SYNTHESIS OF MARINE TRICYCLIC ALKALOIDS

DOI: http://dx.medra.org/10.17374/targets.2026.29.378

Haruhiko Fuwa, Shunta Nakao

Department of Applied Chemistry, Faculty of Science and Engineering, Chuo University
1-13-27 Kasuga, Bunkyo-ku, Tokyo 112-8551, Japan
(e-mail: hfuwa.50m@g.chuo-u.ac.jp)

Abstract. *Marine tricyclic alkaloids, including lepadiformines, cylindricines, and fasicularin, continue to be intriguing targets for the synthetic community because of their unique perhydropyrrolo[2,1-j]quinoline or perhydropyrido[2,1-j]quinoline skeleton. This article summarizes recent advances in the total synthesis of marine tricyclic alkaloids, highlighting creative synthetic strategies developed to construct their synthetically challenging skeletons.*

Contents

1. Introduction

The family of marine tricyclic alkaloids, including lepadiformines, cylindricines, and fasicularin, has long been an intriguing target for the synthetic community because of their unique perhydropyrrolo[2,1-*j*]quinoline or perhydropyrido[2,1-*j*]quinoline skeletal structure (Figure 1).[1-3] The structural diversity within this family of alkaloids arises from the substituent, oxidation, and stereochemistry of the tricyclic skeleton.

(−)-Lepadiformine A **1**, the representative member of this family of marine alkaloids, was isolated by Biard from the marine Tunisian tunicate *Clavelina lepadiformis* Müller as a moderately cytotoxic constituent.[4] The gross structure and relative configuration of this natural alkaloid was initially assigned by chemical and spectroscopic analyses. However, Kibayashi eventually corrected the structure by total synthesis.[5] The absolute configuration of (−)-**1** was established by Weinreb through enantioselective total synthesis and derivatization/spectroscopic analysis of natural and synthetic materials.[6] Almost simultaneously, Kibayashi also reached the same conclusion on the absolute configuration through enantioselective total synthesis and chiral HPLC analysis of natural and synthetic (−)-**1**.[7] Lepadiformines B **2** and C **3** were later identified by Sauviat from *C. moluccensis* collected in Djibouti. Importantly, lepadiformines inhibited inward rectifying K^+ current in cardiac muscle.[8]

Cylindricines A-K **4**-**14** were isolated by Blackman from Tasmanian ascidian *Clavelina cylindrica*.[9-11] The gross structure including relative configuration of cylindricines A **4** and B **5** was established through single crystal X-ray crystallographic analysis.[9] The remainder of cylindricines was structurally characterized mainly by NMR spectroscopic analysis in comparison with **4** and **5**.[10,11] Because Blackman did not report the specific rotation of cylindricines in the isolation papers, the absolute configuration of these natural alkaloids cannot be established unambiguously. However, it is more than likely that the absolute configuration of cylindricines should be the same as that of (−)-lepadiformine A **1**.

Fasicularin **15** was isolated by Patil from the ascidian *Nephteis fasicularis* collected in Pohnpei.[12] The gross structure and relative configuration of **15** were assigned based on NMR spectroscopic analysis coupled with HRMS and IR data. Meanwhile, the absolute configuration was left unassigned, and the specific rotation of the natural isolate was not described in the isolation paper. Fasicularin **15** exhibits DNA damaging activity by alkylation of guanine residues *via* the formation of an aziridinium ion and moderate cytotoxic activity in Vero cells.[13]

Because of their compact yet complex structures, marine tricyclic alkaloids have been a source of inspirations for synthetic chemists; and a body of publications has illustrated creative synthetic approaches toward this family of natural alkaloids.[1-3] This article will give an overview of further advances in total syntheses of marine tricyclic alkaloids from 2017 to 2024.

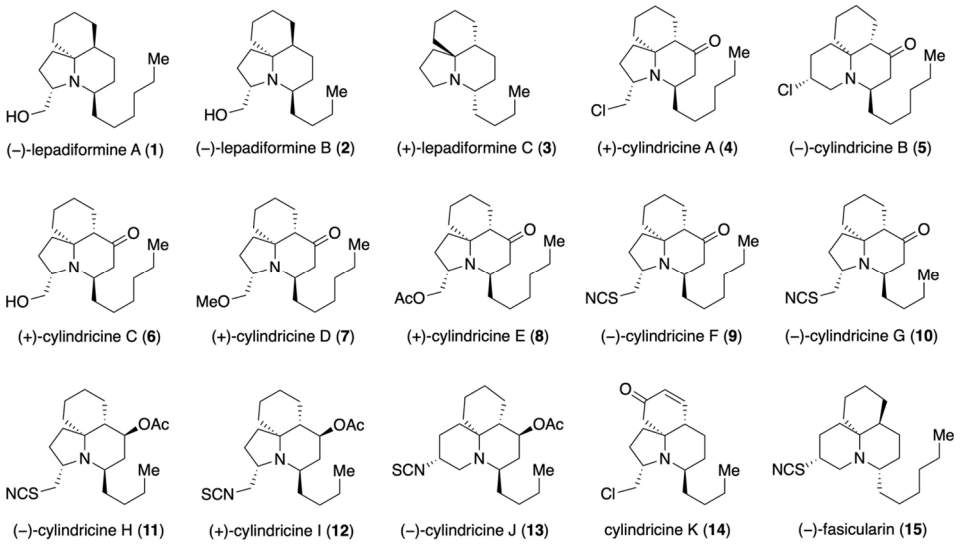
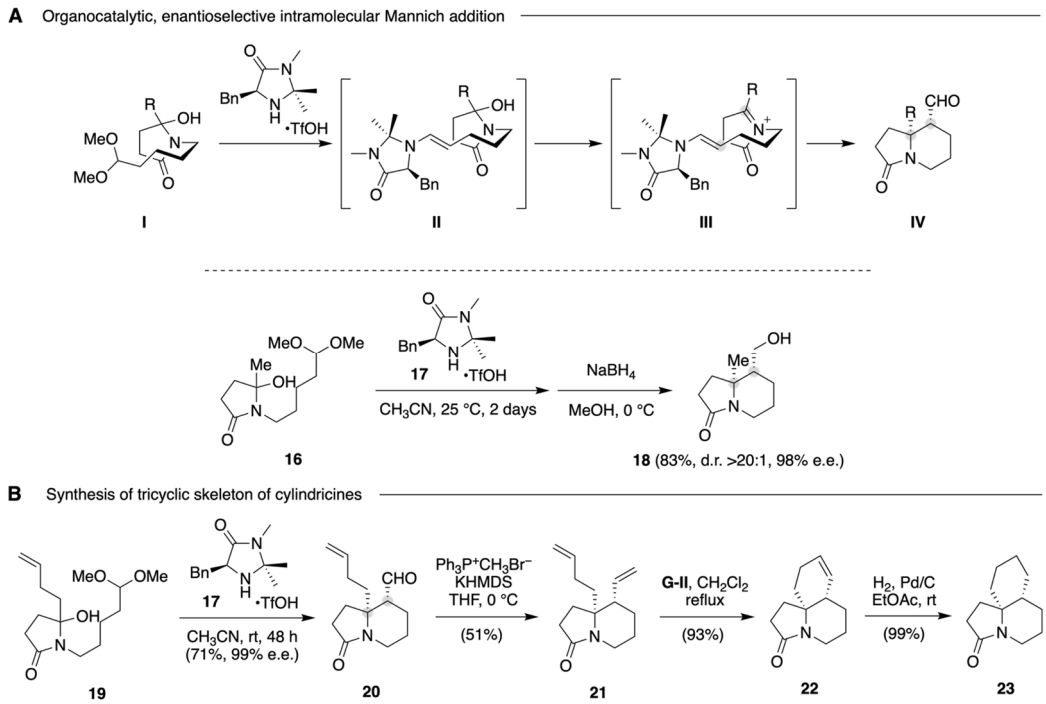


Figure 1. Structures of marine tricyclic alkaloids.

2. Synthesis of the tricyclic skeleton of cylindricines by Koley

One of the challenging issues common to the synthesis of marine tricyclic alkaloids would be the stereocontrolled construction of the nitrogen-substituted quaternary carbon center. Koley envisioned an organocatalytic asymmetric Mannich cyclization of dimethyl acetal-tethered *N*,*O*-hemiaminals for the synthesis of bicyclic lactams having a bridgehead nitrogen-substituted quaternary carbon (Scheme 1).[14] Specifically, *N*,*O*-hemiaminals **I** could be transformed into enamines **II** through an acetal deprotection-enamine formation with a chiral imidazolidinone catalyst.[15,16] Enamines **II** then undergo an *N*-acyl iminium ion formation and subsequent intramolecular Mannich addition[17,18] of the derived iminium ions **III** to deliver bicyclic lactams **IV** (Scheme 1A). The relative configuration of the two contiguous stereogenic centers would be controlled *via* a chair-like transition state. Using *N*,*O*-hemiaminal **16** as a model compound, screening of chiral imidazolidinone catalysts and reaction conditions determined the optimal conditions. Thus, **16** was exposed to catalyst **17** (10 mol%) in CH_3CN at 25 °C to give, after $NaBH_4$ reduction, bicyclic lactam **18** in 83% yield with >20:1 diastereoselection and 98% e.e.

The organocatalytic, asymmetric Mannich cyclization reaction was eventually applied to the synthesis of the tricyclic skeleton of cylindricines (Scheme 1B). *N*,*O*-Hemiaminal **19** was prepared from the corresponding imide *via* an addition of 3-butenylmagnesium bromide (85%). Treatment of **19** with chiral imidazolidinone catalyst **17** (10 mol%) in CH_3CN at room temperature for two days provided bicyclic lactam **20** in 71% yield with 99% e.e. Wittig methylenation of **20** gave olefin **21** (51%), which underwent ring-closing metathesis[19,20] under the influence of the second-generation Grubbs catalyst **G-II** to furnish tricycle **22** (93%). Hydrogenation of **22** furnished the tricyclic skeleton **23** of cylindricines in a near quantitative yield.[14] Thus, an expedient access to the tricyclic skeleton of cylindricines was achieved by exploiting Koley's asymmetric Mannich cyclization strategy.



Scheme 1. Koley's enantioselective Mannich cyclization strategy for the synthesis of tricyclic skeleton of cylindricines.

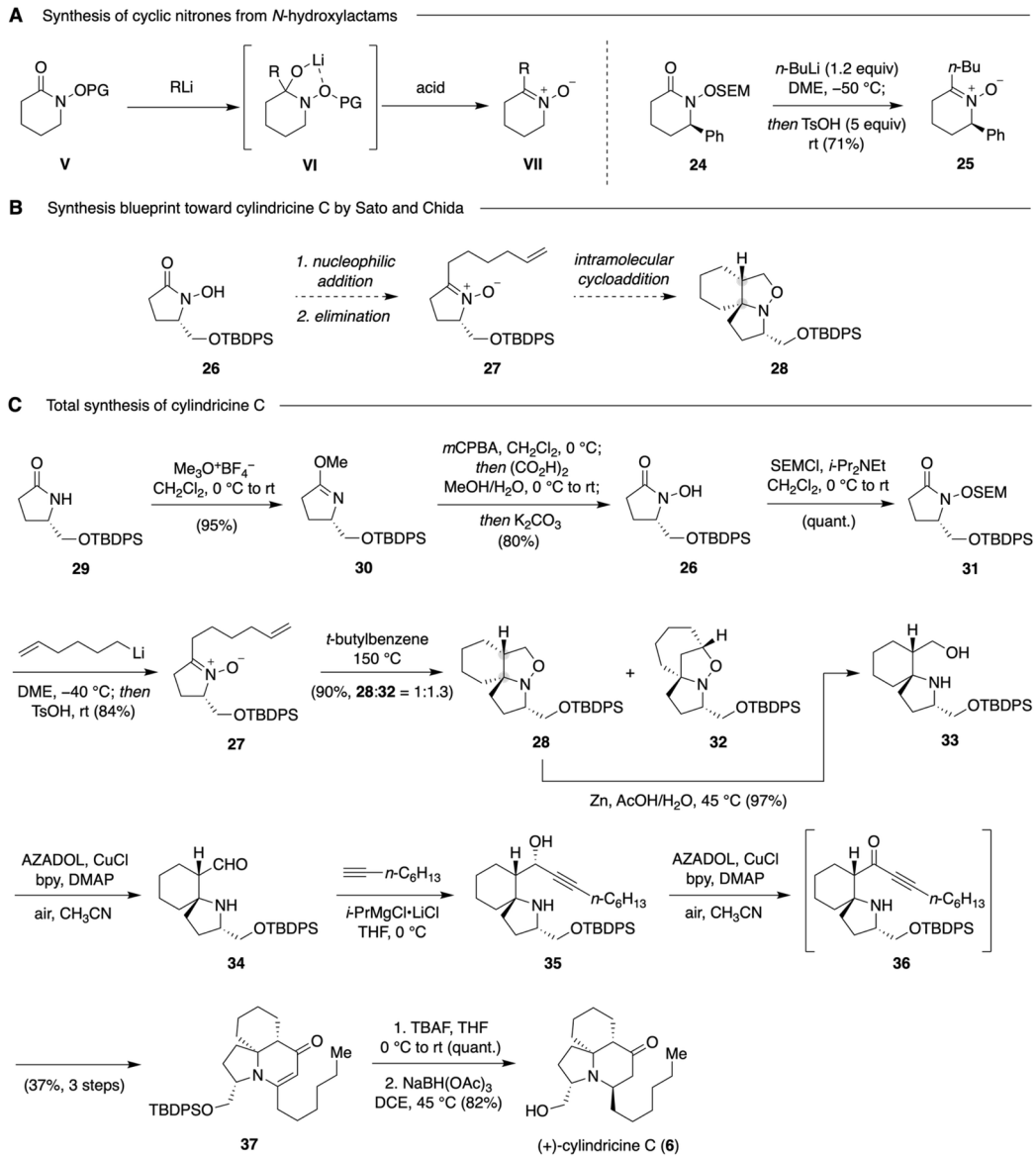
3. Total syntheses of (+)-cylindricine C and (−)-fasicularin by Sato and Chida

3.1. Total synthesis of (+)-cylindricine C

The Sato/Chida group developed an efficient method for the synthesis of fully substituted cyclic nitrones from *N*-hydroxyamide derivatives (Scheme 2A). A nucleophilic addition of organolithiums to *N*-hydroxylactams **V**[21] generates five-membered coordinated intermediates **VI**. An elimination of H_2O and removal of the protecting group from **VI** occur upon *in situ* acid treatment, giving rise to cyclic nitrones **VII**. A series of protecting groups and acids were screened to optimize the reaction using six-membered *N*-hydroxylactams and *n*-BuLi to identify a combination of SEM group and TsOH as the best choice. Specifically, SEM-protected *N*-hydroxylactam **24** was reacted with *n*-BuLi (1.2 equiv) in DME at −50 °C and then with TsOH (5 equiv) at room temperature to afford cyclic nitrone **25** in 71% yield.[22]

The above encouraging result led the Sato/Chida group to envision that *N*-hydroxylactam **26** would be transformable to cyclic nitrone **27**, which in its turn should participate in an intramolecular [3+2]-cycloaddition[23,24] to produce isoxazolidine **28** (Scheme 2B). Compound **28** represents the spirocyclic pyrrolidine framework embedded within (+)-cylindricine C **6**.

Total synthesis of (+)-cylindricine C **6** started with treatment of lactam **29** with Meerwein reagent to deliver *O*-methylimidate **30** (95%), which was transformed to *N*-hydroxylactam **26** (80%) through a sequence of *m*CPBA oxidation, hydrolysis of the derived oxaziridine, and subsequent lactamization (Scheme 2C). After protection of **26** as its SEM ether (quant.), nucleophilic addition of 5-hexenyl lithium to *N*-OSEM lactam **31** afforded, after *in situ* acid treatment, cyclic nitrone **27** (84%).



Scheme 2. Total synthesis of (+)-cylindricine C by the Sato/Chida group.

Intramolecular [3+2]-cycloaddition of **27** in *t*-butylbenzene at 150 °C provided a mixture of isoxazolidine **28** and its isomer **32** in 90% yield with 1:1.3 selectivity (Scheme 2C). These isomers were

separated by MPLC purification. Reductive cleavage of the N–O bond of **28** gave amino alcohol **33** (97%). Chemoselective oxidation of the resultant primary alcohol under Iwabuchi conditions (AZADOL, CuCl, bpy, DMAP, air),[25] addition of an acetylide prepared from 1-octyne/*i*-PrMgCl•LiCl to the derived aldehyde **34**, and subsequent Iwabuchi oxidation of the resultant propargylic alcohol **35** delivered dihydropyridone **37** through an intramolecular aza-Michael addition of amino ynone **36**. Finally, removal of the TBDPS group with TBAF (quant.), followed by directed reduction with $NaBH(OAc)_3$, furnished (+)-cylindricine C **6** in 82% yield.[22] The brevity of the present synthesis of (+)-cylindricine C, completed in 12 steps from L-pyroglutaminol, is ascribable to the rapid generation of complex isoxazolidine **28** from *N*-hydroxylactam **26** through cyclic nitrone **27**.

3.2. Total synthesis of (−)-fasicularin

N-Alkoxyamides are known to show unique reactivity when compared to typical amides. Specifically, the most nucleophilic reaction site of amides is the oxygen atom, whereas that of *N*-alkoxyamides is the nitrogen atom. The Sato/Chida group exploited the unique reactivity of *N*-alkoxyamides to generate cyclic iminium ions for the synthesis of fasicularin (Scheme 3A).

Thus, they envisioned that, by taking advantage of the enhanced nucleophilicity of the nitrogen atom of *N*-alkoxyamides,[26,27] keto *N*-alkoxyamides **VIII** should serve as a viable precursor for cyclic iminium ions **IX**,[27–29] which would then undergo an intramolecular allylation to furnish spirocyclic lactam **X** in a stereocontrolled fashion. The stereochemical consequence of the intramolecular allylation could be rationalized by a chair-like transition state. Moreover, they anticipated that an enantioselective synthesis of **X** might be possible by introducing chirality to 'R' of the *N*-alkoxy group.

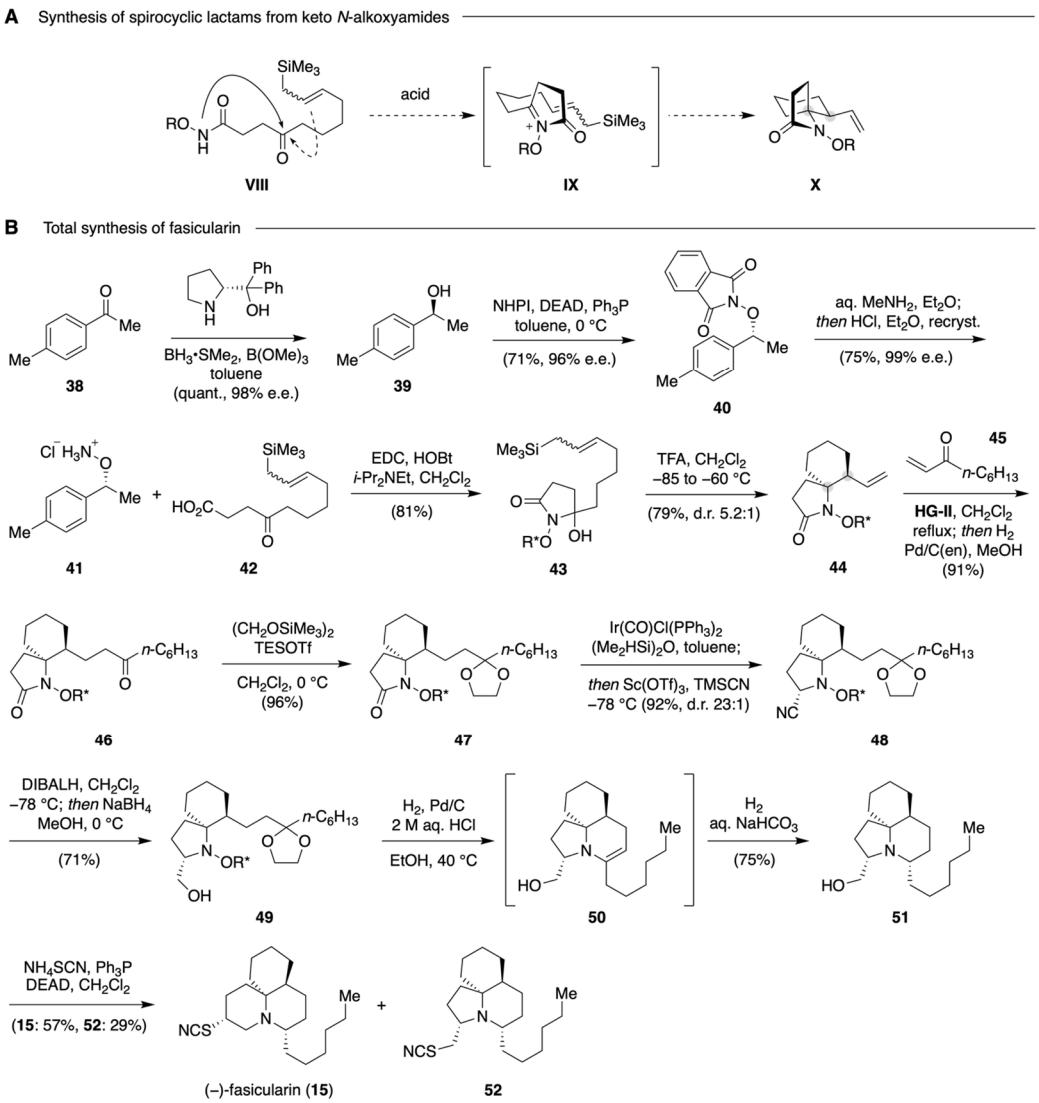
Total synthesis of (−)-fasicularin **15**, shown in Scheme 3B, commenced with Corey-Bakshi-Shibata (CBS) reduction[30] of ketone **38** to give alcohol **39** (quant., 98% e.e.). Mitsunobu reaction[31] of **39** with *N*-hydroxyphthalimide provided *N*-alkoxyimide **40** (71%, 96% e.e.). After cleavage of the phthalimide moiety by methylamine, *N*-alkoxyamine hydrochloride **41** was obtained in 75% yield with 99% e.e. after recrystallization. Condensation of **41** with keto carboxylic acid **42** under standard conditions delivered cyclic hemiaminal **43** (81%). Upon treatment of **43** with TFA (CH_2Cl_2, −85 to −60 °C), intramolecular allylation of cyclic iminium ion generated from **43** occurred to afford spirocyclic lactam **44** in 79% yield with 5.2:1 diastereoselectivity. Olefin cross-metathesis of **44** with vinyl ketone **45** under the influence of the second-generation Hoveyda-Grubbs (**HG-II**) complex, followed by *in situ* hydrogenation, gave ketone **46** (91%). After masking the keto group under Noyori conditions (96%), iridium-catalyzed hydrosilylation[32] of **47** and *in situ* Strecker reaction provided nitrile **48** (92%, d.r. 23:1). Reduction of **48** with DIBALH and then with $NaBH_4$ gave alcohol **49** (71%). Hydrogenolysis of the chiral auxiliary and spontaneous acidic hydrolysis of the dioxolanyl group led to enamine **50**, which was then reduced to tricycle **51** in a stereoselective manner upon basification of the reaction medium. According to the Kiyabashi procedure,[33] **51** was reacted with NH_4SCN under Mitsunobu conditions to furnish (−)-fasicularin (57%) along with its non-ring-expanded isomer **52** (29%). The undesired isomer **52** could be isomerized to (−)-fasicularin *via* an aziridinium ion, simply by stirring **52** in CH_3CN at room temperature (57%). The present total synthesis of (−)-fasicularin **15** proceeded in 11 steps from 4'-methylacetophenone.[34]

4. Formal syntheses of (−)-lepadiformines A and C and (−)-fasicularin by Takashima and Toyooka

The Toyooka group described the stereodivergent syntheses of indolizidine, quinolizidine, and decahydroquinoline alkaloid natural products by exploiting stereoselective derivatization of chiral lactam scaffolds.[35] The synthetic blueprint toward marine tricyclic alkaloids, (−)-lepadiformines A **1** and C (*ent*-**3**) and (−)-fasicularin **15**, made by the Toyooka group is summarized in Scheme 4A. Here, the ring designation is according to that of the isolation papers of cylindricines[9] and fasicularin.[12] According to their earlier works,[36,37] chiral lactam **53** should serve as a precursor for oxazolidinone **54**. A diastereoselective double allylation of **54** and a ring-closing metathesis of the resultant diene would enable an access to the common decahydroquinoline skeleton **55** of marine tricyclic alkaloids.

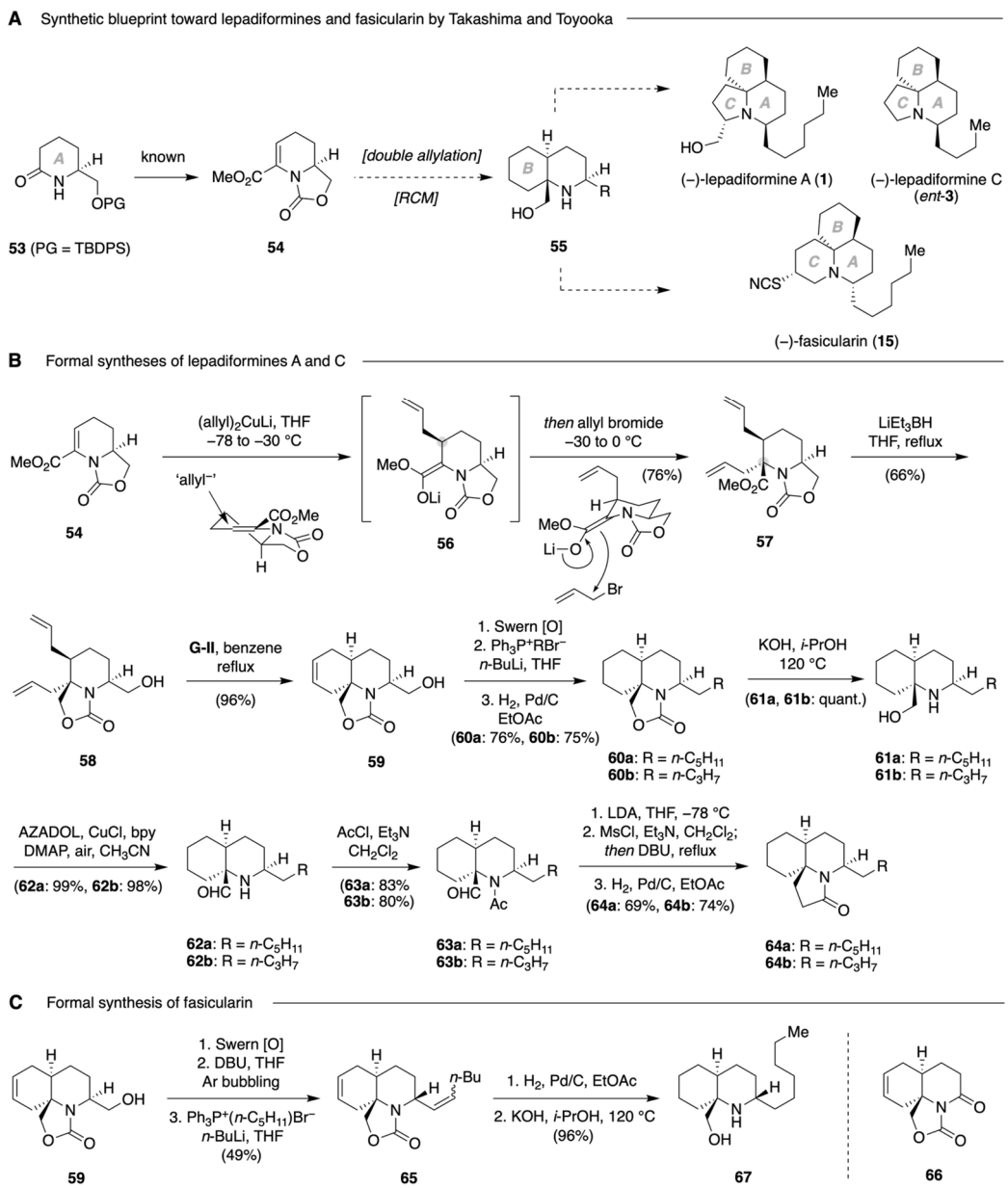
Diastereoselective diallylation of **54** was achieved by initial treatment with $(allyl)_2CuLi$ (THF, −78 to −30 °C) to generate lithium enolate **56** through a stereoelectronically favored, chair-like transition state. (Scheme 4B). Subsequent addition of allyl bromide resulted in stereoselective allylation of **56** from the α-face

to avoid unfavorable torsional strain, giving rise to diallylated product **57** in 76% yield as a single diastereomer. Reduction of **57** with $LiEt_3BH$ delivered, after an intramolecular *O*-acyl migration, alcohol **58** (66%). Upon exposure of **58** to **G-II** in benzene under reflux, ring-closing metathesis occurred to afford tricyclic alcohol **59** (96%). Oxidation under Swern conditions, Wittig olefination, and hydrogenation provided decahydroquinolines **60a**,**b**. Alkaline cleavage of the oxazolidinone gave alcohols **61a**,**b**, which were oxidized chemoselectively under Iwabuchi conditions (AZADOL, bpy, CuCl, DMAP, air) to afford aldehydes **62a**,**b**. After *N*-acetylation, the resultant acetamides **63a**,**b** underwent intramolecular cyclization upon exposure to LDA.



Scheme 3. Total synthesis of (−)-fasicularin by the Sato/Chida group.

Mesylation of the derived alcohols, DBU-mediated elimination, and ensuing hydrogenation furnished tricyclic lactams **64a**,**b**, which successfully intercepted the total synthesis of (±)-lepadiformine A **1** by Renaud[38] and the total synthesis of (±)-lepadiformine C (*ent*-**3**) by Aubé,[39] respectively.



Scheme 4. Formal syntheses of lepadiformines A and C and fasicularin by Takashima and Toyooka.

Meanwhile, Swern oxidation of **59**, epimerization of the derived aldehyde with DBU, and Wittig olefination provided olefin **65** (49%, three steps), as shown in Scheme 4C. Here, it was essential to bubble

argon gas into the reaction mixture during the DBU-mediated epimerization; otherwise, oxidative deformylation by residual oxygen in the reaction medium occurred to give lactam **66** as the major product.[41] Hydrogenation of **65** followed by alkaline hydrolysis afforded decahydroquinoline **67** (96%, two steps), which represents the advanced intermediate in the total synthesis of (±)-fasicularin **15** by Funk.[40] Thus, formal syntheses of (−)-lepadiformines A **1** and C (*ent*-**3**) and (−)-fasicularin **15** were achieved by diversification of tricyclic alcohol **59**.

5. Total synthesis of (−)-lepadiformine A by Tokuyama

Tokuyama and coworkers developed a radical translocation/cyclization strategy toward stereoselective synthesis of azaspirocyclic alkaloid natural products, such as (±)-lepadiformine A[42] and (−)-histrionicotoxin.[43] It was envisioned that *N*-(2-iodo-4-methoxybenzyl)lactam **68** should serve as a suitable precursor for their prospective radical translocation/cyclization to deliver spirocyclic lactam **71** through radical intermediates **69** and **70** (Scheme 5A). The spirocyclic lactam **71** represents the B/C-ring skeleton of (−)-lepadiformine A **1**.

The Tokuyama synthesis of (−)-lepadiformine A **1**, shown in Scheme 5B, started with alkylation of sulfone **72**, available in three steps from succinimide,[42] to give olefin **73** (64%). Ozonolysis of **73** and reductive workup (O_3; then $NaBH_4$) delivered alcohol **74** (75%). Krische asymmetric allylation[44] of **74** under standard conditions afforded homoallylic alcohol **75** in 81% yield with 94% e.e. After migration of the double bond (**HG-II**, ethyl vinyl ether, 85%),[45] alcohol **76** was acylated with acryloyl chloride/*i*-Pr_2NEt (84%) and then subjected to ring-closing metathesis under the influence of **HG-II**, giving rise to the key intermediate **68** (86%). Upon treatment of **68** with Bu_3SnH in the presence of AIBN in refluxing benzene, radical translocation/cyclization occurred to afford spirocyclic lactam **71** in 71% yield with 94% e.e. as the sole product. The stereochemical consequence of the cyclization would be accounted for by a Beckwith-Houk chair-like transition model, in which inversion of the sp^3 radical occurs rapidly to avoid unfavorable steric crash, thereby installing the C5 and C10 stereogenic centers simultaneously with complete stereochemical control. Reductive opening of the γ-lactone within **71** gave a diol ($LiBH_4$, 88%), which was silylated selectively to deliver alcohol **77** (TBDPSCl, imidazole, 92%). Barton-McCombie deoxygenation of **77** *via* a xanthate provided silyl ether **78**. After desilylation with TBAF (quant.), the resultant alcohol was transformed into ketone **79** through a sequence of mesylation (MsCl, Et_3N, 91%), cyanation (KCN, 97%), and Grignard addition (*n*-hexylMgBr, 77%). Reduction of **79** with L-selectride provided alcohol **80** in 85% yield albeit with moderate diastereoselectivity (1.6:1). These diastereomers were separated by flash column chromatography using silica gel, and the minor diastereomer could be oxidized back to **79** quantitatively. After silylation of **80** (TBDPSCl, imidazole, 90%), the PMB group was removed with CAN to afford lactam **81** (74%). Treatment of **81** with $Ti(O\textit{i}\text{-}Pr)_4/Ph_2SiH_2$[46] generated the corresponding imine, which without isolation was reacted with allylmagnesium bromide/$ZnCl_2$ to deliver olefin **82** in 78% yield as a single diastereomer. Desilylation of **82** with TBAF (92%), followed by intramolecular cyclization under Kibayashi conditions (CBr_4, Ph_3P, Et_3N, DMAP),[7,33] afforded tricycle **83** (76%). Olefin migration (**HG-II**, ethyl vinyl ether, 80%) and subsequent ozonolysis/reductive workup (O_3; then $NaBH_4$) then furnished (−)-lepadiformine A **1** (93%).[47]

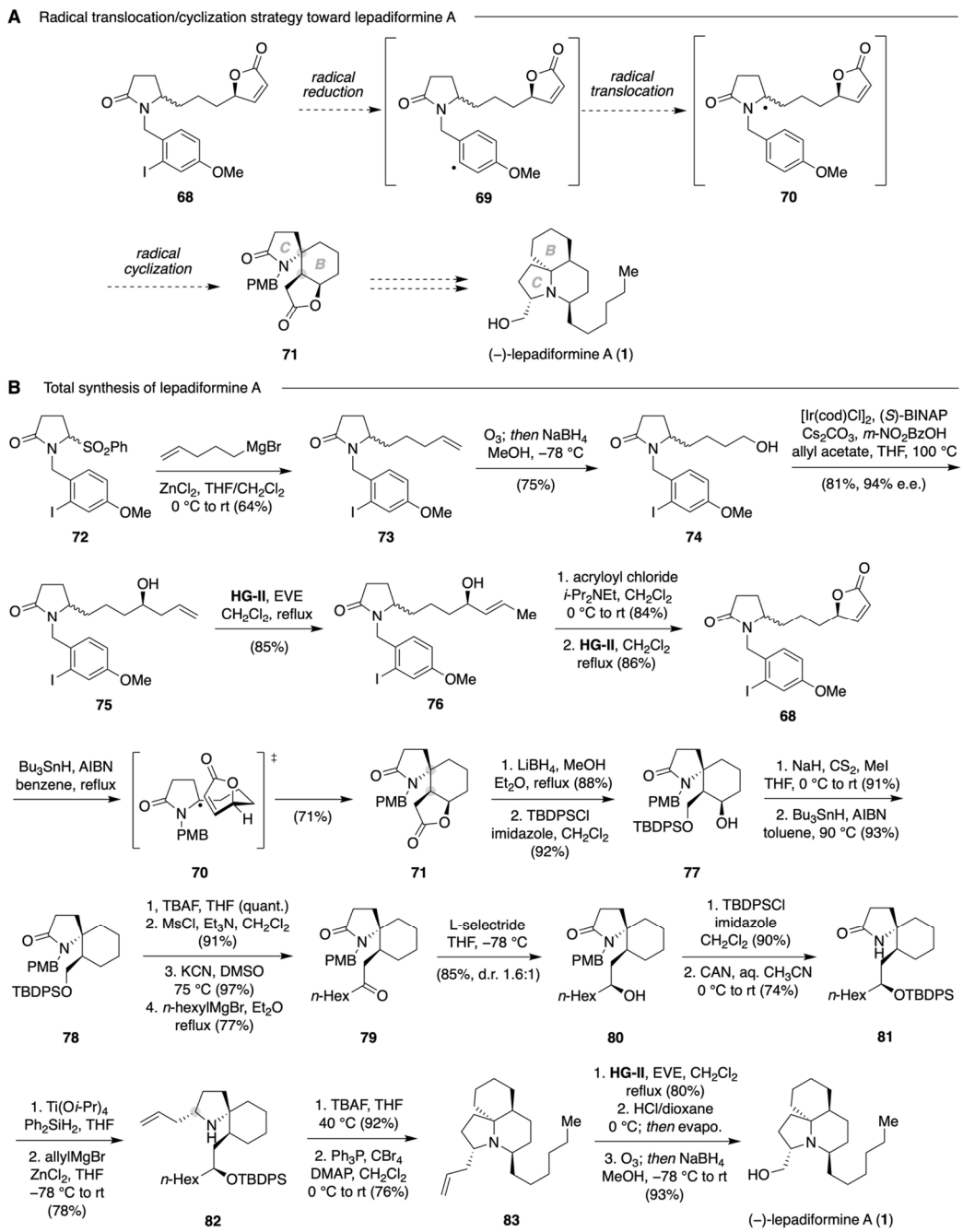
6. Total synthesis of (±)-fasicularin and formal syntheses of (±)-lepadiformines A-C by Chiou

6.1. Formal syntheses of (±)-lepadiformines A-C

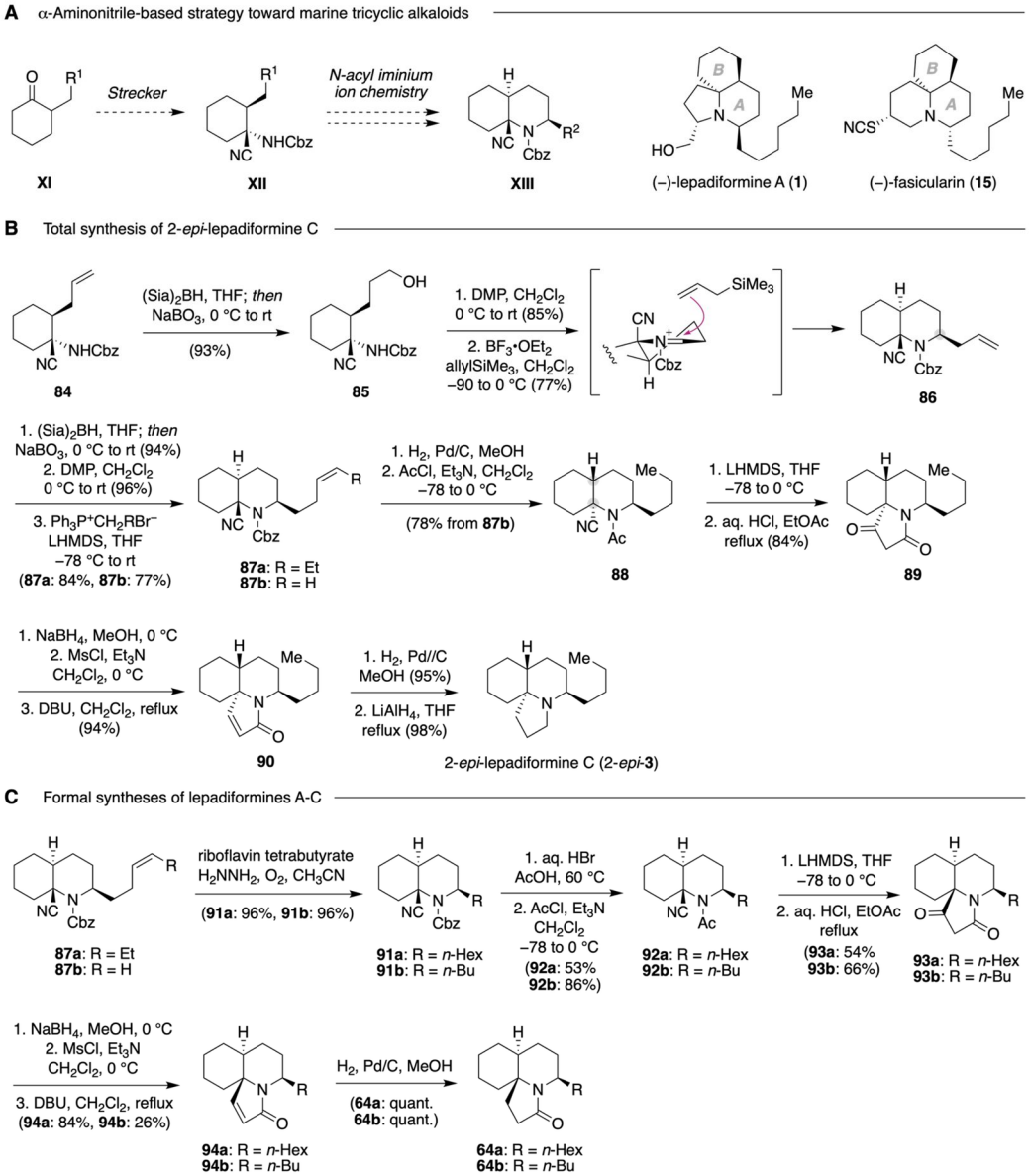
The Chiou group developed a concise access to α-aminonitriles **XII** from readily available 2-substituted cyclohexanones **XI** *via* a Strecker reaction (Scheme 6A). The product α-aminonitriles **XII** is suitably functionalized for the subsequent construction of decahydroquinolines **XIII** through *N*-acyl iminium ion chemistry. The decahydroquinolines **XIII** correspond to the AB-ring skeleton of marine tricyclic alkaloids.

As illustrated in Schemes 6B and 6C, formal syntheses of lepadiformines A–C **1**-**3** began with hydroboration of α-aminonitrile **84** ($(Sia)_2BH$, THF; then $NaBO_3$) to give alcohol **85** (93%). Dess-Martin oxidation of **85** (85%) led to an equilibrating mixture of the corresponding amino aldehyde and hemiaminal. Upon treatment of this mixture with $BF_3{\bullet}OEt_2$/allyl trimethylsilane, olefin **86** was obtained in 77% yield as a single diastereomer, where the stereochemical outcome would be ascribable to stereoelectronic effect avoiding unfavorable allylic strain in the transition state. Hydroboration of **86** with $(Sia)_2BH$ (94%), Dess-Martin oxidation (96%), and Wittig olefination gave olefins **87a**,**b** (77-84%).

Interestingly, hydrogenation/hydrogenolysis of **87b** followed by *N*-acylation provided acetamide **88** (78%), in which the bridgehead stereocenters were both epimerized.



Scheme 5. Total synthesis of lepadiformine A by Tokuyama.



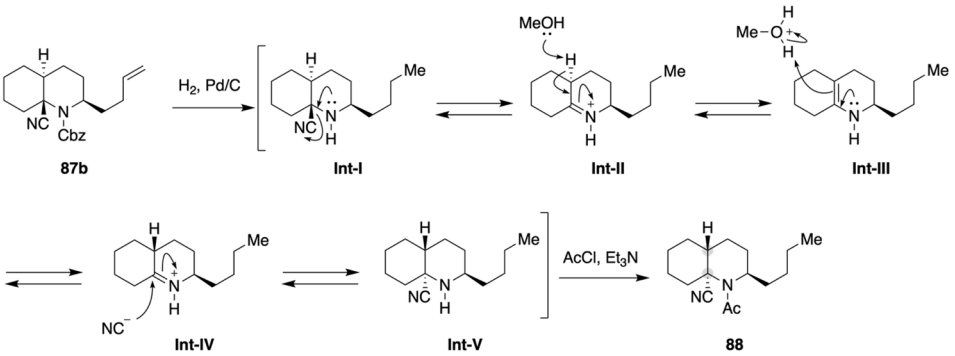
Scheme 6. Formal syntheses of lepadiformines A–C by Chiou.

The configuration of **88** was confirmed by derivatization and X-ray crystallographic analyses. Detailed NMR experiments using isotope-labeling technique demonstrated that the double epimerization occurred through an intriguing sequence of retro-Strecker reaction, imine-enamine tautomerization, and Strecker reaction, involving intermediates **Int-I** to **Int-V** (Scheme 7). **Int-V** should be the most stable intermediate within this reaction sequence.

Treatment of acetamide **88** with LHMDS followed by acidic hydrolysis of the derived imine gave ketone **89** (84%). $NaBH_4$ reduction, mesylation, and DBU-mediated elimination delivered α,β-unsaturated lactam **90**

(94%). Hydrogenation of **90** (H_2, Pd/C, 95%), followed by $LiAlH_4$ reduction of the derived lactam, afforded 2-*epi*-lepadiformine C (2-*epi*-**3**) (98%).

Formal syntheses of lepadiformines A-C **1**-**3** were achieved from olefins **87a**,**b** by avoiding double epimerization under hydrogenation/hydrogenolysis conditions (Scheme 6C). After saturation of olefins **87a**,**b** with diimide, the *N*-Cbz group was removed from **91a**,**b** under acidic conditions (HBr, AcOH), and the resultant amine hydrobromide salt was acetylated carefully to give acetamides **92a**,**b** (53-86%). As described for the synthesis of 2-*epi*-lepadiformine C (2-*epi*-**3**), additional six-step manipulations furnished tricyclic lactams **64a**,**b** through the intermediacy of keto lactam **93a,b** and α,β-unsaturated lactam **94a,b**,[38,39] thereby successfully completing formal syntheses of lepadiformines A-C **1**-**3**.[48]



Scheme 7. Mechanism of double epimerization of bridgehead stereocenters.

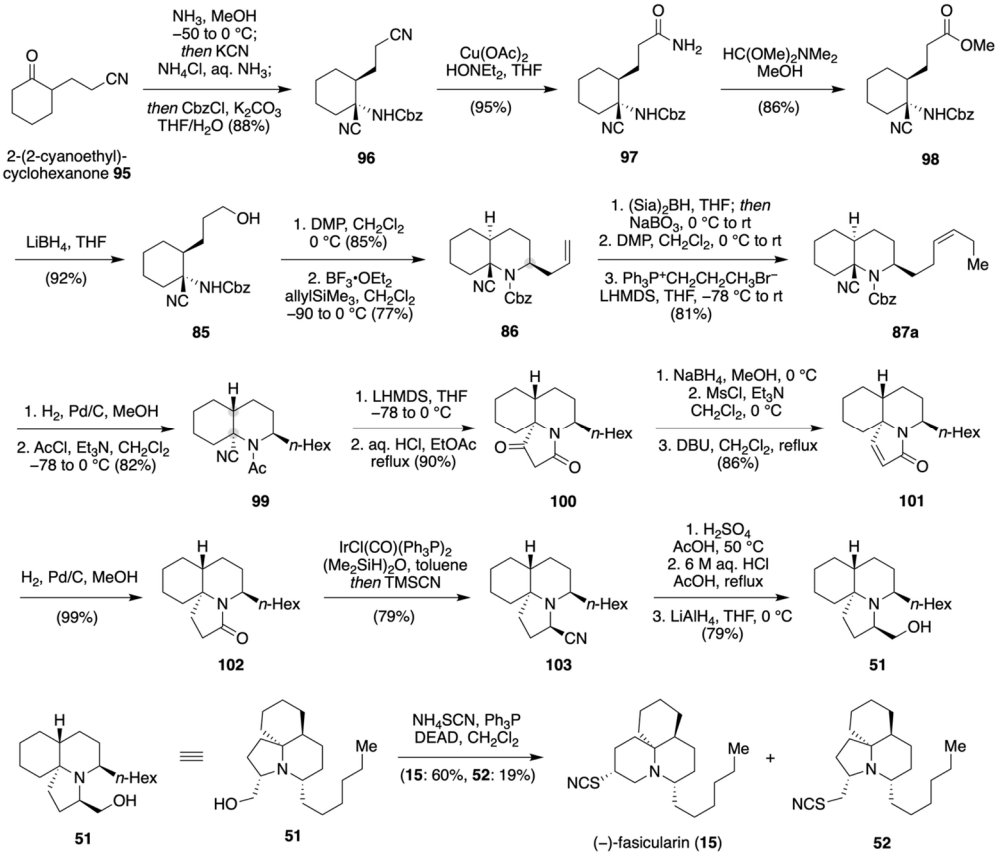
6.2. Total synthesis of (±)-fasicularin

After completing the formal syntheses of lepadiformines,[48] the Chiou group embarked on the total synthesis of fasicularin **15** by leveraging their intriguing 'retro-Stecker/imine-enamine tautomerization/Strecker' sequence for double epimerization of the bridgehead stereocenters of *cis*-2-alkyl-8a-cyanodecahydroquinolines (Scheme 8). The Chiou synthesis of fasicularin **15** commenced with Strecker reaction of 2-(2-cyanoethyl)cyclohexanone **95** to deliver dinitrile **96** (88%). Treatment of **96** with $Cu(OAc)_2$/$HONEt_2$[49] provided carboxamide **97** (95%), which was exposed to dimethylformamide dimethylacetal[50] to give ester **98** (86%). Reduction of **98** with $LiBH_4$ led to alcohol **85** (92%). Dess-Martin oxidation of **85** (85%), followed by allylation of the derived mixture of an amino aldehyde and a cyclic hemiaminal (BF_3•OEt_2, allyl trimethylsilane), provided olefin **86** (77%), which was homologated to olefin **87a** (81%) through a three-step sequence of hydroboration, Dess-Martin oxidation, and Wittig olefination. Hydrogenation/hydrogenolysis of **87a** and subsequent acetylation delivered acetamide **99** (82%), in which the bridgehead stereocenters were successfully epimerized, as anticipated. Intramolecular cyclization of **99** using LHMDS gave, after acidic hydrolysis, keto lactam **100** (90%), which was reduced with $NaBH_4$ and then eliminated *via* a mesylate to afford α,β-unsaturated lactam **101** (86%). Hydrogenation of **101** led to tricyclic lactam **102** (99%), which was transformed into nitrile **103** (79%) through a reductive cyanation under Dixon conditions ($Ir(CO)Cl(PPh_3)_2$, $(Me_2SiH)_2O$; then TMSCN).[51] A two-stage acidic hydrolysis of **103** and reduction with $LiAlH_4$ delivered alcohol **51** (79%). Finally, Mitsunobu reaction of **51** with NH_4SCN afforded fasicularin **15** in 60% yield, along with its isomer **52** in 19% yield. The minor isomer **52** could be transformed into **15** as described earlier (70%).[52]

7. Total synthesis of (−)-cylindricine H by Amat

The *cis*-decahydroquinoline ring system is frequently found in alkaloid natural products and corresponds to the AB-ring skeleton of lepadiformines and cylindricines. Amat and coworkers worked on the synthesis of *cis*-decahydroquinoline alkaloids by exploiting chiral phenylglycinol-derived tricyclic lactams.[53-56] As an application of their synthetic strategy, the Amat group envisioned that chiral tricyclic lactam **104** should represent a suitable precursor for the *cis*-decahydroquinoline skeleton of (−)-cylindricine H **11** (Scheme 9A). Thus, an addition of a carbon nucleophile to C10 (cylindricine carbon numbering) with simultaneous cleavage

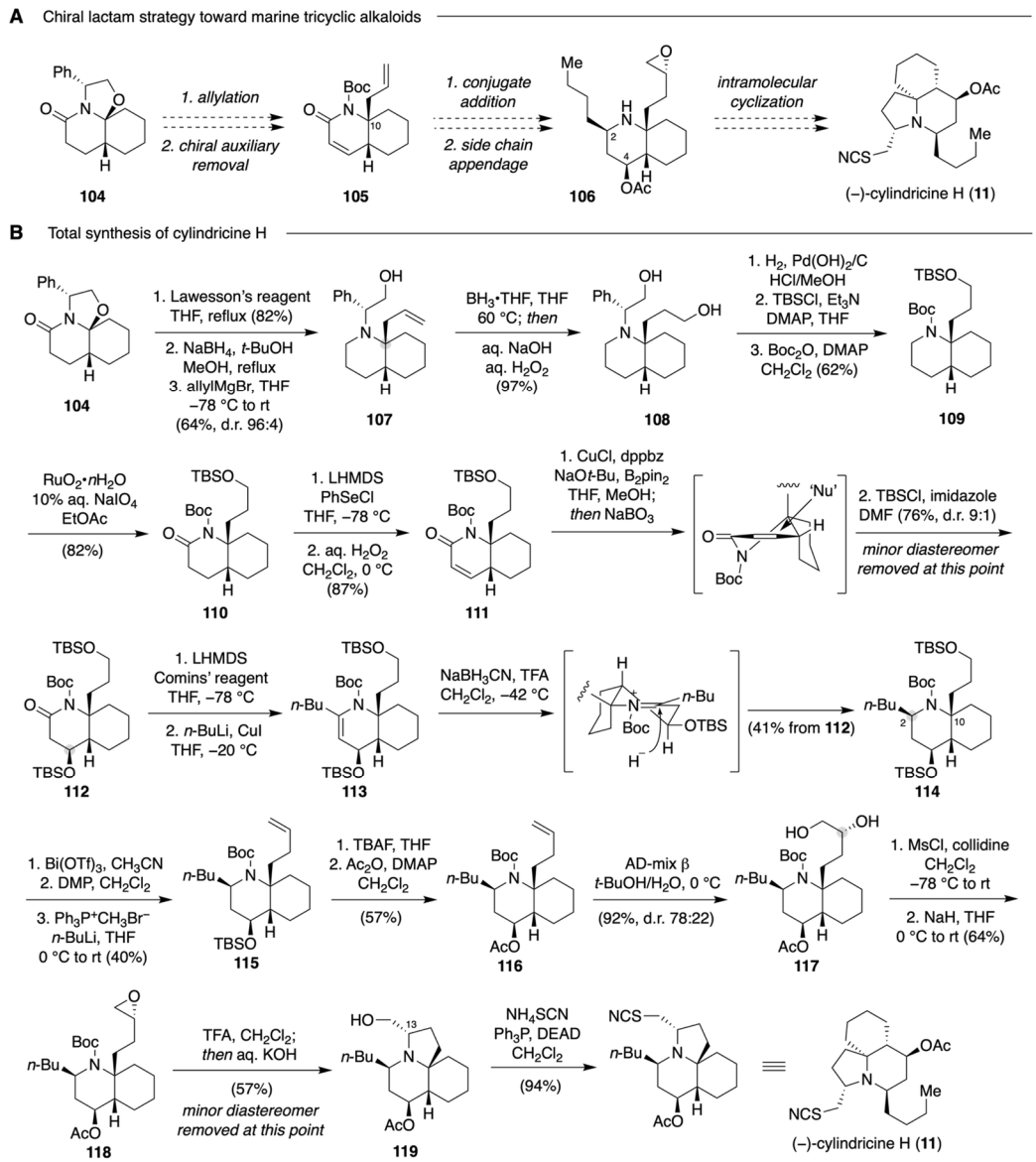
of the oxazolidine ring of **104** should generate the C10 quaternary carbon in a stereocontrolled fashion. After introducing the requisite substituents at C2 and C4 by manipulating the δ-lactam of **105**, closure of the pyrrolidine ring *via* an intramolecular cyclization of epoxide **106** would complete the synthesis of (−)-cylindricine H **11**.



Scheme 8. Total synthesis of fasicularin by Chiou.

However, direct allylation of **104** with $TiCl_4$/allyl trimethylsilane only resulted in a failure, possibly due to the low reactivity of the δ-lactam-fused oxazolidine (Scheme 9B). Accordingly, **104** was treated with Lawesson's reagent to give the corresponding thionolactam (82%), which was reduced with $NaBH_4$ and the derived oxazolidine was allylated with allylmagnesium bromide to deliver olefin **107** (64%, d.r. 96:4). Hydroboration of **107** and oxidative workup gave alcohol **108** (97%). The chiral auxiliary of **108** was removed by hydrogenolysis. After silylation of the hydroxy group, the secondary amine was protected with Boc_2O/DMAP to deliver carbamate **109** (62%). Oxidation of **109** with $RuO_2/NaIO_4$ provided lactam **110** (82%). Selenylation of **110** with LHMDS/PhSeCl followed by oxidation resulted in α,β-unsaturated lactam **111** (87%). Copper-catalyzed conjugate borylation[57] of **111** proceeded from the sterically less encumbered β-face of the molecule to give, after oxidative workup, a β-hydroxy lactam, which was treated with TBSCl/imidazole to afford silyl ether **112** (76%, d.r. 9:1). The minor diastereomer was removed by flash column chromatography using silica gel. Silyl ether **112** was transformed into the corresponding enol triflate (LHMDS, Comins' reagent) and then allowed to react with *n*-Bu_2CuLi to afford cyclic enecarbamate **113**. Stereoselective reduction of **113** with $NaBH_3CN$/TFA provided decahydroquinoline **114** in 41% yield from

112. The stereochemical consequence could be rationalized by a chair-like transition state that minimizes allylic strains between the *N*-Boc group and the C2/C10 substituents. Compound **114** was desilylated using $Bi(OTf)_3$, and the resultant alcohol was oxidized and then methylenated to give olefin **115** (40%). After replacing the TBS group with an acetyl group (57%), the derived olefin **116** was subjected to Sharpless asymmetric dihydroxylation using AD-mix β to afford 1,2-diol **117** in 92% yield with a moderate 78:22 diastereoselectivity. After mesylation of the primary hydroxy group (MsCl, collidine), exposure of the obtained mesylate to NaH provided epoxide **118** (64%).

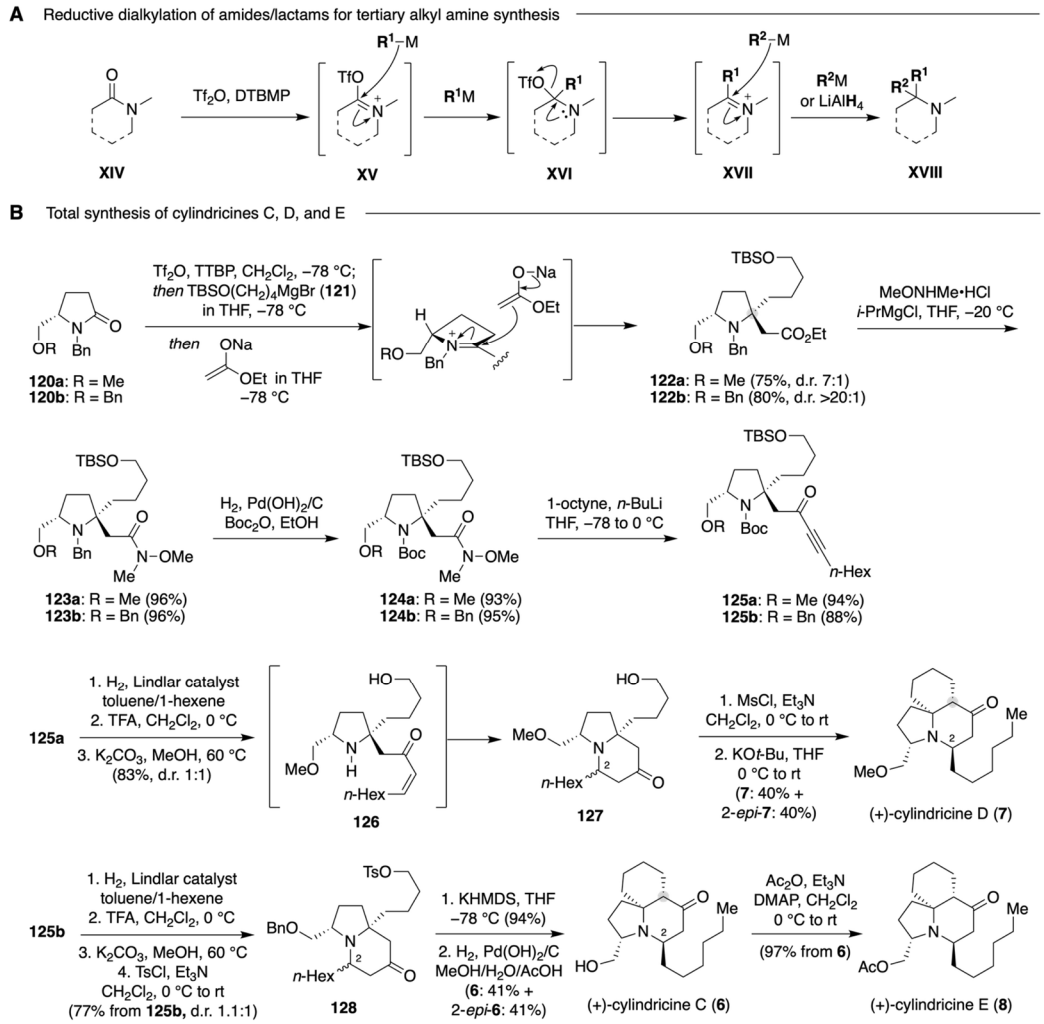


Scheme 9. Total synthesis of cylindricine H by Amat.

Cleavage of the Boc group with TFA, followed by alkaline treatment, resulted in the closure of the pyrrolidine ring, giving rise to tricyclic alcohol **119**. At this point, the C13 minor diastereomer could be removed by flash column chromatography using silica gel. Mitsunobu reaction of **119** with NH_4SCN proceeded cleanly to furnish (−)-cylindricine H **11** in 94% yield. Interestingly, the corresponding ring-expanded product was not observed in this case (Scheme 9B).[58]

8. Total synthesis of (+)-cylindricine C, D, and E by Huang

Huang and coworkers developed a direct, sequential reductive alkylation of amides/lactams with organolithium/magnesium reagents for the synthesis of tertiary alkyl amines (Scheme 10A).[59,60]



Scheme 10. Total synthesis of cylindricine C, D, and E by Huang.

Specifically, the reaction starts from activation of amide/lactam **XIV** with Tf_2O/2,6-di-*t*-butyl-4-methylpyridine (DTBMP) to generate iminium ion **XV**, which reacts with an

organometallic nucleophile to give *N*,*O*-acetal **XVI**. Elimination of OTf^- from **XVI** delivers iminium ion **XVII**, which then reacts with a second organometallic nucleophile or $LiAlH_4$ to provide tertiary alkyl amine **XVIII**. The Huang group has further applied this method to the synthesis of α-substituted or α,α'-disubstituted pyrrolidine/piperidine alkaloid natural products.[60]

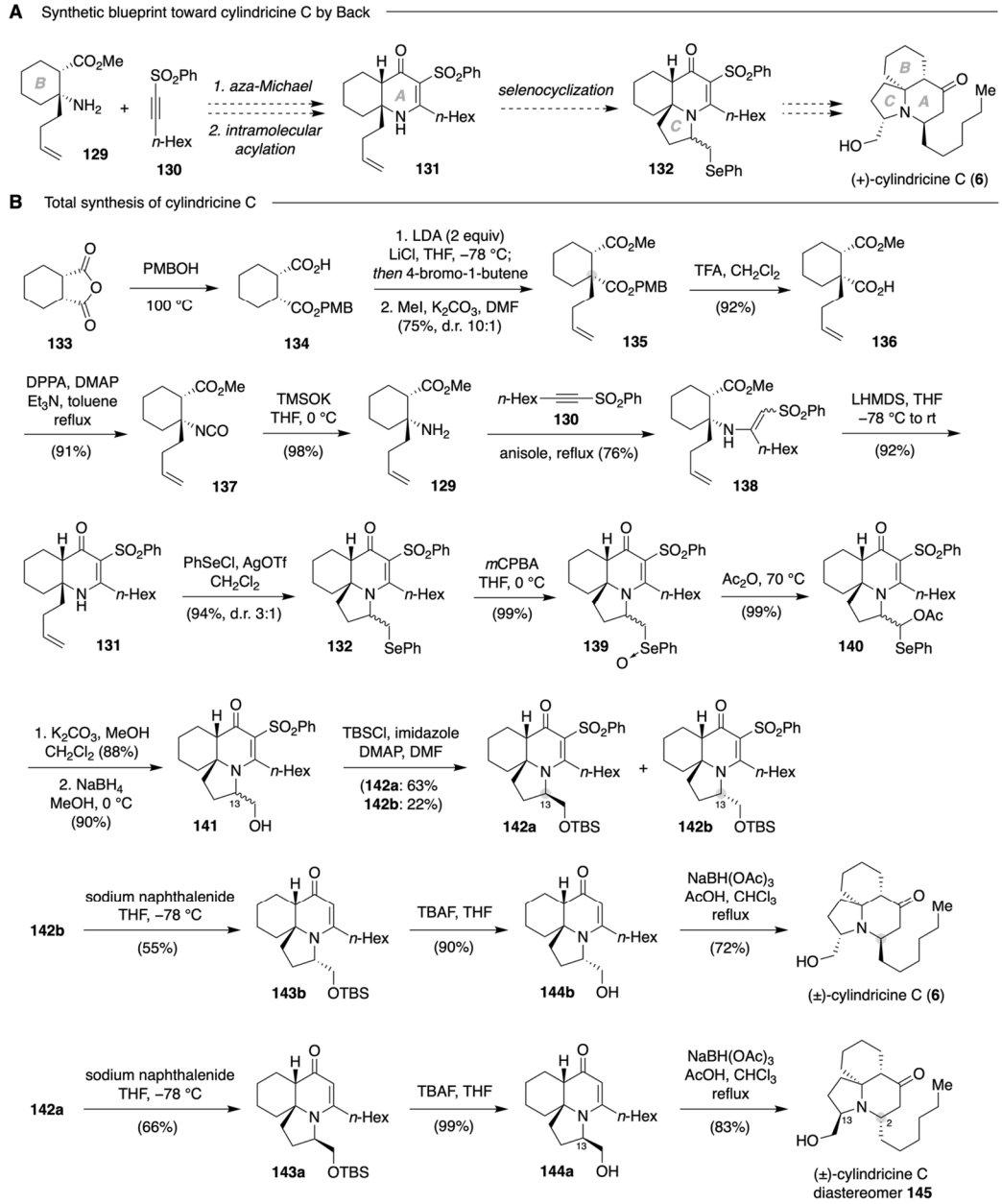
The reductive amide dialkylation methodology enabled the Huang group to investigate a concise approach toward cylindricines C, D, and E **6**, **7**, and **8**. The authors envisioned that the C-ring of cylindricines should be easily accessible from L-pyroglutaminol derivatives (Scheme 10B). Eventually, reductive dialkylation of γ-lactams **120a**,**b** was achieved in a one-pot manner by initial activation with Tf_2O/2,4,6-tri-*t*-butylpyrimidine (TTBP), followed by nucleophilic addition of Grignard reagent **121**, and subsequent addition of a sodium enolate prepared from EtOAc/NaHMDS, to give esters **122a** (75%, d.r. 7:1) and **122b** (80%, d.r. >20:1), respectively. It appears that the second nucleophile, the sodium enolate of EtOAc, attacked to the iminium ion intermediate from the β-face of the molecule to avoid unfavorable steric repulsion with the alkoxymethyl substituent. Treatment of esters **122a**,**b** with MeONHMe•HCl/*i*-PrMgCl afforded Weinreb amides **123a**,**b** (96%). After exchanging the nitrogen protecting group, the derived Boc carbamates **124a**,**b** were allowed to react with a lithium acetylide derived from 1-octyne/*n*-BuLi to provide alkynyl ketones **125a**,**b** (88-94%). Hydrogenation of alkynyl ketone **125a** over Lindlar catalyst, followed by removal of the Boc and TBS groups with TFA, and subsequent treatment with K_2CO_3/MeOH to promote intramolecular aza-Michael addition afforded bicyclic alcohol **127** (83%), although no diastereoselectivity was observed at the C2 position (d.r. 1:1), possibly because of the conformational flexibility of the aza-Michael precursor **126**. In fact, an earlier study by Hsung et al. demonstrated that an intramolecular aza-Michael addition of a spirocyclic pyrrolidine derivative, representing the BC-ring of cylindricine C **6**, provided the corresponding tricyclic ketone with correct configuration at the C2 position in a stereocontrolled manner.[61] After mesylation of **127**, the resultant keto mesylate was subjected to intramolecular alkylation to deliver (+)-cylindricine D **7** (40%) along with 2-*epi*-cylindricine D (2-*epi*-**7**: 40%). These diastereomers were separated by flash column chromatography using silica gel. In a similar manner, alkynyl ketone **125b** was transformed into (+)-cylindricine C **6** and (+)-cylindricine E **8**. Half-reduction, deprotection, and intramolecular aza-Michael addition provided, after treatment with TsCl/Et_3N, tosylate **128** (77% from **126b**). Intramolecular alkylation of **128** occurred upon exposure to KHMDS (94%) and subsequent hydrogenolytic removal of the benzyl group furnished (+)-cylindricine C **6** in 41% yield and 2-*epi*-cylindricine C (2-*epi*-**6**) in 41% yield, after separation by silica gel flash column chromatography. Acetylation of **6** afforded (+)-cylindricine E **8** in 97% yield.[62] While the stereocontrol at the C2 position remains to be addressed, the Huang synthesis of (+)-cylindricine C, D, and E is remarkable in its efficiency.

9. Total synthesis of (±)-cylindricine C by Back

Back and coworkers described the total synthesis of (±)-cylindricine C **6**, which was highlighted by: 1) an inexpensive starting material, *cis*-1,2-cyclohexanedicarboxylic anhydride, as a source of the B-ring; 2) an aza-Michael addition/intramolecular acylation of amine **129** to acetylenic sulfone **130** for forging the A-ring; and 3) a selenium-mediated intramolecular cyclization of amino olefin **131** for the closure of the C-ring to give tricycle **132** (Scheme 11A).

The Back synthesis of (±)-cylindricine C **6** started with alcoholysis of 1,2-cyclohexanedicarboxylic anhydride **133** using PMBOH to give carboxylic acid **134** quantitatively (Scheme 11B). Stereoselective alkylation of **134** was achieved by exhaustive deprotonation with LDA (2 equiv) and subsequent addition of 4-bromo-1-butene to afford, after esterification of the remaining carboxylic group, diester **135** (75%, d.r. 10:1). After removal of the PMB group (TFA, 92%), the derived carboxylic acid **136** was subjected to Curtius rearrangement (DPPA, DMAP, Et_3N), giving isocyanate **137** (91%). Hydrolysis/decarboxylation of **137** using TMSOK delivered amine **129** (98%). Aza-Michael addition of **129** to acetylenic sulfone **130** was achieved in refluxing anisole to afford enamine **138** (76%). Intramolecular acylation of **138** occurred upon exposure to LHMDS (THF, −78 °C to rt), giving rise to cyclic enaminone **131** (92%). Treatment of **131** with PhSeOTf, *in situ* generated from PhSeCl/AgOTf upon anion exchange, induced selenium-mediated intramolecular cyclization to provide selenide **132** in 94% yield with 3:1 diastereoselectivity. Attempts to improve/reverse the diastereoselectivity using camphor-derived chiral selenium chlorides/triflates were non-productive. Asymmetric epoxidation or dihydroxylation of **131** was also unfruitful. Oxidation of **132** with *m*CPBA gave

selenoxide **139** (99%), which underwent seleno-Pummerer reaction through selenoacetal **140** (Ac_2O, 99%; then K_2CO_3, MeOH, 88%) to deliver, after $NaBH_4$ reduction, alcohol **141** (90%, d.r. 3:1). At this point, small quantities of a mixture of diastereomers at C13 were separated by silica gel flash column chromatography and individually subjected to X-ray crystallographic analysis.



Scheme 11. Total synthesis of cylindricine C by Back.

Unfortunately, it turned out that the minor diastereomer had the correct configuration at the C13 position. After silylation of alcohol **141**, diastereomers **142a**,**b** were eventually separated by flash column chromatography using silica gel [**142a** (63%) **142b** (22%)]. Desulfonylation of **142b** with sodium naphthalenide gave cyclic enaminone **143b** (55%). After desilylation (TBAF, 90%), directed reduction of **144b** with $NaBH(OAc)_3$ furnished (±)-cylindricine C **6** in 72% yield. In the same manner, **142a** was transformed into cylindricine C diastereomer **145**.[63] The configuration at the C2 position was also inverted in **145** due to $NaBH(OAc)_3$ reduction directed from the incorrectly configured C13 position (Scheme 11B).

10. Total synthesis of (−)-lepadiformine A, cylindricines A-J, and (−)-fasicularin by Fuwa

10.1. Total synthesis of (−)-lepadiformine A

Au-catalyzed reactions have become a powerful means for constructing complex natural products.[64-66] Intramolecular alkyne hydroamination under Au catalysis enables an efficient generation of *N*-acyl or *N*-sulfonyl iminium ions, which then undergo nucleophilic addition to provide substituted pyrrolidine derivatives.[67] Given prior successes by Weinreb[6] and Sato/Chida[34] in the stereoselective synthesis of (−)-lepadiformine A **1** and facisularin **15** through intramolecular allylation of *N*-acyl iminium ions, we envisioned a Au-catalyzed tandem intramolecular alkyne hydroamination/iminium formation/intramolecular allylation reaction for the stereoselective synthesis of spirocyclic pyrrolidines[68] (Scheme 12A).

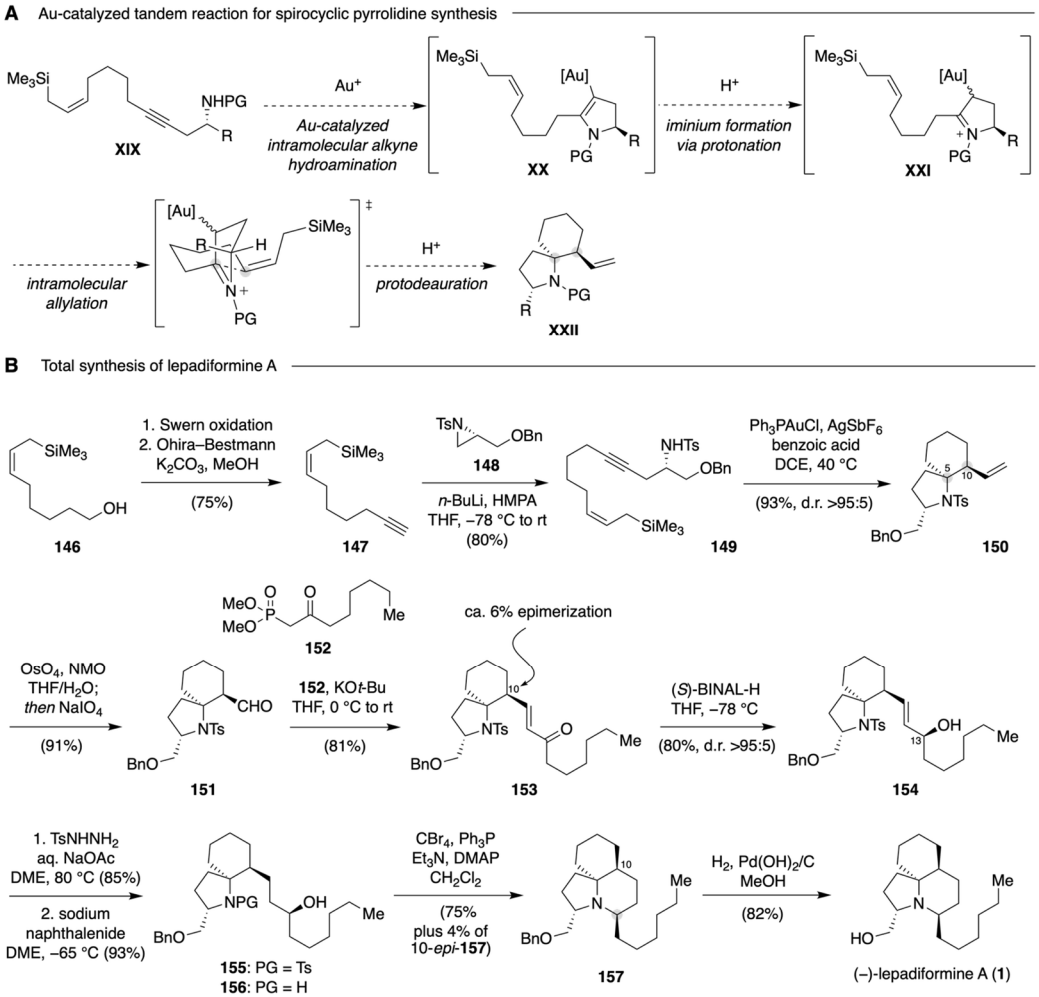
Thus, activation of amino alkynes **XIX** with a cationic Au complex induces an intramolecular alkyne hydroamination to give enamines **XX**. Upon protonation, enamines **XX** are transformed into iminium ions **XXI**, which then undergo an intramolecular allylation to deliver spirocyclic pyrrolidines **XXII**. The stereochemical outcome could be reasoned by an inside attack of the allylsilane moiety onto the iminium ion *via* a chair-like transition state, thereby avoiding unfavorable allylic strain between the nitrogen protecting group and the substituent 'R'.

Total synthesis of (−)-lepadiformine A **1**, summarized in Scheme 12B, started from allylic silane **146**, available in one step from 7-octen-1-ol.[69] Oxidation of **146** under Swern conditions and Ohira-Bestmann alkynylation[70] of the derived aldehyde gave alkyne **147** (75%). Deprotonation of **147** with *n*-BuLi, followed by addition of *N*-Ts aziridine **148**, prepared in two steps from benzyl (*R*)-glycidyl ether, provided amino alkyne **149** (80%). Treatment of **149** with a cationic Au complex, generated *in situ* from $(Ph_3P)AuCl/AgSbF_6$, in the presence of benzoic acid as a proton source in DCE at 40 °C afforded spirocyclic pyrrolidine **150** in 93% yield with greater than 95:5 diastereoselectivity. The relative configuration of **150** was confirmed by detailed conformational analysis based on *J* values and NOE correlations. Cleavage of the double bond of **150** (OsO_4, NMO; then $NaIO_4$, 91%) and Horner-Wadsworth-Emmons olefination of the derived aldehyde **151** using phosphonate **152** (KO*t*-Bu, THF, 0 °C to rt) delivered α,β-unsaturated ketone **153** (81%). At this point, approximately 6% epimerization at the C10 position (carbon numbering according to the isolation paper by Biard[4]) was observed by ^1H NMR analysis. Reduction of **153** with (*S*)-BINALH (THF, −78 °C)[33,71] provided allylic alcohol **154** in 80% yield with greater than 95:5 diastereoselectivity. Diimide reduction of the double bond of **154** (*p*-$TsNHNH_2$, aq. NaOAc, 85%), followed by desulfonylation of **155** with sodium naphthalenide, gave amino alcohol **156** (93%). Intramolecular cyclization of **156** under Kibayashi conditions (CBr_4, Ph_3P, Et_3N, DMAP)[33] afforded tricyclic amine **157** (75%) along with its C10 epimer 10-*epi*-**157** (4%), which were separated by flash column chromatography using silica gel. Finally, hydrogenolysis of **157** furnished (−)-lepadiformine A **1** in 82% yield. The present synthesis of (−)-lepadiformine A **1** was completed in 12 steps from commercially available 7-octen-1-ol, demonstrating the synthetic efficiency of our Au-catalyzed tandem intramolecular alkyne hydroamination/iminium formation/intramolecular allylation strategy.

10.2. Total synthesis of cylindricines A-J

The structural differences between lepadiformines and cylindricines are the configuration of the decahydroquinoline bridgehead C5 position (carbon numbering according to the isolation paper by Blackman[9]) and the oxidation state at the C4 position (Figure 1). An earlier study by Hsung[61] showed that treatment of α,β-unsaturated ketone **158**, corresponding to the configuration of (−)-lepadiformine A **1**, with TFA resulted in deprotection of the Boc group with simultaneous intramolecular aza-Michael addition of **159** to provide tricyclic amine **160**, which upon exposure to TBAF underwent desilylation and concomitant epimerization at C5 to afford (+)-cylindricine C **6**, as shown in Scheme 13A. This result suggested that our

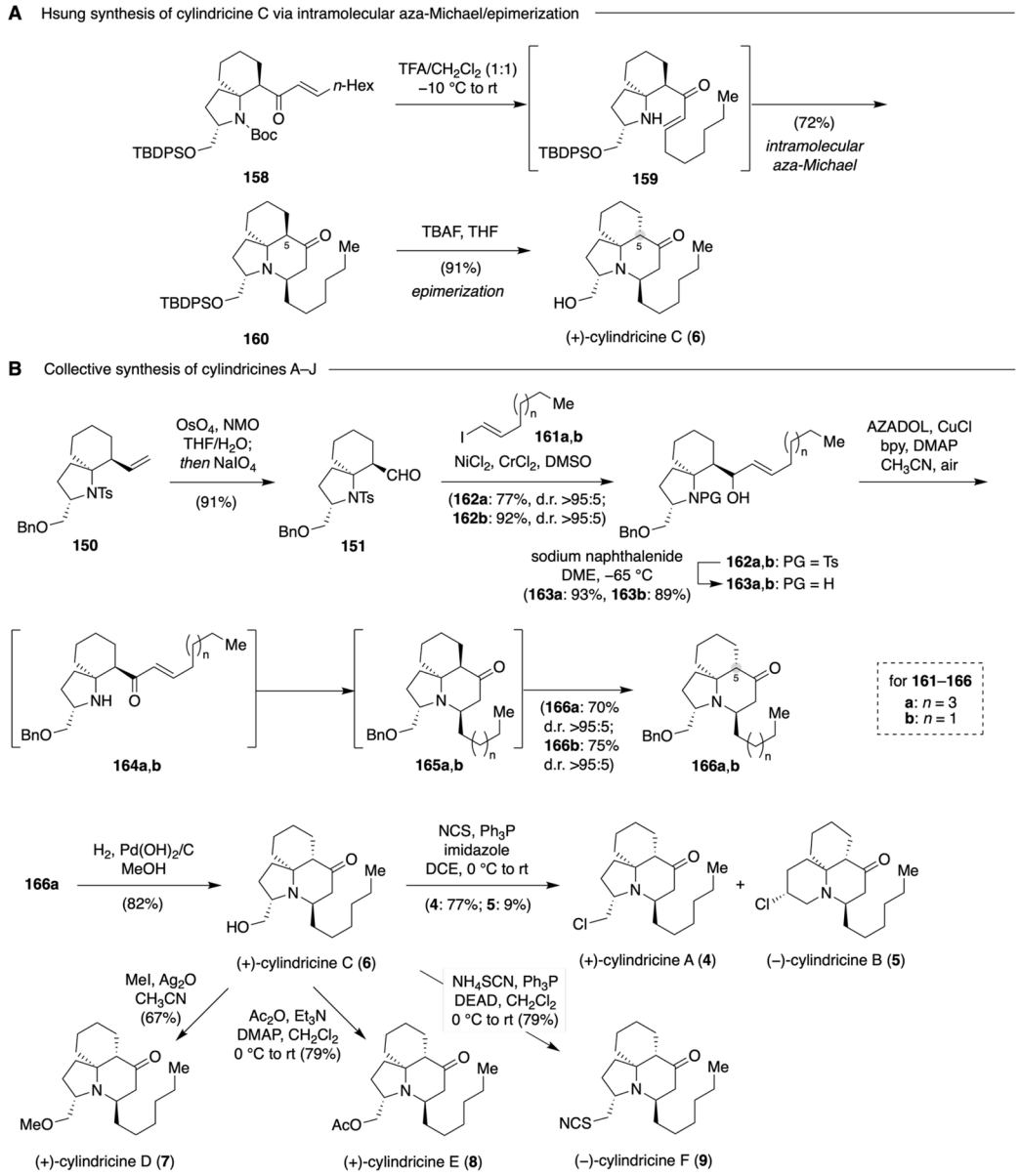
spirocyclic pyrrolidine **150** having the lepadiformine-type configuration would represent a potential precursor for the synthesis of cylindricines.



Scheme 12. Total synthesis of lepadiformine A by Fuwa.

Inspired by the Hsung synthesis of (+)-cylindricine C, we embarked on the collective synthesis of cylindricines from **150** as illustrated in Scheme 13B. Oxidative cleavage of the olefin within **150** gave aldehyde **151**, as described earlier. Nozaki-Hiyama-Kishi reaction[72] of aldehyde **151** with iodoolefins **161a**,**b** ($NiCl_2$, $CrCl_2$, DMSO) delivered allylic alcohols **162a**,**b** (77-92%). After deprotection of the tosyl group with sodium naphthalenide (89-93%), the derived amino alcohols **163a**,**b** were transformed into tricyclic amines **166a**,**b** through a tandem chemoselective oxidation/intramolecular aza-Michael addition/epimerization. Thus, oxidation of **163a**,**b** under Iwabuchi conditions (AZADOL, CuCl, bpy, DMAP, air) provided α,β-unsaturated ketones **164a**,**b**, which readily underwent intramolecular aza-Michael addition to afford tricyclic amines **165a**,**b**. Adsorption of crude **165a**,**b** to silica gel, followed by purification by flash column chromatography, induced epimerization at the C5 position and furnished tricyclic amines **166a**,**b** (70-75%, d.r.>95:5).

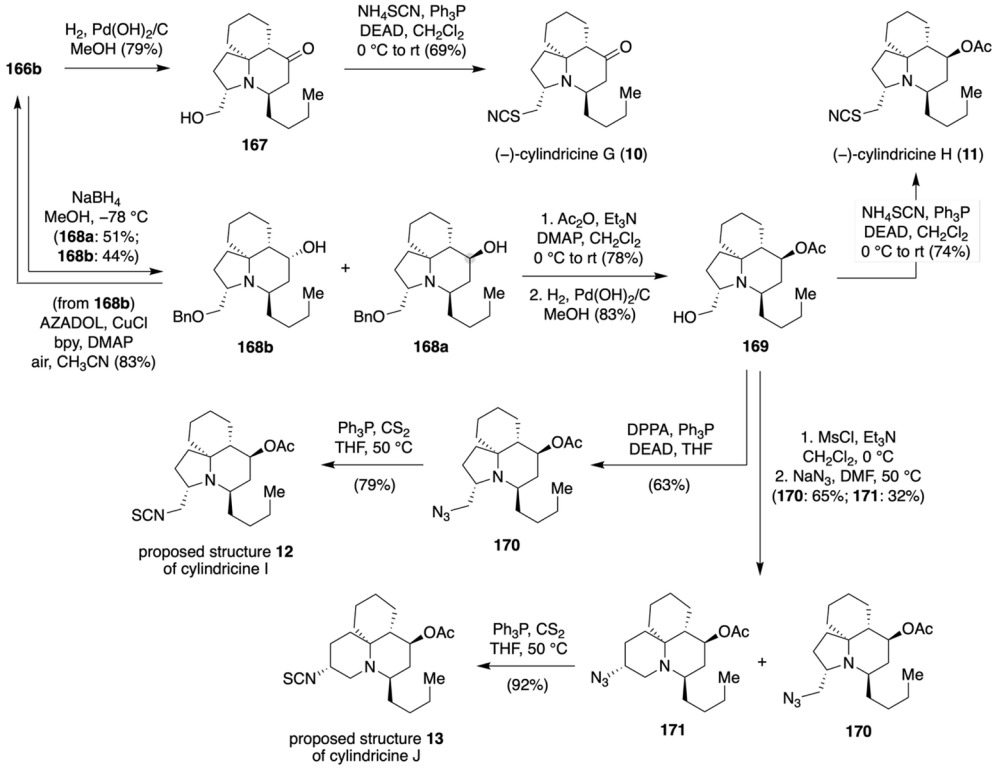
Cylindricines A-F **3**-**9** were synthesized from **166a**. Hydrogenolysis of **166a** delivered (+)-cylindricine C **6** in 82% yield. Chlorination of **6** with NCS/Ph_3P afforded (+)-cylindricine A **4** in 77% yield along with (−)-cylindricine B **5** in 9% yield. Treatment of **6** with MeI/Ag_2O provided (+)-cylindricine D (**7**) in 67% yield. Acetylation of **6** gave (+)-cylindricine E **8** in 79% yield. Mitsunobu reaction of **6** using NH_4SCN, DEAD, and Ph_3P furnished (−)-cylindricine F **9** in 79% yield.



Scheme 13. Total synthesis of cylindricines A–J by Fuwa.

Cylindricines G-J **10**-**13** were synthesized from **166b**. Hydrogenolysis of **166b** (79%), followed by Mitsunobu reaction of the derived alcohol **167** (NH_4SCN, DEAD, Ph_3P), gave (−)-cylindricine G **10** in 69% yield. $NaBH_4$ reduction of **166b** provided alcohols **168a**,**b**, which were separable by flash column chromatography using silica gel. The undesired diastereomer **168b** was recycled back to **166b** *via* Iwabuchi oxidation. Acetylation of **168a** (78%) and subsequent hydrogenolysis delivered alcohol **169** (83%). Mitsunobu reaction of **169** with NH_4SCN afforded (−)-cylindricine H **11** in 74% yield. Azidation of **169** under Mitsunobu conditions (DPPA, DEAD, Ph_3P, THF) led to azide **170** (63%).

Staudinger-aza-Wittig reaction of **170** (Ph_3P, CS_2, THF, 50 °C) furnished cylindricine I **12** in 79% yield (Scheme 13B). Meanwhile, mesylation of **169** and subsequent azidation with NaN_3 in DMF at 50 °C delivered azide **170** (65%) and its ring-expanded isomer **171** (32%), which were separated by flash column chromatography using silica gel. Staudinger-aza-Wittig reaction of **171** (Ph_3P, CS_2, THF, 50 °C) completed the synthesis of cylindricine J **13** in 92% yield.[73] It was found that the ^1H and ^{13}C NMR spectroscopic data of our synthetic cylindricine I **12** and J **13** did not match those of the authentic materials, respectively. Thus, the originally assigned structures of cylindricines I and J are questionable.

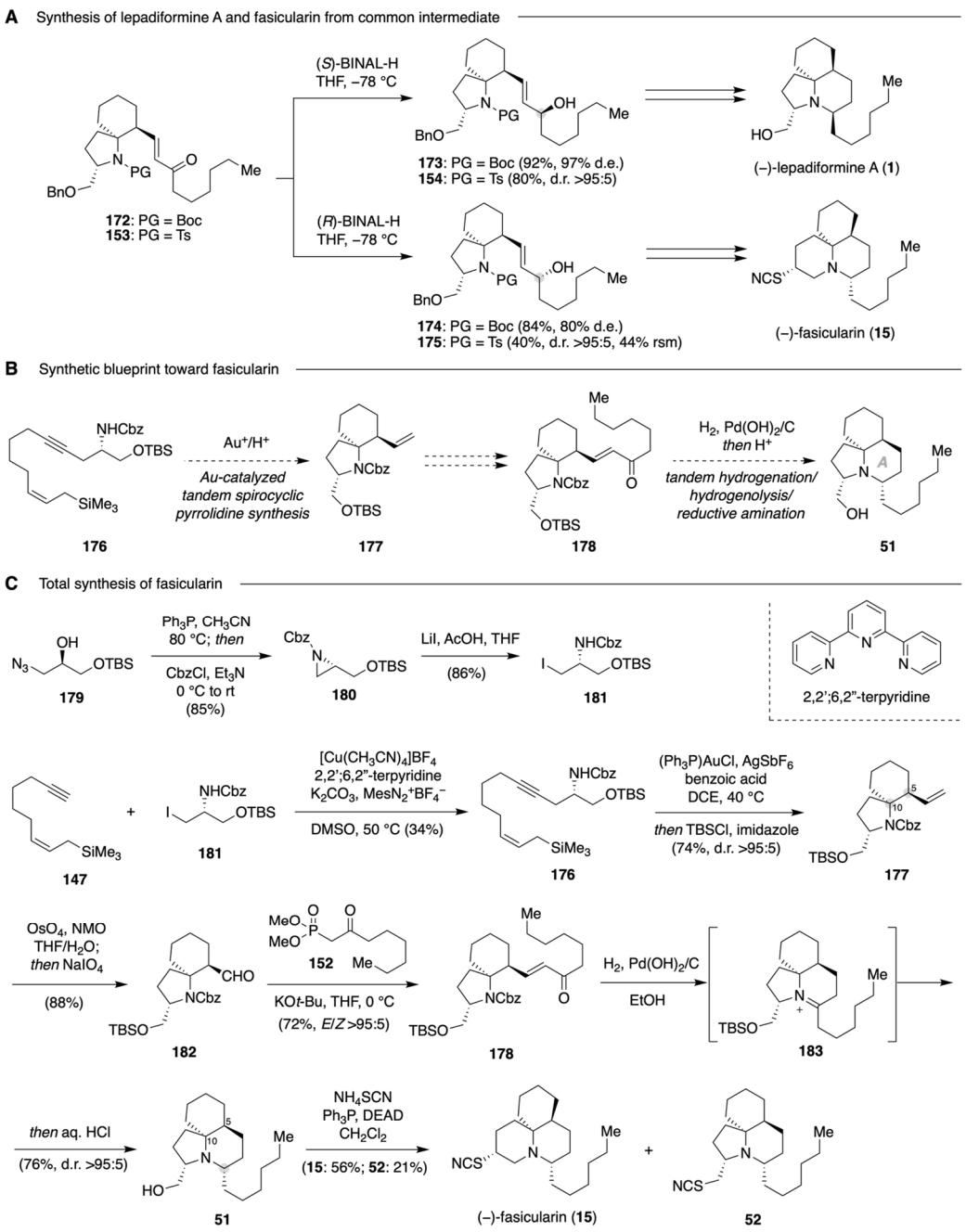


Scheme 13. (*Continued*) Total synthesis of cylindricines A–J by Fuwa.

10.3. Total synthesis of (−)-fasicularin

Finally, we focused our efforts to synthesize (−)-fasicularin **15** by capitalizing on our Au-catalyzed tandem intramolecular alkyne hydroamination/iminium formation/intramolecular allylation. In an earlier study, Kibayashi and coworkers demonstrated that (−)-lepadiformine A (**1**) and (−)-fasicularin **15** could be synthesized from a common precursor, α,β-unsaturated ketone **172**, by switching the chirality of the reducing agent, *i.e.*, (*S*)- or (*R*)-BINALH, to afford allylic alcohol **173** or **174**, respectively (Scheme 14A).[33] Actually, in accordance with the Kibayashi synthesis, α,β-unsaturated ketone **153**, which served as a synthetic

intermediate of our total synthesis of **1**, could be transformed into **15** through the intermediacy of allylic alcohol **175**. Thus, we achieved the total synthesis of (−)-fasicularin **15** in 13 steps from 7-octen-1-ol.



Scheme 14. Total synthesis of fasicularin by Fuwa.

Nevertheless, a much shorter synthesis of **15** was envisioned by expediting the A-ring construction, as shown in Scheme 14B. Specifically, Au-catalyzed tandem intramolecular alkyne hydroamination/iminium formation/intramolecular allylation of amino alkyne **176** would deliver spirocyclic pyrrolidine **177**. After extending the carbon chain, tandem hydrogenation/hydrogenolysis/intramolecular reductive amination of α,β-unsaturated ketone **178** was anticipated to afford tricyclic amine **51**. A relevant strategy for piperidine synthesis has been demonstrated in the total synthesis of pinnaic acid[74,75] and in the Sato/Chida synthesis of (−)-fasicularin.[34]

Our total synthesis of fasicularin **15**, summarized in Scheme 14C, started with Blum–Ittah aziridine synthesis[76] from known azide **179**, available in one step from *t*-butyldimethylsilyl (*R*)-glycidyl ether by epoxide-opening with NaN_3, followed by *in situ* protection of the derived aziridine, to give *N*-Cbz aziridine **180** (85%). Treatment of **180** with LiI in the presence of AcOH provided iodide **181** (86%). Copper-catalyzed aryl radical-mediated cross-coupling of alkyne **147** and iodide **181** ($[Cu(CH_3CN)_4BF_4]$, 2,2':6,2"-terpyridine, $MesN_2^+BF_4^-$, K_2CO_3, DMSO, 50 °C)[77] afforded amino alkyne **176** in 34% yield.

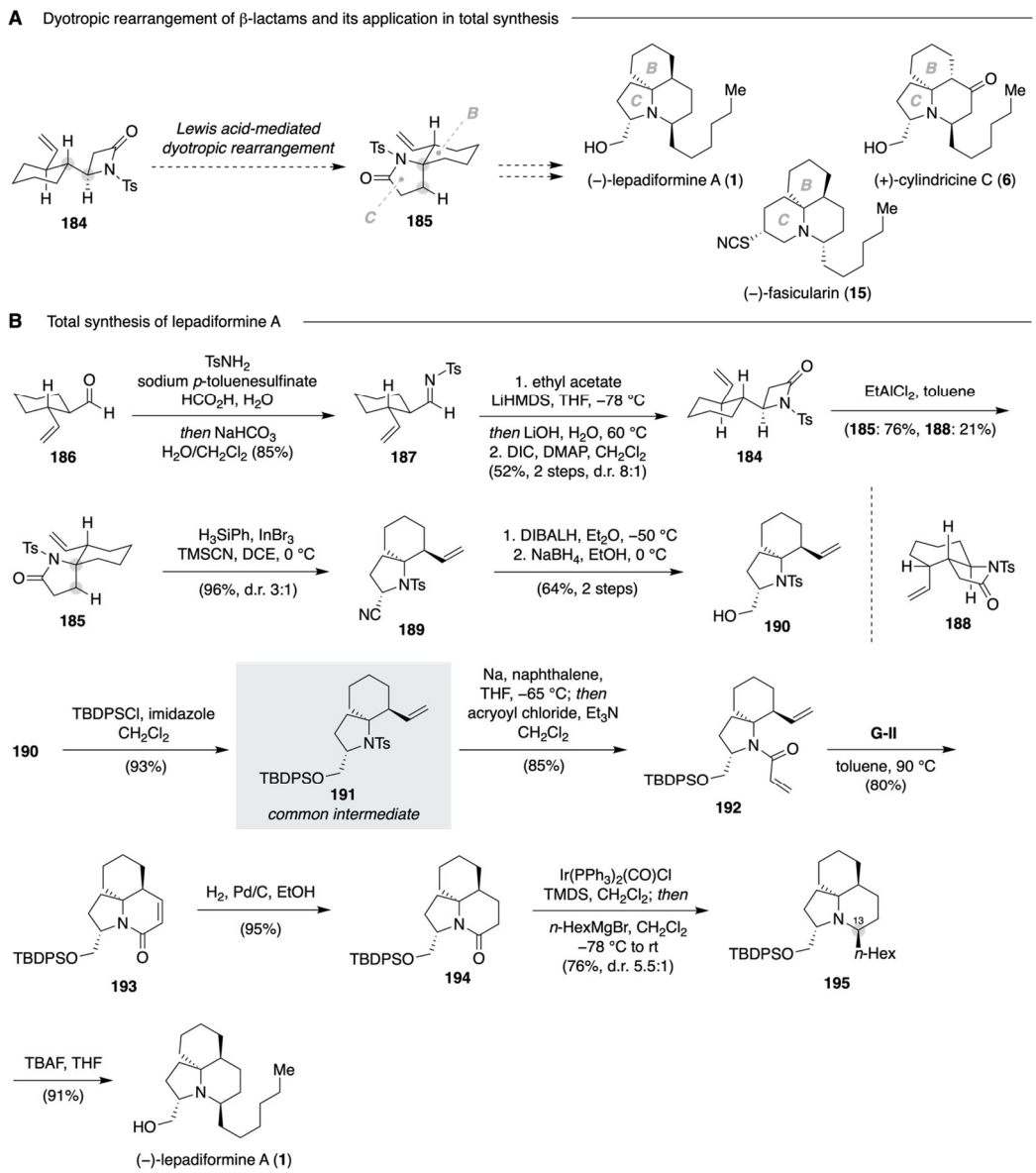
Exposure of **176** to a cationic Au(I) complex, generated *in situ* from $(Ph_3P)AuCl/AgSbF_6$, and benzoic acid in DCE at 40 °C furnished, after *in situ* reprotection with TBSCl/imidazole, spirocyclic pyrrolidine **177** in 74% yield as a single diastereomer (d.r.>95:5). The configuration of the newly created C5 and C10 stereogenic centers was confirmed by derivatization and detailed conformational analysis based on *J* values and NOE correlations. After cleavage of the double bond (OsO_4, NMO; then $NaIO_4$, 88%), Horner-Wadsworth-Emmons olefination of the derived aldehyde **182** using phosphonate **152** (KO*t*-Bu, THF, 0 °C) led to α,β-unsaturated ketone **178** (72%, *E*/*Z* >95:5). Hydrogenation of **178** over Pearlman's catalyst resulted in concomitant hydrogenolysis of the Cbz group and stereoselective reductive amination of the resultant imine **183** to give, after *in situ* removal of the TBS group, tricyclic amine **51** in 76% yield (d.r. >95:5). Mitsunobu reaction of **51** with NH_4SCN, DEAD, and Ph_3P completed the synthesis of (−)-fasicularin **15** in 56% yield along with its isomer **52** in 21% yield. The present synthesis proceeded in nine steps from a commercially available material and represents the shortest synthesis of (−)-fasicularin **15**.[78]

11. Total synthesis of (−)-lepadiformine A, (+)-cylindricine C, and (−)-fasicularin by Tang

Dyotropic rearrangement is a reaction in which two σ-bonds migrate intramolecularly in a simultaneous fashion.[79] Tang and coworkers established a dyotropic rearrangement of *N*-sulfonyl β-lactams and demonstrated its synthetic potential in natural product synthesis. Inspired by known dyotropic rearrangement of β-lactones, it was envisioned that *N*-Ts β-lactam derivative **184** could serve as a suitable precursor for the prospective Lewis acid-mediated dyotropic rearrangement to deliver spirocyclic lactam **185** (Scheme 15A). Spirocyclic lactam **185** represents the B/C-ring (common 5/6 azaspirocycle core) of marine tricyclic alkaloids.

Total synthesis of (−)-lepadiformine A **1**, summarized in Scheme 15B, started from aldehyde **186**, synthesized from (1*R*,2*R*)-1,2-cyclohexanedimethanol in three steps.[80,81] Condensation of **186** with *p*-toluenesulfonamide furnished *N*-Ts aldimine **187**[82] (85%). Diastereoselective Mannich reaction of **187** with a lithium enolate derived from ethyl acetate, followed by *in situ* ester hydrolysis, gave a carboxylic acid. Subsequent intramolecular condensation using DIC/DMAP gave β-lactam **184** (52%, two steps, d.r. 8:1). The diastereoselectivity of the Mannich reaction could be rationalized by the Felkin-Anh model. The key dyotropic rearrangement was achieved by treatment of **184** with $EtAlCl_2$ in toluene to afford the desired spirocyclic lactam **185** in good yield with a high enantiopurity (76%, >99% e.e.). In addition, allyl-migrated product **188** was observed as a side product (21%). According to model investigations, the choice of nitrogen protecting group and Lewis acid was found to be important for the success of the dyotropic rearrangement. In(III)-catalyzed silane-mediated reductive cyanation[83] introduced a one-carbon unit, and the desired cyanide **189** was obtained in an excellent yield and with moderate diastereoselectivity (96%, d.r. 3:1). Sequential reduction of **189** with DIBALH and then with $NaBH_4$ gave primary alcohol **190** (64%, two steps). Treatment of **190** with TBDPSCl/imidazole yielded silyl ether **191** (93%), which served as a common intermediate for the synthesis of (−)-lepadiformine A, (+)-cylindricine C, and (−)-fasicularin (*vide infra*). Deprotection of the *N*-Ts group with sodium naphthalenide, and subsequent *N*-acylation of the derived amine with acryloyl chloride provided **192** (85%). Ring-closing metathesis under the catalysis of **G-II** led to α,β-unsaturated lactam **193** (80%), which upon hydrogenation furnished tricyclic lactam **194** (95%). After various investigations for introducing an alkyl side chain at the C13 position (lepadiformine numbering), Dixon's

Ir-catalyzed reductive alkylation[84] was found to provide tricyclic amine **195** (76%, d.r. 5.5:1). Finally, desilylation with TBAF afforded (−)-lepadiformine A **1** (91%).

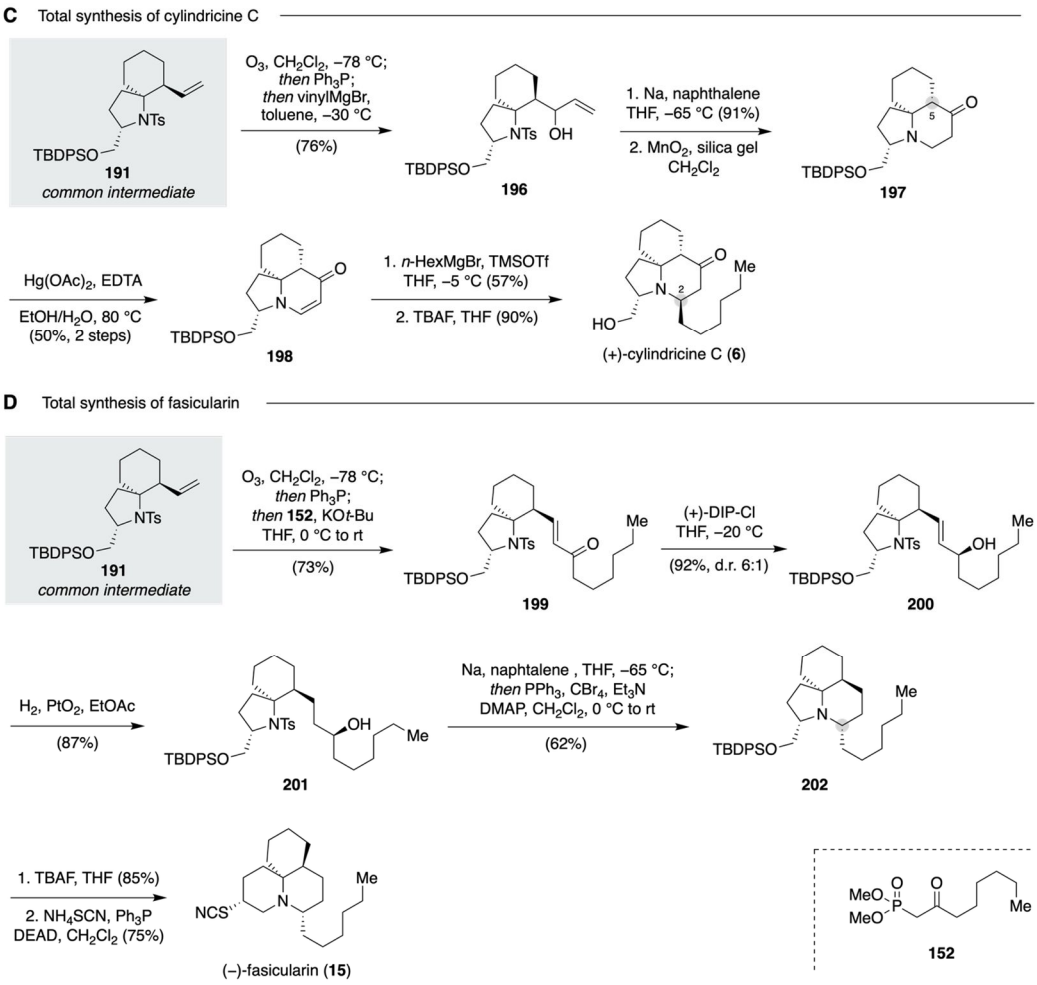


Scheme 15. Total synthesis of lepadiformine A, cylindricine C, and fasicularin by Tang.

As illustrated in Scheme 15C, total synthesis of (+)-cylindricine C **6** was completed from common intermediate **191** in six steps. Ozonolysis of the double bond, followed by reductive workup with Ph_3P, gave the corresponding aldehyde, to which addition of vinyl Grignard reagent provided allylic alcohol **196** (76%). Subsequently, deprotection of the *N*-Ts group with sodium naphthalenide delivered an amino alcohol (91%), whose MnO_2 oxidation triggered spontaneous intramolecular aza-Michael addition/epimerization to afford

tricyclic compound **197** with inversion of the C5 configuration (cylindricine numbering). To introduce the requisite alkyl chain at the C2 position, Hg(II)-promoted desaturation reaction[85] of **197** gave α,β-unsaturated ketone **198** (50%, two steps). Lewis acid-promoted nucleophilic addition[86] of *n*-HexMgBr (57%), followed by deprotection of the silyl group, furnished (+)-cylindricine C **6** in 90% yield.

Finally, total synthesis of (−)-fasicularin **15** was accomplished from the common intermediate **191** in six steps (Scheme 15D). Ozonolysis of **191** and reductive workup, followed by Horner-Wadsworth-Emmons reaction of the derived aldehyde with phosphonate **152** afforded α,β-unsaturated ketone **199** (73%). Asymmetric reduction of **199** with (+)-DIPCl gave allylic alcohol **200** (92%, d.r. 6:1). Hydrogenation of **200** with H_2/PtO_2 provided alcohol **201** in a high yield (87%). Removal of the *N*-Ts group and intramolecular cyclization under Kibayashi conditions (CBr_4, Ph_3P, Et_3N, DMAP, CH_2Cl_2)[33] furnished tricyclic compound **202** (62%). Removal of the silyl group with TBAF (85%) and Mitsunobu reaction of the resultant alcohol according to the Kibayashi protocol[33] (Ph_3P, DEAD, NH_4SCN) accompanied ring-expansion reaction *via* an aziridinium ion to furnish (−)-fasicularin **15** in 75% yield.



Scheme 15. (*Continued*) Total synthesis of lepadiformine A, cylindricine C, and fasicularin by Tang.

12. Conclusions

Over the past three decades, marine tricyclic alkaloids have attracted huge interest from the synthetic community, and diverse synthetic approaches toward this class of alkaloids have been developed. The total syntheses of marine tricyclic alkaloids summarized herein are all enjoyable as fine art. In the meantime, there has recently been a strong trend for pursuing step-economy[87,88] in natural product synthesis. Several pieces of work covered in this article certainly reflect this trend; as it is now possible to access marine tricyclic alkaloids in around ten steps from commercially available materials. Because tandem reactions are a promising means to achieve complex molecule synthesis with high step-economy, our group has been involved in the development of tandem reactions for concise synthesis of complex natural products[89-92] and successfully completed the total synthesis of (−)-lepadiformine A (12 steps),[68] (+)-cylindricine C (10 steps),[73] and (−)-fasicularin (9 steps).[78] We may expect further advances in the synthesis of marine tricyclic alkaloids, fueled by innovative reactions and strategies.[93,94]

Acknowledgements

Past graduate students of our group, Ryohei Hanzawa, Atsushi Yoshimura, and Yuki Takatori (the 'alkaloids' members), are gratefully acknowledged for their significant contribution to total syntheses of marine tricyclic alkaloids completed within our research group.

References

1. Weinreb, S. M. *Chem. Rev.* **2006**, *106*, 2531-2549.
2. Kaga, A.; Chiba, S. *Synthesis* **2018**, *50*, 685-699.
3. Li, Y.; Yuxin, Z.; Yefeng, T. *Chin. J. Org. Chem.* **2025**, *45*, 837-851.
4. Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691-2694.
5. Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583-4592.
6. Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.* **2002**, *67*, 4337-4345.
7. Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3017-3020.
8. Sauviat, M.-P.; Vercauteren, J.; Grimaud, N.; Jugé, M.; Nabil, M.; Petit, J.-Y.; Biard, J.-F. *J. Nat. Prod.* **2006**, *69*, 558-562.
9. Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. W.; White, A. H. *Tetrahedron* **1993**, *49*, 8645-8656.
10. Li, C.; Blackman, A. J. *Aust. J. Chem.* **1994**, *47*, 1355-1361.
11. Li, C.; Blackman, A. J. *Aust. J. Chem.* **1995**, *48*, 955-965.
12. Patil, A. D.; Freyer, A. J.; Reichwein, R.; Carte, B.; Killmer, L. B.; Faucette, L.; Johnson, R. K.; Faulkner, D. J. *Tetrahedron Lett.* **1997**, *38*, 363-364.
13. Dutta, S.; Abe, H.; Aoyagi, S.; Kibayashi, C.; Gates, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 15004-15005.
14. Srinivas, K.; Singh, N.; Das, D.; Koley, D. *Org. Lett.* **2017**, *19*, 274-277.
15. Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.
16. Koley, D.; Krishna, Y.; Srinivas, K.; Khan, A. A.; Kant, R. *Angew. Chem., Int. Ed.* **2014**, *53*, 13196-13200.
17. Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797-5815.
18. Verkade, J. M. M.; van Hemerrt, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29-41.
19. Cheng-Sánchez, I.; Sarabia, F. *Synthesis* **2018**, *50*, 3749-3786.
20. Jahan, N.; Ansary, I. *SynOpen* **2023**, *7*, 209-242.
21. Shirokane, K.; Kurosaki, Y.; Sato, T.; Chida, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 6369-6372.
22. Hiraoka, S.; Matsumoto, T.; Matsuzaka, K.; Sato, T.; Chida, N. *Angew. Chem. Int. Ed.* **2019**, *58*, 4381-4385.
23. Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Org. React.* **2017**, *94*, 1-529.
24. Murahashi, S.; Imada, Y. *Chem. Rev.* **2019**, *119*, 4684-4716.
25. Sasano, Y.; Nagasawa, S.; Yamazaki, M.; Shibuya, M.; Park, J.; Iwabuchi, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 3236-3240.

26. Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13681-13736.
27. Maryanoff, B. E.; Zhang, H.-C.; Cohen, J.-H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431-1628.
28. Wu, P.; Nielsen, T. E. *Chem. Rev.* **2017**, *117*, 7811-7856.
29. Basson, A. J.; McLaughlin, M. G. *Tetrahedron* **2022**, *114*, 132764.
30. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553.
31. Mitsunobu, O. *Synthesis* **1981**, 1-28.
32. Motoyama, Y.; Aoki, M.; Takaoka, N.; Aoto, R.; Nagashima, H. *Chem. Commun.* **2009**, 1574-1576.
33. Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2005**, *127*, 1473-1480.
34. Minamikawa, R.; Fukaya, K.; Kobayashi, A.; Komiya, Y.; Yamamoto, S.; Urabe, D.; Chida, N.; Sato, T. *Synthesis* **2021**, *53*, 4621-4635.
35. Okada, T.; Toyooka, N. *Adv. Heterocycl. Chem.* **2024**, *144*, 49-88.
36. Toyooka, N.; Fukutome, A.; Nemoto, H.; Daly, J. W.; Spande, T. F.; Garraffo, H. M.; Kaneko, T. *Org. Lett.* **2002**, *4*, 1715-1717.
37. Toyooka, N.; Okumura, M.; Nemoto, H. *J. Org. Chem.* **2002**, *67*, 6078-6081.
38. Schär, P.; Renaud, P. *Org. Lett.* **2006**, *8*, 1569-1571.
39. Meyer, A. M.; Katz, C. E.; Li, S.-W.; Vander Velde, D.; Aubé, J. *Org. Lett.* **2010**, *12*, 1244-1247.
40. Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2002**, *4*, 331-333.
41. Takashima, K.; Hayakawa, D.; Gouda, H.; Toyooka, N. *J. Org. Chem.* **2019**, *84*, 5222-5229.
42. Fuijtani, M.; Tsuchiya, M.; Okano, K.; Takasu, K.; Ihara, M.; Tokuyama, H. *Synlett* **2010**, 822-826.
43. Sato, M.; Azuma, H.; Daigaku, A.; Sato, S.; Takasu, K.; Okano, K.; Tokuyama, H. *Angew. Chem. Int. Ed.* **2017**, *56*, 1087-1091.
44. Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891-14899.
45. Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153-2164.
46. Bower, S.; Kreutzer, K. A.; Buchwald, S. L. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1515-1516.
47. Shimomura, M.; Sato, M.; Azuma, H.; Sakata, J.; Tokuyama, H. *Org. Lett.* **2020**, *22*, 3313-3317.
48. Wu, J.-L.; Chiou, W.-H. *J. Org. Chem.* **2020**, *85*, 9051-9063.
49. Marcé, P.; Lynch, J.; Blacker, A. J.; Williams, J. M. J. *Chem. Commun.* **2016**, *52*, 1436-1438.
50. Anelli, P. L.; Brocchetta, M.; Palano, D.; Visigalli, M. *Tetrahedron Lett.* **1997**, *38*, 2367-2368.
51. Fuenetes de Arriba, A. L.; Lenci, E.; Sonawane, M.; Formery, O.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2017**, *56*, 3655-3659.
52. Wang, Y.-T.; Wu, J.-L.; Chiou, W.-H. *Org. Lett.* **2022**, *24*, 5957-5961.
53. Amat, M.; Girera, R.; Fabregat, R.; Molins, E.; Bosch, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3348-3351.
54. Amat, M.; Ghirardi, E.; Navío, L.; Griera, R.; Llor, N.; Molins, E.; Bosch, J. *Chem. Eur. J.* **2013**, *19*, 16044-16049.
55. Piccichè, M.; Pinto, A.; Griera, R.; Bosch, J.; Amat, M. *Org. Lett.* **2017**, *19*, 6654-6657.
56. Pinto, A.; Piccichè, M.; Griera, R.; Molins, E.; Bosch, J.; Amat, M. *J. Org. Chem.* **2018**, *83*, 8364-8375.
57. Mun, S.; Lee, J.-E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887-4889.
58. Piccichè, M.; Pinto, A.; Griera, R.; Bosch, J.; Amat, M. *Org. Lett.* **2022**, *24*, 5356-5360.
59. Xiao, K.-J.; Luo, J.-M.; Ye, K.-Y.; Wang, Y.; Huang, P.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 3037-3040.
60. Xiao, K.-J.; Wang, Y.; Ye, K.-Y.; Huang, P.-Q. *Chem. Eur. J.* **2010**, *16*, 12792-12796.
61. Liu, J.; Swidorski, J. J.; Peters, S. D.; Hsung, R. P. *J. Org. Chem.* **2005**, *70*, 3898-3902.
62. Huang, Y.-H.; Liu, Z.-J.; Huang, P.-Q. *Org. Chem. Front.* **2022**, *9*, 58-63.
63. Pastor, A.; Prinsloo, R.; Burford, K. N.; Macdonald, A. R.; Parvez, M.; Gendy, C.; Back, T. G. *J. Org. Chem.* **2023**, *88*, 13813-13824.
64. Pflästerer, D.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2016**, *45*, 1331-1367.
65. De, S.; Dan, A. K.; Sahu, R.; Parida, S.; Das, D. *Chem. Asian J.* **2022**, e202200896.
66. Lin, B.; Liu, T.; Luo, T. *Nat. Prod. Rep.* **2024**, *41*, 1091-1112.
67. Tan, T.-D.; Chen, Y.-B.; Yang, M.-Y.; Wang, J.-L.; Su, H.-Z.; Hong, F.-L.; Zhou, J.-M.; Ye, L.-W. *Chem. Commun.* **2019**, *55*, 9923-9926.
68. Yoshimura, A.; Hanzawa, R.; Fuwa, H. *Org. Lett.* **2022**, *24*, 6237-6241.
69. Moret, E.; Franzini, L.; Schlosser, M. *Chem. Ber.* **1997**, *130*, 335-340.

70. Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521-522.
71. Noyori, R.; Tomino, I.; Nishizawa, M. *J. Am. Chem. Soc.* **1979**, *101*, 5843-5844.
72. Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644-5646.
73. Hanzawa, R.; Fuwa, H. *Org. Lett.* **2023**, *25*, 1984-1988.
74. Christie, H. S.; Heathcock, C. H. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12079-12084.
75. Xu, S.; Arimoto, H.; Uemura, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 5746-5749.
76. Ittah, Y.; Sasson, Y.; Shahak, I.; Tsaroom, S.; Blum, J. *J. Org. Chem.* **1978**, *43*, 4271-4273.
77. Zeng, X.; Wang, C.; Yan, W.; Rong, J.; Song, Y.; Xiao, Z.; Cai, A.; Liang, S. H.; Liu, W. *ACS Catal.* **2023**, *13*, 2761-2770.
78. Takatori, Y.; Fuwa, H. *J. Org. Chem.* **2024**, *89*, 11693-11700.
79. Fernández, I.; Cossío, F. P.; Sierra, M. A. *Chem. Rev.* **2009**, *109*, 6687-6711.
80. Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 3485-3488.
81. Bunce, R. A.; Kotturi, S. V.; Peeples, C. J.; Holt, E. M. *J. Heterocycl. Chem.* **2009**, *39*, 1049-1054.
82. Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, 75-77.
83. Inamoto, Y.; Kaga, Y.; Nishimoto, Y.; Yasuda, M.; Baba, A. *Org. Lett*. **2013**, *15*, 3452-3455.
84. Xie, L.-G.; Dixon, D. J. *Chem. Sci*. **2017**, *8*, 7492-7497.
85. Möhrle, H.; Claas, M. J. P. *Pharmazie* **1988**, *43*, 749-753.
86. Hugelshofer, C. L.; Palani, V.; Sarpong, R. *J. Am. Chem. Soc*. **2019**, *141*, 8431-8435.
87. Wender, P. A.; Croatt, M. P.; Witulski, B. *Tetrahedron* **2006**, *62*, 7505-7511.
88. We define a reaction step as one in which a substrate is transformed into a product without intermediate work-up or purification.
89. Mizukami, D.; Iio, K.; Oda, M.; Onodera, Y.; Fuwa, H. *Angew. Chem., Int. Ed.* **2022**, *61*, e202202549.
90. Nakazato, K.; Oda, M.; Fuwa, H. *Org. Lett.* **2022**, *24*, 4003-4008.
91. Nakazato, K.; Oda, M.; Fuwa, H. *Bull. Chem. Soc. Jpn.* **2023**, *96*, 257-267.
92. Nakagawa, H.; Fuwa, H. *Chem. Commun.* **2023**, *59*, 10121-10124.
93. During the preparation of this manuscript, total synthesis of (−)-lepadiformine A by the Vaitla group and total syntheses of (±)-lepadiformines B and C by the Chiou groups were reported. Sen, R.; Vaitla, J. *J. Org. Chem.* **2025**, *90*, 8806-8811; Hsiao, W.-T.; Wu, J.-L.; Chiou, W.-H. *J. Org. Chem.* **2025**, *90*, 10104-10108.
94. During the preparation of this manuscript, a review article on the synthesis of lepadiformines was published. Gu, X.; Zhao, M.; Sun, L.; Xiong, Y. *Tetrahedron* **2025**, *185*, 134804.