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Tricyclic Marine Alkaloids: Synthetic Approaches to Cylindricines, Lepadiformine, and Fasicularin

Pascal Schär, Sylvaine Cren, and Philippe Renaud*

Abstract: Cylindricines, lepadiformine, and fasicularin are marine alkaloids with a common novel pyrrolo- and pyrido[1,2-*j*]quinoline skeleton. They have recently been isolated from various tunicates and have shown interesting cytotoxic effects which could be attributed to covalent interactions with DNA, as well as cardiovascular effects. The promising biological activities together with the unique structural features make these alkaloids interesting targets for natural product synthesis. This review focuses on the different approaches developed for their synthesis with a particular emphasis on the key step where the quaternary amino substituted carbon center is created.

Keywords: Alkaloids · Azaspirocycles · Natural products · Perhydroquinolines · Total synthesis

1. Introduction: Isolation, Structural Assignment, and Biological Activity

The pyrrolo-/pyrido[1,2-*j*]quinoline frameworks **1** and **2** (Fig. 1) [1] are a common structural feature of a series of alkaloids which have been recently isolated from various tunicate sources. Named after their respective parent organisms, this class of compounds can be divided into the cylindricines A–K (**3a**–**k**) [2–4], lepadiformine (**4**) [5], and fasicularin (**5**) [6]. Structurally, they differ in their relative configurations, the length of the unbranched side chain, the functionalization of the pyrrolidine or piperidine ring C, and the oxidation state of rings A and B.

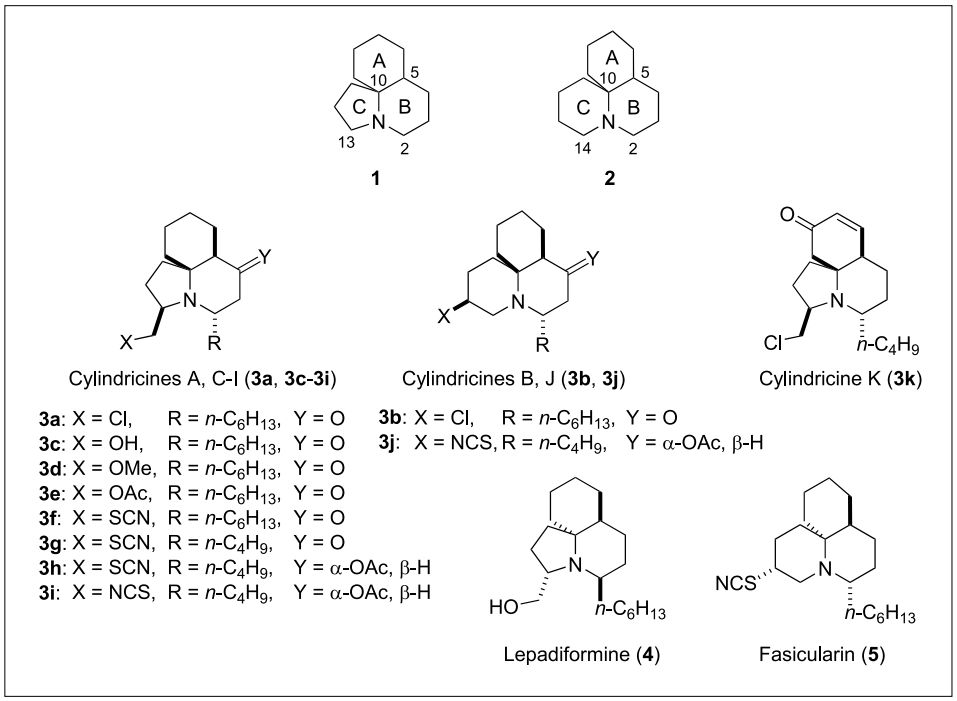


Fig. 1. The structures of the cylindricines, lepadiformine and fasicularin

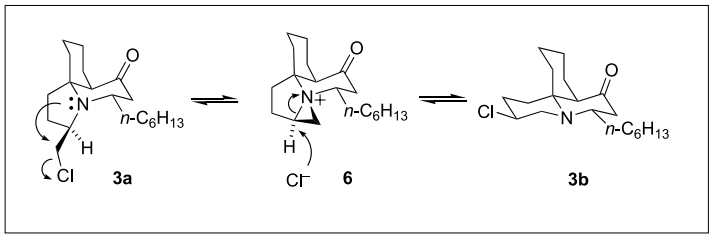
1.1. *Cylindricines*

The cylindricines were isolated from *Clavelina cylindrica* around the eastern coast of Tasmania by Blackman and coworkers in the early 1990s [2–4]. It is a class of compounds with a large structural variety. In particular the substitution pattern on the C ring is varied and seems to correlate with the geographical location of the collection of the samples [4].

Some cylindricines interconvert slowly as the free bases and form thermodynamic mixtures in solutions. For example, cylindricines A (**3a**) and B (**3b**) form a 3:2 equilibrium in an aqueous medium (Scheme 1) [2]. This conversion presumably occurs *via* the aziridinium ion intermediate **6**.

Cylindricines C–F could be obtained from this equilibrium mixture by reaction with the appropriate nucleophile [3]. This

*Correspondence: Prof. Dr. P. Renaud
Universität Bern
Departement für Chemie und Biochemie
Freiestrasse 3
CH-3012 Bern
Tel.: +41 31 631 4359
Fax: + 41 31 631 3426
E-Mail: philippe.renaud@ioc.unibe.ch



Scheme 1. Interconversion of cylindricines A (**3a**) and B (**3b**) [2]

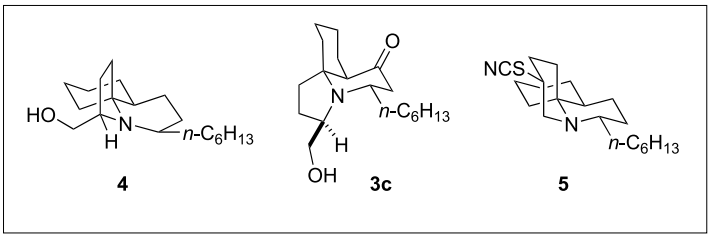
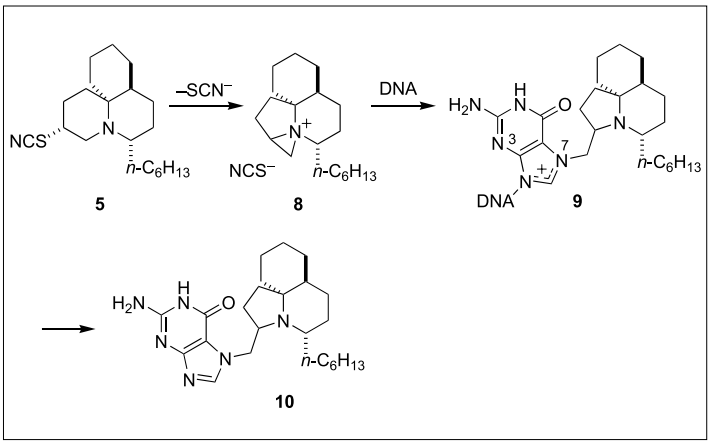


Fig. 3. Conformation of lepadiformine (**4**), cylindricine C (**3c**) and fasicularin (**5**)

suggests a common biosynthetic pathway with aziridinium ion **6** as a late stage intermediate. However, little is known about the biogenesis of the whole class of alkaloids. X-ray crystallography of the picrate salts of **3a** and **3b** was pivotal for the unequivocal structural assignment and especially for the determination of the relative configuration [2]. The structure of the rest of the series was assigned by a combination of chemical conversion, high-resolution mass spectrometry, and NMR experiments. Although Molander and Rönn completed the first asymmetric synthesis of (–)-cylindricine C in 1999 [7], the absolute configuration has never been compared to the natural material and therefore remains undetermined. Cylindricines A and B showed some biological activity in the brine shrimp assay [2].



Scheme 2. DNA-alkylating properties of fasicularin (**5**) [12]

1.2. *Lepadiformine*

Lepadiformine (**4**) was isolated in 1994 by Biard and coworkers from *Clavelina lepadiformis* off the coast of Tunisia and later from *Clavelina moluccensis* near Djibouti [5][8]. The unusual zwitterionic structure **7** was proposed based on elaborate NMR experiments (Fig. 2). However, because the high field region (2.1–0.8 ppm) of the ^{1}H NMR spectrum exhibits 28 out of the 35 signals the relative configuration was not surprisingly wrongly assigned. The correct structure was later proven to be **4** after the first total synthesis of lepadiformine had been achieved by Kibayashi and coworkers in 2000 [9].

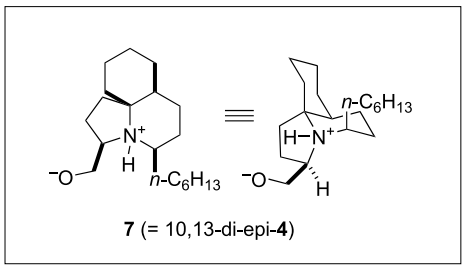


Fig. 2. Zwitterionic structure **7** of lepadiformine initially proposed by Biard *et al.* [5]

Compared to (–)-cylindricine C (**3c**), lepadiformine lacks C(4) oxygenation and is epimeric at C(2), C(10), and C(13). This has an important effect on the shape of the molecule (Fig. 3). While the cylindricines (**3**) exist in a *cis*-1-azadecalin configuration, lepadiformine (**4**) presents a *trans*-1-azadecalin that features an unusual twist-boat conformation of the A ring.

Originally, the optical rotation of lepadiformine at the sodium D-line was reported to be 0 suggesting that it may be present as a racemic mixture. Later, a small positive rotation was found and the absolute configuration was proven independently by the groups of Kibayashi [10] and Weinreb [11] by HPLC on a chiral column and comparison of the NMR spectra of the Mosher esters. Lepadiformine showed moderate cytotoxic activity against several tumor cell lines as well as various cardiovascular effects *in vivo* and *in vitro* [8].

1.3. *Fasicularin*

Fasicularin (**5**) was isolated in 1997 by the team of Patil and coworkers of SmithKline Beecham Pharmaceuticals and Faulkner from Scripps Institution of Oceanography from *Nephteis fasicularis*, collected in Pohnpei [6]. It showed biological activity against a DNA repair-deficient strain of yeast and cytotoxicity against Vero cells [6]. The structural assignment was achieved by NMR and suggested a *trans*-1-azadecalin ring fusion like lepadiformine, but epimeric at C(2). Recent investigations have shown that the cytotoxicity of fasicularin might be attributed to the alkylating properties of aziridinium ion **8**, generated in analogy to **6** (Scheme 2) [12]. Aziridinium ion **8** alkylates the most nucleophilic site in DNA, which is the N(7) position of guanine. The resulting adduct **9** can then easily undergo strand scission. As evidence for this mechanism, fragment **10** was identified as a product of induced cleavage by MS/MS analysis.

These findings offer a reasonable chemical basis for the biological activity of fasicularin and possibly the other alkaloids and they may give a new impetus to the evaluation of these compounds as potential clinical agents.

2. Total Syntheses

The whole family of compounds has attracted considerable synthetic interest over the last decade [13][14]. More than a dozen research groups worldwide have made contributions in more than thirty articles. Given that none of the target molecules has found any practical application so far, the main motivation for this effort might come from the challenging structure of these alkaloids.

The main structural feature of the alkaloids is the azadecalin framework with an amino-substituted quaternary carbon center at C(10). The stereocontrolled introduction of this quaternary center at C(10) represents the main synthetic challenge. The present review aims at highlighting and comparing the solutions developed by different groups

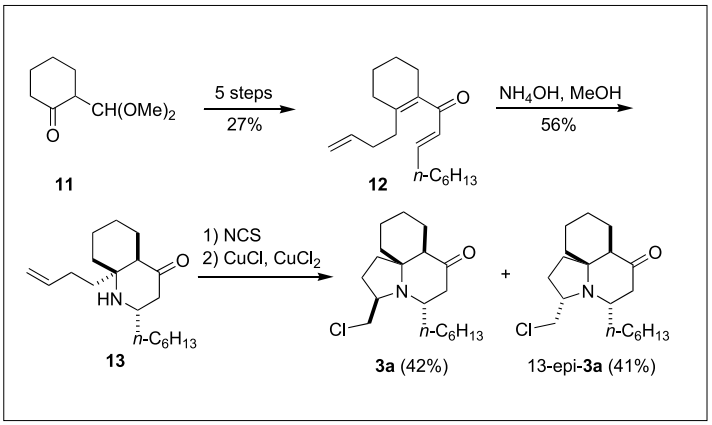
and is divided according to the synthetic strategy used to create the quaternary center at C(10). As these alkaloids are structurally closely related, some of the strategies were applied to the synthesis of several members of the family.

2.1. *Michael Addition*

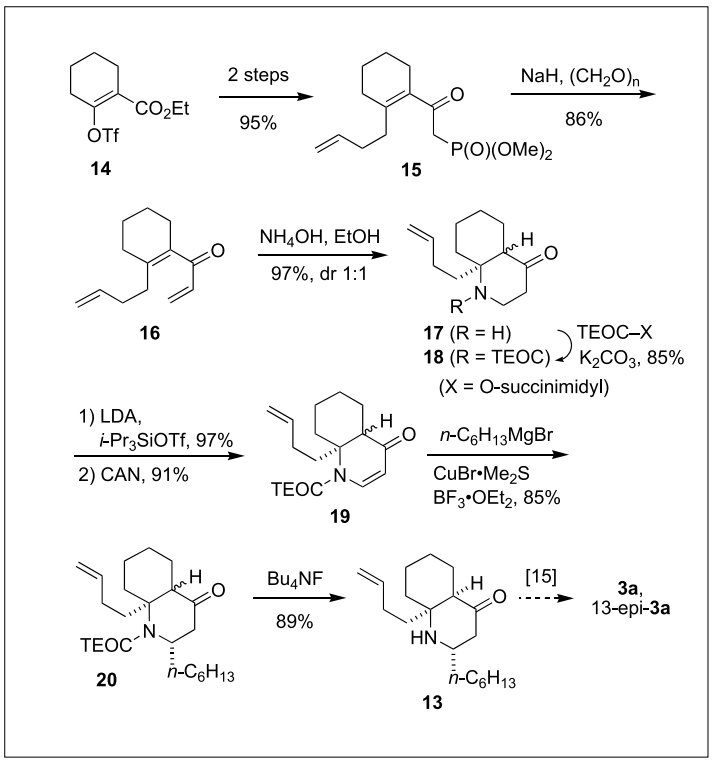
The first total synthesis of racemic cylindricines A, D, and E was reported by Snider and Liu in 1997 [15]. The key step consisted in a double Michael addition of ammonia to dienone **12**, derived from acetalcylohexanone (**11**) (Scheme 3). This gave a mixture of diastereomers with the desired *cis*-perhydroquinolinone **13** isolated in 56% yield. Lowering the pH favored the undesired *trans* isomer. The amine was then converted to the corresponding chloramine which could be cyclized *via* a radical pathway. This gave a nearly 1:1 mixture of **3a** and 13-epi-**3a**, the latter being recycled to **13** by reduction with zinc dust. Cylindricines D and E were prepared by reacting the equilibrium mixture of **3a** and **3b** with NaOMe or NaOAc, respectively.

The same approach was also pursued by Heathcock and Liu in 1999 who prepared dienone **12** from enolester **14** [16]. However, due to the low diastereoselectivity in the double Michael addition of ammonia to dienone **12**, the hexyl chain was installed at a later stage in the synthesis. Michael addition on substrate **16** gave a 1:1 mixture of *cis*- and *trans*-fused products **17** (Scheme 4). Different protecting group strategies for the amine were then investigated, but only the TEOC (trimethylsilylethoxycarbonyl) group could be removed at a later stage of the synthesis. The vinylogous amide **19** was then prepared by CAN (ceric ammonium nitrate) oxidation of the triisopropylsilyl enol ether of **18**. The organocopper addition of the *n*-hexyl side chain to both isomers of **19** proceeded with high diastereoselectivity, as anticipated from molecular modeling. Removal of the protecting group from both isomers of **20** led to known **13** as a single isomer, due to epimerization of the *trans*-perhydroquinolinone to the more stable *cis*-isomer. The synthesis was completed by a radical cyclization of the chloramine, as previously described (Scheme 3) [15], leading to a 1:1 mixture of cylindricine A (**3a**) and its epimer 13-epi-**3a**.

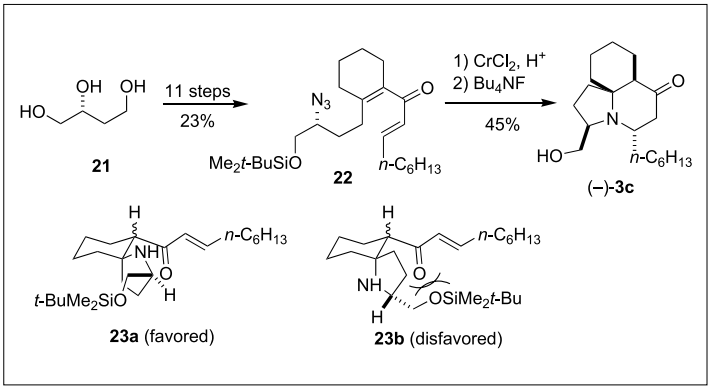
The problem of low diastereoselectivity in the last step was overcome by Molander and Rönn in 1999, who chose an intramolecular approach, where the absolute configuration at C(13) was predetermined by the building block (–)-1,2,4-butanetriol (**21**) derived from L-malic acid (Scheme 5) [7]. The key intermediate **22** was prepared in 11 straightforward steps. The azide moiety of **22** was then reduced with $CrCl_2$ to the corresponding amine that underwent a double



Scheme 3. Synthesis of cylindricine A (**3a**) by Snider and Liu (NCS = N-chlorosuccinimide) [15]



Scheme 4. Synthesis of cylindricine A (**3a**) by Heathcock and Liu, second approach (Tf = SO_2CF_3; TEOC = $CO_2CH_2CH_2SiMe_3$; LDA = $(i\text{-Pr})_2NLi$; CAN = $(NH_4)_2Ce(NO_3)_6$) [16]

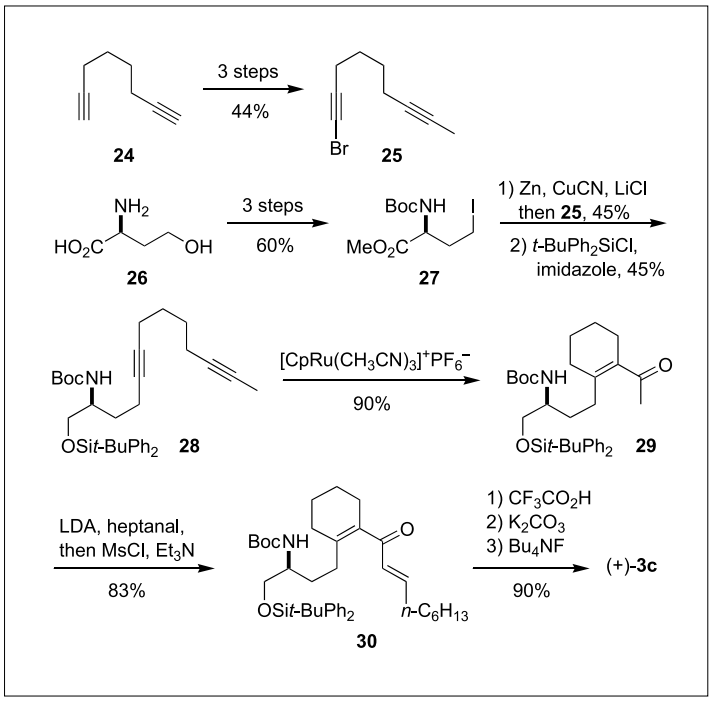


Scheme 5. Synthesis of (–)-cylindricine C ((–)-**3c**) by Molander and Rönn [7]

Michael addition to give, after deprotection of the primary alcohol, (–)-cyclindricine C ((–)-**3c**) as a single stereoisomer.

The stereoselective formation of three new stereocenters represents the highlight of this synthesis. The stereochemical outcome can be explained by a first stereoselective Michael addition leading preferentially to **23a**. Severe steric interactions between the bulky silyl ether and the enone side chain disfavor the formation of **23b**. The stereochemistry in the second Michael addition is created by the reversibility (retro-Michael addition) allowing the *n*-hexyl side chain to occupy an equatorial position. The stereochemistry α to the ketone is established by an epimerization process leading to the more stable *cis*-fused cyclohexanone system.

Trost and Rudd prepared intermediate **30** which is epimeric to **22** at the carbon bearing the nitrogen atom using a ruthenium-catalyzed hydrative diyne cyclization of **28** derived from L-serine (Scheme 6) [17]. This led to the total synthesis of (+)-**3c** in a slightly shorter reaction sequence than the one of Molander (10 *vs.* 13 steps).



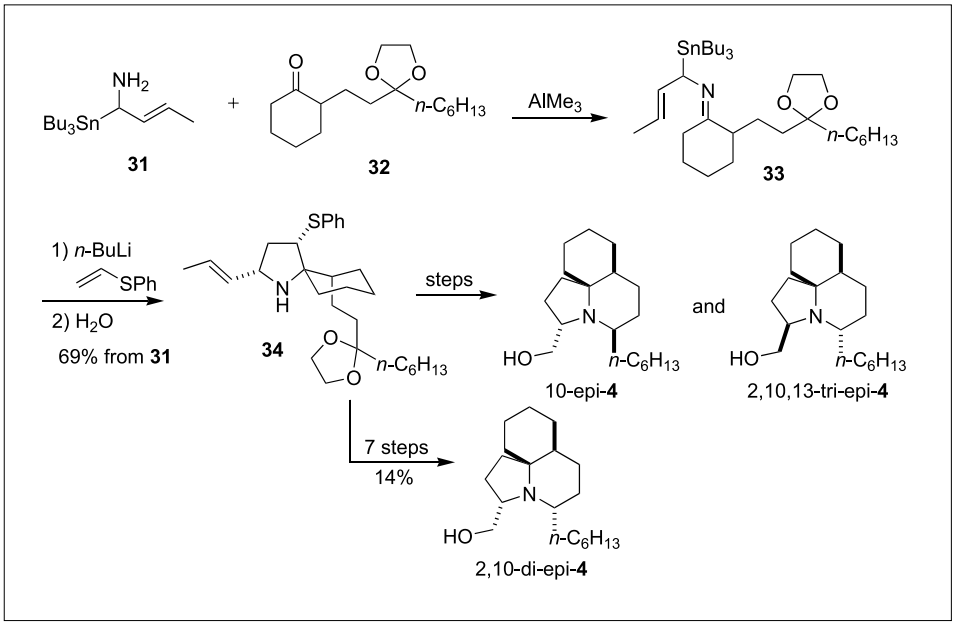
Scheme 6. Synthesis of (+)-cylindricine C ((+)-**3c**) by Trost and Rudd (Boc = CO_2t-Bu; Cp = cyclopentadienyl; Ms = SO_2CH_3) [17]

2.2. *Cycloaddition*

Different types of cycloadditions have been used as the key step to install the C(10) quaternary center in the synthesis of lepadiformine, fasicularin and cylindricines.

2.2.1. *[3+2]-Cycloaddition of 2-Azaallyl Anions*

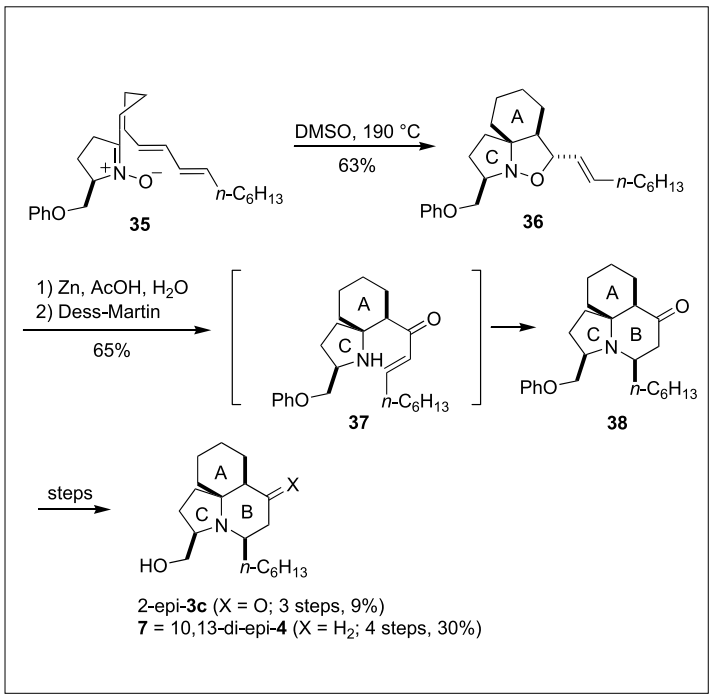
Pearson and coworkers applied their methodology involving a [3+2]-cycloaddition of a 2-azaallyl anion to the synthesis of the three diastereomers of the putative structure of lepadiformine at C(2) and C(13) (Scheme 7) [18][19]. Imine **33** was treated with phenyl vinyl sulfide and *n*-butyllithium, and after work-up spirocycle **34** was obtained in 69% as a single regio- and stereoisomer. The quaternary center was now in place, and this spirocycle was converted into three of the four possible diastereomers of the putative structure of lepadiformine **7**, which were shown not to correspond to the natural product. The fourth diastereomer **7** (10,13-di-epi-**4**) was prepared by Weinreb and was also found to be different from naturally occurring lepadiformine (Scheme 8) [20]. As a consequence, it was deduced that unlike cylindricines (**3**), lepadiformine (**4**) possesses a *trans*-1-azadecalin subunit.



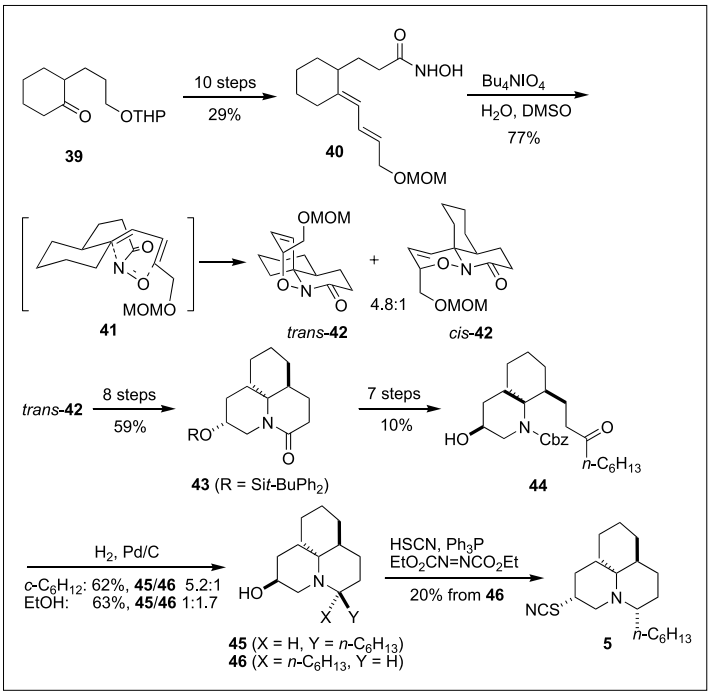
Scheme 7. Preparation of stereoisomers of lepadiformine (**4**) by Pearson and coworkers [18][19]

2.2.2. *[3+2]-Dipolar Cycloaddition of Nitrones*

In 1999, Weinreb and coworkers reported the synthesis of the putative structure **7** of lepadiformine and of 2-epi-cylindricine C (2-epi-**3c**) *via* a common intermediate [20][21]. Their strategy was based on an intramolecular [3+2]-cycloaddition of a nitrone (Scheme 8). Nitrone **35** was synthesized starting from acetone oxime in a total of nine steps. Although the preparation of the precursor was rather tedious, the cycloaddition afforded the desired product **36** as a single stereoisomer in 63% yield. Conversion of **36** into tricycle **38** was achieved by reductive cleavage of the N–O bond followed by Dess-Martin periodinane oxidation of the allylic alcohol to the corresponding enone **37** that underwent spontaneous and stereoselective intramolecular conjugate addition. The exclusive formation of the C(2) axial epimer was rationalized by the transition state initially leading to a boat ketone, which ring flips to the final product **38**. Tricycle **38** was transformed into 2-epi-cylindricine (2-epi-**3c**) in three steps, and into the putative structure of lepadiformine **7** in four steps. Comparison of the spectroscopic data of this product with those of an authentic sample of the natural product revealed that the two compounds were different. All attempts to isomerize 2-epi-**3c** to cylindricine C (**3c**) failed.



Scheme 8. Synthesis of the putative structure of lepadiformine **7** and of 2-epi-cyclindricine C (2-epi-**3c**) by Weinreb, Werner and coworkers [20][21]



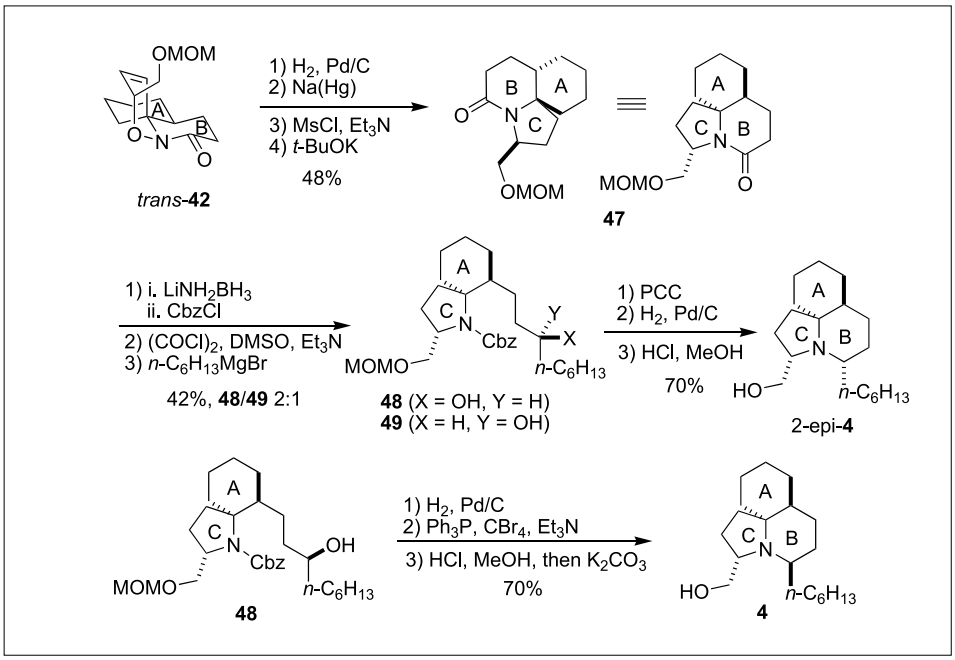
Scheme 9. Synthesis of fasicularin (**5**) by Kibayashi and coworkers (MOM = CH_2OCH_3; Cbz = $CO_2CH_2C_6H_5$) [9]

2.2.3. *[4+2]-Cycloaddition of Acylnitroso Derivatives*

In 2000, Kibayashi and coworkers reported the first total syntheses of racemic fasicularin **5** and lepadiformine **4** [9]. These first syntheses involved a stereocontrolled [4+2]-cycloaddition of acylnitroso derivatives.

The preparation of fasicularin is depicted in Scheme 9. α-Alkylated cyclohexanone **39** was converted to hydroxamic acid **40** in ten steps. Upon treatment with tetrabutylammonium periodate, the acylnitroso compound was generated and underwent a [4+2]-cycloaddition through transition state **41** to afford tricyclic compound **42**. The B/C ring junction was obtained as a 4.8:1 *trans*/*cis* mixture. Compound *trans*-**42** was converted to fasicularin (**5**) *via* a long reaction sequence involving tricyclic intermediate **43** and bicyclic ketone **44**. Reductive amination of **44** afforded **45** and **46** with a solvent-dependent moderate stereoselectivity. Conversion of **46** to fasicularin (**5**) was achieved *via* a Mitsunobu reaction with thiocyano acid in 20% yield.

Lepadiformine (**4**) and its epimer at C(2) (2-epi-**4**) were also prepared from *trans*-**42** (Scheme 10). After hydrogenation of the double bond of *trans*-**42** and reductive cleavage of the N–O bond with sodium amalgam, the pyrrolidine ring was built by mesylation of the alcohol followed by intramolecular nucleophilic substitution. Tricylic compound **47** was converted in four steps to a 2:1 mixture of **48** and **49**. Not surprisingly, the addition of *n*-hexylmagnesium bromide to the aldehyde resulted in a low stereoselectivity. The mixture of **48** and **49** was converted to 2-epi-lepadiformine (2-epi-**4**) *via* oxidation of the alcohol to the corresponding ketone, reductive amination and deprotection of the methoxymethyl protecting group. The diastereomerically pure alcohol **48** was converted to lepadiformine (**4**) *via* removal of the Cbz protecting group followed by cyclization upon treatment of the free amino alcohol with CBr_4 and Ph_3P, and hydrolysis of the methoxymethyl group. Unlike the optically active material, the hydrochloride of the racemic compound gave crystals suitable for X-ray analysis. Therefore the relative configuration of lepadiformine was unambiguously secured since comparison of NMR data of the synthetic compound with those of natural (–)-lepadiformine ((–)-**4**) revealed an exact match.

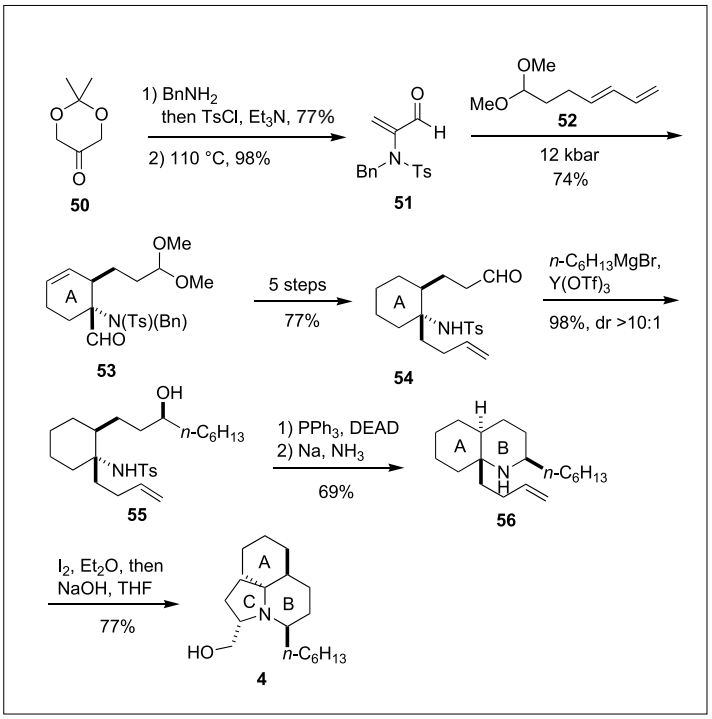


Scheme 10. Synthesis of lepadiformine (**4**) by Kibayashi and coworkers (PCC = pyridinium chlorochromate) [9]

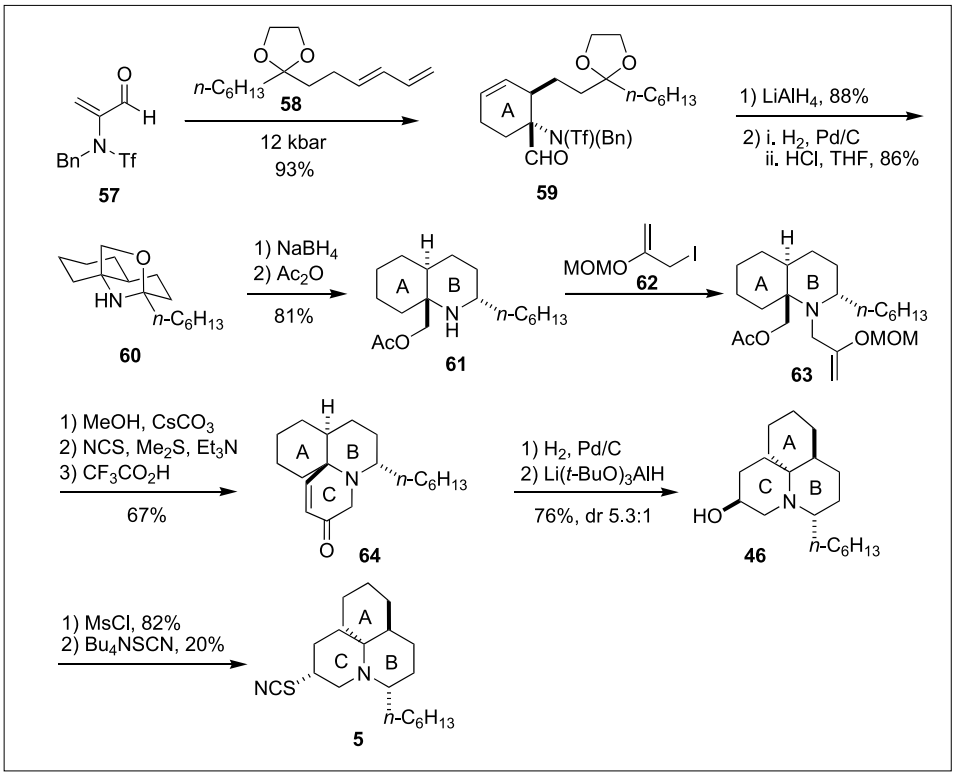
2.2.4. *[4+2]-Cycloaddition of Amidoacroleins*

In 2001, Greshock and Funk reported the total synthesis of lepadiformine using a [4+2]-cycloaddition of an amidoacrolein (Scheme 11) [22]. Amidoacrolein **51** was prepared from protected dihydroxyacetone **50** by condensation with benzylamine, tosylation of the resulting imine and thermally induced retro hetero-Diels-Alder reaction. Cycloaddition of diene **52** with amidoacrolein under high pressure afforded cyclohexene **53** in 74% yield as a single diastereomer *via* an endo transition state. This approach allows the preparation of the A ring of lepadiformine with the desired relative stereochemistry at C(9), C(5) and C(10). Conversion of **53** into aldehyde **54** was carried out in five steps. Reaction of **54** with *n*-hexylmagnesium bromide in the presence of ytterbium triflate afforded alcohol **55** with a good stereoselectivity and excellent chemical yield. Cyclization of **55** under Mitsunobu conditions followed by removal of the N-tosyl group afforded *trans*-1-azadecalin **56**. Finally, the pyrrolidine ring C was built *via* an iodine-promoted amine cyclization in the presence of sodium hydroxide and lepadiformine (**4**) was isolated in 77% yield.

As this approach proved suitable for the preparation of the *trans*-1-azadecalin subunit of lepadiformine, it was also applied to the synthesis of fasicularin (Scheme 12) [23]. In this synthesis, diene **58** containing the *n*-hexyl side chain was used for the cycloaddition with amidoacrolein **57**. The cycloaddition proceeded again with complete selectivity and **59** was obtained in high yield. Reduction of the aldehyde and concomitant removal of the trifluoromethanesulfonyl group followed by hydrogenation of the double bond and hydrogenolysis of the N-benzyl protecting group (H_2, Pd/C) gave an aminoalcohol which upon treatment with HCl in THF afforded oxazolidine **60**. The B ring was prepared with the desired configuration at C(2) by reduction of **60** with $NaBH_4$. Acetylation afforded *trans*-1-azadecalin **61**. The C ring was built by N-allylation followed by deprotection of the acetate in **63**, oxidation of the primary alcohol under Corey-Kim conditions (NCS, Me_2S) and aldol condensation promoted by trifluoroacetic acid. Enone **64** was hydrogenated and stereoselectively reduced to **46** with lithium tris(*tert*-butoxy)aluminum hydride (dr 5.3:1). Finally, mesylation of the secondary alcohol followed by treatment with tetrabutylammonium thiocyanate gave fasicularin (**5**) in only 20% together with the corresponding isothiocyanate and an alkene resulting from an elimination reaction. This last step accounts for the poor overall yield of the synthesis (less than 3%).



Scheme 11. Synthesis of lepadiformine (**4**) by Funk and Greshock (Bn = $CH_2C_6H_5$; Ts = 4-$CH_3C_6H_4SO_2$; DEAD = $EtO_2CN{=}NCO_2Et$) [22]



Scheme 12. Synthesis of fasicularin (**5**) by Funk and Maeng (Ac = $C(O)CH_3$) [23]

2.3. *Inter- and Intramolecular Reactions of Iminium Ions*

Inter- and intramolecular addition of iminium and N-acyliminium ions to alkenes is a classical strategy for the synthesis of alkaloids [24][25]. Several research groups decided to apply this chemistry to the synthesis of the azaspiro moiety of cylindricines, lepadiformine and fascicularin.

2.3.1. *Intermolecular Allylation of an Iminium Ion*

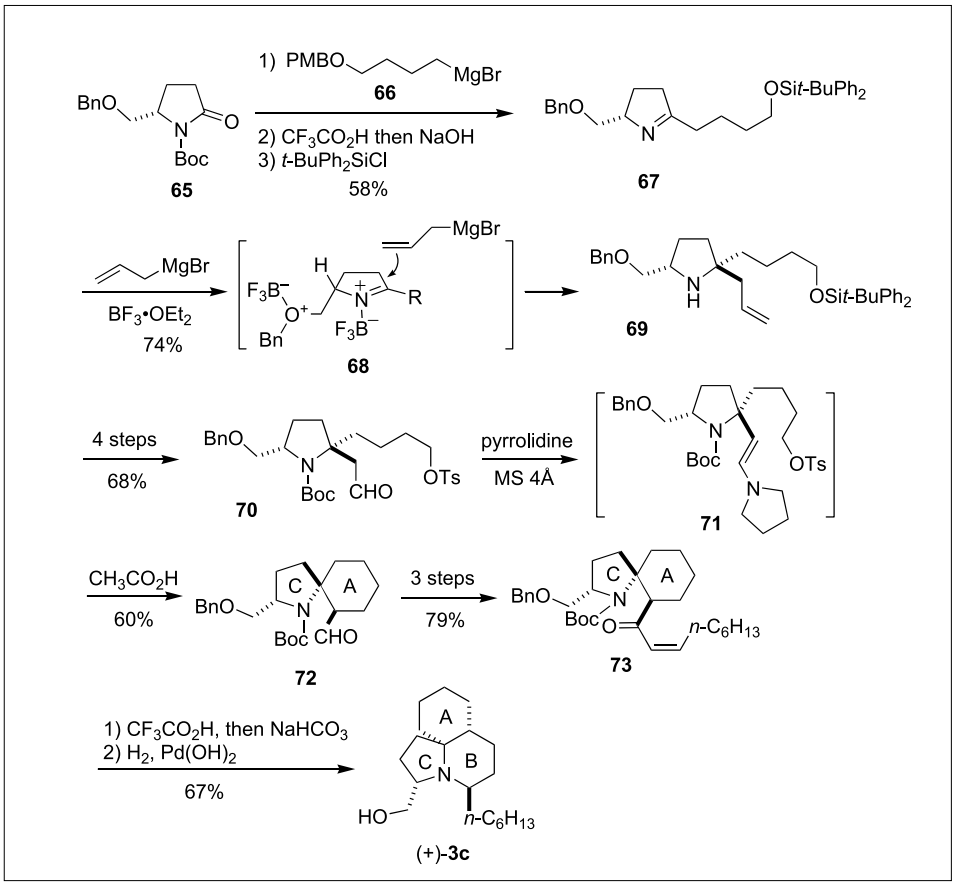
The first synthesis of (+)–cylindricine C ((+)-**3c**) by Kibayashi's group starts from pyrrolidinone **65**, which is easily available from (*S*)-pyroglutamic acid (Scheme 13) [26]. Lactam **65** was converted into pyrroline **67** by reaction with Grignard reagent **66** followed by treatment with tri-

fluoroacetic acid and replacement of the *para*-methoxybenzyl protecting group by a (*tert*-butyl)diphenylsilyl ether. The crucial C(10) stereogenic center was installed in the next step by treating pyrroline **67** with allylmagnesium bromide in the presence of BF_3•OEt_2 and **69** was obtained in 74% yield as a single diastereomer. The *anti* stereochemical outcome is explained by reaction of iminium ion **68** under non-chelation control. Conversion of **69** to aldehyde **70** was achieved in four steps and 68% overall yield. Treatment of **70** with pyrrolidine afforded enamine **71** which spontaneously cyclized to give, after debenzylation of the hydroxymethyl side chain, the azaspirodecane derivative **72** in 60% yield as a single diastereomer. During the intramolecular conjugate addition, a complete inversion of the stereoselectivity at C(5) next to the carbonyl group was observed.

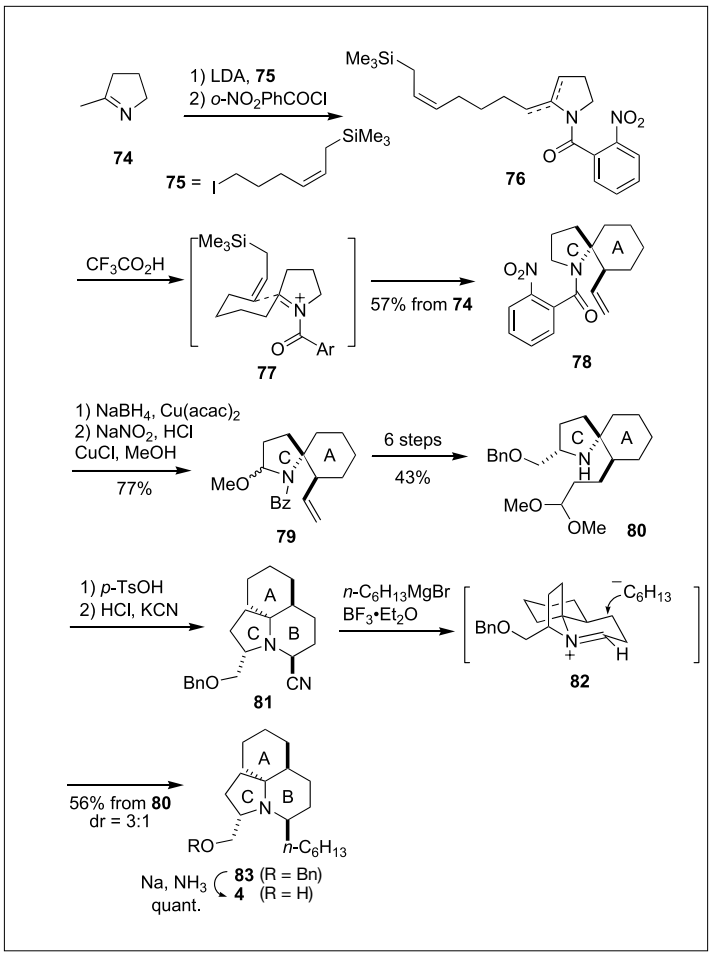
2.3.2. *N-Acyliminium Ion Cyclization: Weinreb Approach*

Since the nitrone-based strategy developed by Weinreb's group (Scheme 8) could not be used to produce the requisite *trans*-tetrahydroquinoline skeleton of lepadiformine, Weinreb and coworkers developed a second approach based on the cyclization of an acyliminium ion intermediate (Scheme 14) [11][27]. Imine **74** was metalated with LDA and alkylated with iodide **75**. After acylation with *o*-nitrobenzoyl chloride, enamide **76** was obtained as a mixture of regioisomers. This crude mixture was treated with trifluoroacetic acid to afford **78** as a single spirocyclization product *via* N-acyliminium ion **77**. After reduction of the nitro group, the aromatic amine was then used to install a methoxy group by radical decomposition of a diazonium salt followed by 1,5-hydrogen transfer and oxidation to methoxyamide **79**. Conversion of **79** to **80** was achieved in six steps. The B ring was built by an intramolecular aminocyanation process leading to the α-aminonitrile **81** under kinetic control. Finally, the *n*-hexyl side chain was introduced by treating **81** with *n*-$C_6H_{13}MgBr$ in the presence of BF_3•OEt_2. The intermediate iminium ion **82** reacted preferentially from the top face (axial attack, dr 3:1) to deliver **83** in 56% yield. Lepadiformine (**4**) was obtained in quantitative yield from **83** upon debenzylation with sodium in liquid ammonia.

This synthetic strategy was easily adapted to the synthesis of the optically pure natural compound (Scheme 15). Thus, lactam **84** was prepared from (*S*)-pyroglutamic acid and treated with organolithium compound **85** to give adduct **86**. Without purification, **86** gave upon treatment with boron trifluoride-acetic acid complex spirocycle **88** as a single stereoisomer in 52% yield from **84**. The reaction goes through an acyliminium



Scheme 13. Synthesis of (+)-cylindricine C ((+)-**3c**) by Kibayashi and coworkers (PMB = 4-$CH_3OC_6H_4CH_2$) [26]



Scheme 14. Synthesis of lepadiformine (**4**) by Weinreb and coworkers (acac = acetylacetonate) [11][27]

ion cyclization according to model **87**. Compound **88** was then converted into intermediate **89** and the rest of the synthesis of (–)-lepadiformine ((–)-**4**) was carried out as described in Scheme 14. This first synthesis of enantiomerically pure (–)-lepadiformine definitively proved the absolute configuration of the natural product.

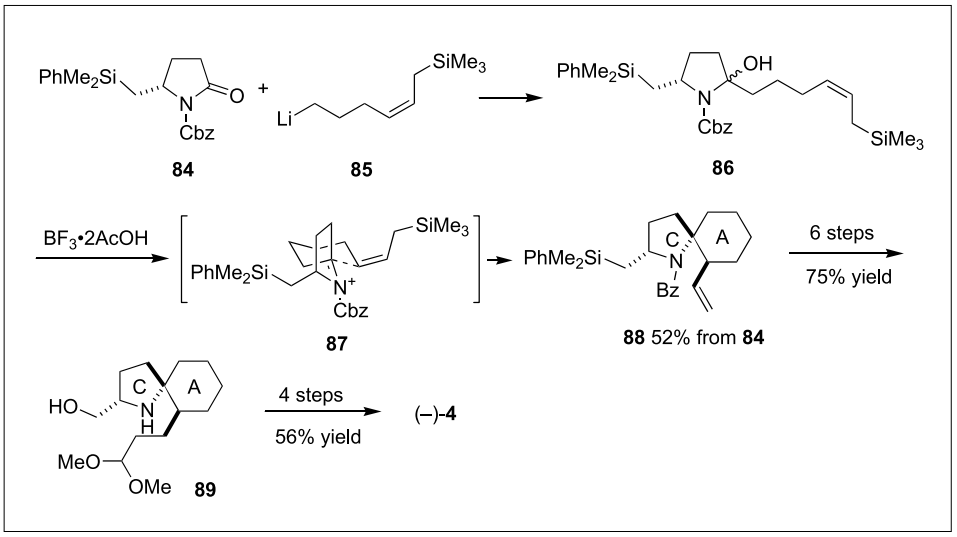
2.3.3. *N-Acyliminium Ion Cyclization: Kibayashi Approach*

Besides the acylnitroso cycloaddition approach (2.2.3.) and the intermolecular allylation of iminium ions (2.3.1.), Kibayashi *et al.* developed a third strategy involving an acyliminium ion cyclization [14]. The efficiency and versatility of this approach is demonstrated by their synthesis of (–)-lepadiformine [10], (+)-cylindricine C, and (–)-fasicularin *via* a common intermediate **93** [28]. The preparation of **93** is shown in Scheme 16. Reaction of pyrrolidinone **65** with Grignard reagent **90** afforded acyclic ketone **91**. A formic acid induced spirocyclization ('*aza*-Prins' cyclization) afforded product **93** *via* acycliminium ion **92** in 88% yield as a mixture of epimeric allylic formates. The relative configuration of the rings A and C corresponds to that of lepadiformine and fasicularin.

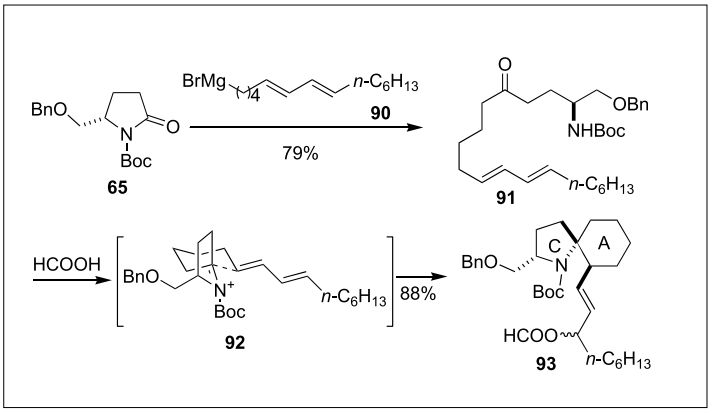
Intermediate **93** was easily transformed into (–)-lepadiformine ((–)-**4**) by first converting the mixture of epimeric allylic formates to diastereomerically pure allylic alcohol **94** *via* hydrolysis, oxidation and stereoselective reduction with Noyori's (*S*)-BINAL-H (Scheme 17). Hydrogenation of the double bond and removal of the Boc protecting group afforded an aminoalcohol which underwent cyclization upon treatment with Ph_3P and CBr_4. Final deprotection of the benzyl group gave (–)-lepadiformine ((–)-**4**) in a remarkable 31% total yield from **65**.

In order to synthesize cylindricine C, it was necessary to oxygenate the C(4) position and to invert the stereochemistry at C(5). This was done according to Scheme 18. Epoxidation of allylic alcohol **94** and reductive opening of the resulting epoxide with $LiAlH_4$ afforded diol **95** which was selectively mesylated at the less hindered position to give **96**. Tricyclic compound **97** was obtained by removal of the N-Boc group and treatment of the free amine with $NaHCO_3$. Oxidation of the alcohol under Swern conditions gave a ketone which epimerized to the more stable *cis*-perhydroquinoline by treatment with K_2CO_3. Finally, debenzylation afforded (+)-cylindricine C ((+)-**3c**).

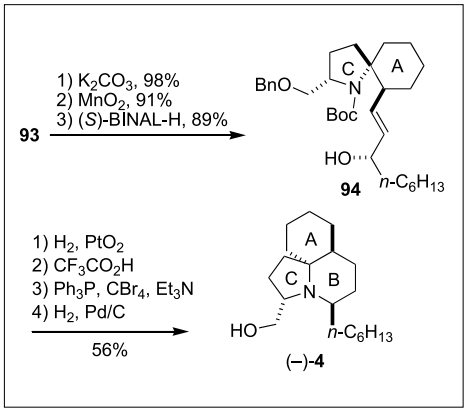
Considering that fasicularin is epimeric to lepadiformine at C(2), allylic alcohol **98**, obtained from **93** *via* the method developed for **94** by using (*R*)-BINAL-H instead of the (*S*)-enantiomer, was used as an advanced intermediate (Scheme 19). Cyclization of **98** under the conditions described for the synthesis of (–)-lepadiformine (Scheme 17) afforded 2-epi-**4** in 67% yield. Upon treatment with ammonium thiocyanate under Mitsunobu conditions, 2-epi-**4** gave a 1:1 mixture of fasicularin ((–)-**5**) and **99**. When standing at room temperature for three days, **99** was converted into (–)-fasicularin ((–)-**5**) in 91% yield. A combined yield of 90% for the conversion of 2-epi-**4** to (–)-**5** was thus obtained. This represents the first synthesis of optically pure fasicularin, which was prepared in a remarkable 28% yield over ten steps from **65**. Since the optical rotation of naturally occurring **5** has not been measured, determination of the absolute configuration of fasicularin (**5**) is not possible without reisolating the natural product.



Scheme 15. Synthesis of (–)-lepadiformine ((–)-**4**) by Weinreb and coworkers [11]



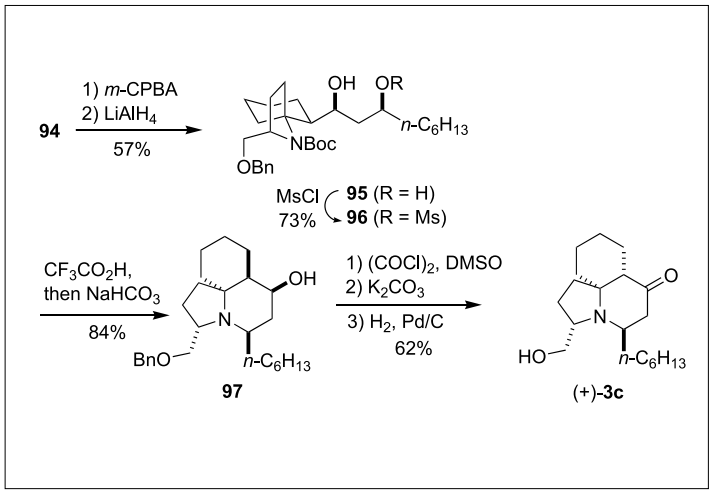
Scheme 16. Preparation of advanced intermediate **93** in Kibayashi's synthesis of (–)-lepadiformine, (–)-fasicularin and (+)-cylindricine C [28]



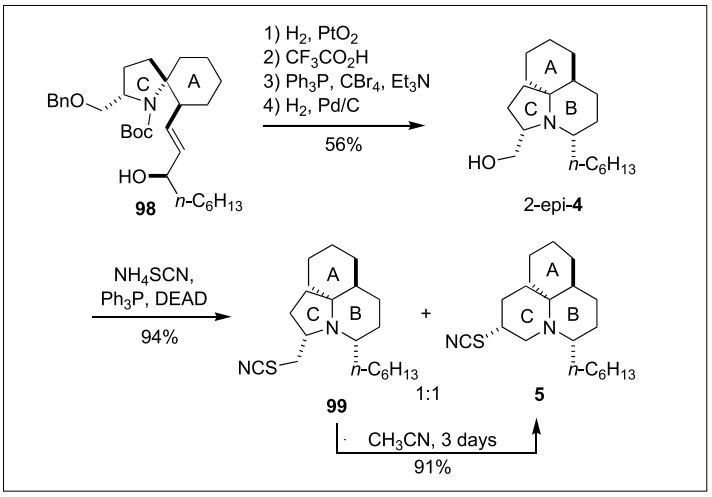
Scheme 17. Synthesis (–)-lepadiformine ((–)-**4**) from **93** by Kibayashi and coworkers (BINAL-H = 2,2'-dihydroxy-1,1'-binaphthylaluminum hydride) [28]

2.3.4. *N-Acyliminium Ion Cyclization: Hsung Approach*

Hsung and coworkers first investigated a strategy based on a Mannich reaction, however, this approach rapidly proved problematic [29]. Therefore, they reported a synthesis based on Kibayashi's *aza*-Prins cyclization (Scheme 20). Allylic alcohol



Scheme 18. Synthesis of (+)-cylindricine C ((+)-**3c**) by Kibayashi and coworkers (m-CPBA = meta-chloroperbenzoic acid) [28]

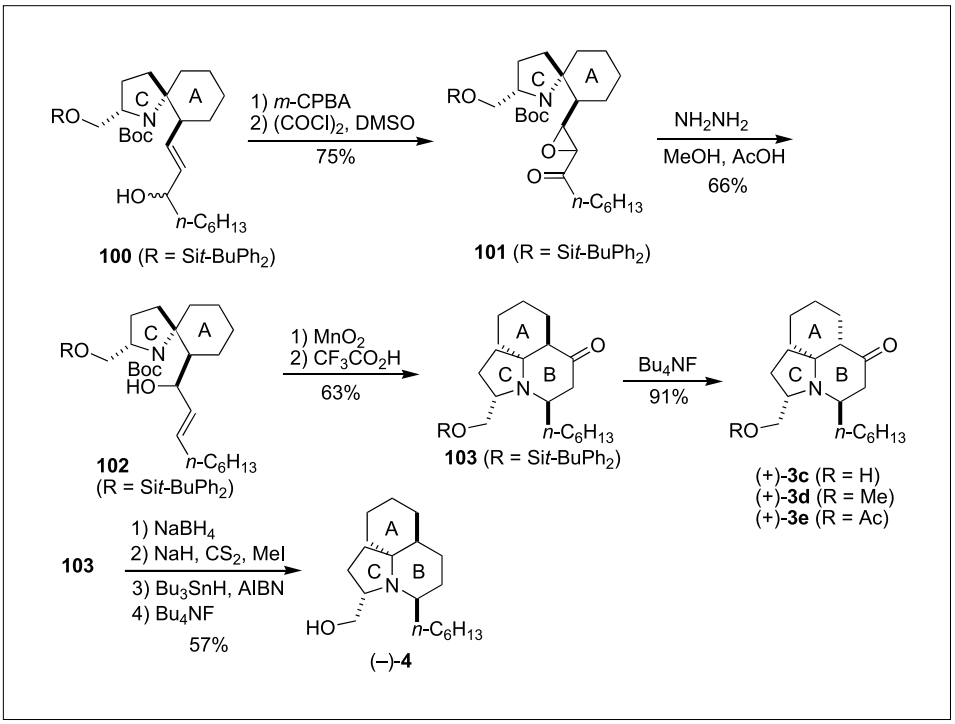


Scheme 19. Synthesis of (–)-fasicularin ((–)-**5**) by Kibayashi and coworkers [28]

100 was prepared from pyroglutamic acid according to the procedure of Kibayashi described in Schemes 16 and 17. A Wharton rearrangement was used to isomerize **100** to **102** *via* epoxide **101**. Oxidation of the rearranged allylic alcohol **102** with MnO_2 followed by treatment with trifluoroacetic acid afforded tricyclic ketone **103**. Conversion of **103** to (+)-cylindricine C ((+)-**3c**) was easily achieved by deprotection and epimerization at C(5). Methylation and acetylation delivered (+)-cylindricines D ((+)-**3d**) and E ((+)-**3e**). The conversion of **103** to (–)-lepadiformine ((–)-**4**) was achieved by reduction of the ketone with $NaBH_4$ followed by a Barton-McCombie deoxygenation.

2.4. *Intramolecular Oxidative Amidation of Phenols*

A unique and elegant synthesis of (–)-cylindricine C ((–)-**3c**) was reported by Ciufolini's group (Scheme 21) [30]. Sulfonamide **104** was prepared from D-homotyrosine, and when treated with diacetoxyiodobenzene, it underwent an oxidative cyclization to give **105** after silylation of the primary alcohol. This oxidative cyclization allows the introduction of the quaternary C(10) center of cylindricine. Deprotonation of the methanesulfonamide with $KN(SiMe_3)_2$ gave cyclized product **106** as a 7:1 mixture of diastereomers. Compound **107** containing a side chain suitable for further elaboration of the B ring was prepared in six steps from **106** by taking advantage of the sulfonamide group. The total synthesis of (–)-cylindricine C ((–)-**3c**) was achieved by deprotection of the silyl group followed by reductive amination with $NaBH(OAc)_3$ in the presence of a catalytic amount of acetic acid. This reaction afforded **108** in good yield and high stereoselectivity. The highly stereoselective reduction is best explained by the directing effect of the free

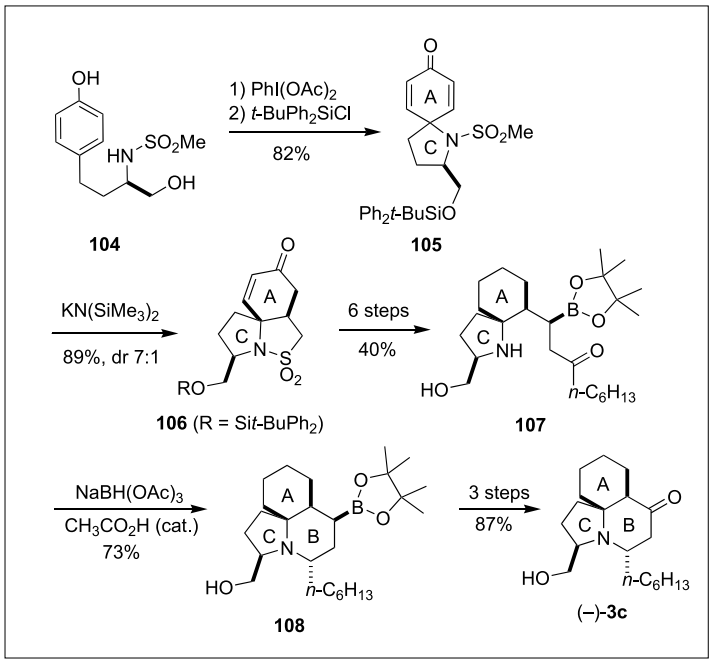


Scheme 20. Synthesis of lepadiformine ((–)-**4**) and (+)-cylindricines C-E ((+)-**3c**, (+)-**3d**, (+)-**3e**) by Hsung and coworkers [29]

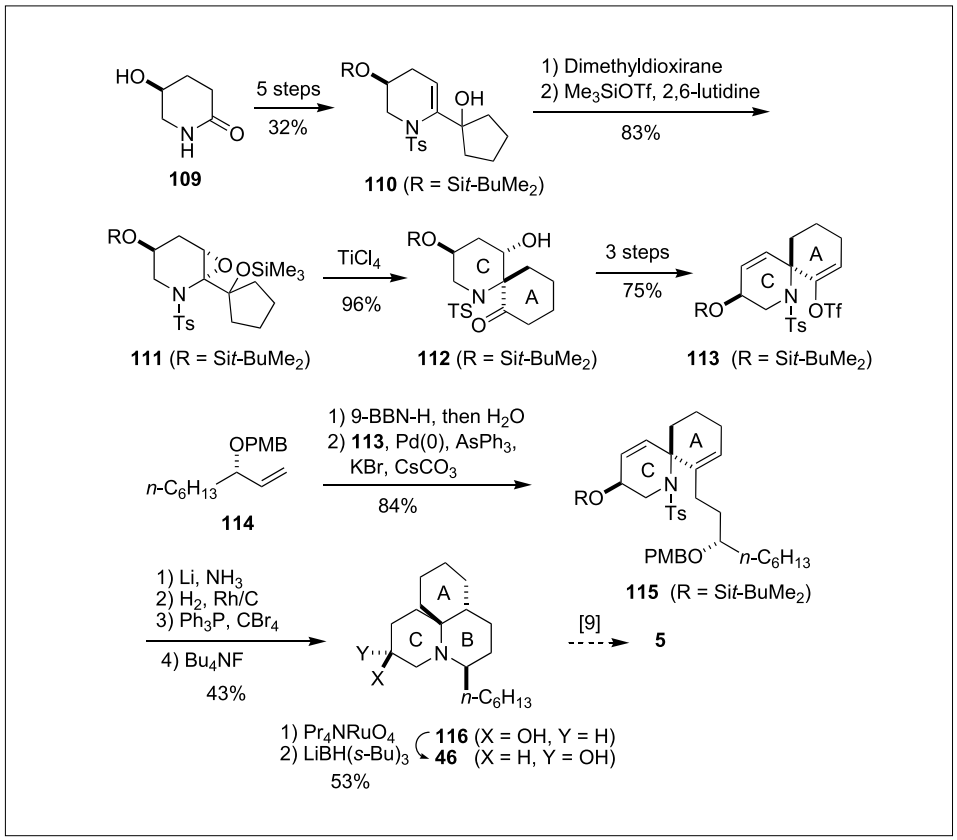
OH group. Conversion of **108** to (–)-cylindricine C ((–)-**3c**) was readily achieved in three steps.

2.5. *Semipinacol Rearrangement*

In 2005, Fenster and Dake reported the use of a semipinacol rearrangement in order to construct the azaspirobicylic framework of fasicularin and set the stereochemical identity at C(10) in a single operation (Scheme 22) [31]. For this purpose, (5*S*)-5-hydroxy-2-piperidinone **109** derived from L-glutamic acid was converted into allylic alcohol **110** in five steps. Epoxidation with dimethyldioxirane followed by silylation of the alcohol afforded epoxide **111**, the key substrate for the semipinacol rearrangement. Treatment of **111** with $TiCl_4$ gave azaspirobicyclic compound **112** in excellent yield as a single diastereomer. The rest of the synthesis is more classical: Suzuki type cross-coupling of enol triflate **113** with protected allylic alcohol **114** under Johnson-Braun conditions gave **115** in good yield. Preparation of the B ring was achieved in four steps. Treatment of **115** with lithium in ammonia to remove both the N-tosyl and O-*para*-methoxybenzyl protecting groups followed by stereoselective hydrogenation of the two double bonds and cyclization with Ph_3P and CBr_4 afforded tricyclic compound **116** after desilylation of the secondary alcohol with Bu_4NF. Inversion of the C(15) asymmetric center by oxidation to



Scheme 21. Synthesis of (–)-cylindricine ((–)-**3c**) by Ciufolini and coworkers [30]



Scheme 22. Formal synthesis of optically pure fasicularin (**5**) by Dake and Fenster (9-BBN = 9-borabicyclo[3.3.1]nonane) [31]

the ketone with tetrapropylammonium perruthenate and stereoreduction with lithium tris(*sec*-butyl)borohydride gave alcohol **46**, a known intermediate in Funk's and Kibayashi's syntheses of fasicularin (Schemes 9 and 12). However, the final conversion of **46** to optically pure fasicularin (**5**) according to Kibayashi's procedure did not afford an analytically pure sample of **5**.

2.6. *Radical Carboazidation*

Recently, radical carboazidation has proved a very attractive tool for the synthesis of alkaloids and related nitrogen-containing heterocyclic compounds [32–34]. The total synthesis of racemic lepadiformine starting from cyclohexanone and using the radical carboazidation is described in Scheme 23 [35]. Methylenecyclohexane derivative **117** was prepared from cyclohexanone in a straightforward manner and underwent radical carboazidation with ethyl iodoacetate and pyridylsulfonyl azide. The resulting azide **118** was obtained in good yield and moderate stereoselectivity. During this process, the key quaternary center C(10) of lepadiformine was created with the major diastereomer possessing the desired relative configuration of the A ring of lepadiformine. The *trans*-1-azadecalin skeleton of lepadiformine was obtained from **118** *via* a one-pot hydrogenation of the azide and intramolecular reductive amination of the ketone. The stereochemical outcome of the hydrogenation of the imine intermediate is best explained by model **119**. Lactamization of γ-aminoester **120** promoted by dimethylaluminum chloride afforded **121** in 75% overall yield from **118**. The functionalization of the C ring was performed according to a modified Takahata procedure after conversion of lactam **121** into thiolactam **122**. A sequence of S-methylation, addition of lithium phenylacetylide to the intermediate iminium ion and treatment with lithium aluminum hydride afforded **123** with the desired stereochemistry at C(13). Conversion of **123** to racemic lepadiformine (**4**) was carried out by ozonolysis of the alkenyl side chain under acidic conditions to avoid oxidation of the tertiary amine. In summary, lepadiformine (**4**) was synthesized in ten steps and 15% overall yield from cyclohexanone. Since **117** should be easily synthesized in enantiomerically pure form, this very short reaction sequence is expected to be extendable to the preparation of optically active lepadiformine.

3. Conclusion

The total synthesis of marine alkaloids containing pyrrolo- and pyrido[1,2-*j*]quinoline skeletons has led to several innovative and efficient methods to prepare their tricyclic core containing a hindered aminated quaternary carbon center at C(10). These approaches should enable the preparation of cylindricines, lepadiformine, and fasicularin in sufficient amounts for more detailed investigations of their biological activities. They could also be applied to the synthesis of derivatives and analogs of the natural products in the view of further studying and enhancing their biological activity.

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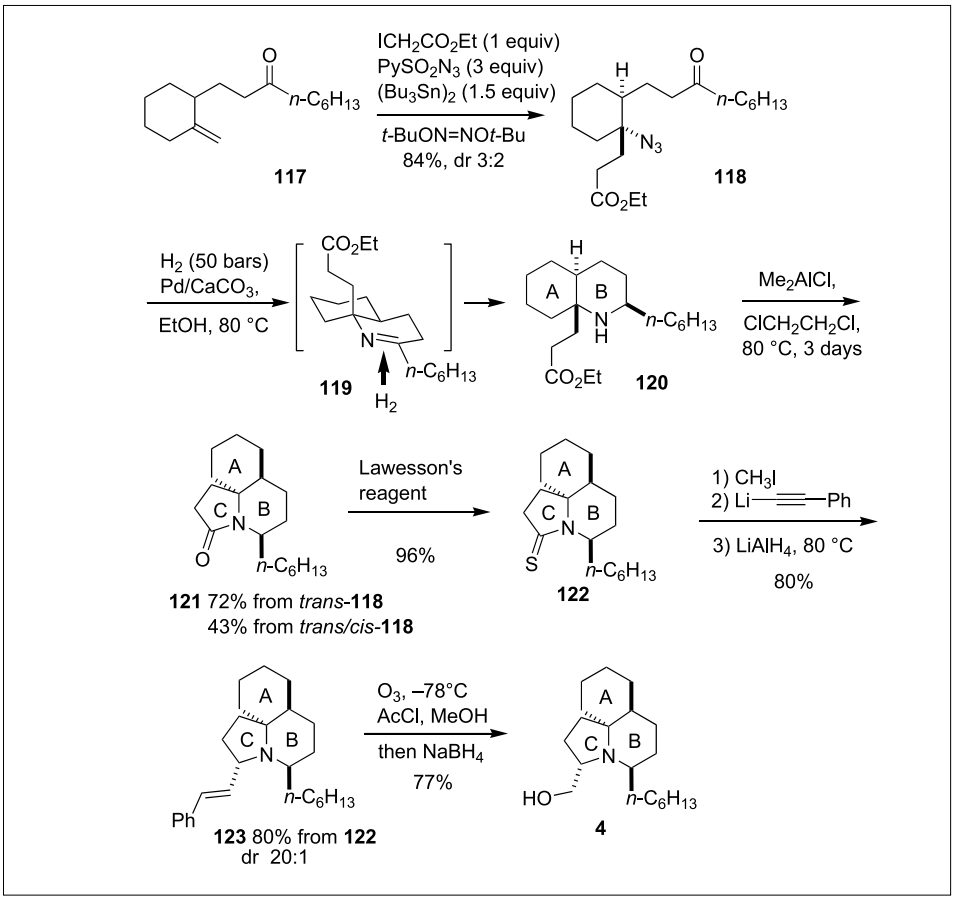

Scheme 23. Synthesis of lepadiformine (**4**) *via* radical carboazidation by Schär and Renaud [35]

[1] The depicted atom-numbering does not correspond to the IUPAC recommendations but was adopted for commodity reasons and is used consistently throughout this text.
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