Synthesis of tricyclic marine alkaloids, cylindricines, lepadiformines, fasicularin, and polycitorols: a recent update

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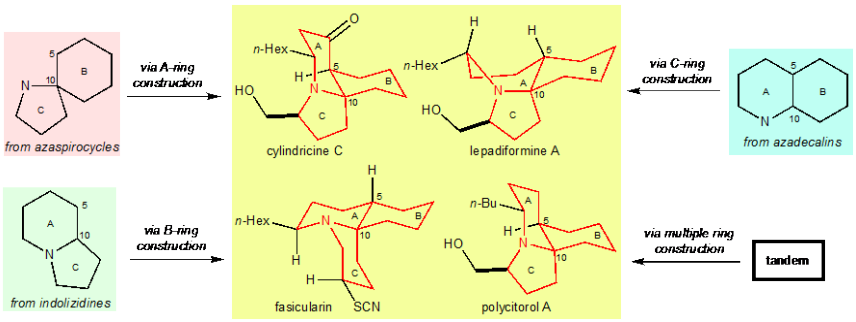

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Abstract Cylindricines, lepadiformines, and fasicularin are tricyclic marine alkaloids bearing perhydropyrrolo- and pyrido[2,1-j] framework having divergent chemical functionalities. They were isolated from marine tunicates in last two decades and found to have a range of cytotoxicity such as DNA-alkylating ability. Recently, polycitorols emerged as a new member of this alkaloid family. Their unique structural features and biological activities intrigued attention of many researchers to challenge their synthesis. This review describes recent syntheses of the tricyclic alkaloids based on the key synthetic approaches.

Key words tricyclic alkaloids, natural products, total synthesis, azaspirocycles, indolizidines, azadecalins, tandem cyclization

1. Introduction

Marine ascidians are rich sources for various fascinating bioactive natural products.[1] Tricyclic alkaloids having a saturated ring system of perhydropyrrolo[2,1-j]quinoline **1** or perhydropyrido[2,1-j]quinoline **2** were found from marine ascidians (Figure 1A). Cylindricine A (**3**) and B (**4**) were isolated from *Clavelina cylindrica* around the east coast of Tasmania by Blackman and co-workers in the early 1990s (Figure 1B).[2] Cylindricine A (**3**) and B (**4**) were the first members of the family based on the perhydropyrrolo[2,1-j]quinoline (**1**) and the perhydropyrido[2,1-j]quinoline (**2**) frameworks, respectively. The structures of cylindricine A (**3**) and B (**4**) were confirmed by X-ray crystallography of their picrate salts. The interconversion between cylindricine A (**3**) and B (**4**) was observed to produce a 3:2 equilibrium mixture in aqueous solution via aziridinium intermediate (**3'**). Cylindricine A (**3**) and B (**4**) possess modest toxicity in brine shrimp assay. Subsequent investigations revealed the different metabolites, cylindricine C-K (**5**-**13**), which were mainly assigned by the NMR experiments (Figure 1B).[3] Although the absolute configuration of natural cylindricines has not been determined, several groups accomplished the asymmetric syntheses of cylindricines.[4] All cylindricines possess the *cis*-1-azadecalin AB ring with an alkyl side chain at C(2) connected with the functionalized C ring.

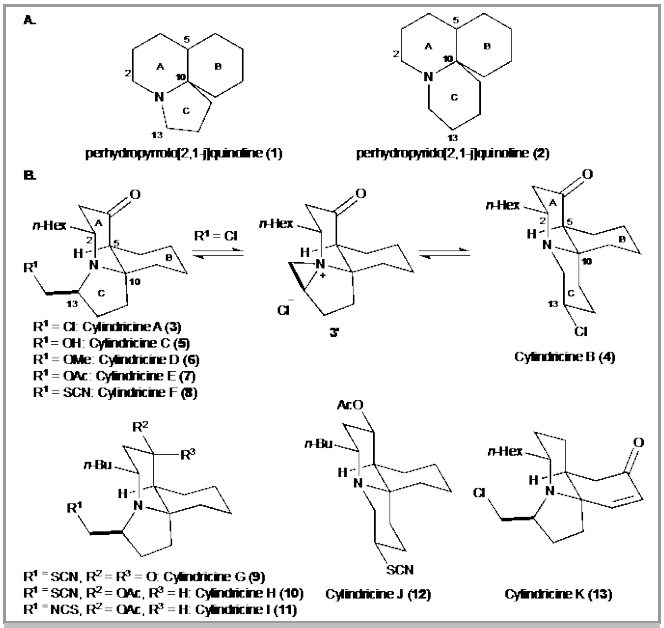


Figure 1 The chemical structure of common framework in tricyclic alkaloids (A) and cylidricines (B).

Lepadiformine A (**14**) was isolated from the tunicate *Clavelina lepadiformis* by Biard and co-workers in 1994 (Figure 2).[5] Structual reassignment of Lepadiformine A (**14**) was completed by the first total synthesis of (±)-lepadiformine A (**14**) by Kibayashi and co-workers.[6] Subsequent asymmetric syntheses of (−)-lepadiformine A (**14**) determined its absolute configuration.[7] This tricyclic alkaloid features the unique twist boat–chair *trans*-1-azadecalin AB-ring fused with the hydroxymethyl pyrrolidine C-ring analogous to the structure of cylindricine C (**5**). Structural differences between lepadiformine A (**14**) and cylindricine C (**5**) are the conformation of 1-azadecalin AB ring as well as lack/presence of carbonyl group at C(4). Their congener, namely lepadiformine B (**15**) and C (**16**) were discovered from *C. moluccensis* by Sauviat and co-workers in 2006.[8] The absolute configuration of (−)-lepadiformine B (**15**) was determined by the Rychnovsky's work in 2012 (vide infra, Scheme 3). Very recently, Morimoto and co-workers accomplished asymmetric synthesis of (+)-lepadiformine C (**16**), which showed the opposite absolute configuration to that of lepadiformine A (**14**) and B (**15**) (vide infra, Scheme 11). Lepadiformines (**14**-**16**) exhibits strong cardiovascular effects as well as moderate cytotoxicity against several tumor cell lines.[5,8,9]

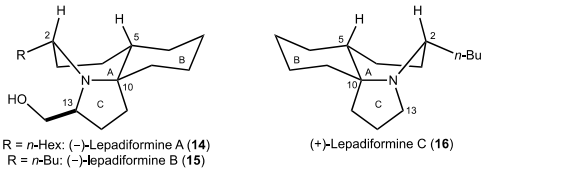
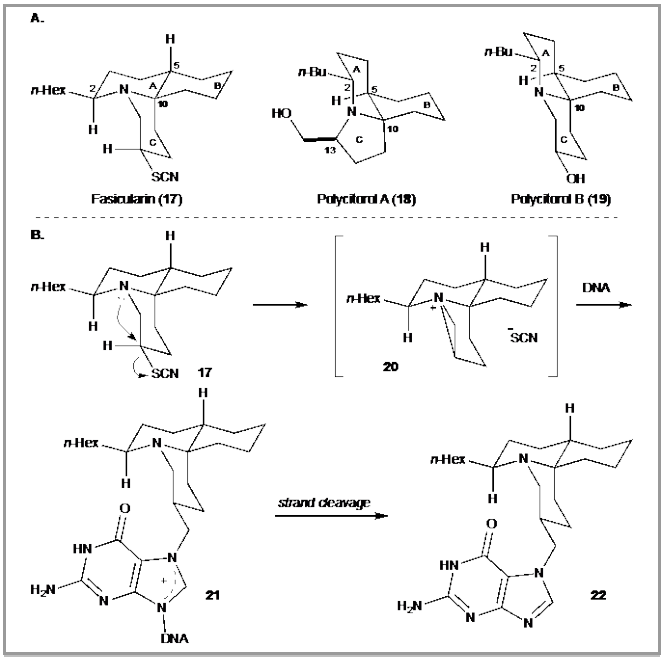


Figure 2 The chemical structure of lepadiformines.

Other tricyclic alkaloids similar to cylindricines and lepadiformines include fasicularin (**17**) as well as polycitorol A (**18**) and B (**19**). Fasicularin (**17**) was isolated from the ascidian *Nephteis fasicularis* in 1997 (Scheme 1A).[10] The structure of fasicularin (**17**) was assigned by the NMR analyses, although the absolute configuration of natural one has not been settled.[4b] Fasicularin (**17**) is composed by the perhydropyrido[2,1-j]quinoline ABC framework including a *trans*-1-azadecalin AB ring similar to that of lepadiformines (**14**-**16**) but epimeric at C(2) with alkyl group. Fasicularin (**17**) possesses cytotoxic activity through alkylation of cellular DNA (Scheme 1B).[11] The ability of DNA alkylation would be attributed to the formation of aziridinium ion **20** along with the release of thiocyanate group. Alkylation of **20** by the N(7) position of guanine residues in DNA would produce intermediate **21**. Subsequent strand cleavage in **21** would give alkylated guanine adduct **22**. On the other hand, polycitorols (**18**-**19**), isolated from a marine ascidian of the family Polycitoridae, have *cis*-1-azadecalin AB skeleton related to cylindricines, while polycitorols lacks carbonyl group at C(4) (Scheme 1A).[12] The first synthesis of polycitorols by Kim and co-workers revealed that the NMR spectroscopic data of the synthetic sample were not identical with those of natural polycitorols (vide infra, Scheme 14). Biological activity of polycitorols has not been reported.



Scheme 1 (A) The chemical structure of fasicularin and polycitorols. (B) DNA-alkylation with fasicularin.

2. Total and Formal Syntheses

2.1. Overview of the synthetic strategies

Stimulated by their unique structures, many research groups have contributed syntheses of these tricyclic alkaloids for the last decades.[13] The challenges in the synthesis of these tricyclic alkaloids are stereoselective construction of the fully substituted carbon center at C(10) as well as steteoselective installation of the alkyl side chain at C(2) in the 1-azadecalin AB ring. The review by Weinreb[13a] highlighted the synthetic studies of these alkaloids reported by 2006. Since then, further new approached for their syntheses have been disclosed. This review updates syntheses of these tricyclic alkaloids in this decade through classification of the synthetic tactics, that can be grouped into four approaches based on the key bicyclic intermediates in their routes such as azaspirocycle (BC ring), indolizidine (AC ring) and azadecalin (AB ring) as well as the tandem cyclization approaches (Figure 3).

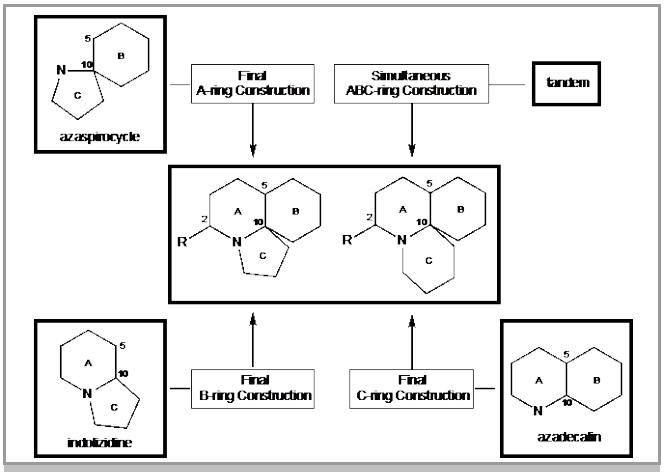
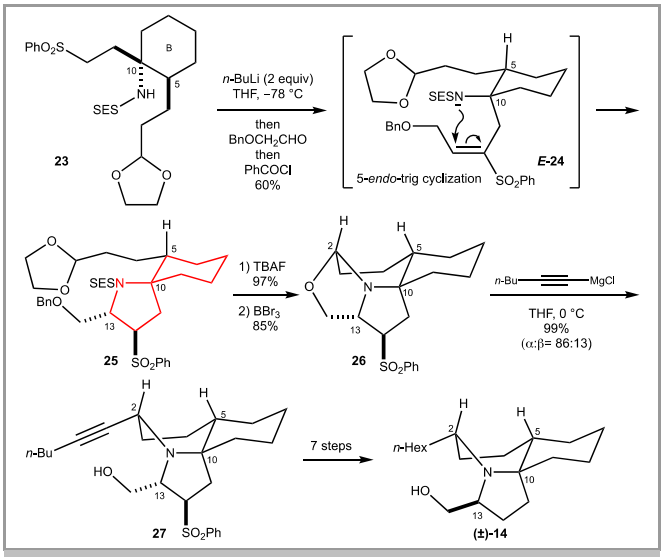


Figure 3 Overview of the synthetic strategies towards the family of tricyclic alkaloids

2.2. Azaspirocycle (BC ring) approaches

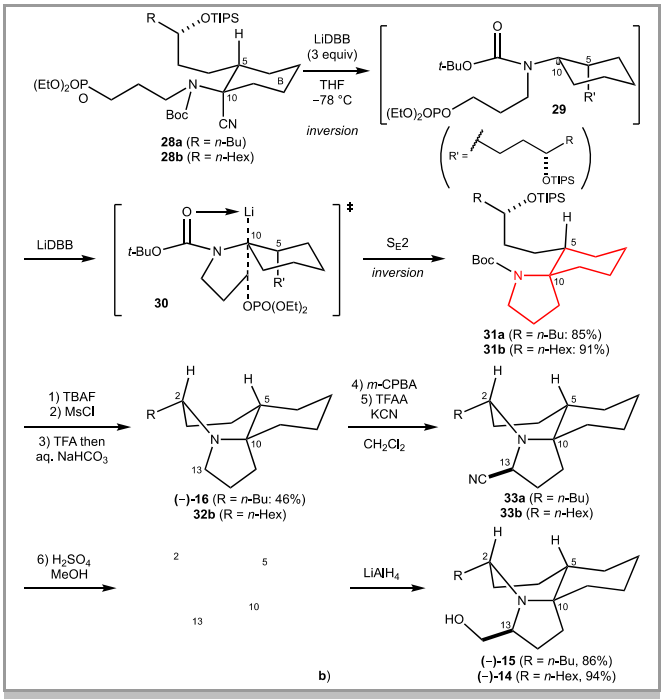
2.2.1. From B-ring

Craig and Caldwell reported the synthesis of (±)-lepadiformine A (**14**) based on azaspirocycle approach in 2007 (Scheme 2).[14] The key step involves base-mediated 5-*endo*-trig cyclization of vinyl sulfone.[15] Vinyl sulfone **24** was prepared in situ from the reaction of sulfone **23** with two equivalents of *n*-butyllithium followed by the treatment with 2-benzyloxyethanal and quenching with benzoyl chloride. The resulting *E*-isomer of vinyl sulfone ***E*-24** underwent 5-*endo*-trig cyclization with the resulting amide anion to provide key azaspirocycle **25** in 60% yield along with the recovery of *Z*-vinyl sulfone ***Z*-24** in 13% yield. Azaspirocycle **25** was converted to tetracyclic *N,O*-acetal **26** by the treatment with TBAF followed by BBr_3. To install the hexyl side chain oriented to α at C(2), *N,O*-acetal **26** was treated with hex-1-ynylmagnesium chloride, affording α-alkynylated amino alcohol **27** as a major isomer (α:β = 86:13). This substitution reaction presumably proceeded via S_N1-like attack of the less sterically hindered linear alkynyl nucleophile. Completion of the synthesis of (±)-lepadiformine A (**14**) was accomplished in seven steps including formation of the saturated hexyl group and stereochemical adjustment at C(13).



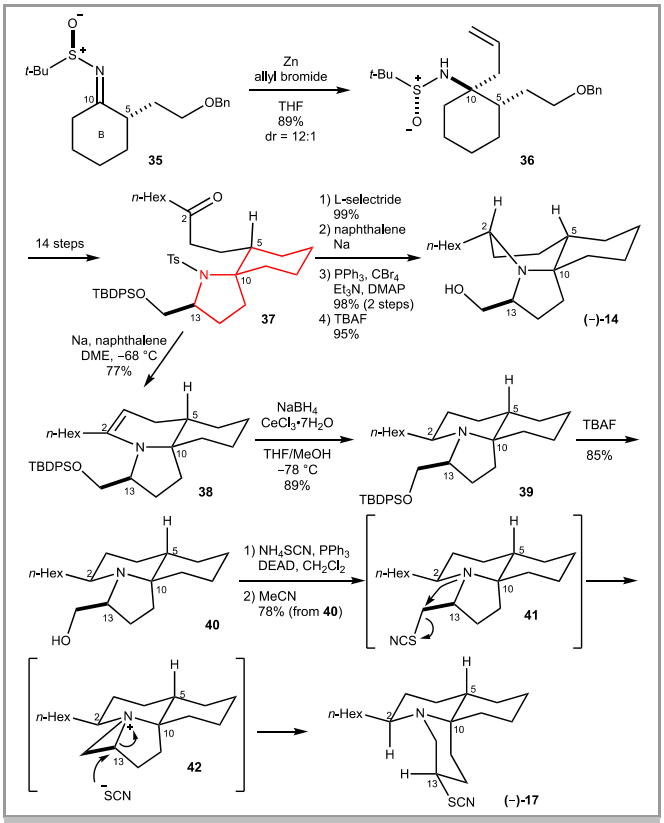
Scheme 2 Synthesis of (±)-lepadiformine A (**14**) by Craig and Caldwell.

Rychnovsky and co-workers accomplished the synthesis of (−)-lepadiformine A (**14**), B (**15**), and C (**16**) utilizing reductive spirocyclization of aminonitriles (Scheme 3).[16,17] The stereoselective cyclization of aminonitrile **28** using LiDBB (lithium di-*tert*-butyl biphenylide) gave key azaspirocycle **31** in overall retention of stereoconfiguration. Treatment of nitriles **28** with LiDBB underwent reductive decyanation to give α-amino radical **29** through the inversion of stereoconfiguration at C(10). This stereoinversive pathway would be attributed to the steric crash between the equatorial alkyl side chain at C(5) and the amide-substituents at C(10). Further reduction of **29** generated conformationally restricted α-amino alkyllithium **30** having chelation with *tert*-buthoxy carbonyl group. Due to this rigid conformation, the phosphate could approach from the back side of the alkyllithium **30** via S_E2_{inv} (electrophilic aliphatic substitution) mechanism to produce azaspirocycle **31**. Further construction of the A-ring from azaspirocycle **31** via the intramolecular substitution reaction afforded (−)-lepadiformine C (**16**) and C(13)-dehydroxymethyl lepadiformine A (**32b**). In order to install hydroxymethyl substituent at C(13), (−)-**16** and **32b** were treated under the Polonovski-Potier reaction conditions (*m*-CPBA followed by KCN, TFAA)[18] to give aminonitrile **33**. Conversion of nitrile **33** to ester **34** followed by reduction with $LiAlH_4$ finally provided (−)-lepadiformine A (**14**) and (−)-lepadiformine B (**15**). Optical rotation of synthetic (−)-lepadiformine B (**15**)·HCl ($[\alpha]_D^{22}$ +3.2 (*c* 0.3, $CHCl_3$)) was identical to that of natural product ($[\alpha]_D$ +3.0 (*c* 1.00, $CHCl_3$)).[8]



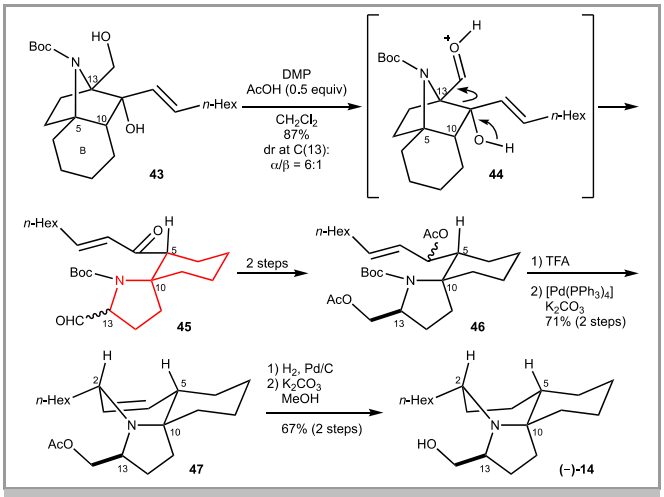
Scheme 3 Synthesis of (−)-lepadiformines (**14**-**16**) by Rychnovsky and co-workers.

Zhao and Mei applied zinc-mediated allylation of chiral *N*-*tert*-butanesulfinylimines towards the synthesis of (−)-lepadiformine A (**14**) and (−)-fasicularin (**17**) in 2010 (Scheme 4).[19,20] The key addition of an allyl zinc nucleophile to chiral sulfinimine **35** provided sulfinamide **36** bearing the aza-quarternary carbon center in 89% yield and 12:1 dr. Sulfinamide **36** was converted to azaspirocycle **37** in 14 steps including homologation of the alkenyl moiety as well as C ring-closure. For the synthesis of (−)-lepadiformine A (**14**), the A ring was constructed by four steps-transformation including diastereoselective reduction of ketone followed by the Mitsunobu reaction under the modified Kibayashi's condition.[6] For the synthesis of (−)-fasicularin (**17**), desulfonylative cyclization of azaspirocycle **37** to enamine **38** followed by the Luche reduction and removal of TBDPS group of **39** provided C(2)-*epi*-lepadiformine A (**40**) having the β-hexyl side chain at C(2). Final installation of the thiocyanate unit to **40** and ring expansion of **41** via aziridinium intermediate **42** was conducted according to the Kibayashi's protocol,[4b] affording (−)-fasicularin (**17**).



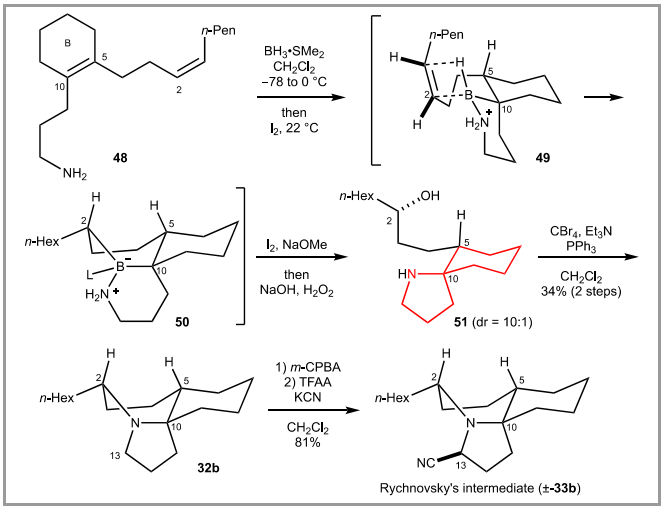
Scheme 4 Synthesis of (−)-lepadiformine A (**14**) and (−)-fasicularin (**17**) by Zhao and Mei.

Pandey and Janakiram reported synthesis of (−)-lepadiformine A (**14**) in 2015 using bridgehead-substituted 1-azabicyclo[2.2.1]heptane **43** as the key starting material (Scheme 5). [21] Oxidative skeletal rearrangement of **43** was conducted using Dess-Martin periodinane (DMP), where the choice of the acid additive was critical to control the reaction courses. Oxidation of **43** with DMP under weak-acidic conditions with acetic acid (AcOH) generated aldehyde **44**. Subsequent retro-aldol reaction of aldehyde **44** underwent to provide azaspirocycle **45** in 87% yield. On the other hand, the treatment of **43** in the presence of trifluoroacetic acid (TFA) instead of AcOH promoted tandem cyclization to construct the tricycle core of cylindricines (vide infra, Scheme 20). Azaspirocycle **45** was converted to allyl acetate **46** in two steps. The synthesis of (−)-lepadiformine A (**14**) was accomplished by the diastereoselective Tsuji-Trost cyclization of **46** to **47** followed by olefin hydrogenation and deacetylation.



Scheme 5 Synthesis of (−)-lepadiformine A (**14**) by Pandey and Janakiram.

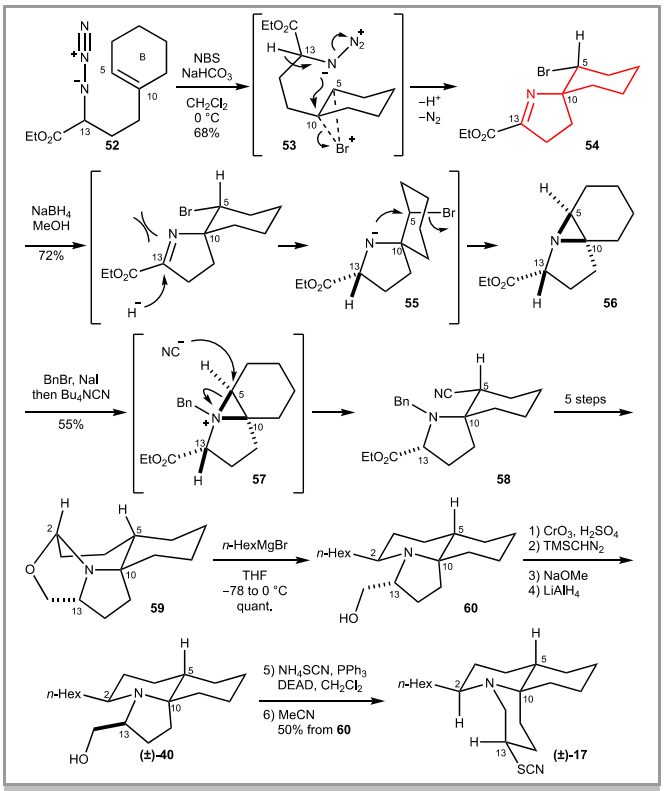
Construction of the key azaspirocycle has also been accomplished utilizing the alkene-hydroamination strategy,[22] that was demonstrated by Shenvi and Tabor in their formal synthesis of (±)-lepadiformine A (**14**) in 2015 (Scheme 6).[23] The reaction of alkenyl amine **48** with $BH_3{\cdot}SMe_2$ followed by rapid addition of iodine promoted double hydroboration via **49**. The resulting boronic amide **50** was subsequently subjected to iodine and sodium methoxide followed by oxidative work-up to afford amino alcohol **51** (dr = 10:1). The further C-ring closure under the Kibayashi's condition[6] constructed the tricycle **32b**. For completion of the formal synthesis of (±)-lepadiformine A (**14**), the resulting triclycle **32b** was treated under the Rychnovsky's conditions to afford aminonitrile **33b**, which is the key intermediate in the synthesis of (−)-lepadiformine A (**14**) by Rychnovsky and co-workers (Scheme 3).[16a]



Scheme 6 Formal synthesis of (±)-lepadiformine A (**14**) by Shenvi and Tabor.

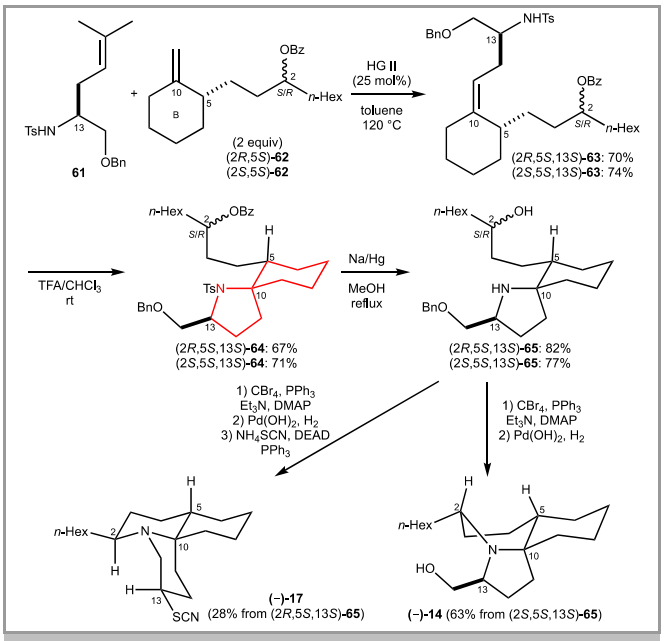
In 2016, Chiba and co-workers accomplished the synthesis of (±)-fasicularin (**17**) using diastereoselective aminobromination of α-azido ester as the key step to construct the azaspirocyclic framework (Scheme 7).[24] Treatment of α-azido ester **52** with NBS in the presence of $NaHCO_3$ underwent denitrogenative spirocyclizing *trans*-aminobromination via bromonium ion **53**

to give spirocyclic imine **54** in good yield. **54** was further converted into tricyclic aziridine **56** through stereoselective hydride reduction of the C=N bond with $NaBH_4$ and successive intramolecular nucleophilic substitution of amine **55**.[25] This stereochemical outcome is attributed to less steric hindrance of the β-face on the C=N bond of **54**. Treatment of aziridine **56** with benzyl iodide formed *N*-benzyl aziridinium salt **57**, which was successively treated with Bu_4NCN to realize regio- and stereoselective ring-opening of the aziridinium ion at C(5), giving azaspirocycle **58** with the cyano group at C(5).[26] Azaspirocycle **58** was further converted to tetracyclic *N*,*O*-acetal **59** in five steps. The subjection of *N*,*O*-acetal **59** with hexylmagnesium bromide successfully installed the β-hexyl side chain at C(2) to provide amino alcohol **60**. This reaction proceeded via S_N2-like displacement of the *N*,*O*-acetal **59**, which is contrast to the α-alkynylation of sulfone-containing hemiaminal **26** in the synthesis of (±)-lepadiformine A (**14**) by Craig and Caldwell (Scheme 2).[14] Final adjustment of the stereochemical configuration at C(13) followed by the Mitsunobu reaction of **40** according to the Kibayashi's protocol[4b] afforded (±)-fasicularin (**17**).



Scheme 7 Synthesis of (±)-fasicularin (**17**) by Chiba and co-workers.

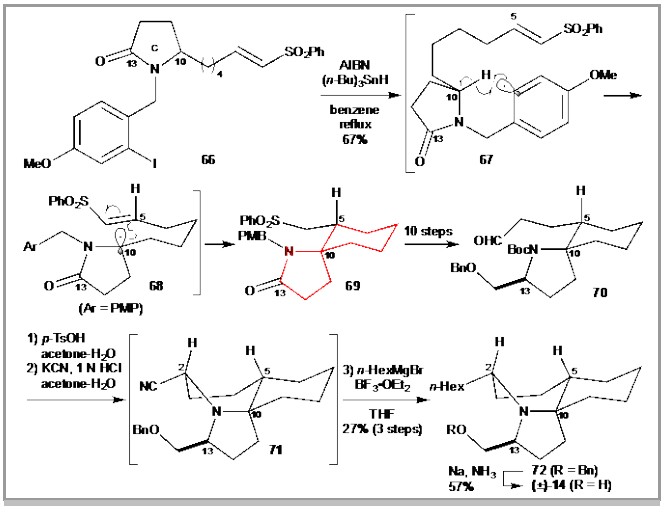
In 2017, Robinson and co-workers reported asymmetric synthesis of (−)-fasicularin (**17**) and (−)-lepadiformine A (**14**) using olefin cross-metathesis as the key reaction tool (Scheme 8).[27,28] As cross-metathesis partners, alkenyl amine **61** bearing a sterically-encumbered tri-substituted olefin as well as exomethylene cyclohexane **62** were selected. The reaction of **61** and two equivalent of **62** in the presence of the Hoveyda-Grubbs 2nd generation catalyst provided desired olefin **63**. Subsequent treatment of olefin **63** under acidic conditions promoted 5-*endo*-trig spirocyclization to give **64** having *trans*-relationship between the C(10)-N bond and the alkyl tether at C(5). After removal of the *N*-tosyl and C(2)-*O*-benzoyl group, annulation of (2*R*,5*S*,13*S*)-**65** under the modified Kibayashi's method[6,19] followed by the Mitsunobu reaction[4b] provided (−)-fasicularin (**17**). The synthesis of (−)-lepadiformine A (**14**) was also accomplished by the analogous cyclization procedure from (2*S*,5*S*,13*S*)-**65**.



Scheme 8 Synthesis of (−)-fasicularin (**17**) and (−)-lepadiformine A (**14**) by Robinson and co-workers.

2.2.2. From C-ring

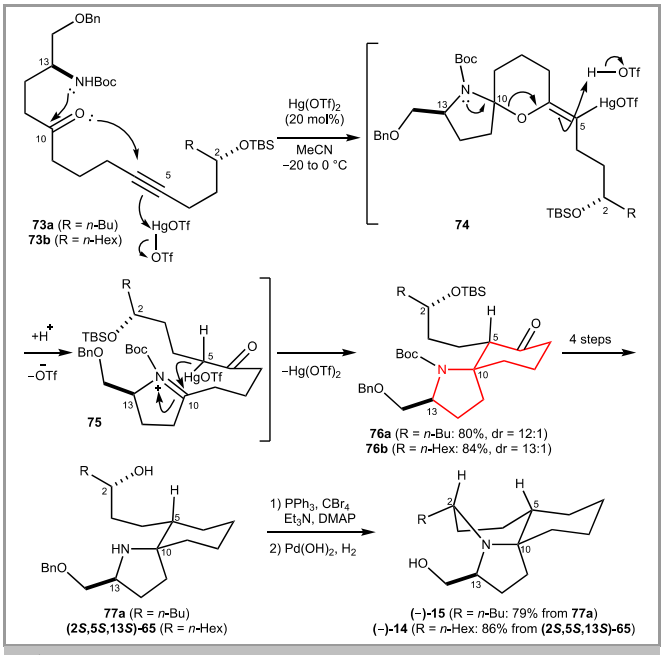
The azaspirocyclic framework in (±)-lepadiformine A (**14**) has been constructed from the 5-membered C-ring intermediate using radical translocation-cyclization strategy by Tokuyama and co-workers in 2010 (Scheme 9).[29,30] The radical translocation reaction of amide **66** would be initiated under the combination of AIBN and *n*-Bu_3SnH for generation of aryl radical **67**. Subsequent 1,5-hydrogen atom transfer provided α-amino alkyl radical **68**, which underwent 6-*exo* cyclization to afford azaspirocycle **69** as a single diastereomer. The excellent diastereoselectivity is attributed to less 1,3-diaxial steric repulsion between benzylic hydrogens of the PMB group and the vinyl sulfone parts. Azaspirocycle **69** was converted to **70** having the benzyloxymethyl tether at C(13) in 10 steps. **70** was subjected under the Weinreb's procedure[7b] including 1) formation of putative aminonitrile **71** and 2) addition of hexylmagnesium bromide to provide **72**, which was converted into (±)-lepadiformine A (**14**) via debenzylation.



Scheme 9 Synthesis of (±)-lepadiformine A (**14**) by Tokuyama and co-workers.

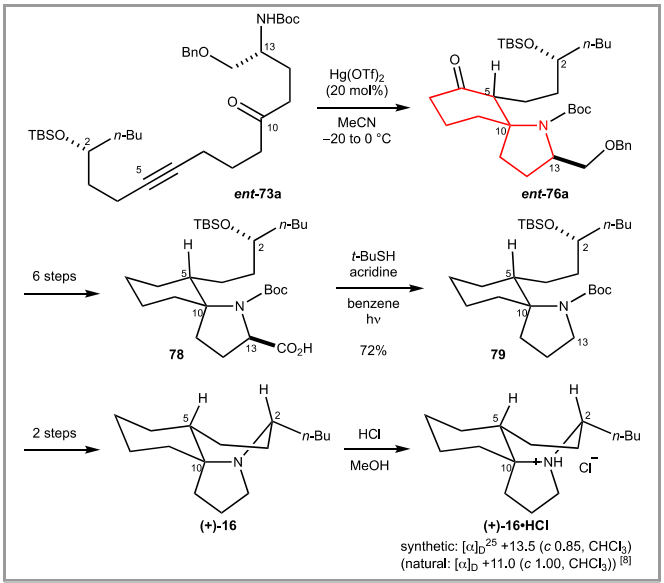
2.2.3. From acyclic substrates

Morimoto and co-workers accomplished asymmetric syntheses of lepadiformines (**14**-**16**) based on azaspirocycle approach using the cycloisomerization reaction of acyclic ynones and determination of the absolute configuration of natural lepadiformine C (**16**).[31] The mercury(II)-catalyzed cycloisomerization reaction of ynone **73** provided azaspirocycle **76** in good diastereoselectivity (Scheme 10). This reaction was initiated by 6-*exo*-dig oxymercuration to generate spirocyclic aminal **74**. Subsequent ring opening of **74** was promoted by protonation with in situ-generated TfOH to give iminium intermediate **75**. The resulting iminium ion **75** underwent the Ferrier-type cyclization[32] to deliver azaspirocycle **76**, where the process minimized steric repulsion between the TBS ether-containing alkyl tether and the benzyloxymethyl group. Further four steps-transformation of **76** including deoxygenation of the carbonyl group provided aminoalcohol **77a** and (2*S*,5*S*,13*S*)-**65**. Finally, cyclodehydration under the modified Kibayashi's conditions[6,19] followed by debenzylation completed the synthesis of (−)-lepadiformine A (**14**) and B (**15**).



Scheme 10 Synthesis of (−)-lepadiformine A (**14**) and B (**15**) by Morimoto and co-workers.

The synthesis of (+)-lepadiformine C (**16**) was also accomplished by the analogous protocol from ynone *ent*-**73a** (Scheme 11). After spirocyclization of *ent*-**73a,** the resulting *ent*-**76a** was converted to carboxylic acid **78**, which was treated under the Okada's photo-decarboxylation conditions[33] to afford **79**. Final C-ring closure of **79** provided (+)-lepadiformine C (**16**). Optical rotation of (+)-lepadiformine C (**16**)·HCl ($[\alpha]_D^{25}$ +13.5 (*c* 0.85, $CHCl_3$)) was identical to that of natural product ($[\alpha]_D$ +11.0 (*c* 1.00, $CHCl_3$)).[8]

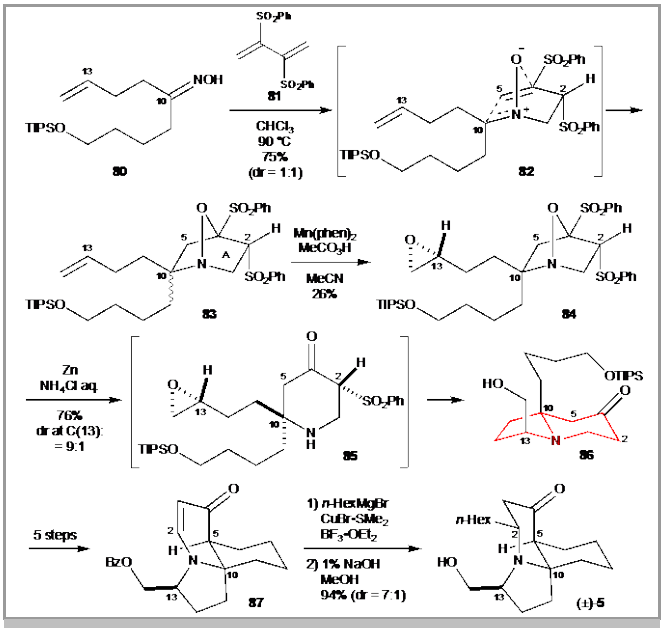


Scheme 11 Synthesis of (+)-lepadiformine C (**16**) by Morimoto and co-workers.

2.3. Indolizidine (AC ring) approaches

2.3.1. From A-ring

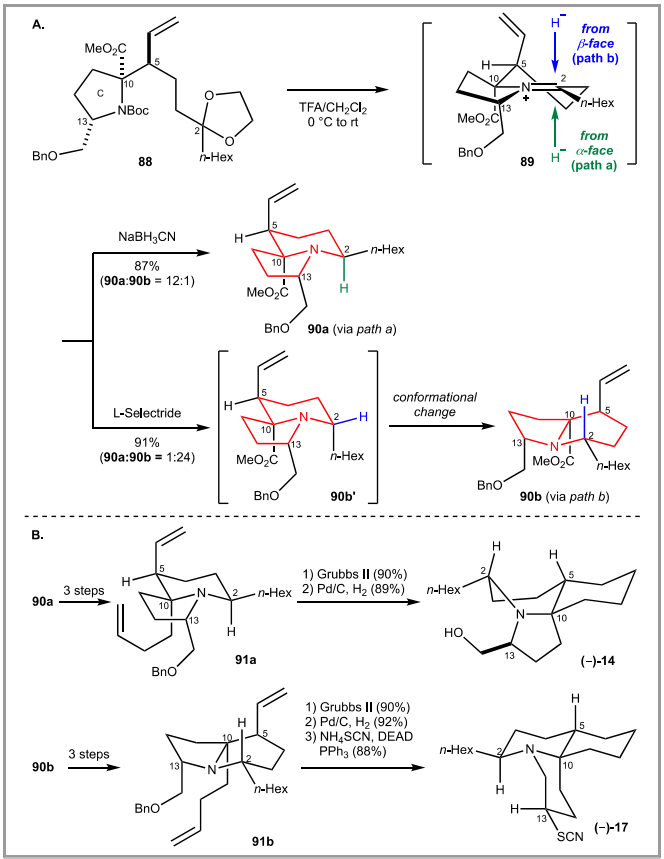
Padwa and co-workers reported the synthesis of (±)-cylindricine C (**5**) based on the indolizidine approach using conjugate addition/dipolar-cycloaddition cascade to construct fully substituted carbon center at C(10) (Scheme 12).[34,35] Conjugate addition of oxime **80** to diene **81** formed nitrone **82** and its subsequent 1,3-dipolar cycloaddition provided bicyclic isoxazolidine **83** as a 1:1 mixture of diastereomers. Epoxidation of a diastereomeric mixture of **83** by 1,10-phenanthroline manganese(II) catalyst with peracetic acid proceeded selectively for *exo*-**83** to provide **84** in 26% yield along with the recovery of *endo*-**83**.[36] The reductive N-O bond cleavage of **84** using combination of zinc and ammonium chloride furnished piperidone **85**.[37] Further reductive desulfonylation followed by construction of the A-ring via ring-opening of epoxide provided indolizidine **86** having the hydroxymethyl tether at C(13) (dr = 9:1). Indolizidine **86** was converted to enone **87** in five steps. Conjugate addition of hexyl cuprate under the modified Donohoe protocol[38] proceeded in diastereoselective manner from the pseudoequatorial position at C(2), that was followed by basic hydrolysis, furnishing (±)-cylindricine C (**5**) as a 7:1 mixture of diastereomers.



Scheme 12 Synthesis of (±)-cylindricine C (**5**) by Padwa and co-workers.

2.3.2. From C-ring

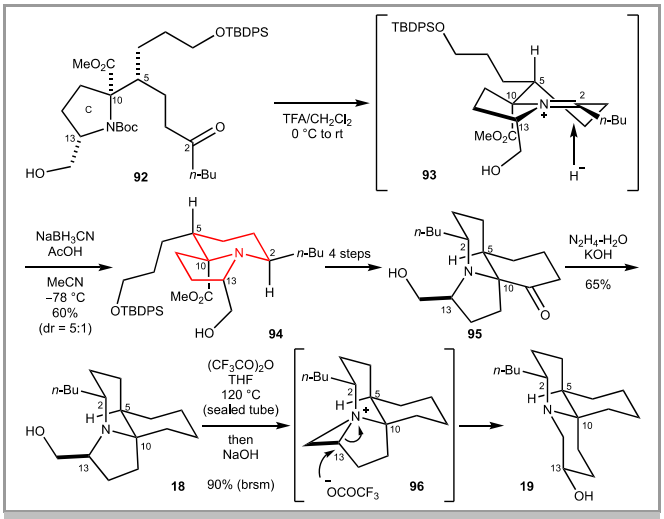
In 2014, Kim and co-workers reported the 2nd-generation synthesis of (−)-lepadiformine A (**14**) and (−)-fasicularin (**17**) (Scheme 13)[39a] since their previous formal synthesis of (−)-**14** reported in 2006.[39b] The key reaction in their 2nd-generation synthesis relied on diastereoselective reduction of iminium AC-ring to control stereochemistry of the hexyl side chain at C(2) (Scheme 13A). First of all, the chiral pyrrolidine **88** was treated with TFA to generate iminium AC-ring **89** through the removal of acetal and Boc protecting groups and subsequent condensation. The size of the hydride reductants affected stereoselectivity of the following reduction of the iminium ion **89**. The use of less hindered reductant, $NaBH_3CN$ provided indolizidine **90a** as a major isomer because a hydride prefers to approach to C(2) from the α-face based on the stereoelectronic effect whereby the nitrogen lone pair and the installed C-H bond are arranged preferentially in anti-coplanar (Scheme 13A, path a).[40] On the contrary, reduction of iminium ion **89** with bulky L-selectride resulted in opposite selectivity to initially form chair-**90b'** as a major isomer, which then flipped over to more stable boat-**90b** (Scheme 13A, path b). Bulky reductant presumably attacked from the β-face at C(2) to avoid its steric crash with the methoxycarbonyl group at C(10). The indolizidines **90a** and **90b** were converted into **91a** and **91b,** respectively, through installation of the homoallylic tether at C(10) (Scheme 13B). Synthesis of (−)-lepadiformine A (**14**) was accomplished by ring-closing metathesis of **91a** followed by debenzylation. Similarly, **91b** was converted into (−)-fasicularin (**17**) via ring-closing metathesis and debenzylation followed by installation of the SCN group and ring-expansion by following the Kibayashi's protocol.[4b]



Scheme 13 Synthesis of (−)-lepadiformine A (**14**) and (−)-fasicularin (**17**) by Kim and co-workers.

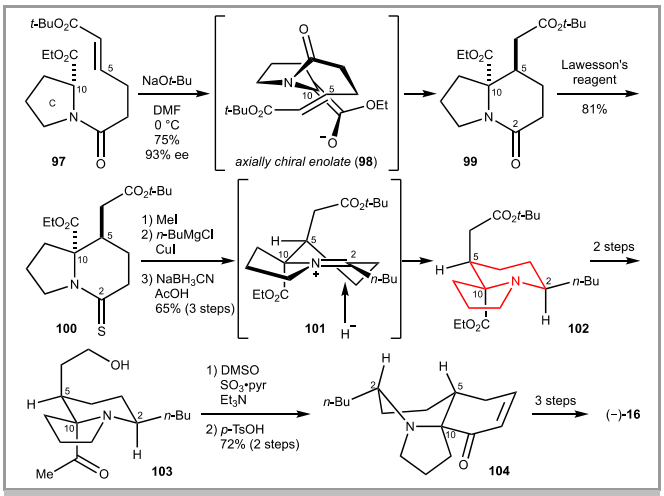
The synthesis of the proposed structure of polycitorol A (**18**) and B (**19**) were demonstrated in the same report by Kim (Scheme 14). After deprotection of the Boc group of pyrrolidine **92**, the resulting bicyclic iminium ion **93** was reduced using $NaBH_3CN$ in MeCN, that took place via the α attack of hydride ion at C(2) to provide indolizidine **94** as a major isomer (dr = 5:1), having *cis*-relationship between the methoxycarbonyl group at C(10) and the alkyl tether at C(5). Indolizidine **94** was further converted to tricycle **95** in four steps including

construction of the B ring. Finally, the Wolff-Kishner-Huang reduction of ketone **95** gave the proposed structure of polycitorol A (**18**).[41] The synthesis of the proposed structure of polycitorol B (**19**) was accomplished by ring expansion of **18** using trifluoroacetic anhydride by the analogous Cossy and Pardo's procedure[42] via aziridinium ion **96**. However, the NMR data of the synthetic samples of polycitorols A (**18**) and B (**19**) were not identical with those of natural ones.[12] The structural determination of polycitorols remains elusive yet.



Scheme 14 Synthesis of proposed structure of polycitorol A (**18**) and B (**19**) by Kim and co-workers.

Kim and co-workers in 2017 showed the asymmetric synthesis of (−)-lepadiformine C (**16**) by the intramolecular Michael addition of chiral proline ester **97** as the key step to construct the indolizidine skeleton (Scheme 15).[43] The treatment of **97** with NaO*t*-Bu generated axially chiral enolate **98**, that underwent subsequent Michael addition to provide indolizinone **99** in 93% ee without loss of the original chirality on **97**.[44] After conversion of the lactam moiety of **99** to thioamide **100**, methylation followed by alkylation with butyl cuprate generated iminium ion intermediate **101**,[45] that was subsequently treated with $NaBH_3CN$ to afford indolizidine **102** via diastereoselective α-attack of hydride. Indolizidine **102** was further transformed to keto alcohol **103** in two steps. The Parikh-Doering oxidation[46] of alcohol of **103** followed by intramolecular aldol condensation under acidic conditions provided tricycle **104**. The synthesis of (−)-lepadiformine C (**16**) was finally accomplished by hydrogenation and deoxygenation of C(9) carbonyl group in three steps.

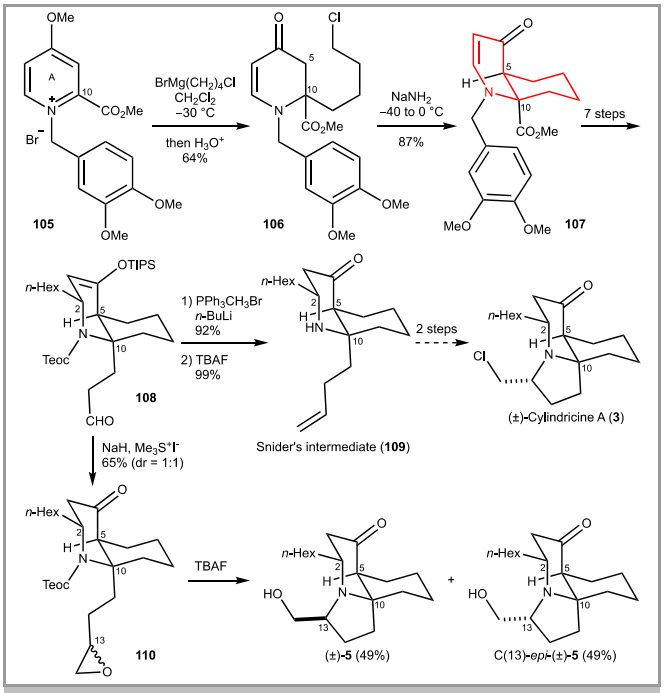


Scheme 15 Synthesis of (−)-lepadiformine C (**16**) by Kim and co-workers.

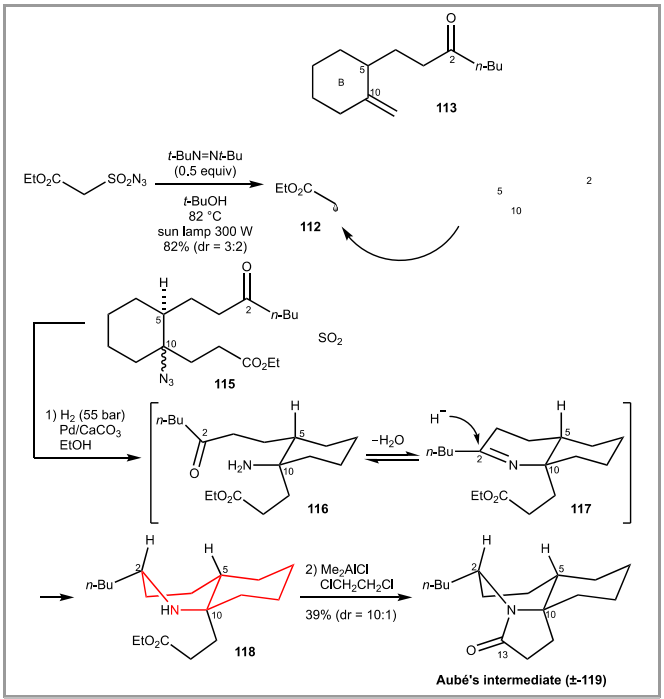
2.4. Azadecalin (AB ring) approaches

2.4.1. From A-ring

Donohoe and co-workers accomplished the formal and total synthesis of (±)-cylindricine A (**3**) and (±)-cylindricine C (**5**) based on the azadecalin approach (Scheme 16).[47] The construction of the azadecalin (AB ring) framework was commenced with regioselective addition of the Grignard reagent to electron-deficient pyridinium salt **105**.[38,48] The reaction of *N*-(3,4-dimethoxybenzyl)-pyridinium salt **105** with chlorobutylmagnesium bromide underwent regioselective addition at the C(10) position to give piperidone **106**. Sodium amide-mediated construction of the B-ring resulted in exclusive formation of *cis*-1-azadecalin **107**, which was converted to silyl enolate **108** in eight steps including installation of the hexyl side chain at C(2) and homologation at C(10). Olefination of the formyl group of azadecalin **108** followed by desilylation gave **109**, which is the reported intermediate for the synthesis of (±)-cylindricine A (**3**) by Snider and co-workers.[49] For the synthesis of (±)-cylindricine C (**5**), azadecalin **108** was treated under the Corey-Chaykovsky epoxidation conditions to give epoxide **110** as a 1:1 mixture of diastereomers.[50] Deprotection of the teoc group of **110** with TBAF promoted the final C-ring construction via aminative ring-opening of the epoxide at C(13) to give (±)-cylindricine C (**5**) and C(13)-*epi*-(±)-**5** in 98% overall yield.



Scheme 16 Formal and total synthesis of (±)-cylindricine A (**3**) and (±)-cylindricine C (**5**) by Donohoe and co-workers.



Scheme 17 Formal synthesis of (±)-lepadiformine C (**16**) by Renaud and co-workers.

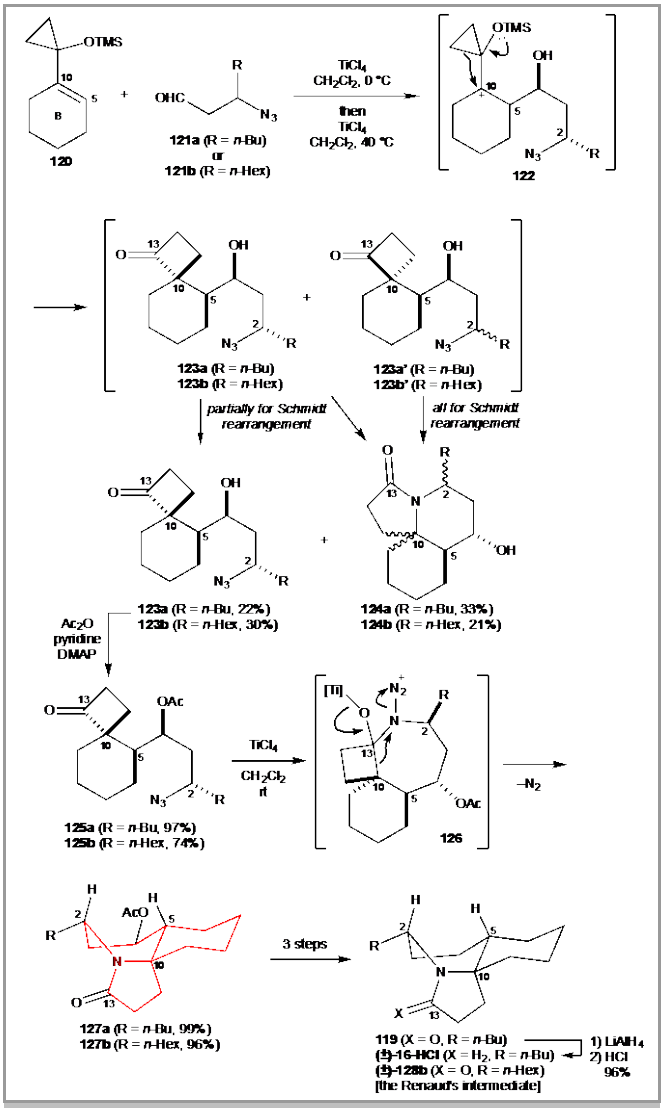
2.4.2. From B ring

Renaud and co-workers reported the formal synthesis of (±)-lepadiformine C (**16**) utilizing radical carboazidation of alkene (Scheme 17),[51,52] which was the updated protocol from their previous synthesis of (±)-lepadiformine A (**14**).[53] The key carboazidation was initiated from the reaction of sulfonyl azide **111** with di-*tert*-butyldiazene to generate electrophilic α-carbonyl radical **112**, that reacted with exo-methylene moiety of the B-ring synthon **113** to give alkyl radical **114**. Further desulfonylative transfer of the azide group from sulfonyl azide **111** provided carboazidation adduct **115** as a 3:2 mixture of diastereomers as well as initial radical **112** to propagate the radical chain process. To construct the azadecalin framework, azide **115** was reduced to amine **116** by hydrogenation. Subsequent formation of imine **117** followed by its hydride reduction from the less hindered β-face furnished *trans*-azadecalin **118** having the α-butyl group at C(2). Final lactamization of azadecalin **118** using Me_2AlCl afforded lactam **119**, which is the key intermediate in the synthesis of (±)-lepadiformine C (**16**) by Aubé and co-workers (vide infra, Scheme 18).

2.5. Tandem cyclization approaches

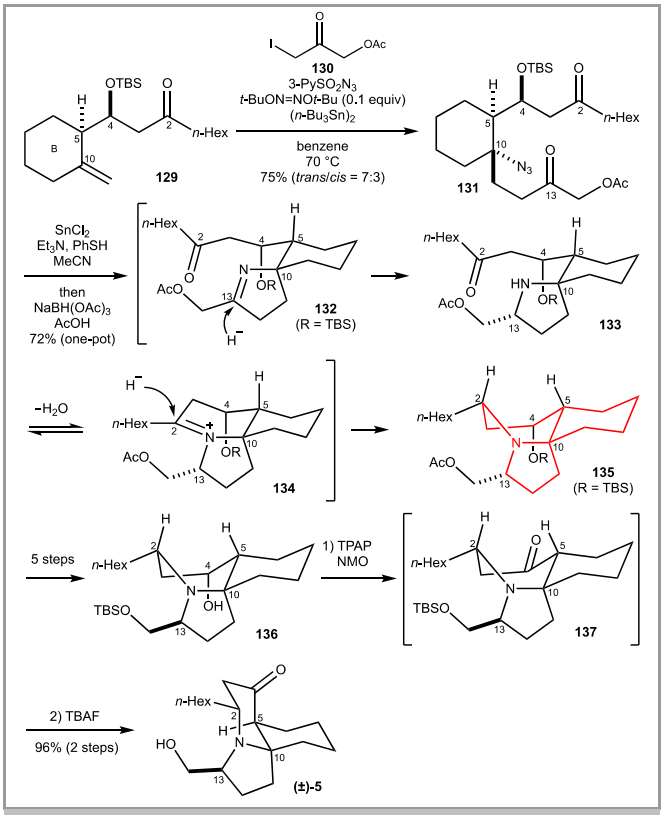
2.5.1. From B-ring

Aubé and co-workers reported the formal and total synthesis of (±)-lepadiformine A (**14**) and (±)-lepadiformine C (**16**) by using a sequence of the Prins and Schmidt reactions (Scheme 18).[54] Treatment of cyclopropane **120** and azidoaldehyde **121a-b** in the presence of $TiCl_4$ promoted the Prins reaction to give carbocation intermediate **122**, which underwent subsequent ring expansion to afford spirocyclobutanones **123a-b** and another diastereomer **123a'-b'**.[55] Interestingly, the subsequent Schmidt rearrangement converted all of **123a'-b'** to tricyclic lactam **124a-b**, while that of **123a-b** occurred partially to retain **123a-b** to allow for its isolation as a single diastereomer. After acetylation of the hydroxyl group of **123a-b**, the resulting acetate **125a-b** were treated with $TiCl_4$ to provide tricyclic lactam **127a-b** through the intramolecular Schmidt rearrangement of aza seven membered-ring intermediate **126**.[56] Formal synthesis of (±)-lepadiformine A (**14**) was accomplished by deoxygenation in the A-ring of lactam **127b**, giving the Renaud's intermediate **128b**.[53] Analogous deoxygenation of **127a** followed by reduction of amide **119** provided (±)-lepadiformine C (**16**), the structure of which was confirmed after formation of hydrochloride salt **16·HCl**.



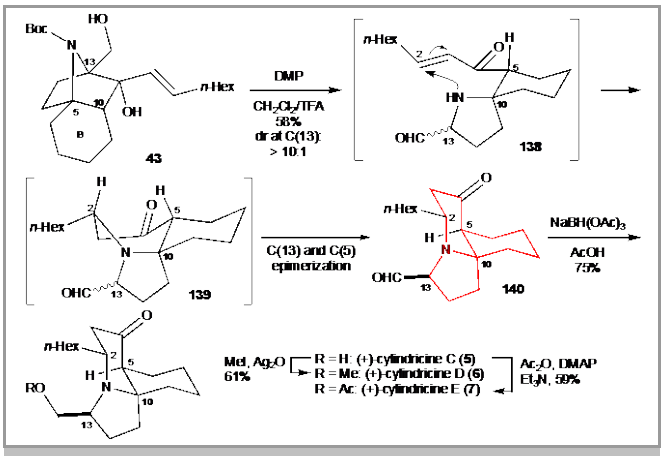
Scheme 18 Formal and total synthesis of (±)-lepadiformine A (**14**) and (±)-lepadiformine C (**16**) by Aubé and co-workers.

Renaud and co-workers reported the synthesis of (±)-cylindricine C (**5**) using double reductive amination for construction of the tricyclic core (Scheme 19).[57] Their synthesis was departed from radical carboazidation of alkene **129** and α-iodo ketone **130** in the presence of 3-pyridinesulfonyl azide for synthesis of tertiary azide **131** (*trans*/*cis* = 7:3). The resulting two diastereomers were separable and *trans*-**131** was utilized for the next double reductive amination, which was initiated from reduction of azide **131** with $SnCl_2$[58] to give cyclic imine **132** followed by the treatment with $NaBH(OAc)_3$ to afford azaspirocycle **133** in diastereoselective manner, in which hydride was delivered from the less hindered β-face of the C=N bond of **132**. Subsequently, the second reductive amination took place from **133** to give tricycle **135** via diastereoselective hydride reduction of iminium intermediate **134**, where hydride is delivered from the opposite side to the silyloxy group at C(4). After the stereochemical adjustment at C(13) (from **135** to **136**), the TPAP oxidation of the C(4)-hydroxy group of **136** to ketone **137** followed by TBAF-mediated desilylation and epimerization at C(5) furnished (±)-cylindricine C (**5**). Epimerization at C(5) under basic conditions readily underwent because the chair-chair conformation of **5** is thermodynamically more stable than the chair-boat conformation of **137**.[4b]



Scheme 19 Synthesis of (±)-cylindricine C (**5**) by Renaud and co-workers.

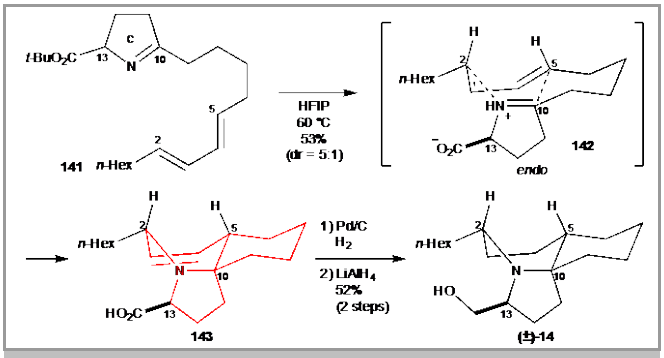
Pandey and Janakiram reported the synthesis of (+)-cylindricine C-E (**5**-**7**) (Scheme 20) during their synthetic study of (−)-lepadiformine A (**14**) (vide supra, Scheme 5).[21] The aforementioned key reaction was initiated by a sequence of oxidation of **43** followed by retro-aldol reaction to generate enone **45** (Scheme 5). Addition of TFA instead of acetic acid promoted further aza-Michael reaction of **138** at C(2) via in situ deprotection of the *N*-Boc moiety. Subsequent epimerization at C(13) and C(5) of **139** afforded tricycle **140**. Final reduction of the formyl group completed the synthesis of (+)-cylindricine C (**5**). (+)-Cylindricine C (**5**) was derivatized to (+)-cylindricine D (**6**) and (+)-cylindricine E (**7**) by *O*-methylation and acetylation, respectively.



Scheme 20 Synthesis of (+)-cylindricine C-E (**5**-**7**) by Pandey and Janakiram.

2.5.2. From C-ring

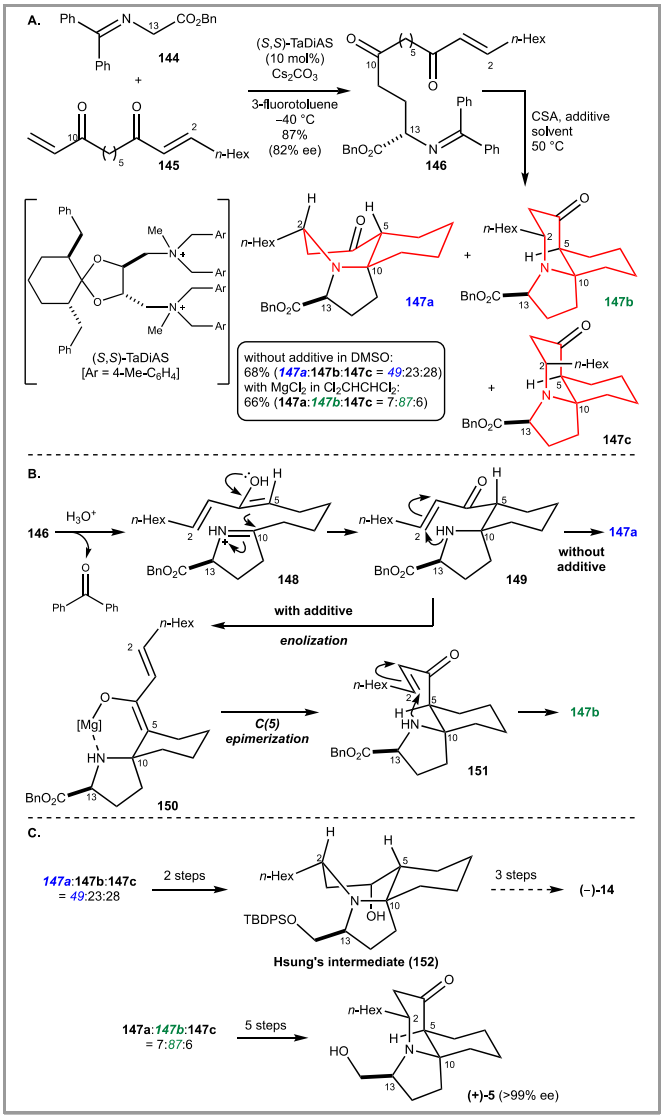
Lygo and co-workers reported the synthesis of (±)-lepadiformine A (**14**) using intramolecular hetero-Diels-Alder cycloaddition as a key step (Scheme 21).[59,60] The reaction of C-ring cyclic imine ester **141** having 1,3-diene moiety in HFIP elevated the cleavage of *tert*-butyl ester to generate iminium-carboxylate zwitter ion **142**. Subsequent intramolecular cycloaddition reaction of **142** via an *endo* transition state provided tricycle **143** as a major isomer (dr = 5:1). Moreover, the carboxyl group at C(13) favored to locate *anti* to the diene part. Finally, a sequence of olefin hydrogenation followed by reduction of the carboxylic acid afforded (±)-lepadiformine A (**14**).



Scheme 21 Synthesis of (±)-lepadiformine A (**14**) by Lygo and co-workers.

2.5.3. From acyclic substrates

Shibasaki and co-workers succeeded in the synthesis of (−)-lepadiformine A (**14**) and (+)-cylindricine C (**5**) using tandem cyclization to construct the tricyclic frameworks (Scheme 22).[61] Their synthesis was started from the asymmetric conjugate addition of imine **144** to dienone **145** using (*S*,*S*)-TaDiAS (tartrate-derived diammonium salt) as a phase transfer catalyst (Scheme 22A).[62] The reaction in the presence of Cs_2CO_3 in 3-fluorotoluene at −40 °C provided Michael adduct **146** in 82% ee. Tandem cyclization of **146** was promoted by CSA (camphorsulfonic acid) in DMSO to afford triclycle **147a** having the *trans*-1-azadecalin framework as a major isomer (68% yield, **147a**:**147b**:**147c** = 49:23:28). Interestingly, the reaction of **146** in the presence of $MgCl_2$ as an additive in $Cl_2CHCHCl_2$ dramatically increased the diastereoselectivity of **147b** bearing the *cis*-1-azadecalin skeleton (66% yield, **147a**:**147b**:**147c** = 7:87:6). This acid-promoted tandem cyclization was initiated by formation of cyclic imine **148** through elimination of benzophenone followed by dehydrative condensation (Scheme 22B). Subsequent intramolecular Mannich reaction of **148** afforded spirocycle **149**. In the absence of $MgCl_2$ additive, the aza-Michael cyclization proceeded to give tricycle **147a**. On the other hand, the addition of $MgCl_2$ promoted enolization of **149** to generate enol **150**, which was stabilized by chelation between the putative magnesium enolate and the pyrrolidine moiety. This enolization resulted in epimerization at C(5) to give *cis*-azadecalin **151**, before undergoing construction of the A-ring to give **147b** as a major product. Finally, formal synthesis of (−)-lepadiformine A (**14**) was accomplished by the conversion of **147a** to the Hsung's intermediate **152** in two steps (Scheme 22C).[4c] The synthesis of enantiopure (+)-cylindricine C (**5**) was achieved via five steps-transformation from **147b** involving installation of the hydroxymethyl group at C(13).



Scheme 22 Formal and total synthesis of (−)-lepadiformine A (14) and (+)-cylindricine C (**5**) by Shibasaki and co-workers.

3. Summary and future perspective

This review highlighted recent syntheses of tricyclic marine alkaloids, cylindricines, lepadiformines, fasicularin, and polycitorols based on the key approaches of the ring construction. Table 1 summarizes reported syntheses of these tricyclic alkaloids according to the types of the key cyclic intermediates in chronological order. Numerous synthetic efforts showcased a variety of unprecedented and elegant linchpin methodologies to construct the tricyclic scaffolds. As majority of the reports in this review relied on linear step synthesis, a next challenge should be to develop divergent strategies for construction of the tricyclic alkaloids using common late-stage intermediates.[63] The employment of divergent total synthesis is able to deliver various analogs of the target natural products and accelerate the discovery of novel and potent biologically active derivatives.

Table 1 A summary of the total syntheses of tricyclic alkaloids.

Author	Approach	Molecules	Steps
Craig (2007)[14]	Azaspirocycle	(±)-lepadiformine A (**14**)	15
Rychnovsky (2010)[16]	Azaspirocycle	(−)-lepadiformine C (**16**)	18
Zhao (2010)[19]	Azaspirocycle	(−)-lepadiformine A (**14**) (−)-fasicularin (**17**)	20 21
Tokuyama (2010)[29]	Azaspirocycle	(±)-lepadiformine A (**14**)	20
Rychnovsky (2012)[16]	Azaspirocycle	(−)-lepadiformine A (**14**) (−)-lepadiformine B (**15**)	22 22
Pandey (2015)[21]	Azaspirocycle	(−)-lepadiformine A (**14**)	29
Shenvi (2015)[23]	Azaspirocycle	(±)-lepadiformine A (**14**)[a]	11[b]
Chiba (2016)[24]	Azaspirocycle	(±)-fasicularin (**17**)	19
Morimoto (2015, 2017)[31]	Azaspirocycle	(−)-lepadiformine A (**14**) (−)-lepadiformine B (**15**) (+)-lepadiformine C (**16**)	16 16 19
Robinson (2017)[27]	Azaspirocycle	(−)-lepadiformine A (**14**) (−)-fasicularin (**17**)	9 10
Padwa (2008, 2010)[34]	Indolizidine	(±)-Cylindricine C (**5**)	14
Kim (2014)[39a]	Indolizidine	(−)-lepadiformine A (**14**) (−)-fasicularin (**17**) Polycitorol A (**18**) Polycitorol B (**19**)	12 13 17 18
Kim (2017)[43]	Indolizidine	(−)-lepadiformine C (**16**)	12
Donohoe (2010)[47]	Azadecalin	(±)-Cylindricine A (**3**)[a] (±)-Cylindricine C (**5**)	15[b] 13
Renaud (2010)[51]	Azadecalin	(±)-lepadiformine C (**16**)[a]	8[b]
Shibasaki (2006, 2007)[61]	Tandem	(+)-Cylindricine C (**5**) (−)-lepadiformine A (**14**)[a]	9 6[b]
Lygo (2008)[59]	Tandem	(±)-lepadiformine A (**14**)	9
Aubé (2010)[54]	Tandem	(±)-lepadiformine A (**14**)[a] (±)-lepadiformine C (**16**)	12[b] 7
Renaud (2011)[57]	Tandem	(±)-Cylindricine C (**5**)	16
Pandey (2015)[21]	Tandem	(+)-Cylindricine C (**5**) (+)-Cylindricine D (**6**) (+)-Cylindricine E (**7**)	24 25 25

[a] Formal syntheses. [b] Number of steps include conversion of the reported intermediates to the natural products in the original total syntheses.

Acknowledgment

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Biosketches

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