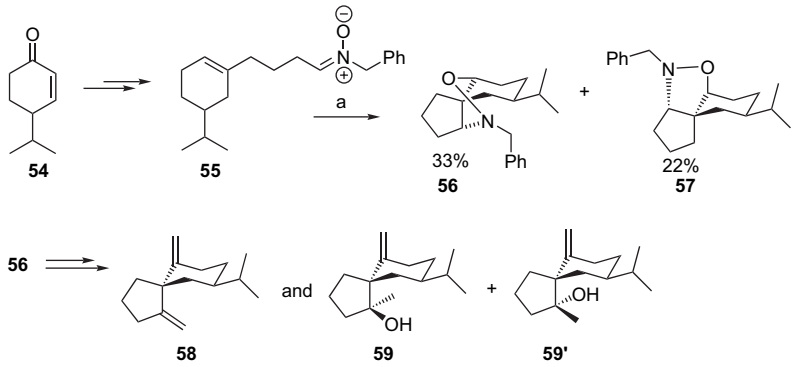
37 38 39 40 41

Scheme 10. (a) MeNHOH·HCl, Py, $CHCl_3$, MeOH, then benzene, reflux, 87%; (b) $NH_2OH \cdot HCl$, Py, 82%; (c) NCS, Py, Et_3N, $CHCl_3$, 71%.



42 43 44 45 46 47

Scheme 11. (a) BnNHOH, toluene, 135 °C; (b) toluene, 135 °C.



Scheme 13. (a) Toluene, 180 °C, sealed tube.

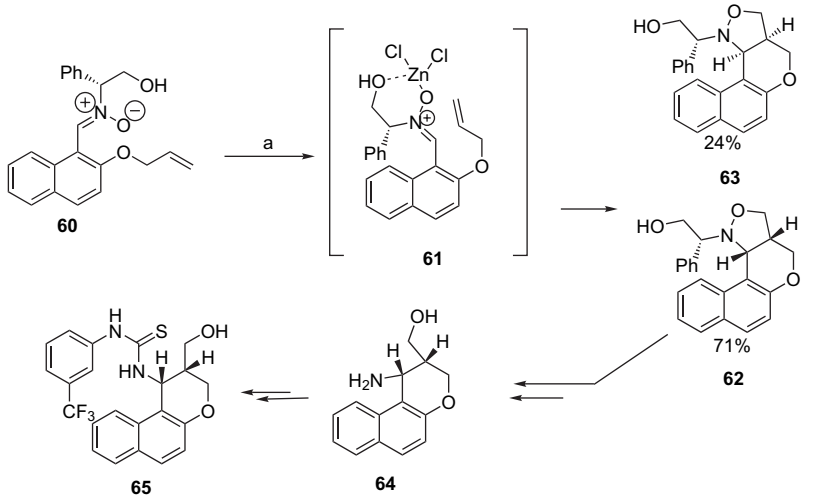
diastereomer **56** possessed the desired stereochemistry. Further reactions on **56** were carried out to synthesize both erythroidene **58** and spirojatamols **59** and **59′** in racemic forms (Scheme 13).[26]

Romero and co-workers have developed a synthetic route to enantiomerically pure chromane derivatives like **65** using an intramolecular dipolar cycloaddition (IDC) of the nitrone and alkene as a key step. Chromane itself is known to exhibit modest antibacterial activity. The authors employed nitrones with a chiral substituent on the nitrogen, which also possessed an oxygen functional group. This allowed for a Lewis-acid chelation involving the nitrone oxygen and, as a result, provided very good diastereoselectivity for the cycloaddition. The cycloadducts were then subjected to routine synthetic operations to furnish various enantiopure chromane derivatives. A representative example is provided in Scheme 14.[27]

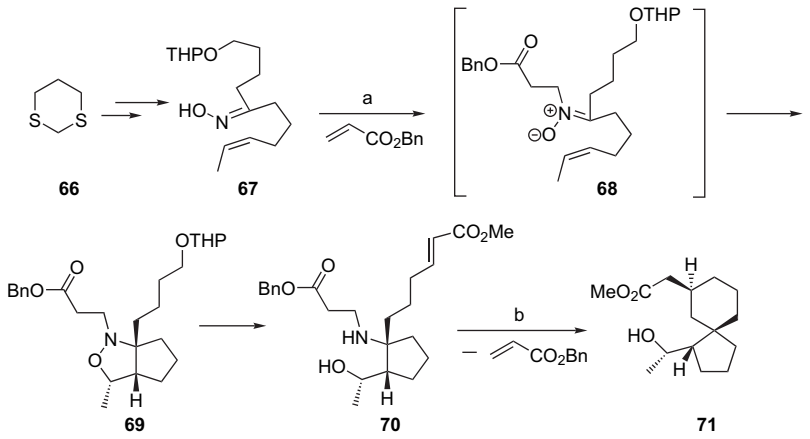
Halichlorine and pinnaic acid are two marine natural products known to exhibit interesting biological properties. Both compounds contain an azaspiro[4.5]decane core structure. A stereospecific synthesis of this structural unit has been achieved by employing the INC reaction. Oxime **67** prepared from dithiane **66** was heated in the presence of benzyl acrylate at 140 °C. Nitrone **68** that was generated underwent smooth cycloaddition to provide a single cycloadduct **69** in 92% yield. The latter adduct was then subjected to various chemical transformations to afford azaspiro[4.5]decane **71** as a single isomer. The conversion of **70** into **71** proceeds through a hetero-Michael addition–reversion sequence with elimination of benzyl acrylate (Scheme 15).[28]

The indolizidine ring system is widespread in many biologically active alkaloids. Polyhydroxylated indolizidines act as structural analogues of sugars and can competitively interact with glycosidases. In an enantioselective synthesis of hydroxylated indolizidines, Brandi employed the INC reaction of a pyrroline nitrone **72** derived from L-malic acid. Initial attempts to deprotect the THP ether and attach an olefinic tether met with difficulties associated with the racemization of the intermediate hydroxynitrone. Therefore, nitrone **72** was initially masked as the adduct **73** by a dipolar cycloaddition with ethyl acrylate (or styrene). Subsequent hydrolysis of the THP ether and attachment of the olefinic tether via a Mitsunobu inversion proceeded without any racemization. The substrate on heating underwent cycloreversion to reveal the nitrone and subsequent INC cycloaddition to furnish the isoxazoline derivative. Deprotection, mesylation, and hydrogenolysis afforded the indolizidine derivative **77** (Scheme 16).[29]

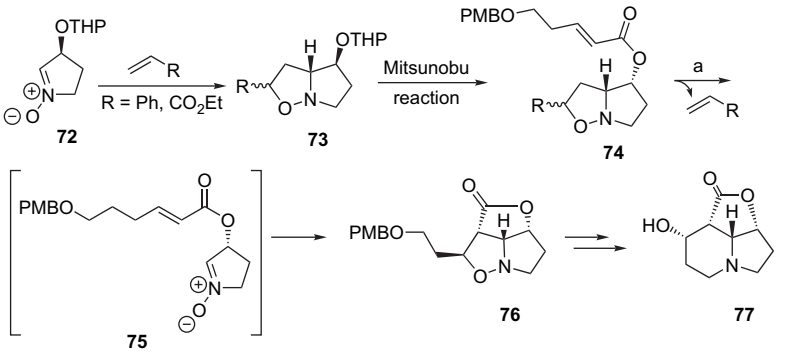
(−)-Histrionicotoxin **85** is a spiropiperidine alkaloid isolated from the brightly colored poison-arrow frog,



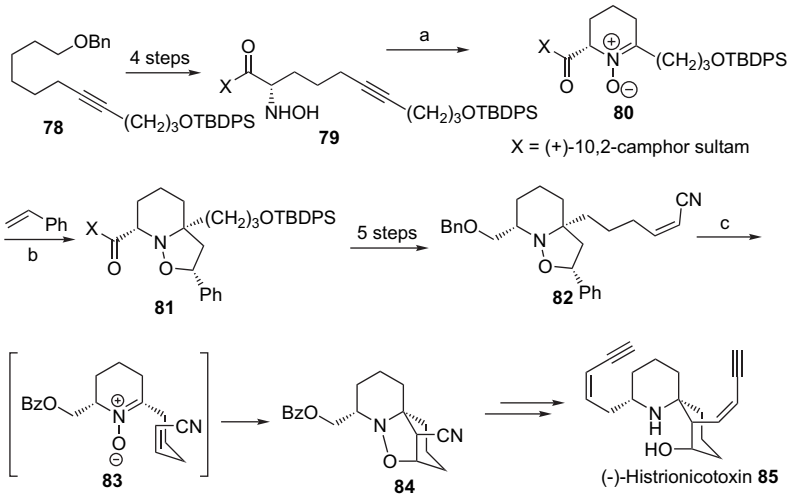
Scheme 14. (a) 2 equiv $ZnCl_2$, 40 °C, CH_2Cl_2.



Scheme 15. (a) Xylene, 140 °C, 92%; (b) 1,2-dichlorobenzene, reflux, 84%.



Scheme 16. (a) *o*-Dichlorobenzene, 150 °C, 3 h, 74%.

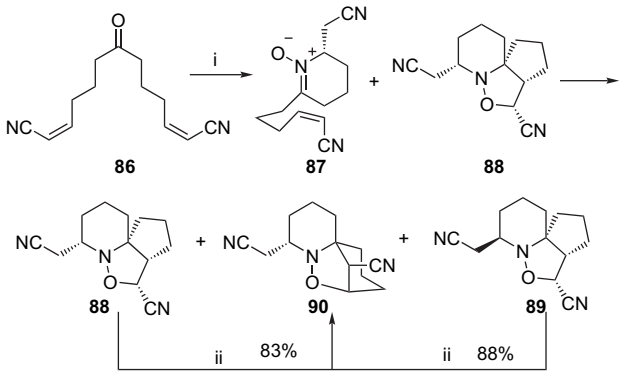


Scheme 17. (a) Toluene, 80 °C, 6 h; (b) 75 °C, 85%; (c) toluene, sealed tube, 190 °C, 3.5 h, 80%.

Dendrobates histrionicus. It is known to act as non-competitive inhibitor of nicotinic acetylcholine receptors and is also employed as probe to study neuromuscular signal transmission. In an enantioselective synthesis of (−)-histrionicotoxin by Holmes and co-workers, an imaginative use of the INC reaction is demonstrated. The cyclic nitrone **80** is generated by a hydroxylamine–alkyne cyclization and is protected as the cycloadduct **81** by treating with styrene. The side chain on isoxazolidine **81** was modified to install the α,β-unsaturated nitrile group. Compound **82** was heated in a sealed tube at 190 °C in toluene to promote the cycloreversion–dipolar cycloaddition sequence. The cycloadduct **84** was obtained as a single isomer in high yield and, in the process, all three chiral centers present in the natural product were fixed. The (*Z*)-enediyne units were installed using Stork's iodophosphorane methodology to complete the synthesis of **85** (Scheme 17).[30]

Holmes has reported another route employing the INC reaction for the synthesis of azaspirocycloundecane skeleton **90**,

which is the precursor of all of the known histrionicotoxin alkaloids (Scheme 18). Conjugate addition of the oxime derived from **86** to the α,β-unsaturated nitrile generates an equimolar mixture of the nitrone **87** and the kinetically favored cycloadduct **88**. Further heating of this mixture generally afforded a mixture of isoxazolidine derivatives **88–90**. The authors have optimized the conditions for the conversion of **88** and the epimer **89** into the required cycloadduct **90**.[31]



Scheme 18. (i) $NH_2OH·HCl$, NaOAc, MeOH, 25 °C; (ii) chlorobenzene, sealed tube, 180 °C.

Lepadiformine, a tricyclic indolizidine alkaloid, isolated from *Clavelina lepadiformis*, exhibits cytotoxic activity toward several tumor strains in vitro. In a convergent stereoselective synthesis by Weinreb, the indolizidine core of lepadiformine was prepared by the INC reaction of the cyclic nitrone **92**. The latter nitrone was derived from the linear acyclic oxime acetal **91**, which contains all of the carbon atoms necessary for the construction of the tricyclic core. The stable nitrone **92** was thermolyzed to obtain a single isoxazolidine cycloadduct **93**. The linking chain of the nitrone assumes a boat-like conformation and the dipolarophile approaches the nitrone from the face opposite to the bulky phenoxymethyl group. Amino alcohol **94**, derived by reduction of the isoxazolidines, was further elaborated into the target lepadiformine **95** (Scheme 19).[32]

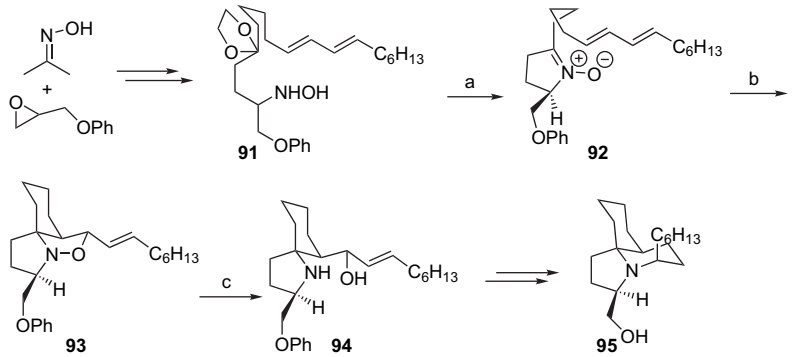
Pretazettine is a member of the crinine class of amaryllidaceae alkaloids, exhibiting antiviral and antitumor activities. An advanced intermediate for the synthesis of pretazettine was constructed by employing an intramolecular nitrone–olefin cycloaddition. Aldehyde **97** was treated with the oxalate salt of *N*-(α-methylbenzyl)hydroxylamine and base in benzene to afford the nitrone **98** as a 5:1 mixture of cis and trans isomers. The nitrone solution was then refluxed to furnish the diastereomeric cycloadducts in a 16:1 ratio. Interestingly, the stereoselectivity of this reaction is rather high when compared to that of similar nitrone–olefin cycloadditions (Scheme 20).[33]

Baldwin has recently employed the INC reaction to synthesize the amaryllidaceae alkaloids, (−)-haemanthidine **105**, (+)-pretazettine **106**, and (+)-tazettine **107**, from D-mannose in enantiopure form. Alkenylhydroxylamine **103** for the INC reaction was produced from the alkenyl acetal, which, in turn, was obtained from α-methyl-D-mannopyranoside. The dipolar cycloaddition was carried out by heating the crude nitrone **103** in benzene. The cycloadduct was further transformed into the alkaloid, (−)-haemanthidine **105**. (+)-Pretazettine **106** and (+)-tazettine **107** were sequentially synthesized from **105** by taking advantage of the well-established chemical relationship between these alkaloids (Scheme 21).[34]

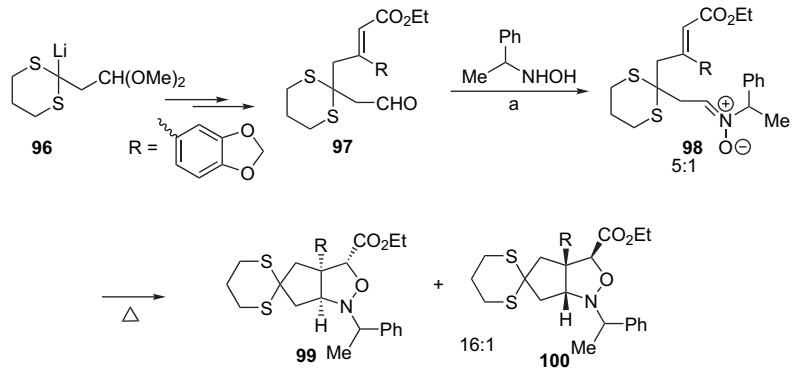
A synthesis of the 1-azaspiro[4.5]decane core found in cylindricine-type alkaloids has been accomplished by the INC reaction (Scheme 22). The stable cyclic nitrone **110** underwent cycloaddition when refluxed in benzene. Electronic effects caused by the presence of the silyl group at the alkene moiety controlled the regiochemistry.[35]

The azaspirocyclic core of pinnaic acid was also synthesized by White and co-workers by employing a transannular nitrone–olefin cycloaddition. Ring-closing metathesis (RCM) of **113** produced a diastereomeric mixture of the macrocyclic oxaziridine **115**. Simultaneous hydrolysis of the oxaziridine and the ketal afforded the hydroxylamine-ketone, which underwent an immediate condensation to afford the nitrone **117**. After chromatographic removal of the minor *Z*-isomer, a toluene solution of the nitrone was refluxed to furnish a single cycloadduct **118** (Scheme 23). Since the cyclic nitrone is not large enough to allow the nitrone oxygen to pass through the ring, the cycloaddition occurs preferentially at the rear face of the trans double bond. Hydrolysis of the lactone and reductive cleavage of the isoxazolidine afforded the dihydroxy amino ester representing the azaspirocyclic core structure of pinnaic acid **119**.[36]

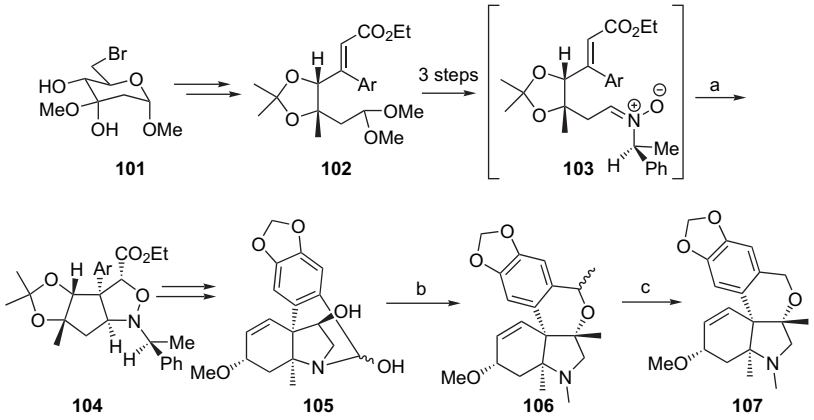
Kita has combined the kinetic resolution of a racemic hydroxynitrone with a subsequent dipolar cycloaddition to achieve a high enantioselectivity for the cycloadducts. He



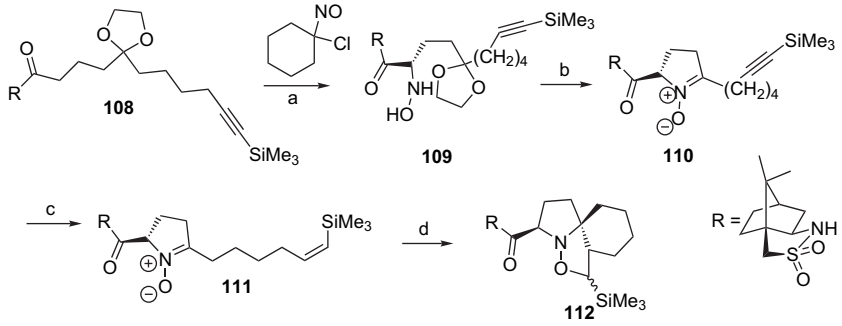
Scheme 19. (a) 3 N HCl, THF, 4 h, rt, 92%; (b) DMSO, 190 °C, 16 h, 63%; (c) Zn dust, AcOH, H_2O, 45 °C, 3 h, 91%.



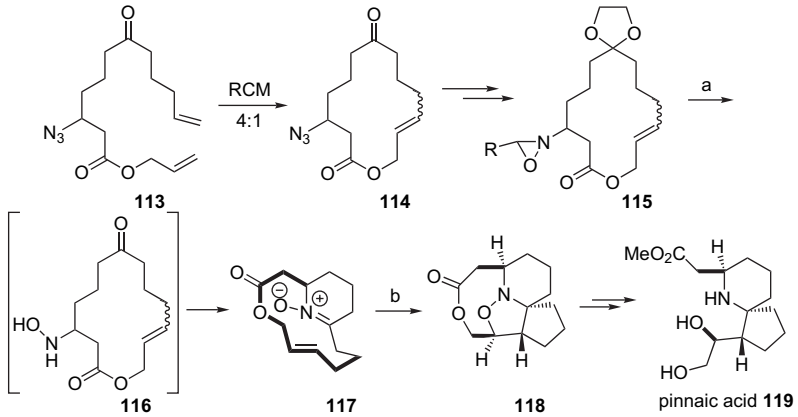
Scheme 20. (a) Benzene, K_2CO_3, rt.



Scheme 21. (a) Benzene, 80 °C, 65%; (b) MeI, MeOH, then HCl and $NaHCO_3$; (c) NaOH, MeOH.

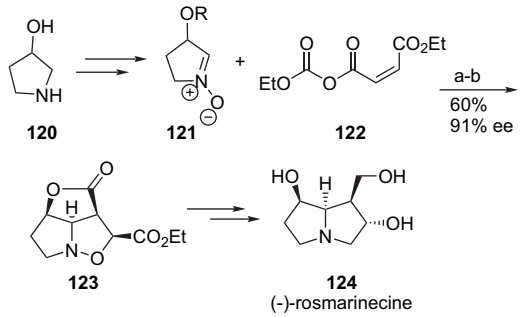


Scheme 22. (a) $NaN(SiMe_3)_2$, THF, −78 °C, then chloronitrosocyclohexane; (b) concd HCl; (c) Ni_2–B, H_2, MeOH; (d) benzene, 80 °C, 208 h.



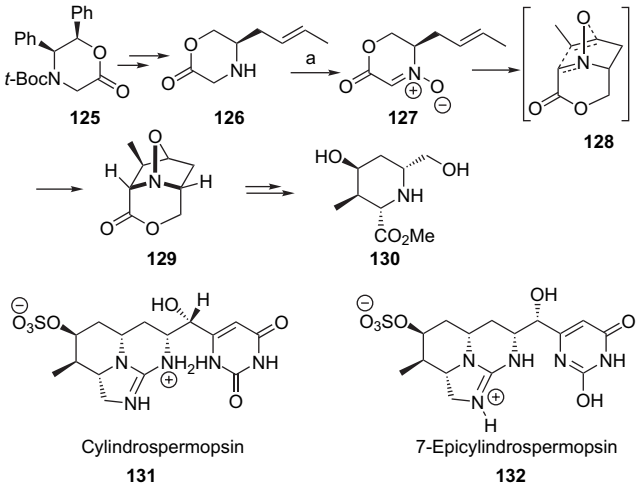
Scheme 23. (a) *p*-TsOH, MeOH/H_2O, 70%; (b) toluene, reflux, 64%.

employed this strategy for the catalytic enantioselective synthesis of (−)-rosmarinecine. The acyl donor **122** functionalized with the dipolarophile was used in the kinetic resolution of the nitrone **121** by *Candida antarctica* lipase fraction B (CAL-B). The enantio-enriched cycloadduct **123** was then used in the synthesis of (−)-rosmarinecine **124** (Scheme 24).[37]



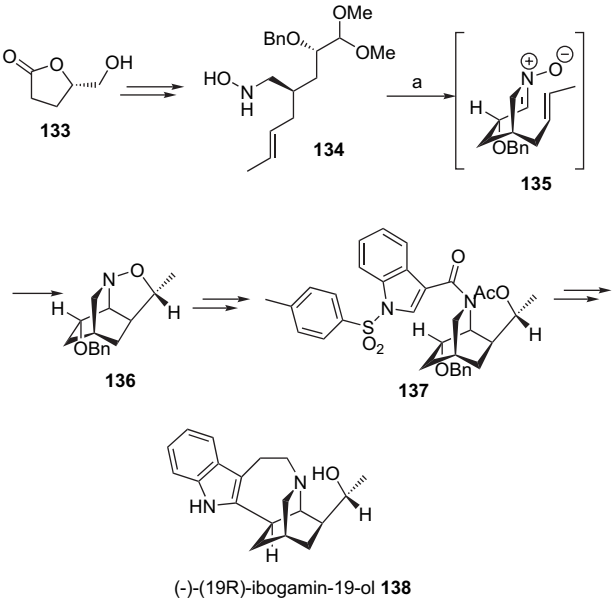
Scheme 24. (a) Ethoxyacetylene, $RuCl_2(p\text{-cymene})_2$, acetone; (b) CAL-B, MeCN.

Cylindrospermopsins are potent hepatotoxins. They inhibit the translational step of protein synthesis and are non-competitive inhibitors of uridine monophosphate synthesis complex. The construction of an A-ring synthon for the cylindrospermopsin **131** has been reported by Williams (Scheme 25). The INC reaction was employed to create three contiguous stereocenters in the target. Nitrone **127**, readily obtainable from the commercially available oxazinone **125**, on heating underwent cycloaddition to afford the adduct with the required stereochemistry, along with traces of a regioisomeric product. Reduction of the isoxazolidine **129** and further transformations afforded the target compound **130**.[38,39] Employing the same methodology, Williams and co-workers later reported a concise asymmetric synthesis of 7-epicylindrospermopsin **132**, a hepatotoxin, which is isolated from *Aphanizomenon ovalisporum*.[40]



Scheme 25. (a) Toluene, 200 °C, sealed tube, 78%.

(−)-(19*R*)-Ibogamin-19-ol is a monoterpene indole alkaloid obtained from *Tabernaemontana quadrangularis*. In its first enantioselective synthesis, the 2-azabicyclo[2.2.2]octane part was constructed by the stereoselective INC reaction of the nitrone **135** derived from hydroxylamine **134**, which, in turn, is made from L-glutamic acid and (+)-2-*S*-but-3-en-2-ol. The dipolar cycloaddition was achieved in the presence of acid and the isoxazolidine **136** was obtained in 67% yield (96:4) selectively (only the major isomer shown in Scheme 26). The *endo* product was obtained as the major isomer from *cis*-nitrone **136** intermediate, which reacts faster than the trans intermediate. Reductive cleavage and amide formation with indoleacetic acid furnished the intermediate **137**, which was further elaborated to complete the synthesis of the natural product **138**.[41]



Scheme 26. (a) 1.5 M H_2SO_4, 8 h, 47 °C, 67%, 96:4.

3. Nitrile oxides

Nitrile oxides are generally prepared by Mukaiyama reaction of primary nitro compounds with isocyanates[42] or by the oxidation of oximes with NaClO in the presence of a weak base.[43] Most nitrile oxides are very reactive and are often generated in situ to avoid dimerization. The cycloadducts, isoxazoles or isoxazolidines, are well-known precursors of amino alcohols and α-hydroxy cyclopentanones (Fig. 1).[44]

Albicanol is a drimane sesquiterpene isolated from *Diplophyllum albican* in 1997. In Fukumoto's approach to the synthesis of albicanol, a diastereoselective formation of the isoxazoline **142** from the alkenyl nitrile oxide **141**, which, in turn, is derived from (+)-Wieland–Miescher ketone **139**, has been employed. A chair-like conformation of the transition state devoid of any unfavorable non-bonding interactions contributes toward the diastereoselectivity. Reductive hydrolysis followed by methylenation afforded the optically pure albicanol **143** (Scheme 27).[45]

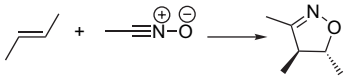
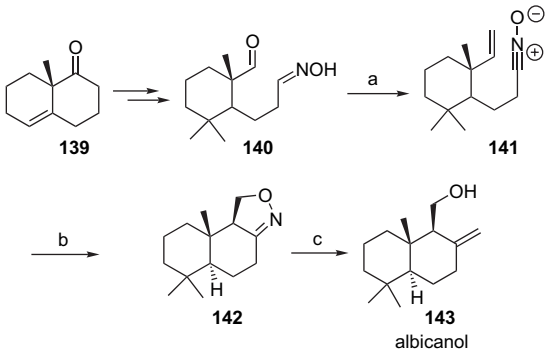


Figure 1.

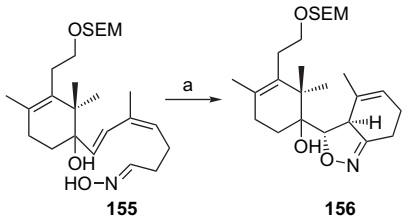


Scheme 27. (a) 7% aq NaOCl, 90%; (b) H_2, Raney-Ni, $B(OMe)_3$, 100%; (c) Zn, CH_2Br_2, $TiCl_4$, 60%.

Limonoids are degraded diterpenes, generally possessing a broad spectrum of biological activities. Azadiradione is a member of the limonoid group of havanensin. An intramolecular dipolar cycloaddition approach has been successfully employed in the synthesis of the CDE fragment of the insect antifeedant, 12-hydroxyazadiradione **151**. Apart from its potent biological activity, the target compound **151** could also serve as a precursor for *C*-secolimonoids. In the approach of Mateos and co-workers, α-cyclocitral **144** was subjected to routine synthetic manipulations to afford the oxime **145**, which was then treated with sodium hypochlorite to generate the corresponding nitrile oxide. The latter underwent cycloaddition to afford the isoxazoline **147** in 50% yield. Parallel operations involving the nitrile oxide generated from the nitro compound **146** afforded the isoxazoline **147** in 73% yield. Subsequently, the isoxazoline ring was cleaved to the hydroxy ketone **148** and further transformations led to the target compound **151** (Scheme 28).[46]

A crucial step in the synthesis of trehazolin **154**, an antibiotic pseudosaccharide, involved the nitrile oxide cycloaddition. The key step for the synthesis of the azide was the oxidation followed by the intramolecular [3+2] cycloaddition reaction of the oxime. Thus, the oxime **152** on treatment with NaOCl in triethylamine afforded the cycloadduct **153**, which is a key intermediate in the synthesis of trehazolin **154** (Scheme 29).[47]

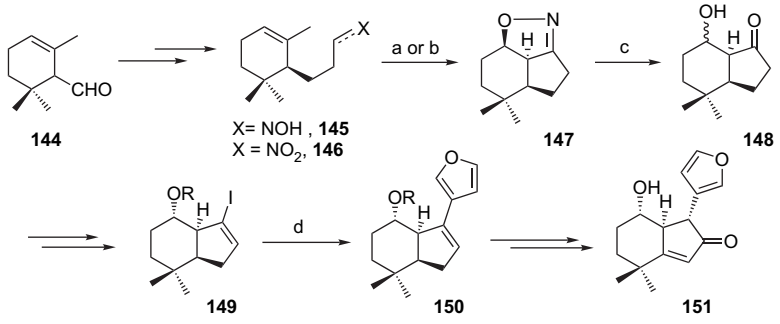
The construction of the C-ring of taxol was accomplished by Mioskowski and co-workers by the intramolecular [3+2] cycloaddition reaction of a nitrile oxide generated in situ. Thus, the oxime **155** on treatment with NaOCl furnished the tricyclic isoxazoline **156** as a separable mixture of diastereomers (4:1) in 46% yield (Scheme 30).[48]



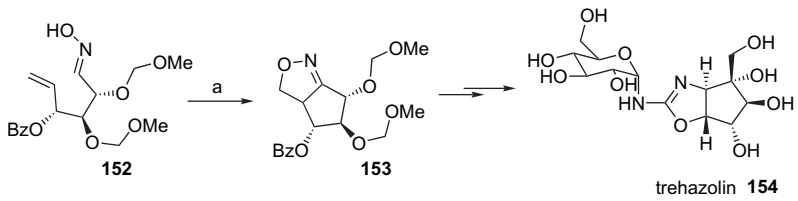
Scheme 30. (a) NaOCl, 46%.

Nicolaou has employed an intramolecular nitrile oxide–olefin cycloaddition to synthesize the urethane-cyclohexenone part of calicheamycinone, the enediyne antibiotic calicheamycin. Oxime **158** was accessed from tetronic acid in a few steps. Treatment of aldoxime **158** with aqueous sodium hypochlorite in dichloromethane afforded the diastereomeric cycloadducts **159** and **160** in a 4:1 ratio (65% combined yield) along with a small amount of the ester **161** (Scheme 31). Further transformations produced keto-isoxazole **162**, which was then employed in the synthesis of the target compound (Scheme 31).[49]

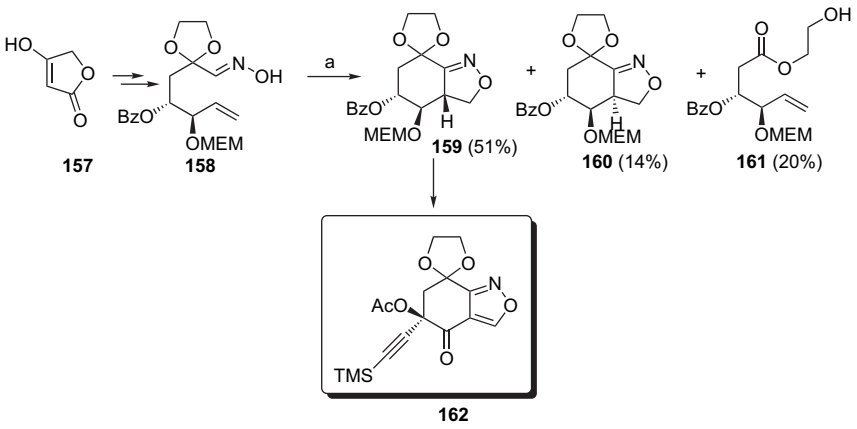
The intramolecular nitrile oxide cycloaddition (INOC) reaction plays a crucial role in the synthesis of the *trans*-hydrindane derivative **165**, a potential intermediate for the synthesis of the C_2-symmetric pentacyclic alkaloid,



Scheme 28. (a) NaClO, CH_2Cl_2 for **145**; (b) PhNCO, Et_3N, benzene, 25 °C for **146**; (c) Pd/C, H_2, AcOH, NaOAc; (d) LiCl, $Pd(PPh_3)_4$, Bu_3(3-furyl)Sn, THF, reflux, 60%.

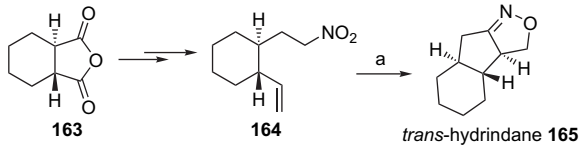


Scheme 29. (a) 5% NaOCl, Et_3N.



Scheme 31. (a) NaOCl, CH_2Cl_2, H_2O, 0 °C.

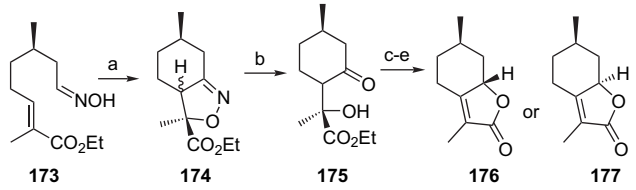
papuamine. Nitroalkene **164** was prepared from racemic anhydride **163** in a few steps. Nitrile oxide formed in situ by the reaction of **164** with PhNCO underwent cyclization to afford the racemic *trans*-hydrindane **165** (Scheme 32).[50]



Scheme 32. (a) PhNCO, benzene, 72%.

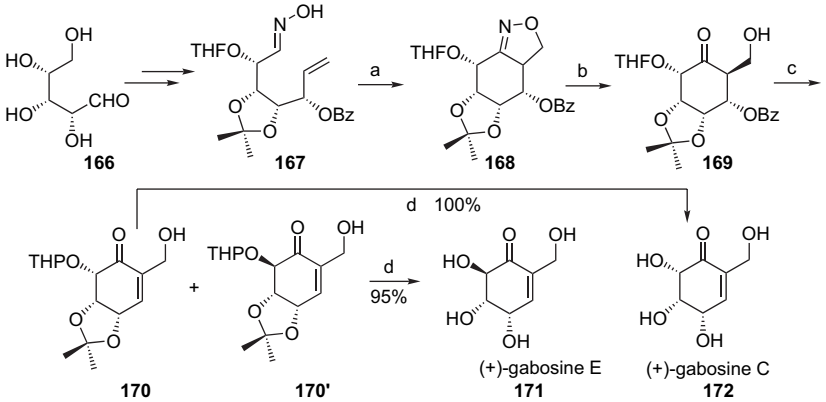
Gabosines C and E are two unusual carbo-sugars that, respectively, exhibit antibiotic and inhibitory activities toward the biosynthesis of cholesterol. An alkenyl oxime **167** derived from D-ribose is employed for the construction of the carbocyclic framework. The INOC reaction of the oxime **167** was conducted by exposing it to sodium hypochlorite, thereby affording the required oxazolidine **168**. The ketone functionality and the hydroxymethyl substituent at the C-2 position were then unmasked by the reductive cleavage of the oxazolidine. Elimination of benzoic acid with DABCO and deprotection of the hydroxyl groups completed the synthesis of gabosine C **172** and gabosine E **171** (Scheme 33).[51]

Butenolides, (−)-mintlactone **176** and (+)-isomintlactone **177**, were enantioselectively synthesized by employing the INOC reaction as the key step (Scheme 34). The generation and cycloaddition of the nitrile oxide from **173** were achieved by treating it with NaClO. The reaction yielded a diastereomeric mixture of isoxazolines in 86% yield (20:1). Catalytic hydrogenation followed by hydride reduction and subsequent dehydration afforded **176** and **177** (Scheme 34).[52]



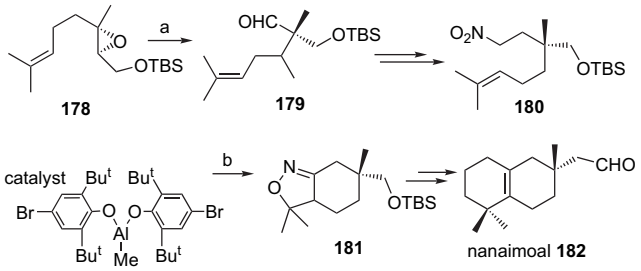
Scheme 34. (a) NaOCl, 84%, 20:1; (b) H_2, Raney-Ni, $B(OMe)_3$; (c) $Me_4NBH(OAc)_2$ for **176** and $Zn(BH_4)_2$ for **177**; (d) *p*-TSOH; (e) $POCl_3$, Py.

Shishido and Omodani reported the first enantioselective synthesis of the fragrant sesquiterpene, nanaimoal **182**, which is isolated from *Acanthodoris nanaimoensis*. Epoxide **178** was prepared by Sharpless asymmetric epoxidation of geraniol. Synthesis of the aldehyde **179** possessing a quaternary stereocenter was achieved by the rearrangement of the epoxide **178** with methylaluminum bis(4-bromo-2,6-di-*tert*-butyl)phenoxide. Chain extension of the aldehyde to nitroolefin **180** was followed by the generation of the nitrile oxide by treatment with isocyanate. A diastereomeric mixture of isoxazolidines was produced by the INOC reaction. Further reactions including the reductive cleavage of the



Scheme 33. (a) NaOCl, Et_3N, CH_2Cl_2, 60%; (b) H_2, Raney-Ni, EtOH, AcOH, 89%; (c) DABCO, THF, 80%; (d) TFA, CH_2Cl_2.

isoxazolidine and its transformation into the bicyclic system yielded the target compound **182** (Scheme 35).[53]

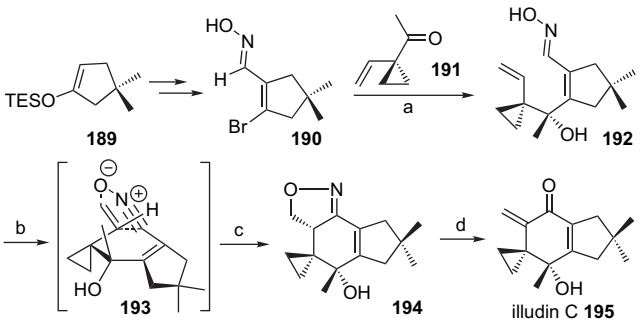


Scheme 35. (a) Catalyst, CH_2Cl_2, 97%; (b) *p*-ClC_6H_4NCO, Et_3N, benzene, 100%.

An unconventional approach to the antibiotic lactone, crassin acetate **188**, also involves the INOC reaction as a key step. Macrocycle **184** was constructed by the intramolecular alkylation of lithioalkyne derived from **183**, with allyl bromide. The secondary alcohol derived from the acetonide was converted into the nitro ether by usual synthetic protocols. Nitro derivative **185** was treated with phenyl isocyanate to generate the nitrile oxide, which underwent concomitant cycloaddition to form the tricyclic isoxazole **187** with newly formed stereocenters at C-1 and C-14 (Scheme 36).[54]

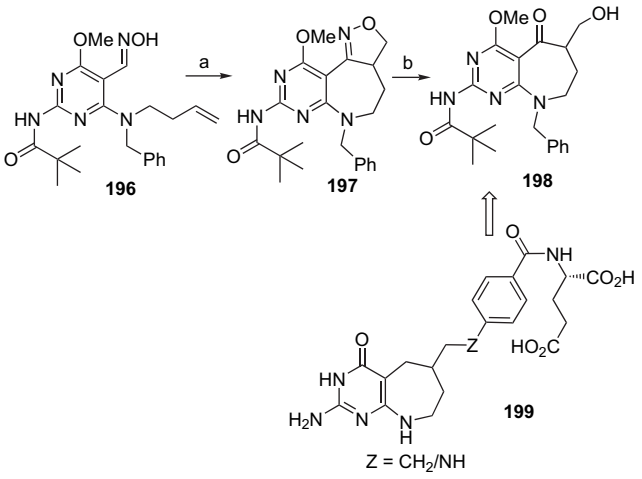
Illudins are a class of tricyclic sesquiterpenes isolated from several fungi. They differ in the number and position of hydroxyl substituents and the degree of unsaturation in the tricyclic framework. They exhibit varying degrees of antimicrobial and anticancer activities. In a concise synthesis of (±)-illudin C **195**, Funk has utilized an intramolecular nitrile oxide–olefin cycloaddition. The dianion generated from the oxime **190** was coupled to cyclopropyl ketone **191** to afford the oxime **192**, which serves as the precursor for the INOC reaction. The treatment of **193** with chloramine T afforded the isoxazoline **194** as a single stereoisomer in nearly quantitative yield. Isoxazole on reductive hydrolysis and dehydration afforded illudin C **195** in 8.2% overall yield (Scheme 37).[55]

Ray and co-workers synthesized a pyrimidoazepinone derivative by employing an INOC reaction. The target compound is a potential intermediate for the synthesis of pyrimidoazepine-based folic acid derivatives. Oxime **196** was treated with *N*-chlorosuccinimide to generate the



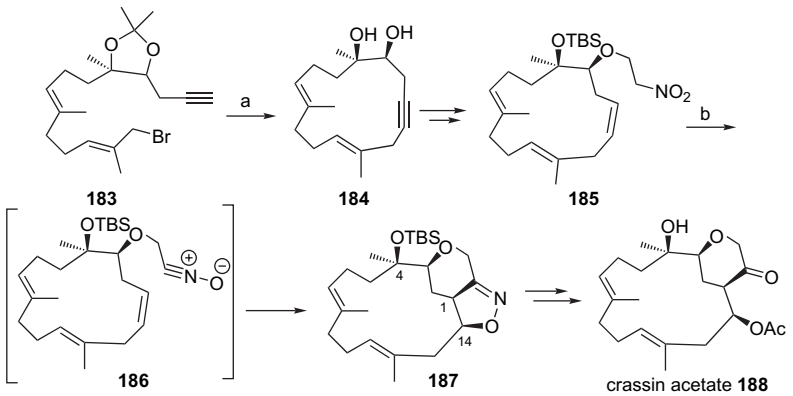
Scheme 37. (a) 3 equiv *t*-BuLi, THF, −78 °C, 68%; (b) chloramine T, EtOH, 40 °C, 99%; (c) Raney-Ni, H_2, $B(OH)_3$, MeOH, H_2O; (d) MsCl, Et_3N, CH_2Cl_2, DBU, rt, 73%.

corresponding oximoyl chloride. Subsequent addition of base effected the generation of the nitrile oxide and its cycloaddition with the terminal olefin. Isoxazoline **197** was then reductively cleaved to afford the hydroxy ketone **198**. Later, they utilized an INOC reaction of oxime with alkyne to construct the oxazole-fused pyrimidoazepine derivative (Scheme 38).[56,57]

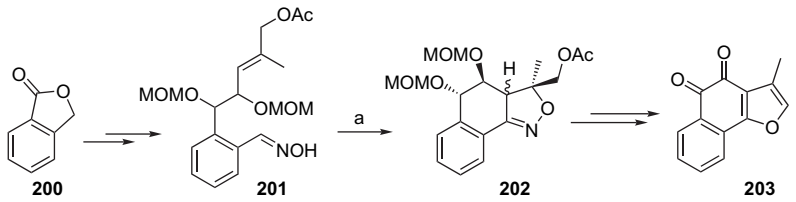


Scheme 38. (a) NCS, CH_2Cl_2, rt, then Et_3N; (b) Raney-Ni, MeOH, AcOH, H_2, 44%.

Tanshinones are quinoidal abietane-derived diterpenes, which constitute the active principle of certain traditional Chinese medicines for the treatment of coronary heart,



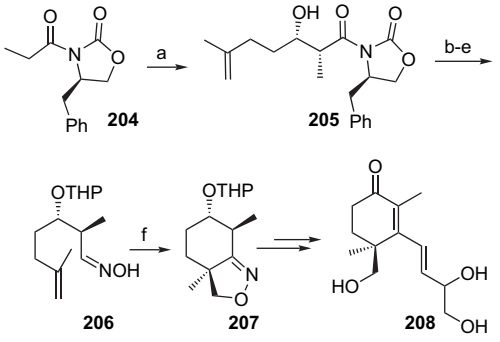
Scheme 36. (a) $LiN(TMS)_2$, THF, 74%, then H_3O^+, 92%; (b) PhNCO, Et_3N, benzene, 80 °C, 74%.



Scheme 39. (a) 7% NaOCl, CH_2Cl_2, 100%, 5.3:1.

cerebrovascular diseases, and neurasthenic insomnia. The tricyclic framework of tanshinones was constructed by the INOC reaction of oxime acetate **201** as a key step, the latter compound being obtained from phthalide **200**. Treatment of **201** with NaOCl quantitatively furnished the isoxazolines **202** as separable diastereomers in a ratio of 5.3:1. Reductive cleavage of the isoxazoline, acid-catalyzed cyclization to form the furan ring, and subsequent oxidation using Fremy's salt afforded *ortho*-quinone **203** (Scheme 39). The tricyclic ring system **203** is the common structural unit (BCD rings) found in the tanshinones.[58]

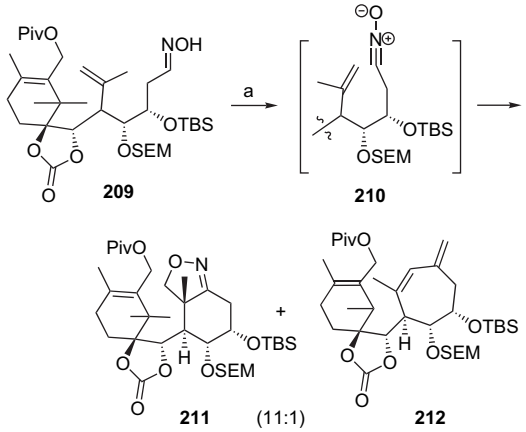
Cassiol **208** is an aglycon of the antiulcerogenic natural product, cassioside. Shishido reported an enantioselective synthesis of (+)-cassiol using INOC strategy for the construction of the cyclohexenone core possessing an asymmetric quaternary carbon center (C-4). Starting from *N*-acyl oxazolidinone **204**, the optically pure oxime **206** was made by a sequence involving an Evans asymmetric aldol condensation, reduction, oxidation, and condensation with NH_2OH. Oxime **206** on treatment with aqueous NaOCl at room temperature underwent an INOC reaction to yield the isoxazole **207** as a single isomer in 88% yield. The introduction of the carbon chain at the C-3 position completed the synthesis of cassiol (Scheme 40).[59]



Scheme 40. (a) *n*-Bn_2BOTf, *i*-Pr_2NEt, 4-methylpent-4-enal, CH_2Cl_2, −78 °C; (b) 2,3-dihydropyran, PPTS, CH_2Cl_2; (c) $LiAlH_4$, THF; (d) Swern oxidation; (e) $NH_2OH{\cdot}HCl$, AcONa, MeOH, rt; (f) 7% aq NaOCl, CH_2Cl_2, rt, 88%.

Takahashi and co-workers have reported the use of the cycloaddition of the nitrile oxide for the synthesis of the C-ring of paclitaxol. The advanced intermediate **209** containing the A-ring was treated with NaClO to generate the nitrile oxide **210**, which underwent an INOC reaction to afford the adduct **210**. A minor amount of an undesired seven-membered ring product **212** was also formed via a cationic cyclization (Scheme 41).[60]

An interesting synthetic approach to bisisoxazolidine-substituted pyridinone tetracycles has been reported. The



Scheme 41. (a) NaClO, CH_2Cl_2, 0 °C, Et_3N, 95%.

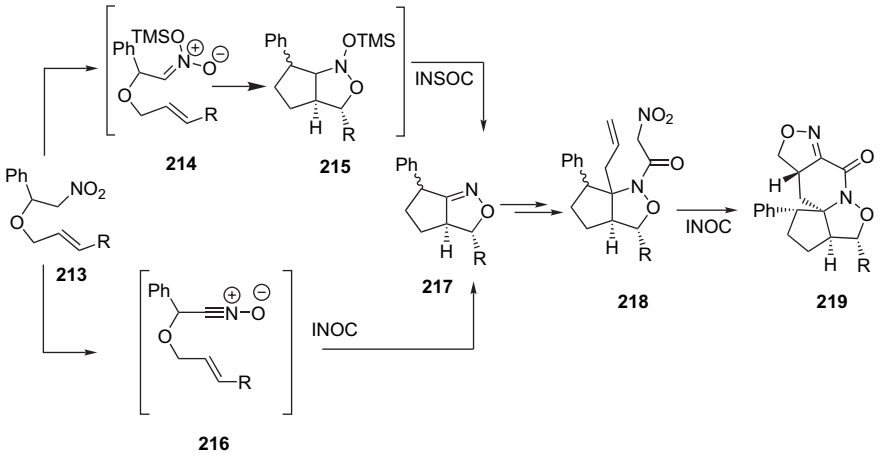
reaction sequence employs either an intramolecular silyl nitronate olefin cycloaddition (INSOC) or an INOC as the key transformation. The second oxazoline ring was constructed by another INOC reaction at a later stage (Scheme 42).[61]

4. Carbonyl ylides[62]

Carbonyl ylides can be generated in situ by thermolysis or photolysis of oxiranes[63a–c] and 1,3,4-oxazolidines.[63d–f] Another well-documented method for the generation of carbonyl ylides involves the rhodium-catalyzed decomposition of α-diazoketones containing another carbonyl group.[64] Oxazolin-4-one is a mesionic carbonyl ylide. Oxidopyrilium ylides available from pyrones also belong to this group (Fig. 2).[65] Carbonyl ylides are generally very reactive and undergo facile dipolar cycloaddition with alkenes and alkynes.[66]

The oxo-bridged tricyclic ring system is the basic structural unit of phorbol. The latter compound is a member of the tigliane family of diterpenes and has been known to possess tumor-promoting activity. The basic tricyclic ring system of phorbol has been synthesized in one step from olefin-tethered diazoketone **221** via an IDC reaction (Scheme 43). The significance of this reaction lies in the formation of an isomer with the correct stereochemistry of the newly formed stereocenters present in the phorbol skeleton.[67]

Pseudolaric acids A and B are two cytotoxic diterpenes identified as the active principles of traditional Chinese medicine. These closely related compounds are characterized by the presence of a perhydroazulene skeleton bearing trans-fused acetoxy and lactone groups. The basic structural framework of pseudolaric acids was constructed by



Scheme 42.

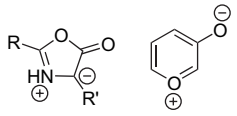
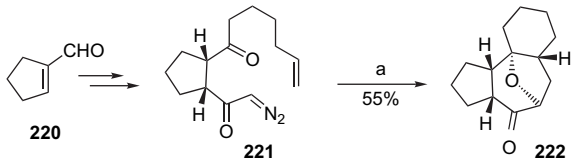
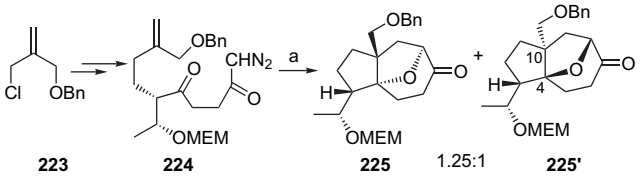


Figure 2.



Scheme 43. (a) $Rh_2(OAc)_4$, CH_2Cl_2.

employing a rhodium-catalyzed cycloaddition of chiral diazoketone **224**. The required trans disposition at C-4 and C-10 was achieved during an IDC reaction (Scheme 44).[68]



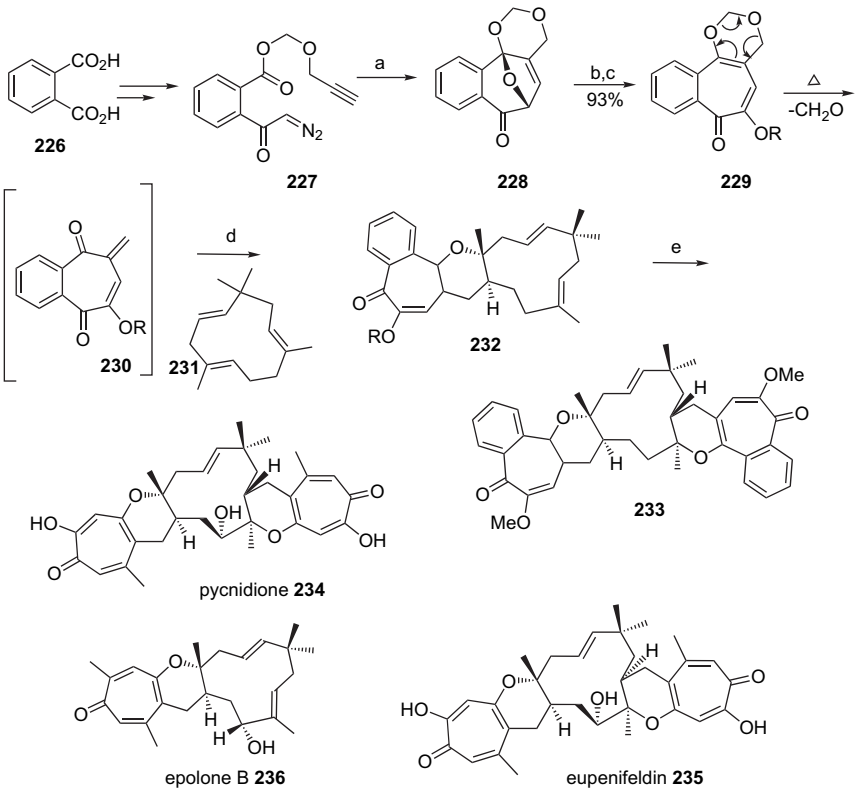
Scheme 44. (a) 1% $Rh_2(OAc)_4$, benzene, rt, 66%.

Pycnidione **234**, eupenifeldin **235**, and epolone B **236** are members of a family of tropolone fungal metabolites known to possess important biological activities. These compounds are structurally similar, with an identical tropolone ring attached to sesquiterpene backbones. Baldwin employed an intramolecular dipolar cycloaddition of a carbonyl ylide to a pendant alkyne for the construction of the tropolone moiety in the synthesis of pycnidione and epolone B analogues. Phthalic acid was transformed into α-diazoketone **227** in two steps. The latter ketone on treatment with $Rh_2(OAc)_4$ in dichloromethane afforded the tetracyclic ring system via the IDC reaction of the carbonyl ylide with the terminal acetylene. Acid-catalyzed cleavage of the oxa-bridge afforded the benzotropolone derivative. The natural product analogues were then synthesized by generating reactive quinone-methides from the benzotropolone intermediate and trapping with humulene in successive Diels–Alder reactions (Scheme 45).[69]

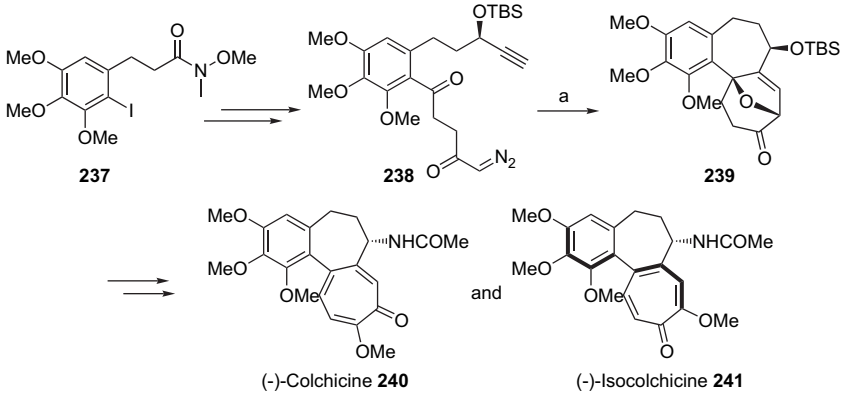
Colchicine is an important alkaloid isolated from meadow saffron and is known to exhibit powerful antimitotic activity. Schmaltz and co-workers have applied a rhodium-catalyzed IDC reaction as the pivotal step in a total synthesis of (−)-colchicine. The key substrate for the domino sequence was prepared from the bifunctional building block **237**. Enantioselective transformation of Weinreb amide unit to the propargyl alcohol derivative and aromatic acylation produced the diazoketone **238**. The $Rh_2(OAc)_4$-triggered intramolecular dipolar cycloaddition of the α-diazoketone **238** with the unactivated alkyne was carried out in toluene at 110 °C to afford the oxatetracyclic compound **239** with nearly complete diastereoselectivity. Having completed the carbon skeleton, the conversion of the C-ring into the α-oxygenated tropolone and the conversion of the oxygen functionality of the B-ring into the acetamide were realized by a series of conventional reactions. The overall yield of (−)-colchicine **240** and (−)-isocolchicine **241** was approximately 1% over 15 steps (Scheme 46).[70]

Recently, Padwa and co-workers synthesized [6.3.1.$0^{0,0}$]-dodecanedione substructure of the icetexane diterpene, komaroviquinone, known for its trypanocidal activity. On treatment with Rh(II) at room temperature, **243** produced epoxyindanone **244**, which, on thermolysis, gave 9,10-benzo-12-oxatricyclo[6.3.1.$0^{0,0}$]dodecanedione **245**. Reaction of **243** at elevated temperature directly afforded **245** as the sole product. Enhanced reactivity was observed, due to the *gem*-dialkyl effect with the substrate having two methyl substituents (R=Me, in **245b**) (Scheme 47).[71]

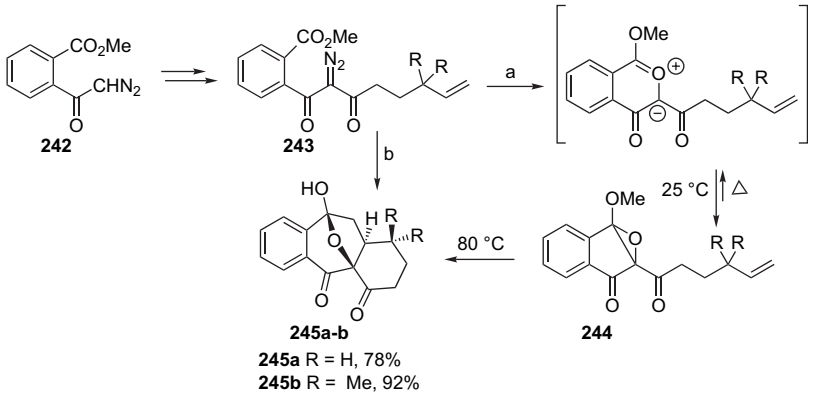
Ergot alkaloids isolable from the ergot fungus *Claviceps purpurea* are famous for their activity in the treatment of hypertension, migraine, and prolactin-dependent disorders. Lysergic acid diethylamide (LSD) is a powerful hallucinogen belonging to this family. Lysergic acid was first isolated by Stoll, and enormous efforts by several groups on the synthesis of this molecule have been reported. Padwa and co-workers applied the IDC reaction of isomünchnone to the alkenyl group for the construction of the CD ring of lysergic acid. Isomünchnone precursor **246** was assembled



Scheme 45. (a) $Rh_2(OAc)_4$, CH_2Cl_2, rt, 74%; (b) 6 N HCl, dioxane, 93%; (c) NaH, MeI, DMF, 73%; (d) *p*-xylene, 150 °C, 60%; (e) *p*-xylene, 150 °C, **231** (4 equiv), 20%.

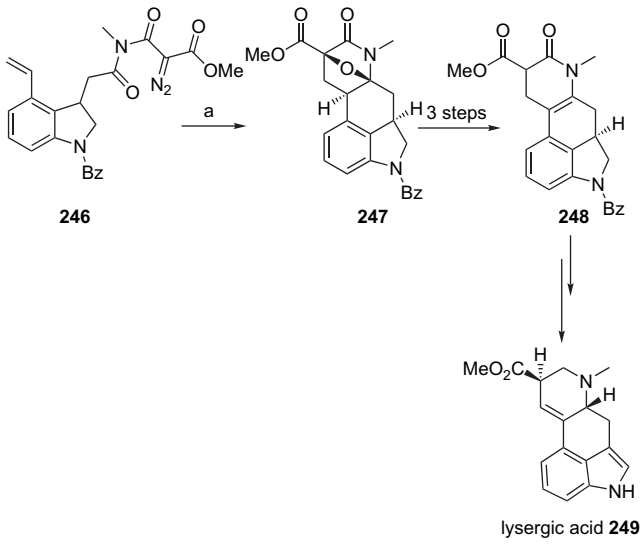


Scheme 46. (a) $Rh_2(OAc)_4$, toluene, 110 °C, 7 h, 98% de.



Scheme 47. (a) Rh(II), 25 °C; (b) Rh(II), 80 °C.

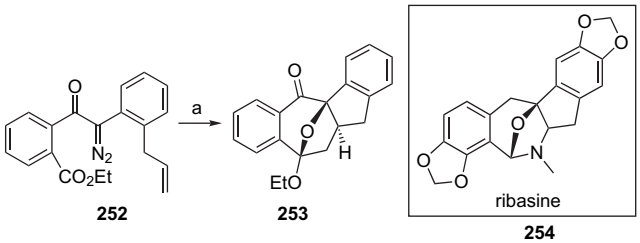
from the tricyclic olefin in eight steps. It underwent a cycloaddition and insertion reaction in the presence of $Rh_2(pfb)_4$. Notably, the reaction showed more chemoselectivity and a faster rate compared to that using $Rh_2(OAc)_4$. Cleavage of oxabicycle followed by Barton–McCombie reaction afforded lysergic acid (Scheme 48).[72]



Scheme 48. (a) $Rh_2(pfb)_4$, CH_2Cl_2.

Padwa and co-workers have investigated extensively the intramolecular dipolar cycloaddition of push–pull carbonyl ylides generated by the action of rhodium(II) on diazoimides. The strategy was employed for the construction of the pentacyclic skeleton of aspidosperma family of alkaloids. Diazoimide **250** derived from 3-carboxy-3-ethyl-2-piperidone and *N*-methyl indol-3-acetyl chloride was treated with $Rh_2(OAc)_4$. The resulting rhodium carbenoid underwent cyclization to generate the carbonyl ylide, which spontaneously reacted with the indole double bond to afford the pentacyclic derivative **251**. The cycloaddition reaction created four new stereocenters with complete diastereoselectivity. The diastereoselectivity is the consequence of an *endo* addition with regard to the dipole and this is also in accord with the lowest-energy transition state. Further transformations of the highly oxygenated polycyclic system **251** afforded a key intermediate of vindoline (Scheme 49).[73]

A successful attempt toward the synthesis of oxabicyclo-[3.2.1]octane ring of (±)-ribasine **254** was made by Padwa and co-workers (Scheme 50). *o*-Allylphenyl-substituted α-diazoketone **252** underwent an IDC reaction by the formation of the cyclic carbonyl ylide along with dipolar cycloaddition of the diazo group in the presence of $Rh_2(tfa)_4$. Incorporation of an aldehyde group instead of ethoxycarbonyl and an imino group for the alkenyl moiety would provide the exact core structure of ribasine.[74]

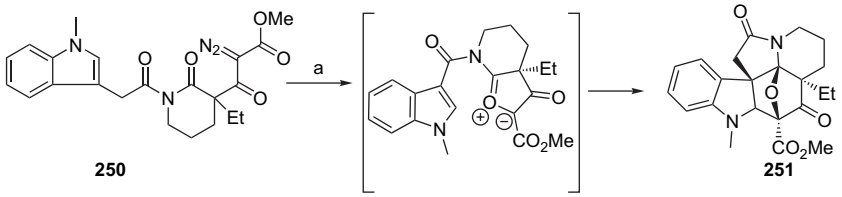


Scheme 50. (a) $Rh_2(tfa)_4$, toluene, 110 °C.

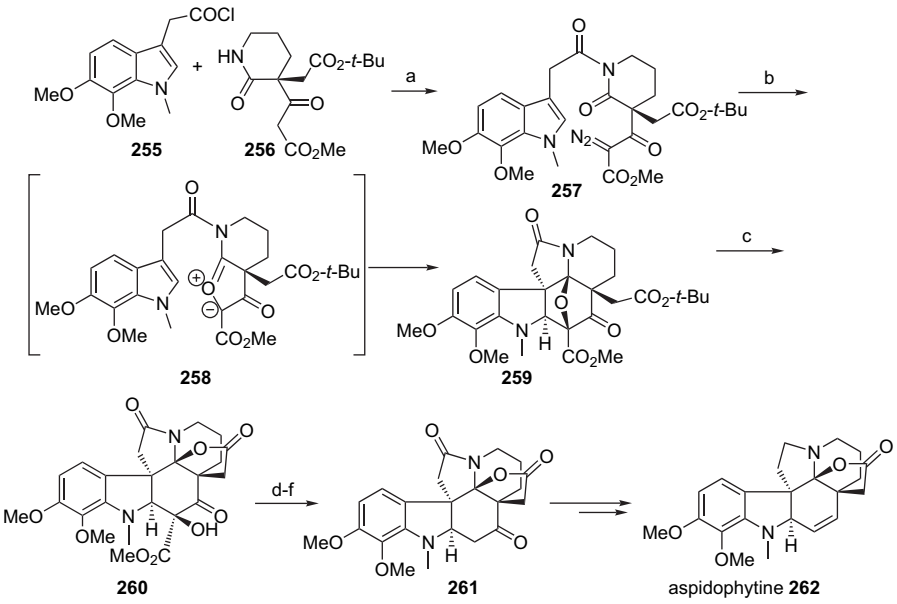
(±)-Aspidophytine **262** is a member of the family of aspidosperma alkaloids. These alkaloids possess a common pentacyclic framework and show diverse biological activities. Synthesis of aspidophytine has been reported by Corey and later by Fukuyama. Recently, Padwa and Oneto employed the IDC reaction as a key step for the construction of the aspidosperma skeleton. Diazoimide **257** was prepared by the coupling of acid chloride **255** and diazolactam **256**. In the crucial $Rh_2(OAc)_4$-catalyzed reaction, the diazoimide **257** underwent carbonyl ylide cycloaddition with the indole ring to afford the pentacyclic indane ABCDE framework. The IDC reaction furnished a single isomer **259** with the required stereochemistry at the newly formed four stereocenters. Acid treatment of **259** afforded the lactone **261**, which was transformed into aspidophytine **262**, by routine protocols (Scheme 51).[75]

Very recently, Padwa extended the IDC reaction of push–pull carbonyl ylides to the synthesis of hexacyclic frameworks associated with kopsifoline alkaloids. These are structurally related to, and possibly derived from, aspidosperma alkaloids. Diazoketone **263** was subjected to rhodium-catalyzed decomposition to afford the cycloadduct **264** as a single isomer. Further synthetic transformations were carried out to construct the hexacyclic skeleton **265** of the kopsifoline alkaloid (Scheme 52).[76]

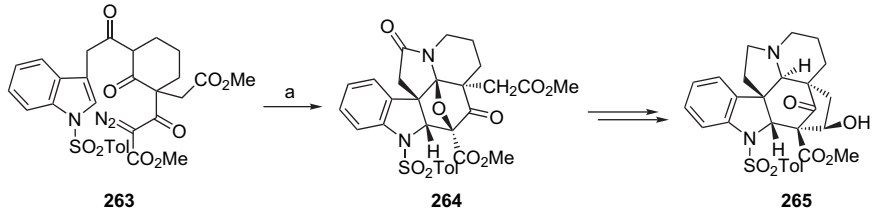
Boger reported the synthesis of both isomers of vindoline **272** by a tandem intramolecular [4+2]/[3+2] cycloaddition cascade reaction. The intramolecular Diels–Alder reaction of the alkene-tethered 1,3,4-oxadiazole **269** followed by the loss of nitrogen furnished the carbonyl ylide **270**, which underwent an *endo* stereoselective dipolar cycloaddition with the indole ring to form the pentacyclic core having six contiguous stereocenters. Substrate **269** for the tandem cycloaddition was prepared from *N*-methyl-6-methoxytryptamine **266**. It is noteworthy that vindoline constitutes the most complex half of vinblastine and vincristine, the two bisindole alkaloids clinically used as antineoplastic drugs (Scheme 53).[77]



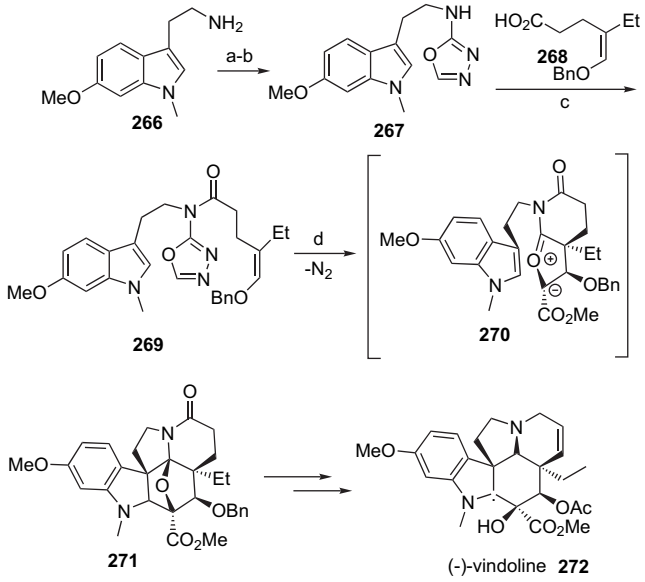
Scheme 49. (a) $Rh_2(OAc)_4$, benzene, 50 °C, 95%.



Scheme 51. (a) MS 4 Å, 92%; (b) $Rh_2(OAc)_4$, 97%; (c) $BF_3 \cdot OEt_2$, 70%; (d) MgI_2, MeCN, 75%; (e) AcCl, Et_3N; (f) SmI_2, 90%.



Scheme 52. (a) $Rh_2(OAc)_4$, benzene, 80 °C, 98%.



Scheme 53. (a) CDI, $H_2NNHCOCO_2Me$; (b) TsCl, Et_3N; (c) EDCI, DMAP; (d) 1,3,5-triisopropylbenzene, 230 °C.

5. Azomethine imines and azomethine ylides

Azomethine ylides are precursors to pyrrolidines, dihydropyrroles, and pyrroles.[78] They have been generated by thermolysis or photolysis of aziridines, fluorine-mediated desilylation protocols, and by the deprotonation of the imines derived from α-amino acids.[79] Azomethine imines act as precursors to pyrazolidines and have been prepared by the reaction of 1,2-disubstituted hydrazines with carbonyl compounds (Fig. 3).[80]

An intramolecular azomethine imine–alkene cycloaddition has been employed for the synthesis of a differentially protected trifunctional spiro-diamino acid scaffold, which finds use in combinatorial synthesis. The sequence of events involves an intramolecular Michael addition of hydrazone **273** to afford the azomethine imine **274**, which then reacts with the terminal olefin in an intramolecular dipolar cycloaddition to afford the tricyclic pyrazoline **275**. Reductive cleavage of the N–N bond and further routine synthetic manipulations afforded spiro-diamino acid **276** in 30% overall yield from **273**. The ketone precursor of **273** can be directly transformed into **275** in one-pot by treating with *tert*-butyl carbazate, albeit in lower yield (Scheme 54).[81]

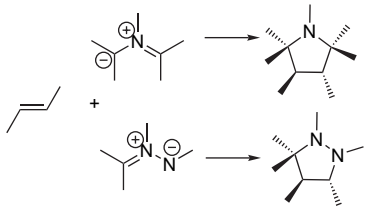
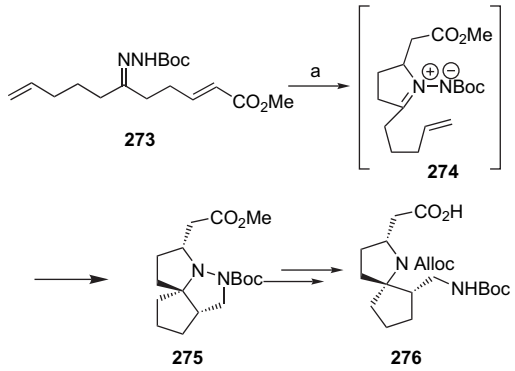
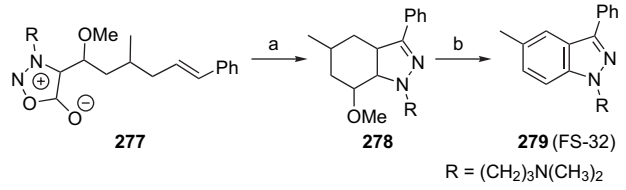


Figure 3.



Scheme 54. (a) EtOH, reflux, 72 h, 75%.

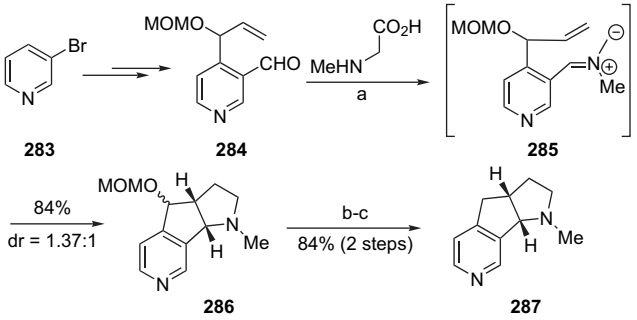
1-[3-(Dimethylamino)propyl]-5-methyl-3-phenyl-1*H*-indazole (FS-32) **279** is a reserpine antagonist and it also potentiates amphetamine-induced self-stimulation and L-dopa-induced increase in motor activity. The fused pyrazole core of FS-32 has been prepared by the intramolecular dipolar cycloaddition (IDC) reaction of a 3-alkyl sydnone **277**, which serves as a masked azomethine imine moiety with an alkene tether. Substrate **277** on boiling in xylene underwent the IDC reaction, followed by a rapid aromatization with the ejection of CO_2, finally resulting in the formation of the fused pyrazole **278**. The cyclohexane ring was oxidized under air using Pt/C, $HClO_4$, and acetic acid to complete the synthesis of the pyrazole-ring system (Scheme 55).[82]



Scheme 55. (a) Xylene, 130 °C, 46%; (b) Pt/C, air, $HClO_4$, AcOH.

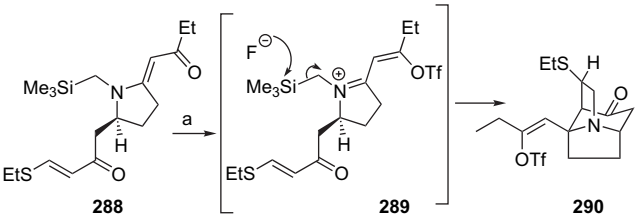
Overman reported the synthesis of triazacyclopenta[*cd*]pentalenes **282** by the IDC reaction of azomethine imines. The dipole was generated by the condensation of dihydropyrrole α-ketoester **280** with thiosemicarbazide. The construction of the target ring system is a crucial step in the synthesis of complex guanidine alkaloids such as palaúamine and stylo-guanidine. It is noteworthy that the IDC reaction exhibits a good degree of functional-group tolerance (Scheme 56).[83]

A facile construction of the hexahydropyrrolo[3,2-*f*]pyridine tricyclic framework has been achieved in six steps. The target heterocyclic system **287** is a conformationally restricted nicotinoid and assumes importance as potential nicotinic acetylcholine receptor (nAChR)-targeting ligand. Starting from 3-bromopyridine, the aldehyde **284** was constructed in three steps. Treatment of **284** with sarcosine in DMF at 100–110 °C generated the azomethine ylide **285**, which was intercepted by the pendant alkene. The intramolecular dipolar cycloaddition afforded a pair of diastereomers **286** (1.37:1) in 84% yield. Subsequent reductive dehydroxylation by zinc and formic acid produced the target compound **287** (Scheme 57).[84]



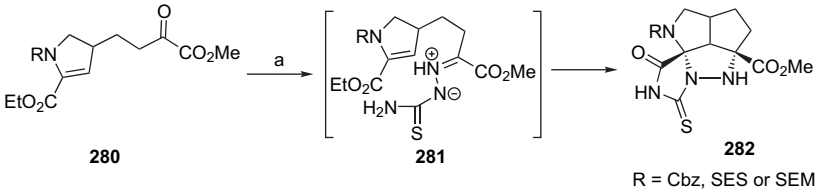
Scheme 57. (a) DMF, heat; (b) HCl, 60 °C; (c) Zn, AcOH.

Epperson and Gin have accomplished the enantiospecific synthesis of the bridged aza-tricyclo[5.3.0.0^{4,8}]decane core of asparagamine A, a pyrrolizidine alkaloid isolated from *Asparagus racemosus* showing potent antioxytocin activity. They employed the optically pure *N*-trimethylsilylmethyl vinylogous amide **288**, synthesized from an L-glutamic acid derivative, as the precursor for the azomethine ylide **289**. The latter ylide was generated by treating **288** with Tf_2O followed by tetrabutylammonium triphenyldifluorosilicate (TBAT). An intramolecular cycloaddition reaction initiated by *Z*-enol triflate formed exclusively then generated the bridged pyrrazolidine core **290** with an angular *C*8-*E*-butenyl substituent in 51% yield with complete regio- and stereospecificity (Scheme 58).[85]



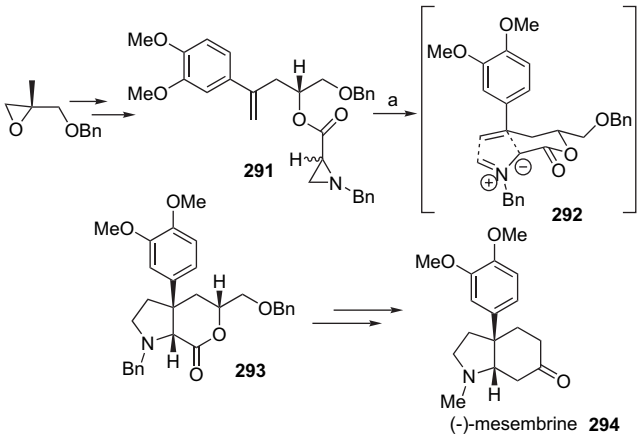
Scheme 58. (a) Tf_2O, $CHCl_3$, 23 °C, TBAT, 65 °C, 24 h, 51%.

Employing the IDC reaction of an azomethine ylide, Takano accomplished the total synthesis of (−)-mesembrine **294**, an alkaloid obtained from *Sceletium namaquense*. Thermolysis of aziridine ester **291** in xylene afforded pyrrolidine lactone **293** in 85% yield. The reaction is noteworthy for the



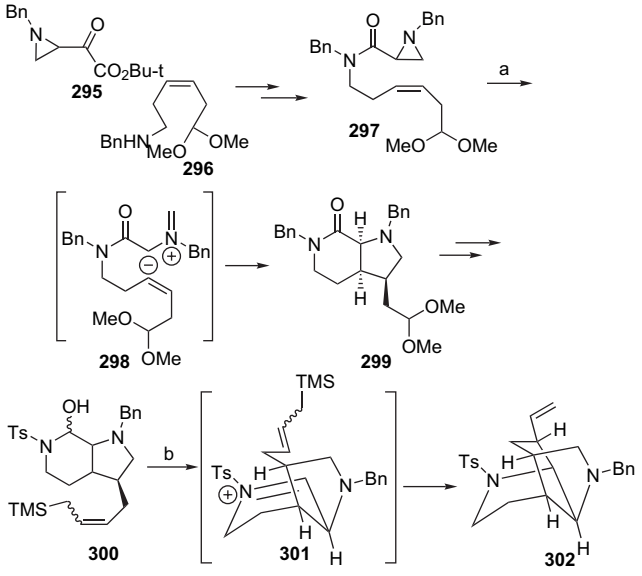
Scheme 56. (a)$NH_2NHCSNH_2$, AcOH, 70 °C.

stereoselective formation of three new chiral centers, including a tertiary carbon. The bulky benzyloxymethyl group occupies the equatorial position in the transient azomethine ylide **292**, thus leading to the formation of a single isomer **293**. Lactone **293** is then converted into (−)-mesembrine **294** and its *N*-methyl derivative through a synthetic sequence involving eight steps (Scheme 59).[86]



Scheme 59. (a) Xylene, sealed tube, 250 °C, 20 min.

Sarain A is a polycyclic alkaloid of marine origin possessing a unique structural array unprecedented in natural products. The tightly fused central tricyclic core of sarain A was constructed by Weinreb and co-workers by employing an intramolecular azomethine ylide–alkene cycloaddition.[87a] Thermolysis of the aziridine moiety in substrate **297** generated a transient azomethine ylide, which subsequently cyclized to afford the adduct **299** in 73% yield (Scheme 60). Interestingly, the efficiency of the cycloaddition was heavily dependent on the nature of the protecting groups on the amide nitrogen and side-chain oxygen. The cycloadduct was then transformed into the allylsilane derivative **300**. Ferric chloride-catalyzed cyclization of the allylsilane onto the *N*-acyliminium species afforded **302**, the tricyclic core



Scheme 60. (a) *o*-Dichlorobenzene, 320 °C, 78%; (b) $FeCl_3$, CH_2Cl_2, −78 °C to rt, 61%.

of Sarain A (Scheme 60). Very recently, Weinreb and co-workers have prepared an advanced intermediate for the total synthesis of sarain A employing a similar strategy.[87b] It is noteworthy that Heathcock had also employed a similar dipolar cycloaddition route to construct the core structure of sarain.[87c,d]

Ogasawara and co-workers have developed a synthetic route to both enantiomers of necine base, dihydroxyheliotridane, starting from (*R*)-*O*-benzylglycidol. The diastereofacial selectivity of the dipolar cycloaddition reaction is controlled by the tether length between the dipole and dipolarophile. The homoallylic aziridinic ester **303a** rapidly transformed into azomethine ylide at 260 °C in diphenyl ether and underwent the IDC reaction to afford δ-lactone **305** along with its 2,3 epimer **305′**. The stereochemical outcome is consistent with the involvement of a chair-like transition state **304**. The allylic aziridine ester **303** underwent the IDC reaction under similar conditions, however, presumably through an envelope-like transition state **306**, as it contains a shorter chain, and afforded γ-lactones **307** and **308** with opposite diastereofacial selectivity. δ-Lactone **305** was further elaborated to complete the synthesis of (−)-dihydroxyheliotridane **309**. The other enantiomer, (+)-dihydroxyheliotridane **309′**, was obtained from the γ-lactone **307** (Scheme 61).[88]

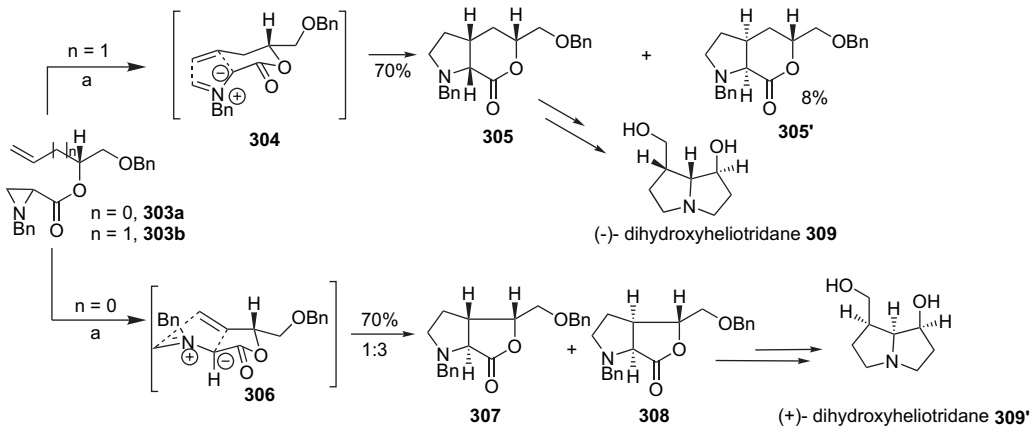
Pandey and co-workers reported a formal total synthesis of (±)-pancracine, which belongs to 5,11-methanomorphanthridine family of alkaloids, utilizing the azomethine IDC reaction (Scheme 62).[89a] The precursor for the IDC reaction was prepared by N-alkylation of α,α-bis(trimethylsilyl)alkylamine **311** with diiodide **310** and further Heck coupling with MVK. The non-stabilized azomethine ylide **314** was generated by the AgF-mediated double desilylation of **313**. The sterically favored *endo* attack of the azomethine ylide on the alkene furnished the 5,11-methanomorphanthridine skeleton with suitable side chains at C-4 and C-11. Hydrolysis of the benzoyl group, mesylation, and subsequent ring closure via the kinetic enolate of the methyl ketone afforded a pentacyclic derivative. Olefin **316** obtained by the reductive elimination of the ketone has been employed as a key intermediate in Overman's total synthesis of (±)-pancracine.[89b,c]

6. Azides

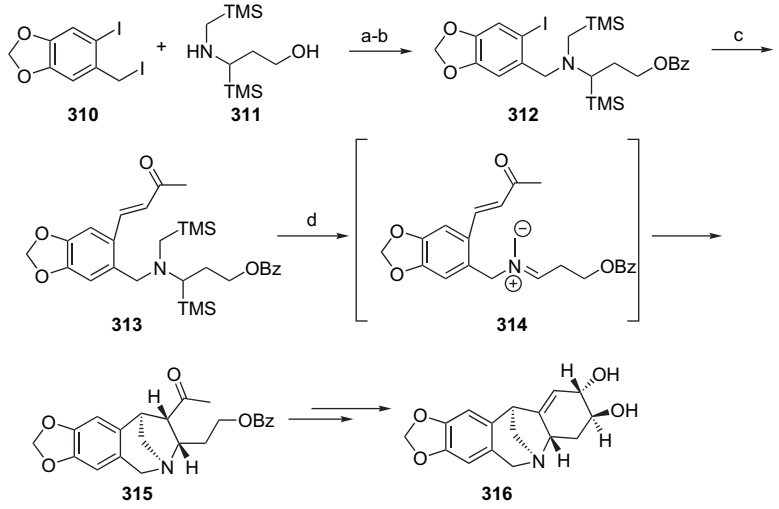
Azides constitute a very important class of dipoles and the azide group can be easily incorporated into organic compounds by nucleophilic displacement reactions.[90] The dipolar cycloaddition of an azide to an alkene furnishes a triazoline derivative (Fig. 4) whereas cycloaddition to an alkyne affords a triazolidine derivative.[91] The latter reaction has received much attention recently, due to its ability to deliver macromolecules.[92,93]

Azide–alkene cycloadducts can extrude nitrogen at elevated temperatures to form aziridines or imines, depending upon the substrate and reaction conditions. Both pathways have been made use of in total synthesis and a few selected examples are described.

The enantioselective synthesis of (−)-slaframine **323**, a toxic indolizidine alkaloid isolated from the fungus *Rhizoctonia*



Scheme 61. (a) Diphenyl ether, 260 °C.



Scheme 62. (a) K_2CO_3, MeCN; (b) BzCl, Et_3N, CH_2Cl_2; (c) $Pd(OAc)_2$, PPh_3, K_2CO_3, MVK; (d) AgF, MeCN, 56%.

leguminicola, has been accomplished via an intramolecular azide dipolar cycloaddition (IAC) as the key step. Starting from **317**, the amino functionality at the C-6 position of (−)-slaframine was introduced by reduction with DIBALH. The IAC precursor was produced by the displacement of tosylate with azide and subsequent thermolysis produced the imine. Neither the azide **319** nor the cycloadduct **320** was isolated. Further structural manipulations delivered **323** (Scheme 63).[94]

An enantioselective synthesis of the pyrrolizidine alkaloid, (+)-crotanecine **326**, also utilizes the IAC reaction as a key step. Tosylate **324** derived from 2,3-*O*-isopropylidene-D-erythrose was treated with sodium azide in DMF to afford the imine **325** directly. Further synthetic transformation of the imine afforded the alkaloid **326** (Scheme 64).[95]

Crinane **332** is a non-natural alkaloid possessing a 5,10b-ethanophenanthridine skeleton, which is typical of the

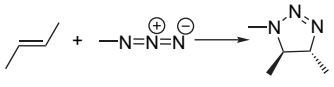
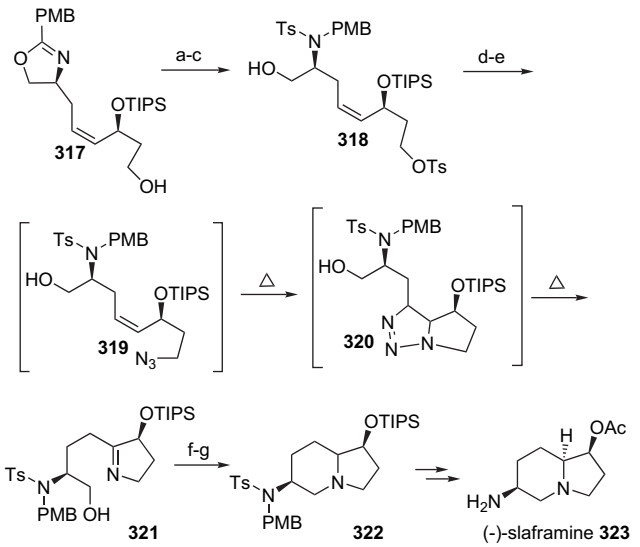
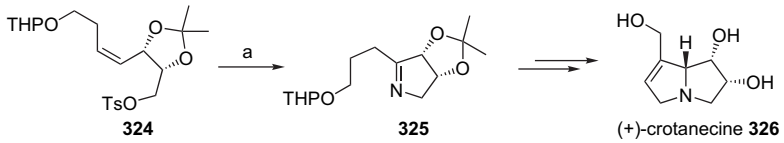


Figure 4.



Scheme 63. (a) TsCl, Et_3N, DMAP, CH_2Cl_2; (b) DIBALH, THF, 0 °C; (c) *N*-tosyl-*N*-methyl pyrrolidine perchlorate, CH_2Cl_2, 0 °C; (d) NaN_3, DMF, 60 °C; (e) toluene, reflux; (f) MsCl, Et_3N, CH_2Cl_2; (g) $NaBH_4$, EtOH, 0 °C, then K_2CO_3, reflux.



Scheme 64.

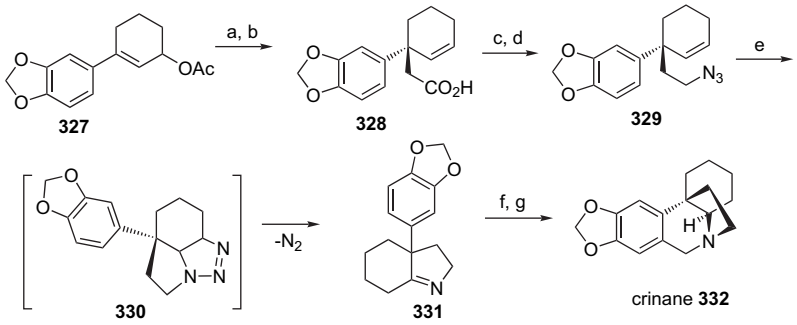
Amaryllidaceae family. Pearson and Schkeryantz utilized the IAC to achieve a racemic synthesis of crinane. Conversion of acetate **327** into the carboxylic acid **328** by Ireland–Claisen rearrangement was followed by reduction and azidation to furnish the precursor **329** for the IAC reaction. Thermolysis of the azido olefin **329** generated the cycloadduct triazoline **330**, which on rapid extrusion of nitrogen quantitatively furnished the imine **331**. The latter imine on reduction and subsequent treatment with Eschenmoser's salt afforded crinane **332** in 23% overall yield (starting from cyclohexenone) (Scheme 65).[96]

Tylophorine **338**, belonging to the phenanthroindolizidine family of alkaloids, is known to possess antitumor activity. Pearson employed the azide–alkene dipolar cycloaddition for the racemic synthesis of **338**. Azido alkene **334** was synthesized starting from homoveratric acid **333**. Thermolysis of the azide **334** followed by sodium borohydride reduction directly afforded the alkaloid tylophorine in 82% yield. Presumably, the iminium salt **337** is formed via the intermediates **335** and **336** (Scheme 66).[97]

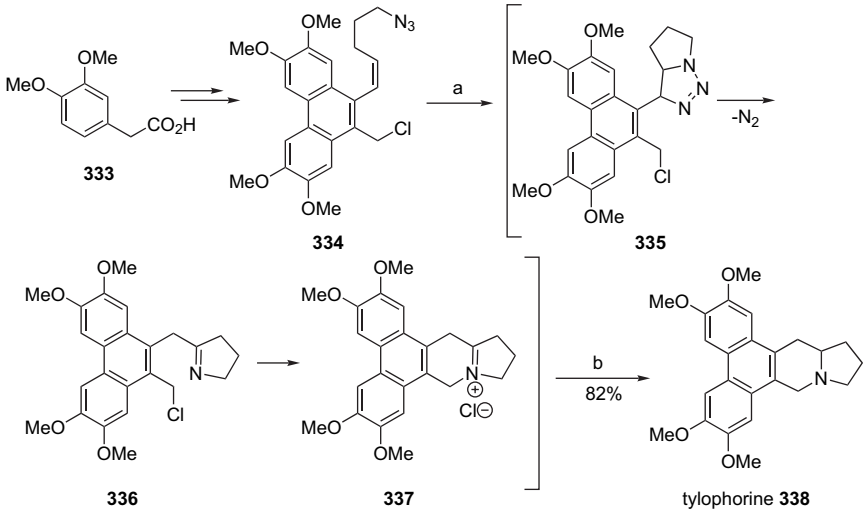
Pearson has also employed a similar strategy for the synthesis of the alkaloids, swainsonine and γ-lycorane.[98]

Molander has employed the intramolecular azide–enone dipolar cycloaddition reaction in the synthesis of an azaspirocyclic ketoaziridine, which could serve as the intermediate for the antitumor alkaloid, cephalotaxine **343**. Azido-enone **341** was constructed by the Pd(0)-catalyzed coupling of vinyl iodide **339** and arylzinc chloride **340**. The cycloadduct presumably loses nitrogen to afford the aziridine **342** (Scheme 67).[99]

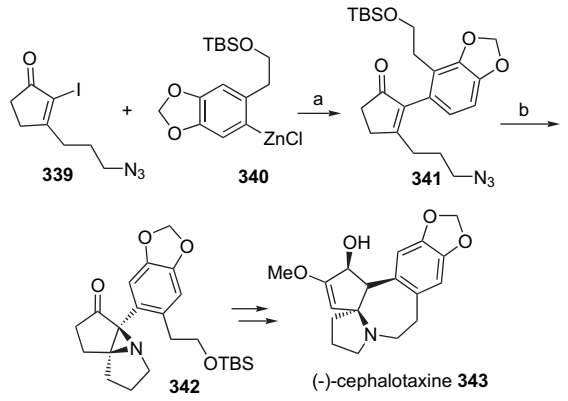
Benzazoc-3-ene unit (e.g., **347**) is a structural moiety, which has been recognized as a useful precursor for the synthesis of the antitumor agents, mitomycin C and FR-900482. An azide–allylsilane 1,3-dipolar cycloaddition has been employed for the construction of the benzazoc-3-ene derivative **347**. A completely diastereoselective dipolar cycloaddition afforded the triazoline **345** and the latter compound on photolysis furnished the aziridine **346** (Scheme 68). Formation of the eight-membered ring was achieved by the action of



Scheme 65. (a) LDA, THF, −78 °C; (b) TBSCl, −78 °C to reflux; (c) $LiAlH_4$, THF; (d) Ph_3P, DEAD, $(PhO)_2P(O)N_3$, CH_2Cl_2; (e) toluene, reflux, 100%; (f) $NaBH_3CN$, AcOH; (g) $CH_2N(Me)_2I$, THF, 50 °C.

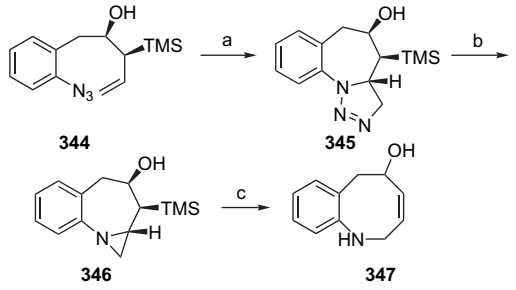


Scheme 66. (a) Benzene, 130 °C; (b) $NaBH_4$, MeOH.



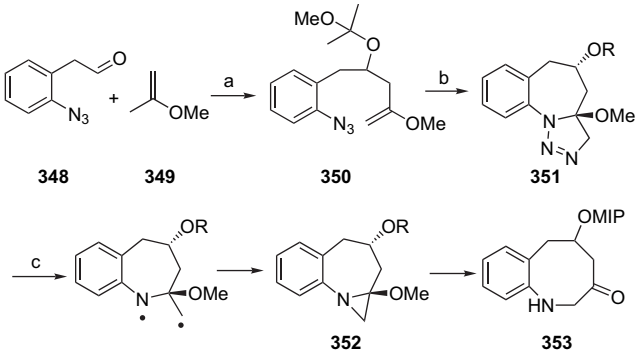
Scheme 67. (a) $Pd(dba)_3$, TFP, DMF, THF, 25 °C; (b) xylene, 131 °C, 48 h, 76%.

fluoride ion on the silylaziridine. It was observed that when the hydroxyl group of **346** was protected, aziridine cleavage did not occur. The authors suggest that the function of the fluoride from TBAF is to reversibly deprotonate the hydroxyl to promote a homo-Brook rearrangement. Various other bases in aprotic media were also found to be effective in promoting the transformation, thus providing support for this mechanistic proposal.[100]



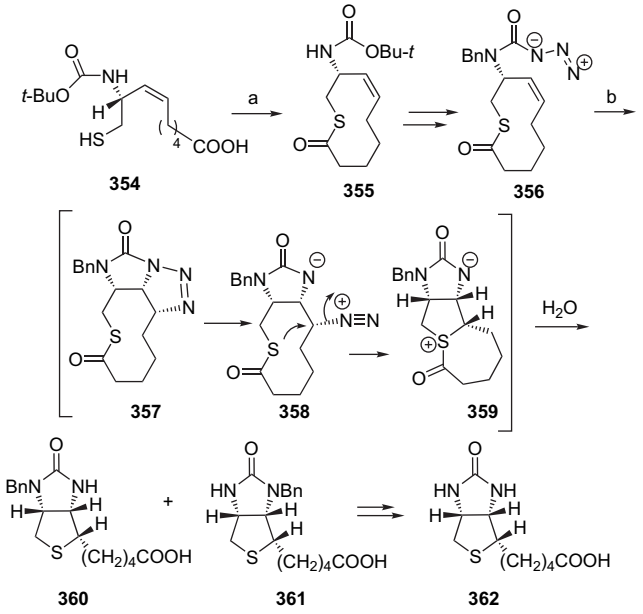
Scheme 68. (a) Toluene, reflux, 90%; (b) benzene, rt, *hν*, 77%; (c) TBAF, DMF, −20 °C.

Ciufolini has also utilized a similar strategy for the synthesis of benzazocenone, a potential intermediate for the synthesis of mitomycinoidic antitumor agents. Azido alkene **350** required for the cycloaddition was synthesized by an ene reaction between 2-methoxypropene and 2-(2-azidophenyl)-acetaldehyde **348**. Azide **350** underwent an IAC reaction to yield the triazoline **351** as a mixture of *anti* and *syn* (7:1) isomers. Photochemical extrusion of nitrogen and subsequent hydrolysis furnished **353** (Scheme 69).[101]



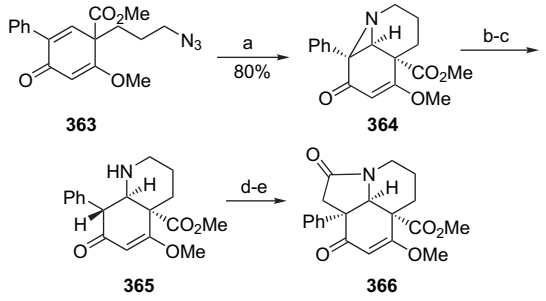
Scheme 69. (a) Lewis acid, CH_2Cl_2, rt; (b) toluene, reflux, cat. K_2CO_3, 55%; (c) *hν*, moist THF.

An intramolecular azide–alkene cycloaddition features as the key step in the enantioselective synthesis of the water-soluble B-vitamin, (+)-biotin **362**. The macrothiolactonization of the carboxylic acid **354**, available in a few steps from L-(+)-cysteine, affords the 10-membered thiolactone **355**, albeit in low yield. The urethane moiety was then replaced with a carbamoyl azide **356** and the latter azide on thermolysis in water afforded a mixture of isomers **360** and **361** in a 3:2 ratio. Both isomers are carried through the synthesis to furnish (+)-biotin. The initially formed cycloadduct **357** presumably loses nitrogen assisted by the proximal nucleophilic sulfur atom to form a tricyclic sulfonium intermediate **359**. The carboxylic acid side chain of biotin is released by the hydrolytic opening of the latter compound (Scheme 70).[102]



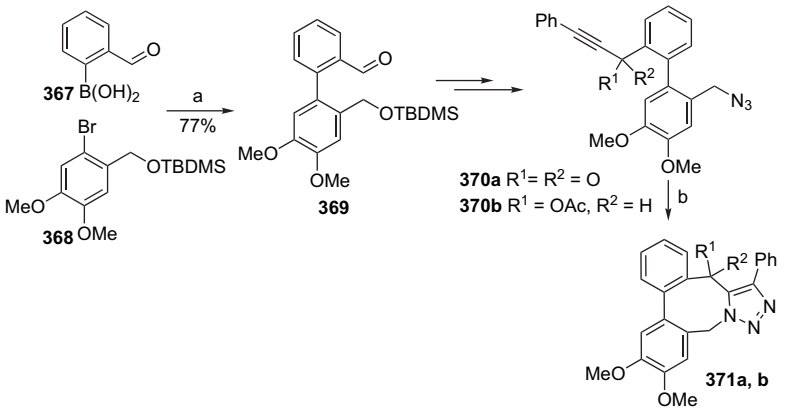
Scheme 70. (a) $PhOP(O)Cl_2$, DMF, CH_2Cl_2, 24%; (b) H_2O, autoclave, 145 °C, 42%.

The tricyclic ring system present in the aspidosperma alkaloid, vindoline, has been constructed by the IAC reaction. Azido olefin **363** underwent cycloaddition, and immediate loss of nitrogen by the intermediate afforded the aziridine **364** as a single isomer. Reductive opening of the aziridine, N-acylation, and C-alkylation completed the construction of the CDE-ring system of vindoline (Scheme 71).[103]



Scheme 71. (a) Benzene, reflux; (b) Li, NH_3, THF, −78 °C; (c) AcOH; (d) $BrCH_2COCl$, $NaHCO_3$, THF; (e) *t*-BuOK, benzene, reflux.

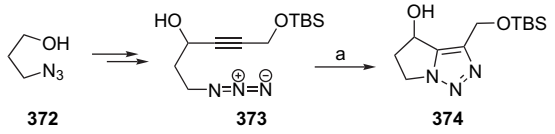
Bisbenzocyclooctadiene lignan lactones like (−)-steganacine and (−)-steganone have been shown to possess



Scheme 72. (a) $Pd(Ph_3P)_4$, Cs_2CO_3, dioxane/EtOH, 130 °C, microwave; (b) *o*-dichlorobenzene, 210 °C, 15 min, microwave, 43% for **371a** or DMF, 120 °C, 15 min, microwave, 76% for **371b**.

significant anticancer activity. Their unnatural 7-aza analogues also exhibit potent biological activity and, at the same time, do not present any stereoselection problems in the synthesis. A microwave-assisted intramolecular azide–alkyne cycloaddition has been employed in the synthesis of such compounds possessing a 1,2,3-triazole ring. Thus, biaryl-azidoalkyne **370**, obtained by sequential Suzuki coupling, propargylation, and azidation, readily afforded dibenzotriazolo[1,5]azocine **371**. Conventional heating was ineffective in promoting the cycloaddition reaction. In the acetate derivative **371b**, the lesser rigidity would account for the lower activation energy and, hence, the high yield of the product (Scheme 72).[104]

The triazole analogue of a dehydropyrrolizidine alkaloid has been constructed through the IDC reaction of azidoalkyne **373** (Scheme 73). The product, 5,6-dihydro-4*H*-pyrrole-[1,2-*c*][1,2,3]triazole **374**, assumes importance, since analogues of dehydropyrrolizidine alkaloids are potent antitumor agents.[105]

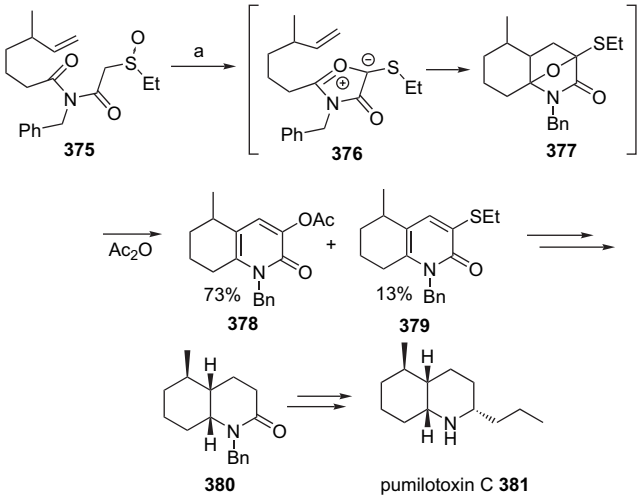


Scheme 73. (a) Toluene, reflux, 24 h, 59%.

7. Mesionic and miscellaneous dipoles[65]

Padwa and Kuethe reported a formal synthesis of decahydroquinoline alkaloid, (±)-pumilotoxin C **381** by employing a tandem Pummerer-isomünchnone dipolar cycloaddition reaction. Pummerer reaction of imidosulfoxide **375** generated an isomünchnone dipole **376**, which underwent a cycloaddition reaction with the tethered olefin. The cycloaddition directly afforded α-pyridones **378** and **379**. Both compounds were independently converted into the pyridine **380**, which is a known precursor to pumilotoxin. α-Pyridones **378** and **379** arise from the oxo-bridge cleavage of **377** and subsequent acetylation by the excess acetic anhydride (Scheme 74).[106]

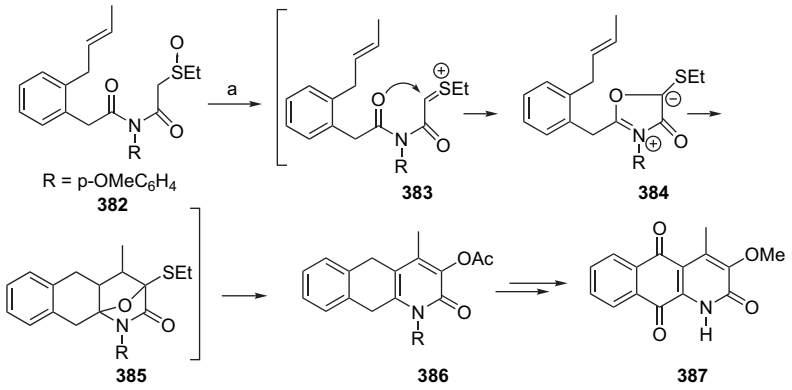
Padwa has also employed Pummerer reaction–deprotonation–cycloaddition cascade for the synthesis of many other



Scheme 74. (a)Ac_2O, *p*-TsOH (trace), Δ.

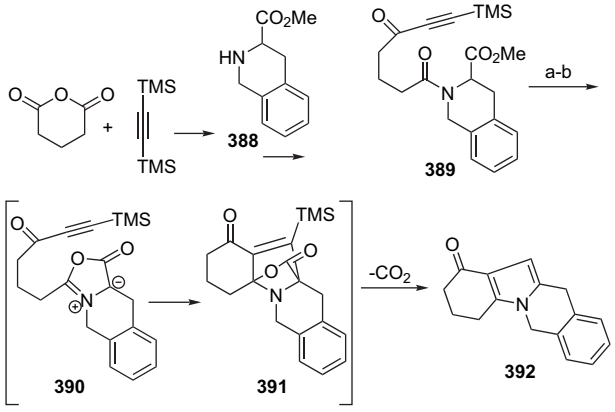
naturally occurring alkaloids. The pivotal step of all these syntheses is the cycloaddition reaction of a mesionic isomünchnone dipole. The alkaloids synthesized by this methodology include onychnine, dielsiquinone, lupinine, anagyrine, and costaclavine. The syntheses of all of these alkaloids are summarized in a single publication. As a representative example, the synthesis of dielsiquinone is presented in Scheme 75. Pummerer-induced generation of the isomünchnone dipole **384**, subsequent cycloaddition with the pendant alkene and oxabicyclic ring cleavage of the cycloadduct were achieved essentially in one step by treating the imidosulfoxide **382** with excess acetic anhydride in the presence of a catalytic amount of *p*-TsOH. Pyridone derivative **386** was further transformed into the alkaloid, dielsiquinone, in a few steps to complete its first total synthesis. The power of this synthetic methodology is evident from the number and variety of the targets that it has achieved.[107]

A general synthesis of tetrahydroindoles via dipolar cycloaddition of münchnones generated from *N*-acyl amino acid derivatives has been reported. An alkynone moiety attached on the acyl unit reacts with the münchnone intermediate (e.g., **390**) to afford a primary cycloadduct, which readily loses CO_2 to furnish the tetrahydroindole derivative (Scheme 76). A topoisomerase-I inhibitor skeleton



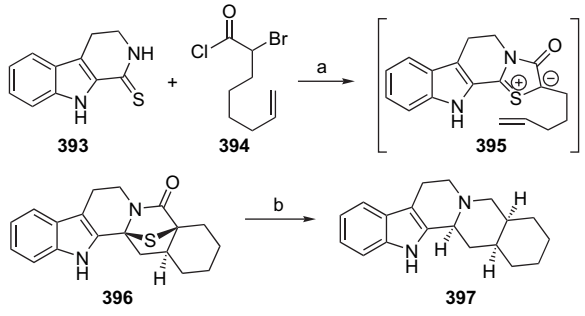
Scheme 75. (a) Ac_2O, *p*-TsOH, 68%.

incorporating some features of camptothecin was synthesized using this methodology.[108]



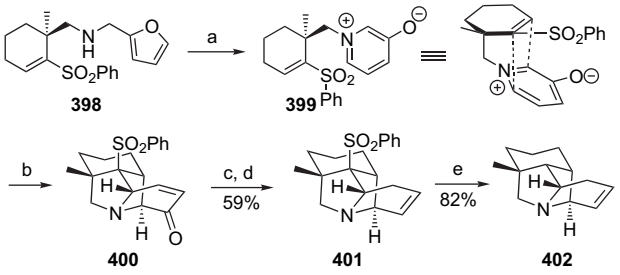
Scheme 76. (a) LiI, EtOAc, heat; (b) Ac_2O, 70–120 °C.

(±)-Alloyohimbane **397** was synthesized by Padwa using the intramolecular dipolar cycloaddition of thioisomünchnone **395** produced by the reaction of thiocarboline **393** and bromo acid chloride **394**. Reduction of polycyclic heterocycle **396** furnished alloyohimbane **397** (Scheme 77).[109]



Scheme 77. (a) Et_3N, heat; (b) Raney-Ni, then LAH.

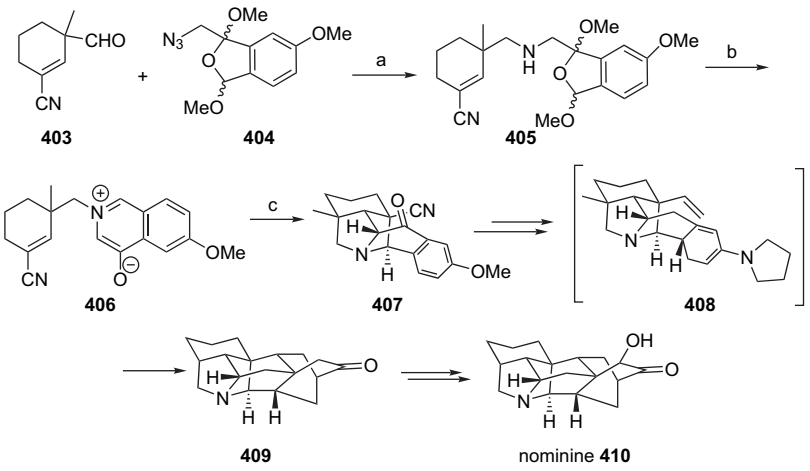
The hetisine class of alkaloids is characterized by the presence of a 3-methyl-1-aza-tricyclo[5.2.1.$0^{3,8}$]decane substructure embedded in the carbon scaffold. Synthetic efforts toward the alkaloids of this class have been scarce, presumably due to the challenges in constructing the tricyclic framework. Gin and Peese recently reported a methodology based on the intramolecular cycloaddition of an oxidopyridinium dipole for the synthesis of the aza-tricyclic unit. Oxidopyridinium betaine **399** was generated by the bromine-mediated oxidative rearrangement of the furfuryl amine derivative **398**. The stable oxidopyridinium betaine underwent cycloaddition on heating in toluene with the endocyclic double bond to afford the adduct **400** in 70% yield. Reductive removal of the sulfonyl and carbonyl groups and double bond isomerization afforded the 3-methyl-1-aza-tricyclo[5.2.1.$0^{3,8}$]decane skeleton **402** (Scheme 78).[110]



Scheme 78. (a) Br_2, AcOH, H_2O, 0 °C, 77%; (b) toluene, reflux, 70%; (c) L-Selectride, $PhNTf_2$, −78 °C; (d) HCO_2H, Et_3N, $PdCl_2(PPh_3)_2$, 60 °C; (e) Na(Hg), Na_2HPO_2, THF, *t*-BuOH.

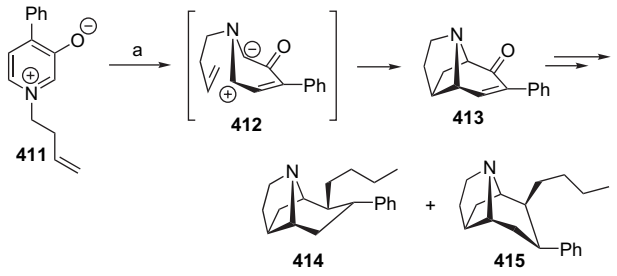
Gin and Peese employed a modification of this strategy in the total synthesis of the hetisine alkaloid nominine. The dipolarophile component was accessed from 3-methylcyclohexenone and was coupled to the oxidopyridinium betaine precursor **404** via a Staudinger reaction–reduction sequence. The diastereomeric mixture was converted into isoquinolinium betaine on treatment with TFA. The betaine on heating at 180 °C afforded two easily separable isomeric cycloadducts. Although the required isomer was the minor product, thermal re-equilibration of the isolated undesired cycloadduct allowed the production of the desired isomer without loss of material. The nitrile functionality of the cycloadduct was converted into a methylene unit and the aromatic ring was subjected to Birch reduction to reveal a diene unit. An intramolecular Diels–Alder reaction furnished the essential carbon framework of nominine. The synthesis of nominine was completed by a Wittig reaction of the ketone and an allylic hydroxylation (Scheme 79).[111]

Kozikowski has synthesized tricyclic cocaine analogues with an extra ring that binds N-8 and C-6, thereby fixing the nitrogen lone pair spatially. The intramolecular dipolar cycloaddition of 3-hydroxypyridinium betaine **411** with the butenyl side chain at nitrogen produced the 6-bridged



Scheme 79. (a) PBu_3, $NaBH(OAc)_3$, CH_2Cl_2; (b) TFA, CH_2Cl_2; (c) THF, 180 °C, 97%, 1:3.6.

tropenone isomer. Further advancement via the reduction of enone and introduction of a butyl moiety at C-2 afforded **414** and **415** as an inseparable mixture of cocaine analogues (Scheme 80).[112]

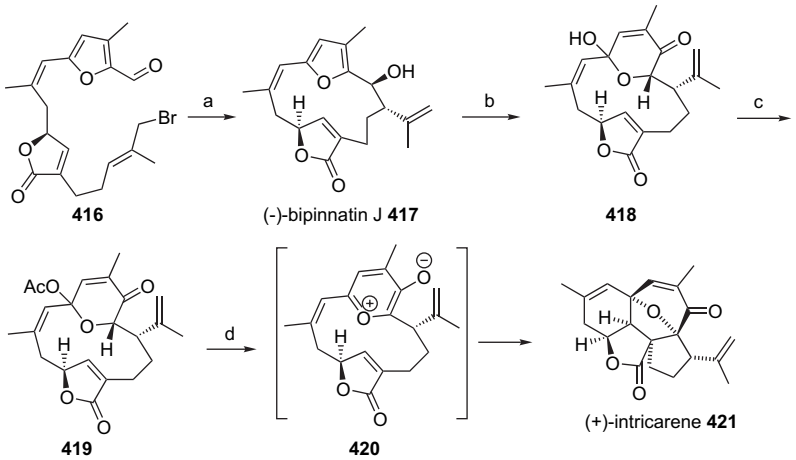


Scheme 80. (a) Xylene, reflux, 36%.

Trauner has employed a [5+2] intramolecular cycloaddition of a pyrilium betaine and a butenolide for the synthesis of (+)-intricarene **421**, which belongs to a class of diterpenes characterized by the presence of a furanocembranoid skeleton and additional transannular carbon–carbon bonds. The authors synthesized a few members of the series and postulated that the dipolar cycloaddition may well feature in the biosynthesis of these diterpenes. (−)-Bipinnatin J **417** is initially synthesized enantioselectively using a Nozaki–Hiyama–Kishi macrocyclization reaction. The biomimetic conversion of (−)-bipinnatin J into (+)-intricarene was best carried out by oxidation with *m*-CPBA, acetylation, and subsequent elimination of acetic acid. Betaine **420** thus formed underwent transannular cycloaddition to afford (+)-intricarene **421** directly (Scheme 81).[113]

8. Conclusions

Undoubtedly the area of dipolar cycloaddition reactions has progressed enormously since Huisgen's seminal contributions and rationalization of the process. The examples of dipolar cycloadditions in targeted syntheses described above span the entire spectrum of organic synthesis. The versatility of this class of reactions makes it a very powerful synthetic tool. Recent advances in computational methods are revealing the fine aspects of the electronic interactions in dipolar cycloadditions and this is likely to trigger more efforts to apply this uniquely powerful class of reactions in targeted syntheses.



Scheme 81. (a) $CrCl_2$, 72%; (b) *m*-CPBA; (c) Ac_2O, DMAP, Py, 81% from **417**; (d) base, DMSO, 150 °C, 26%.

Acknowledgements

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