CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Total Syntheses of Lepadiformine Marine Alkaloids with Enantiodivergency, Utilizing $Hg(OTf)_2$-Catalyzed Cycloisomerization Reaction and their Cytotoxic Activities

Authors: Keisuke Nishikawa, Kengo Yamauchi, Seiho Kikuchi, Shinnosuke Ezaki, Tomoyuki Koyama, Haruka Nokubo, Kunihiro Matsumura, Takeshi Kodama, Momochika Kumagai, and Yoshiki Morimoto

To be cited as: *Chem. Eur. J.* 10.1002/chem.201701475

Link to VoR: http://dx.doi.org/10.1002/chem.201701475

Supported by
ACES

WILEY-VCH

10.1002/chem.201701475

WILEY-VCH

FULL PAPER

Total Syntheses of Lepadiformine Marine Alkaloids with Enantiodivergency, Utilizing $Hg(OTf)_2$-Catalyzed Cycloisomerization Reaction and their Cytotoxic Activities

Keisuke Nishikawa,[a] Kengo Yamauchi,[a] Seiho Kikuchi,[a] Shinnosuke Ezaki,[a] Tomoyuki Koyama,[a] Haruka Nokubo,[a] Kunihiro Matsumura,[a] Takeshi Kodama,[a] Momochika Kumagai,[a, b] and Yoshiki Morimoto*[a]

Abstract: The enantioselective total syntheses of lepadiformine marine alkaloids, azatricyclic natural products isolated from marine tunicates, were completed. These alkaloids have a unique chemical structure characterized by the *trans*-1-azadecalin (AB ring system) fused with the spirocyclic ring (AC ring system). Here we found that a cycloisomerization reaction from functionalized linear substrates to a 1-azaspiro[4.5]decane framework corresponding to the AC ring in lepadiformines is promoted by a catalytic amount of mercury(II) triflate ($Hg(OTf)_2$). The total syntheses of (–)-lepadiformines A and B were achieved in 28% and 21% overall yields, respectively, through the novel cycloisomerization reaction. The syntheses of (+)- and (–)-lepadiformine C hydrochloride salts also enabled us to determine the absolute configuration of natural lepadiformine C. It has been found that a phenomenon of enantiodivergence occurs in lepadiformine alkaloids from a single species of marine tunicate, *Clavelina moluccensis*. The cytotoxic activities of synthesized lepadiformine hydrochloride salts and their synthetic intermediates were evaluated.

Introduction

The compound (–)-lepadiformine A (**1**, Figure 1), an azatricyclic marine alkaloid isolated by Biard *et al.* from the marine tunicate *Clavelina lepadiformis* in 1994, exhibits moderate cytotoxic activity against various cell lines [IC_{50}: 9.20 μg mL^{-1} (KB), IC_{50}: 0.75 μg mL^{-1} (HT29), IC_{50}: 3.10 μg mL^{-1} (P388), IC_{50}: 6.30 μg mL^{-1} (P388 doxorubicin-resistant), and IC_{50}: 6.10 μg mL^{-1} (NSCLS-N6)].[1] Although a chemical structure that was different from **1** was first proposed based on spectroscopic and chemical methods,[1a] the original structure was revised to (–)-**1** through studies on the total synthesis by Kibayashi's, Weinreb's, and Pearson's groups.[2] Lepadiformines B (**2**) and C were also isolated by Sauviat's group from another marine tunicate *Clavelina moluccensis* off Djibouti waters in 2006, along with (–)-**1**. All lepadiformines exhibit an effect on the cardiovascular system and block the cardiac inward rectifying potassium channel.[3] But cytotoxic activities with lepadiformines B and C have not yet been reported. In addition, the absolute configurations of (–)-**1** and (–)-**2** have been completely determined through the total syntheses.[2i,4m] Although the absolute configuration of lepadiformine C was assumed to be **3**, corresponding to that of (–)-**1**, some doubtful points have remained according to Rychnovsky's report.[4m] Establishing a simple synthetic pathway for lepadiformine marine alkaloids is important in elucidating their biological activities and determining the absolute configuration of lepadiformine C.

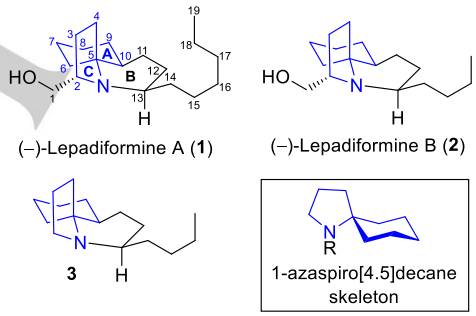


Figure 1. Chemical structures of lepadiformines A (**1**), B (**2**), and **3**.

As regards its structural features, (–)-**1** has a unique skeleton characterized by the *trans*-1-azadecalin AB ring system fused with the AC spirocyclic ring, four asymmetric centers including a nitrogen-containing stereogenic tetrasubstituted carbon, and a B-ring as a boat form produced by a bulky *n*-hexyl side chain. The core skeleton of (–)-**1** is conserved in (–)-**2**, but the aliphatic side chain at C13 is shortened from an *n*-hexyl group to an *n*-butyl group. And **3** has the same framework as (–)-**2** without a hydroxymethyl group at C2. The unique molecular architecture of lepadiformine alkaloids has attracted considerable attention from the organic synthesis community.[2,4] In a previous letter,[5] our laboratory described the enantioselective total synthesis of (–)-**1** *via* an $Hg(OTf)_2$-catalyzed cycloisomerization reaction from a functionalized linear substrate to a 1-azaspiro[4.5]decane skeleton as a key reaction. We then successfully synthesized (–)-**2** and **3** to examine the structure-activity relationships of lepadiformine alkaloids. In this full article, we describe the development of the metal-catalyzed cycloisomerization reaction, the full details of the total syntheses of (–)-**1**, (–)-**2**, and (–)- and (+)-**3**, the determination of the absolute configuration of

[a] Dr. K. Nishikawa, K. Yamauchi, S. Kikuchi, S. Ezaki, T. Koyama, H. Nokubo, K. Matsumura, Dr. T. Kodama, M. Kumagai, Prof. Dr. Y. Morimoto
Department of Chemistry, Graduate School of Science, Osaka City University
Sumiyoshi-ku, Osaka 558-8585 (Japan)
E-mail: morimoto@sci.osaka-cu.ac.jp
[b] M. Kumagai
Japan Food Research Laboratories
Ibaraki-shi, Osaka 567-0085 (Japan)

Supporting information for this article is given via a link at the end of the document.

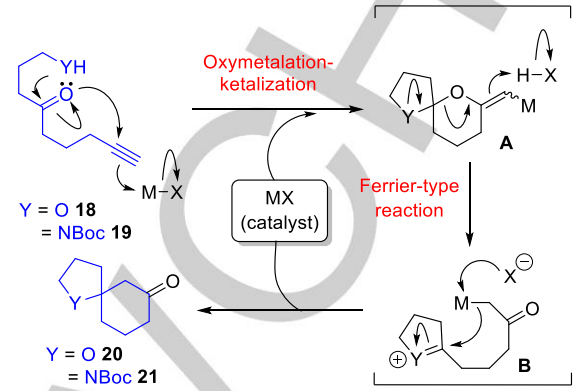
10.1002/chem.201701475

lepadiformine C, and the evaluation of their cytotoxic activities against Hela, HT-29, and P388 cell lines.

Results and Discussion

Our laboratory focused on the construction of a spirocyclic skeleton, which is embedded in several complex alkaloids. Especially, a 1-azaspiro[4.5]decane framework represents not only the AC spirocyclic ring system of lepadiformines, but also the core skeleton of many alkaloids, such as cylindricines **4**−**11**,[6] polycitorol A (**12**),[7] FR901483 (**13**),[8] and *Kopsia* alkaloids **14**−**17** (Figure 2).[9] It was envisioned that the desired spirocyclic compounds, such as 1-heterospiro[4.5]decane frameworks **20** and **21**, could be produced from designed acyclic ynones **18** and **19**, respectively, in one step if 6-*exo*-dig oxymetalation followed by ketalization of the substrates with metal catalysis and Ferrier-type cyclization[10] proceeded as outlined in Scheme 1. Concretely, a 6-*exo*-dig intramolecular oxymetalation initiated by coordination of a catalyst to the alkyne π-electron and nucleophilic addition of the heteroatom to the carbonyl carbon would produce spiroketal **A**. The intermediate **A** would be cleaved by protonation of the enol ether to afford oxonium or iminium ion **B**. The spirocyclic product could be obtained by reforming a carbocycle *via* Ferrier-type cyclization with regeneration of a catalyst. Whether such a metal-catalyzed cycloisomerization reaction proceeds was investigated using designed linear substrates (Tables 1−4).

First, the reaction of ynone **18** possessing a hydroxy group at



Scheme 1. Novel metal-catalyzed cycloisomerization reaction.

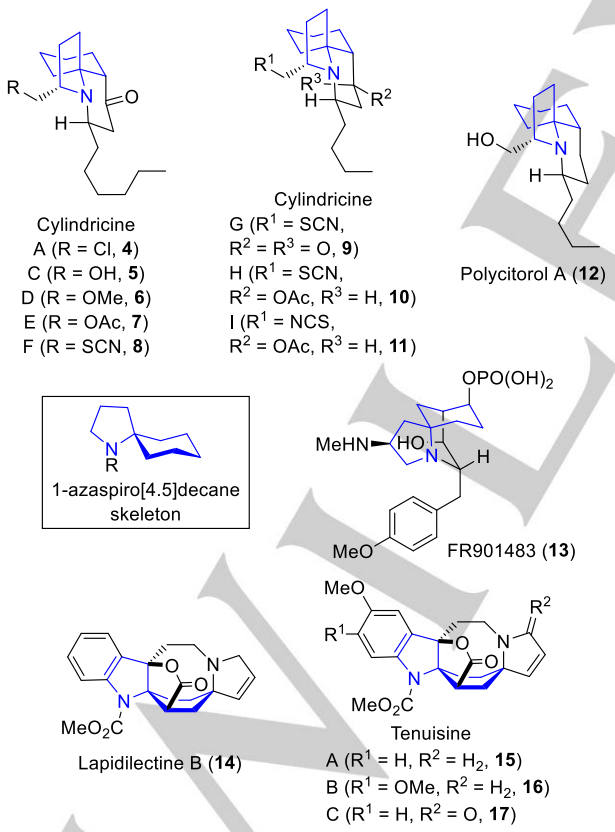
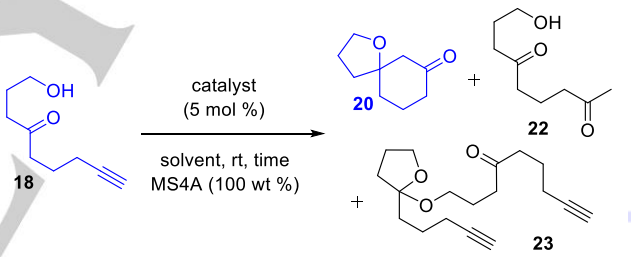


Figure 2. Chemical structures of complex alkaloids having a 1-azaspiro[4.5]decane skeleton.

Table 1. Examination of the metal-catalyzed cycloisomerization reaction of linear substrate **18**.



				yield (%)[a]			
entry	catalyst	solvent	time (h)	**20**	**22**	**23**	**18**
1	AuCl	CH_2Cl_2	2	–	4	26	35
2	$AuCl_3$	MeCN /CH_2Cl_2	17	7	39	9	29
3	$Ph_3PAuOTf$[b]	Toluene	6	26	20	–	42
4	Ph_3PAuBF_4[b,c]	CH_2Cl_2	23	–	–	17	63
5	$PtCl_4$	THF	17	–	16	–	21
6	$Pd(TFA)_2$	CH_2Cl_2	3	–	5	11	37
7	$PdCl_2$	CH_2Cl_2	8	–	–	–	quant.
8	$Hg(OTf)_2$[d]	CH_2Cl_2	3	16	–	–	–

[a] Isolated yield. [b] These catalysts were prepared *in situ* from Ph_3PAuCl and AgOTf or $AgBF_4$ (Ref. 12). [c] 1 mol %. [d] 10 mol %.

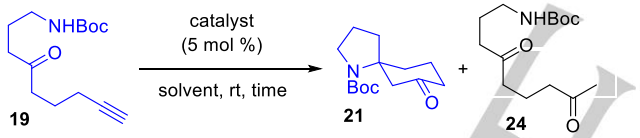
10.1002/chem.201701475

FULL PAPER

the terminal position was investigated (Table 1). To retain dry conditions, 4 Å molecular sieves (MS4A) were added to the reaction. Gold catalysts known as good ynophiles[11] were examined. Although the reaction using AuCl provided only two byproducts, diketone **22**, which was hydrated in the alkyne moiety and dimerized ketal **23** (entry 1), the use of $AuCl_3$ afforded the desired spirocyclic compound **20** albeit in low yield (7%) along with **22** and **23** (entry 2). The reaction using $Ph_3PAuOTf$ improved the yield of **20** (26%) (entry 3),[13] but the use of Ph_3PAuBF_4 resulted in the production of **23** and recovery of the starting material (entry 4). The use of $PtCl_4$[14] afforded the alkyne hydration product **22** without the desired **20** (entry 5). $Pd(TFA)_2$ also generated **22** and **23** (entry 6), and the use of $PdCl_2$ resulted in no reaction (entry 7).[15] Finally, mercury(II) triflate ($Hg(OTf)_2$), a good ynophile developed by Nishizawa *et al.*,[16] was tested. $Hg(OTf)_2$ afforded only the desired **20** in lower yield (16%) than that with $Ph_3PAuOTf$ (entry 8). From these results, it was concluded that ynone **18** was not a good substrate for the cycloisomerization reaction.

Next, we investigated ynone **19** bearing an NHBoc group at the terminal position (Tables 2 and 3). Although the reaction using AuCl and $AuCl_3$ resulted in recovery of the starting material **19** (entries 1 and 2), it was found that $Ph_3PAuOTf$ and Ph_3PAuBF_4 brought about the desired cycloisomerization reaction to provide spirocyclic compound **21** albeit in modest yields (53% and 47%, respectively) (entries 3 and 4). Only the use of AgOTf, which was required for the preparation of $Ph_3PAuOTf$, resulted in recovery of **19** (entry 5). $PtCl_4$ afforded **21** in low yield (22%) along with diketone **24** (entry 6). $Pd(TFA)_2$ also generated **24** (entry 7), and $PdCl_2$ gave a complex mixture (entry 8). $[Ir(cod)Cl]_2$[17] and $Rh_2(TFA)_4$[18] were ineffective catalysts and led only to the recovery of **19** (entries 9 and 10). Finally, mercury catalysts were examined (Table 3). Unfortunately, $Hg(OAc)_2$ and $Hg(TFA)_2$ resulted in recovery of **19** (entries 1 and 2). To our delight, it was found that $Hg(OTf)_2$ effected the cycloisomerization reaction in

Table 2. Examination of the metal-catalyzed cycloisomerization reaction of **19**.



entry	catalyst	solvent	time (h)	yield (%)[a] 21	24	19
1	AuCl	MeCN	14	–	–	65
2	$AuCl_3$	MeCN	22	–	–	57
3	PPh_3AuOTf[b]	CH_2Cl_2	0.5	53	–	–
4	PPh_3AuBF_4[b]	MeCN	30	47	–	–
5	AgOTf	MeCN	23	–	–	73
6	$PtCl_4$[c]	Toluene	42	22	23	–
7	$Pd(TFA)_2$	MeCN	13	–	12	21
8	$PdCl_2$	CH_2Cl_2	8	–	–	–
9	$[Ir(cod)Cl]_2$	MeCN	14	–	–	43
10	$Rh_2(TFA)_4$	MeCN	1	–	–	31

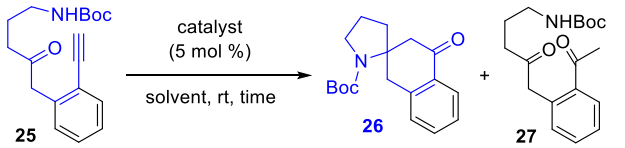
[a] Isolated yield. [b] These catalysts were prepared *in situ* from Ph_3PAuCl and AgOTf or $AgBF_4$ (Ref. 12). [c] 10 mol %.

Table 3. Examination of the mercury-catalyzed cycloisomerization reaction of **19**[a].

entry	catalyst	solvent	time (h)	yield (%)[b] 21	24	19
1	$Hg(OAc)_2$	MeCN	17	–		89
2	$Hg(TFA)_2$	MeCN	2	–	24	57
3	$Hg(OTf)_2$	CH_2Cl_2	0.7	71	16	–
4	$Hg(OTf)_2$	MeCN	0.7	74	–	10
5	$Hg(OTf)_2$	Toluene	1	64	33	–
6[c]	$Hg(OTf)_2$	MeCN	0.4	61	–	–
7	TfOH	MeCN	2	–	–	24

[a] The reaction in Table 3 is the same as that in Table 2. [b] Isolated yield. [c] MS4A (100 wt %) was added to the reaction.

Table 4. Examination of the metal-catalyzed cycloisomerization reaction of **25**.

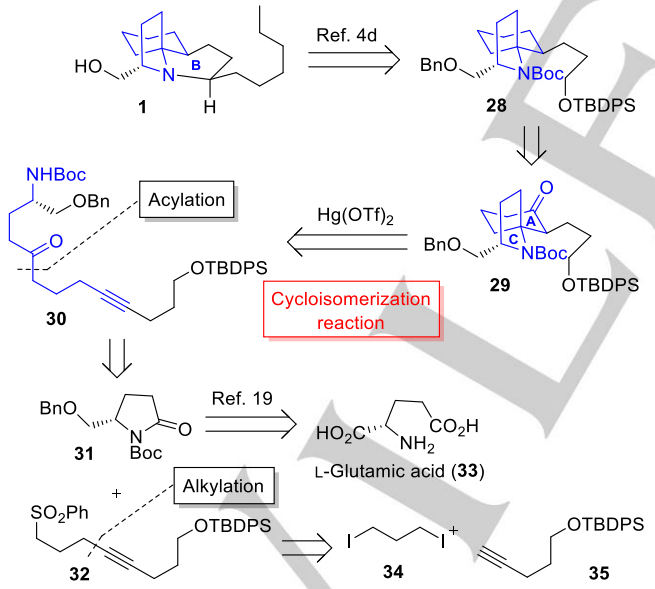


entry	catalyst	solvent	time (h)	yield (%)[a] 26	27
1	$Hg(OTf)_2$	CH_2Cl_2	1	46	19
2	$Hg(OTf)_2$	Toluene	2	60	11
3	$Hg(OTf)_2$	MeCN	1	65	26
4	$Ph_3PAuOTf$[b]	MeCN	2	31	49

[a] Isolated yield. [b] This catalyst was prepared *in situ* from Ph_3PAuCl and AgOTf (Ref. 12).

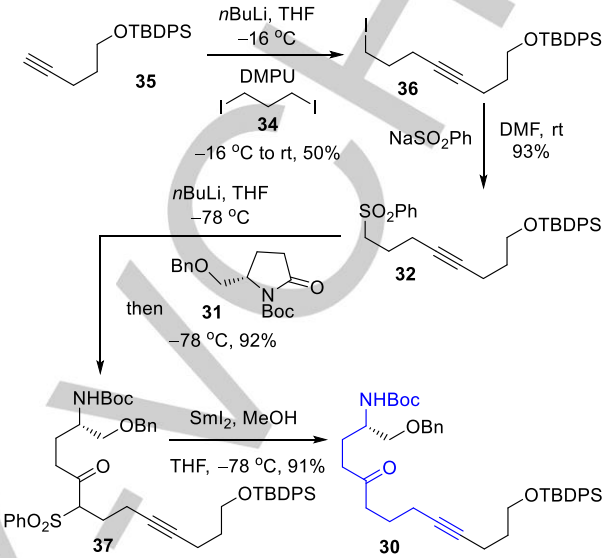
better yields (61–74%) than gold catalysts (entries 3–6). As the alkyne hydration byproduct **24** was observed (entries 3 and 5), the reaction was conducted in the presence of MS4A; however, the yield of **21** could not be improved (entry 6). Treatment with TfOH afforded only the starting material **19**, demonstrating that TfOH does not catalyze this cycloisomerization reaction (entry 7). The cycloisomerization reaction of ynone **25** possessing an aromatic ring was also investigated (Table 4). Among the solvents examined, MeCN was the solvent of choice in terms of the yield of spirocyclic product **26** (65%) (entries 1–3). The reaction with $Ph_3PAuOTf$ resulted in a lower yield (31%) than with $Hg(OTf)_2$ (entry 4). Thus, our laboratory could develop the novel $Hg(OTf)_2$-catalyzed cycloisomerization reaction from linear substrates to a 1-azaspiro[4.5]decane framework frequently occurring in the aforementioned alkaloids. With this reaction in hand, we embarked on the total syntheses of lepadiformine marine alkaloids.

Our first-generation retrosynthetic analysis of (–)-**1** is depicted in Scheme 2. The spirocyclic ring **28** could be converted into (–)-**1** *via* B-ring formation followed by the introduction of an *n*-hexyl group according to the synthesis of (–)-**1** reported by Kim *et al*.[4d] We planned to construct the AC spirocyclic ring by applying the $Hg(OTf)_2$-catalyzed cycloisomerization reaction to linear substrate **30**. The precursor **30** would be prepared by acylation of sulfone **32** with pyrrolidinone **31**, which was derived from L-glutamic acid (**33**) by the use of a known method.[19] Sulfone **32** would be synthesized by alkylation of a lithium acetylide of alkyne **35**[20] with commercially available 1,3-diiodopropane (**34**).



Scheme 2. Our first-generation retrosynthetic analysis of (–)-lepadiformine A (**1**).

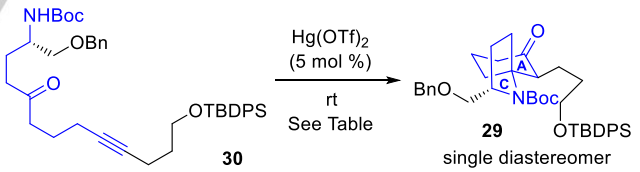
The total synthesis commenced with the known alkyne **35**, prepared by TBDPS protection of commercially available 4-pentyn-1-ol[20] (Scheme 3). The alkylation of a lithium acetylide of **35** with **34** afforded monoiodide **36**. After sulfonylation of the iodo moiety in **36**, acylation of an α-anion of sulfone **32** with **31** followed by SmI_2-mediated desulfonylation[21] afforded the desired cyclization precursor **30** in high yield (78% in 3 steps).



Scheme 3. Synthesis of cyclization precursor **30**.

We examined the $Hg(OTf)_2$-catalyzed cycloisomerization reaction of precursor **30** (Table 5). Firstly, the cycloisomerization reaction in $MeNO_2$ afforded the desired spirocylic product **29** as

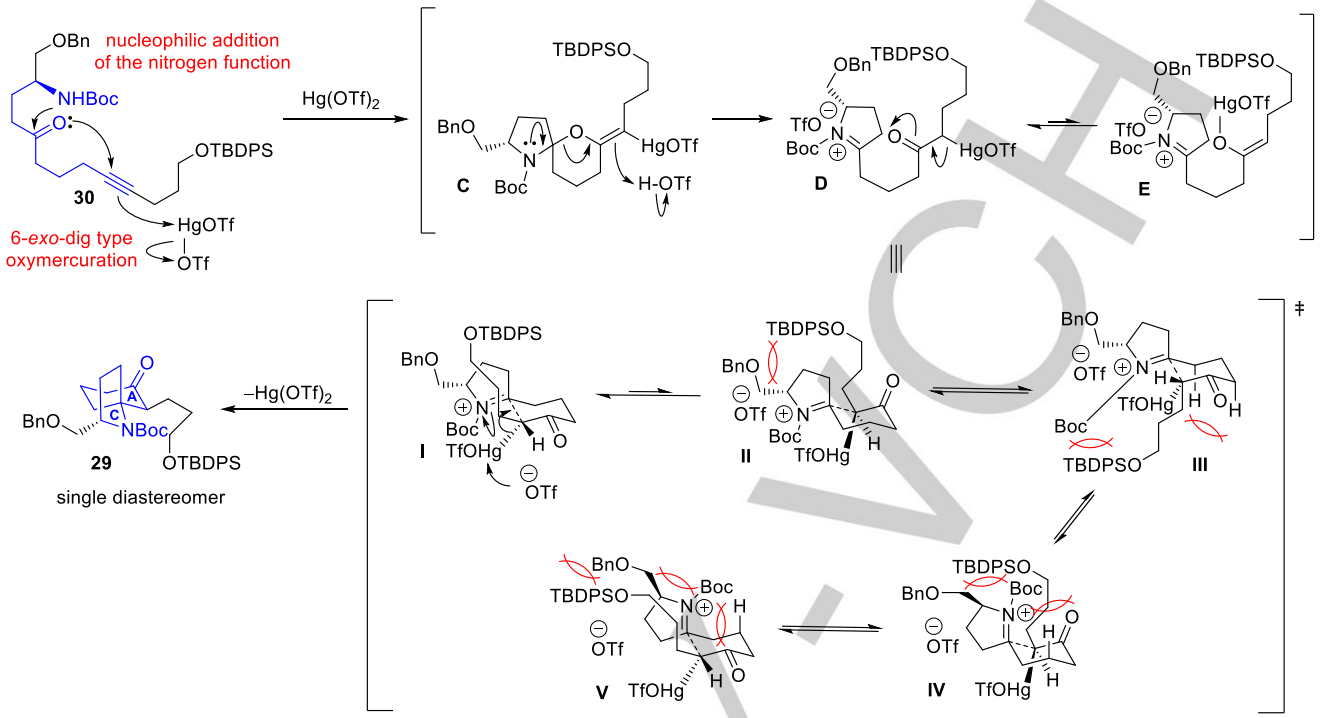
Table 5. Examination of the cycloisomerization reaction of linear substrate **30**.



entry	solvent	temperature	time (h)	yield (%)[a]
1	$MeNO_2$	rt	3	8
2	Toluene	rt	20	17
3	THF	rt	19	12
4	CH_2Cl_2	rt	3	10
5	MeCN	rt	0.5	52
6	MeCN	0 °C	0.75	74

[a] Isolated yield.

10.1002/chem.201701475

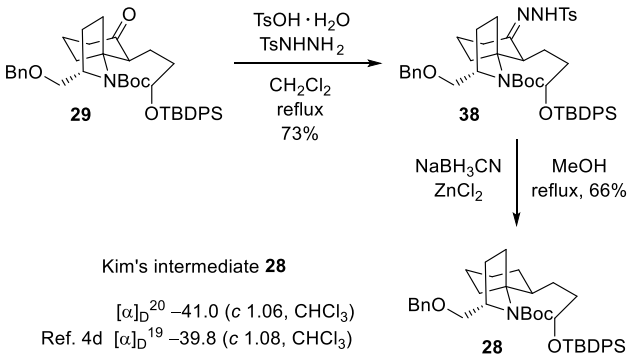


Scheme 4. Proposed mechanism for the cycloisomerization reaction of **30**.

a single diastereomer albeit in low yield (entry 1). Among various solvents examined at room temperature, MeCN was still the solvent of choice (52%) (entries 1–5). The reaction at 0 °C improved the yield (74%) (entry 6). The stereochemistry of **29** was clearly assigned based on the NOESY spectrum; see the Supporting Information (SI).

To sum up, the key cycloisomerization reaction enabled us to conduct the diastereocontrolled construction of the 1-azaspiro[4.5]decane framework. The mechanism and the diastereoselectivity of the reaction that we propose at present are summarized in Scheme 4. The aminoketal **C** would be generated through a 6-*exo*-dig type intramolecular oxymercuration initiated by coordination of $Hg(OTf)_2$ to the alkyne π-electron followed by nucleophilic addition of the nitrogen function. **C** could be cleaved by protonation with generated TfOH to give iminium ion intermediate **D**. Although an α-mercury carbonyl in **D** would be in equilibrium with the enolate form **E**, we presumed that **D** would predominate due to the stability of the C−Hg bond.[22] In addition, although the stereochemistry of the aminoketal **C** and the face selectivity of the protonation in **C** were unknown, we think that the intermediate **D** can have both (*R*) and (*S*) configurations of the C−Hg bond *via* **E**. The construction of a carbocycle *via* Ferrier-type cyclization would result in production of the desired product **29** and regeneration of an $Hg(OTf)_2$ catalyst. Considering chair-like transition states **I**−**V** in the re-cyclization, **I**−**III** could be more stable than **IV** and **V** because in **IV** and **V** a bulky NBoc iminium moiety is disposed in an axial position. In transition states **I**−**III**, **III** with a bulky TBDPSO-containing alkyl group in an axial position and **II** with steric repulsion between benzyloxymethyl and TBDPSO-containing alkyl groups would be less stable than **I** without such steric repulsion. Like transition state **III**, transition states with the bulky TBDPSO-containing alkyl group in an axial position in **II**, **IV**, and **V** should also be disfavored due to steric hindrance. Thus, the desired **29** would be selectively obtained as a single diastereomer *via* transition state **I**.

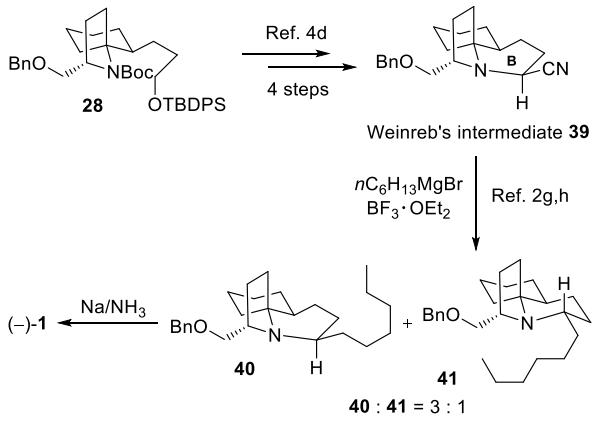
After a ketone moiety in the synthesized **29** was converted into a tosylhydrazone group, $NaBH_3CN$ reduction to a methylene group[23] afforded Kim's synthetic intermediate **28**[4d] (Scheme 5). The spectral characteristics (^1H and ^{13}C NMR) of synthetic **28** were identical to those of Kim's reported sample.[4d] The optical rotation of (−)-**28**, $[\alpha]_D^{20}$ −41.0 (*c* 1.06, $CHCl_3$), was similar to that



Scheme 5. Synthesis of Kim's intermediate **28**.

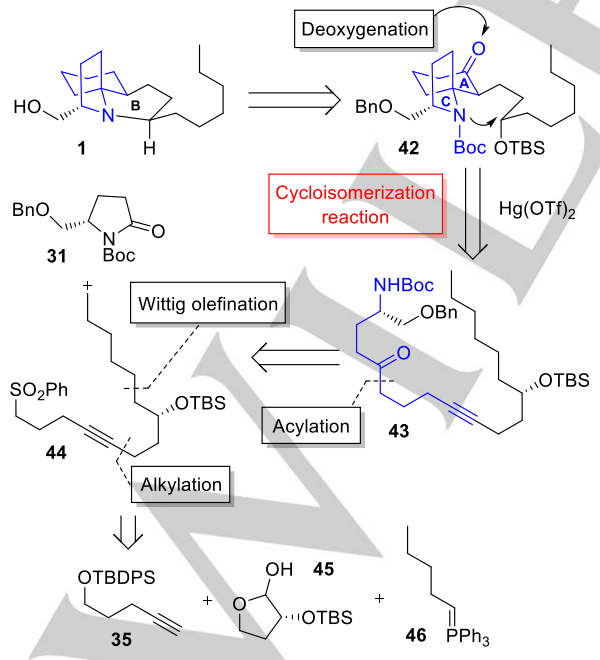
10.1002/chem.201701475

of the reported sample, $[\alpha]_D^{19}$ −39.8 (*c* 1.08, $CHCl_3$).[4d] The synthesis of (−)-**1** by Kim *et al.* was a formal total synthesis wherein **28** was led to Weinreb's synthetic intermediate **39**[2g,h] (Scheme 6). But in the transformation from **39** to (−)-**1**, the stereoselectivity was not sufficient to attach an *n*-hexyl group to the B-ring (**40**:**41** = 3:1). To resolve this problem, we tried to carry out the key cycloisomerization reaction with a new linear substrate having all the carbon atoms required for the total synthesis of (−)-**1**.



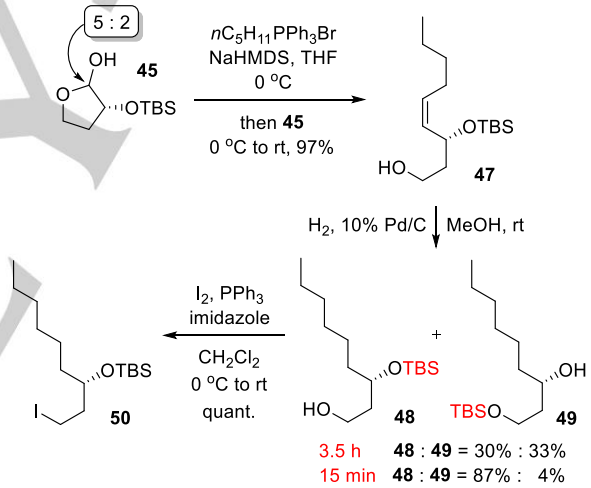
Scheme 6. Formal synthesis of (−)-**1** by Kim *et al.*

Our second-generation retrosynthetic analysis of (−)-**1** is shown in Scheme 7. Deoxygenation of the spirocyclic compound **42** followed by B-ring formation according to Kibayashi's and Zhao's method[4c,j] would generate (−)-**1**. Compound **42** could arise from the key $Hg(OTf)_2$-catalyzed cycloisomerization reaction of functionalized cyclization precursor **43** bearing all the carbon numbers required for the total synthesis of (−)-**1**. Precursor **43** could be prepared by acylation of sulfone **44** with the known **31**. Compound **44** would be synthesized through Wittig olefination of the known lactol **45**[24] with ylide **46** followed by alkylation of a lithium acetylide of **35**.



Scheme 7. Our second-generation retrosynthetic analysis of (−)-**1**.

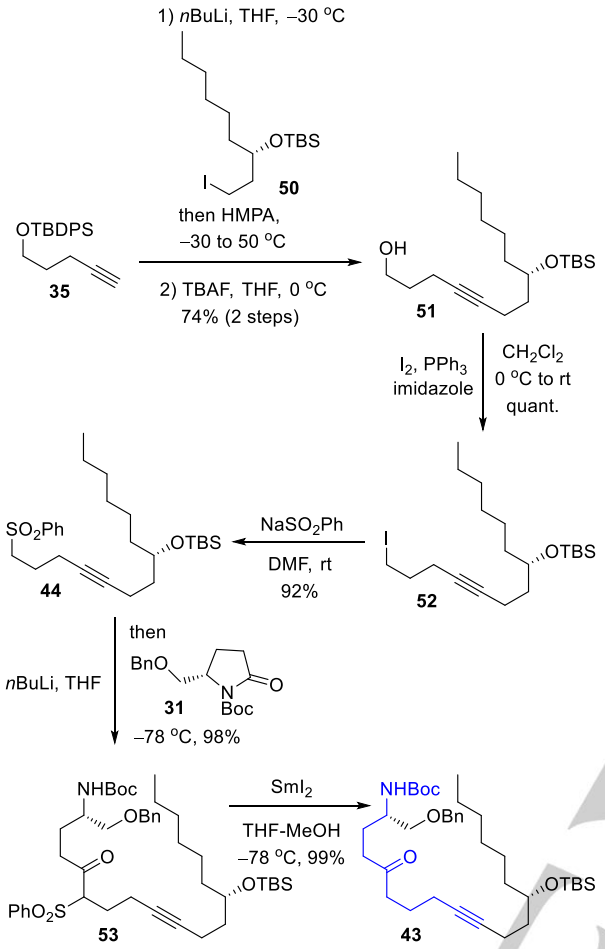
Our second-generation total synthesis started with Wittig olefination of the known optically active lactol **45**[24] to stereoselectively yield *Z*-olefin **47** (Scheme 8). The heterogeneous hydrogenation of **47** for 3.5 h provided the desired alcohol **48** in low yield (30%), along with the TBS-migrated byproduct **49** (33%). But shortening the reaction time (15 min) selectively afforded **48** in high yield (87%). After iodination of **48**, alkylation of a lithium acetylide of **35** with iodide **50** followed by selective deprotection of a TBDPS group using TBAF[25] gave alcohol **51** (Scheme 9), which was transformed to the cyclization precursor **43** in a 4-step reaction sequence: (1) iodination of a hydroxy group, (2) sulfonylation, (3) acylation of an α-anion of sulfone **44** with **31**, and (4) desulfonylation by SmI_2-mediated radical reduction.



Scheme 8. Synthesis of iodide **50**.

The key $Hg(OTf)_2$-catalyzed cycloisomerization reaction of precursor **43** was performed under various reaction conditions (Table 6). As expected, the reaction proceeded in a stereoselective manner to furnish the desired spirocyclic compound **42** in 39% isolated yield as a sole diastereomer, when **43** was allowed to react with $Hg(OTf)_2$ (10 mol %) at −40 °C (entry 1). We supposed that the spirocyclic product **42** would be selectively produced through transition state **VI** corresponding to **I** in Scheme 4. Increasing the catalyst loading to 20 mol % gave a better yield of **42** (52%), along with a minor diastereomer **54** (6%) through transition state **VII** (entry 2). Raising the reaction temperature resulted in a gradual increase in the yield of **42** (entries 3−5). In addition, the reaction time for disappearance of the starting material was gradually shortened as the temperature increased. Entry 5 indicates the best temperature conditions (−20

10.1002/chem.201701475

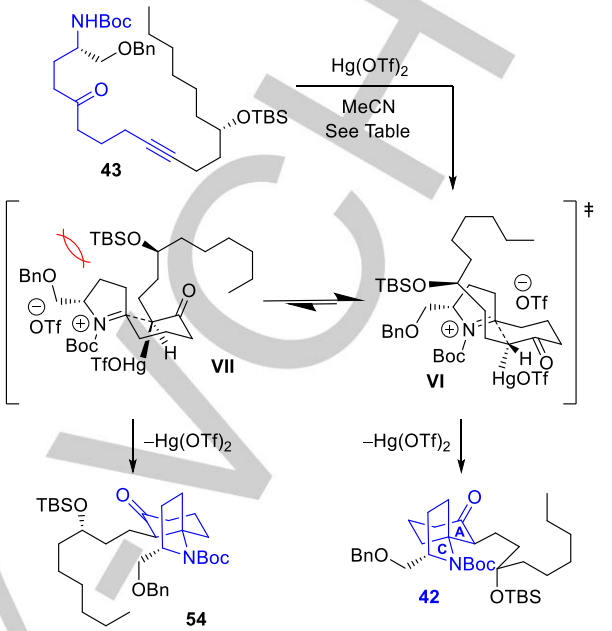


Scheme 9. Synthesis of cyclization precursor **43**.

°C to 0 °C) in terms of the yield and the diastereoselectivity. Increasing the catalyst loading to 30 mol % led to a decrease in the yield of **42** (47%) (entry 6). The stereochemistry of **42** and **54** was apparently assigned based on their NOESY spectra.[5] With regard to the generation of diastereomer **54**, the thermodynamic and kinetic experiments for the $Hg(OTf)_2$-catalyzed cycloisomerization reaction were compared. Treatment of the spirocyclic product **42** under the same reaction conditions as those employed for the cycloisomerization of **43** resulted in recovery of the starting material in quantitative yield. And treatment of the diastereomer **54** also resulted in recovery of the starting material. Therefore, we think that the above cycloisomerization reaction is under kinetic control.

We synthesized Kibayashi's synthetic intermediate **59**[4c] from **42** (Scheme 10). For deoxygenation of the carbonyl group, we applied the previous method *via* a tosylhydrazone to yield the desired methylene **55**. But the method resulted in a modest yield (44% in 2 steps) and poor reproducibility. Instead, Markó-Lam's deoxygenation method utilizing SmI_2-HMPA[26] was employed after the diastereocontrolled reduction to axial alcohol **56**

Table 6. Optimization of the $Hg(OTf)_2$-catalyzed cycloisomerization reaction of cyclization precursor **43**.

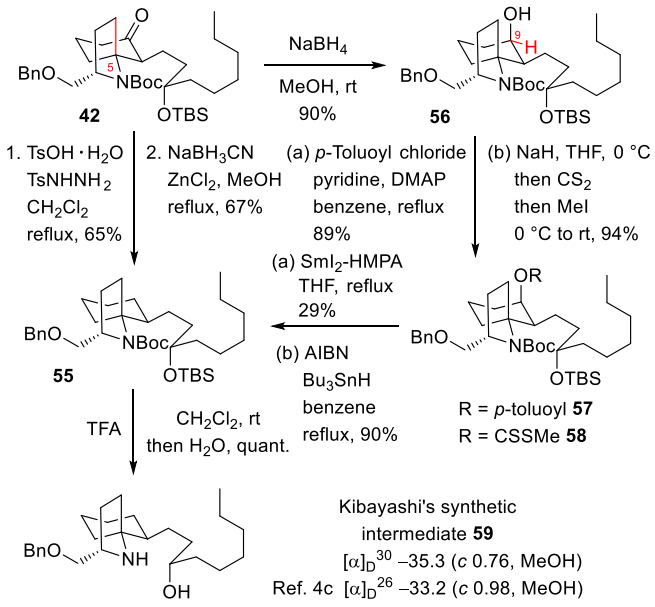


entry	$Hg(OTf)_2$ (mol %)	temper-ature (°C)	time (min)	yield (%)[a] 42	54	43	selectivity 42 : 54
1	10	−40	60	39	N.D.[b]	–	–
2	20	−40	40	52	6	6	8.9 : 1
3	20	−30	40	60	5	–	12.0 : 1
4	20	−20	15	77	12	–	6.4 : 1
5	20	−20 to 0	5	78	6	–	13.0 : 1
6	30	0	10	47	4	4	11.8 : 1

[a] Isolated yield. [b] N.D. = Not Determined.

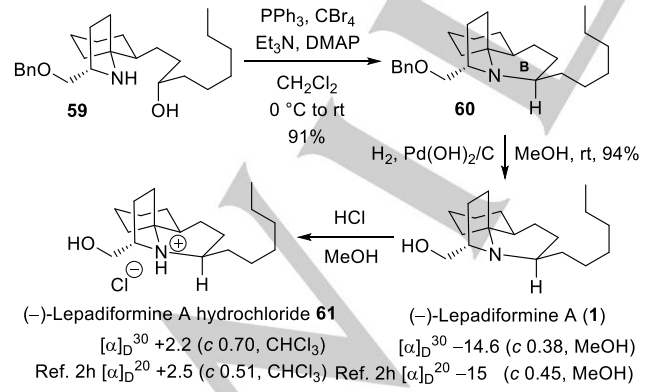
(Scheme 10, synthetic pathway a) to furnish **55** in low yield (23% in 3 steps from **42**) along with the recovered **56**. As a result of this examination, it was found that Barton-McCombie's deoxygenation method[27] (Scheme 10, synthetic pathway b) provided the desired **55** in high yield (76% in 3 steps from **42**). In the $NaBH_4$ reduction of **42**, an equatorial hydride attack could predominate as a result of avoiding the axial alkyl group at C5. In the ^1H NMR spectrum of a major rotamer of **56**, the coupling pattern of C9−H at 4.12 ppm was observed as a doublet with J = 2.2 Hz showing an equatorial proton. Removal of both Boc and TBS protecting groups in **55** with TFA afforded the amino alcohol **59**. The spectral characteristics (^1H and ^{13}C NMR) and the optical rotation, $[\alpha]_D^{30}$ −35.3 (*c* 0.76, MeOH), of synthetic **59** were identical to those of Kibayashi's reported sample.[4c]

10.1002/chem.201701475



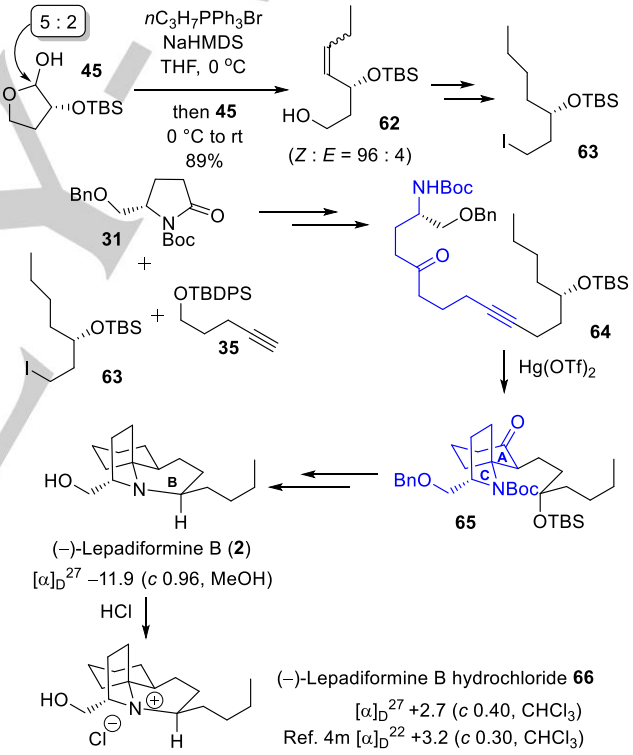
Scheme 10. Synthesis of Kibayashi's intermediate **59**.

The total synthesis of (–)-lepadiformine A was completed from **59** as outlined in Scheme 11. Compound **59** was subjected to Kibayashi's and Zhao's procedure[4c,j] to give an azatricyclic ring system **60** *via* B-ring formation accompanied by inversion of configuration. Finally, deprotection of a Bn group in **60** afforded (–)-lepadiformine A (**1**). The total synthesis of (–)-**1** was achieved in 16 steps from the known lactol **45** with 28% overall yield. The spectral data (^{1}H and ^{13}C NMR) and the optical rotation of synthetic **1**, $[\alpha]_D^{30}$ −14.6 (*c* 0.38, MeOH), were in agreement with those reported previously, $[\alpha]_D^{20}$ −15 (*c* 0.45, MeOH).[2h] We confirmed that the spectral data and the optical rotation of the hydrochloride salt **61**, $[\alpha]_D^{30}$ +2.2 (*c* 0.70, $CHCl_3$), are also comparable to those reported for the authentic sample, $[\alpha]_D^{20}$ +2.5 (*c* 0.51, $CHCl_3$).[2h]



Scheme 11. Synthesis of (–)-lepadiformine A (**1**).

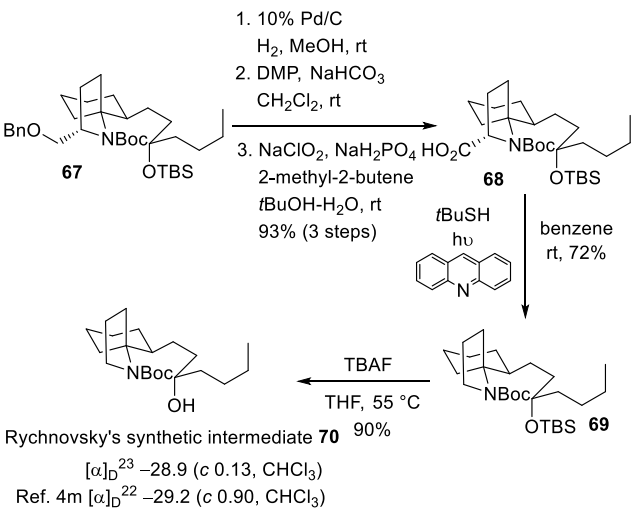
We performed the enantioselective total synthesis of (−)-lepadiformine B (**2**) in a similar manner in order to explore the structure-activity relationships of lepadiformine marine alkaloids (Scheme 12; see the SI for details). Iodide **63** was prepared through a 3-step synthesis including Wittig olefination of **45** with propyltriphenylphosphorane.[28] The corresponding cyclization precursor **64** was synthesized from pyrrolidinone **31**, alkyne **35**, and synthesized **63** by the same synthetic procedure as that of **1**. The $Hg(OTf)_2$-catalyzed cycloisomerization reaction of **64** afforded the desired spirocyclic compound **65** (dr = 12:1). Compound **65** was converted to (−)-**2** *via* Barton-McCombie's deoxygenation and construction of the B-ring. The total synthesis of (–)-**2** was also achieved in 16 steps from the known lactol **45** with 21% overall yield. The spectral characteristics (^{1}H and ^{13}C NMR) of synthetic (−)-lepadiformine B hydrochloride salt **66** were identical to those of the authentic sample.[3, 4m] The optical rotation of synthetic **66**, $[\alpha]_D^{27}$ +2.7 (*c* 0.40, $CHCl_3$), was similar to that of the authentic sample, $[\alpha]_D^{22}$ +3.2 (*c* 0.30, $CHCl_3$).[4m]



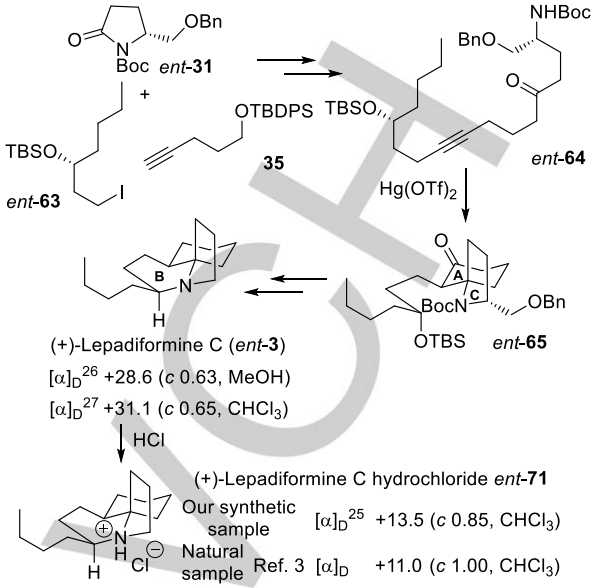
Scheme 12. Synthesis of (−)-lepadiformine B (**2**).

Finally, we successfully synthesized (–)-**3** from the synthetic intermediate **67** during the synthesis of (–)-**2** (Scheme 13). The starting material **67** was transformed to carboxylic acid **68** through deprotection of a benzyl group, Dess-Martin oxidation, and Pinnick oxidation. A carboxy group in **68** was removed by applying photodecarboxylation using acridine, as developed by Okada *et al.*,[29] to provide methylene **69** in modest yield (72%). Deprotection of a TBS group with TBAF afforded Rychnovsky's synthetic intermediate **70**.[4m] The spectral characteristics (^{1}H and

^{13}C NMR) of synthetic **70** were identical to those of Rychnovsky's sample.[4m] The optical rotation of (–)-**70**, $[\alpha]_D^{23}$ –28.9 (*c* 0.13, $CHCl_3$), was similar to previous data, $[\alpha]_D^{22}$ –29.2 (*c* 0.90, $CHCl_3$).[4m]

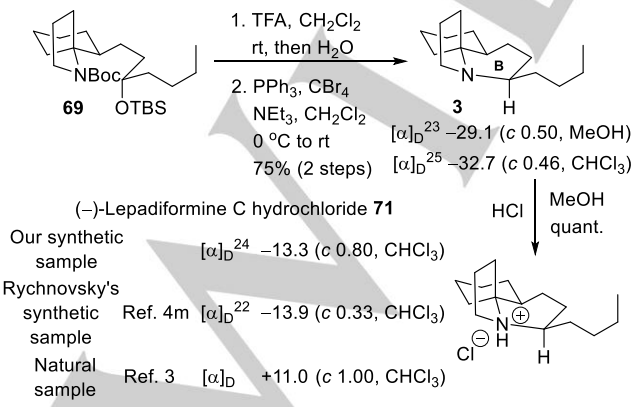


Scheme 13. Synthesis of Rychnovsky's intermediate **70**.



Scheme 15. Synthesis of (+)-lepadiformine C (*ent*-**3**).

The total synthesis of **3** was completed from **69** as outlined in Scheme 14. Compound **69** was subjected to Kibayashi's and Zhao's procedure[4c,j] to provide **3** in modest yield (75% in 2 steps). The spectral characteristics (^{1}H and ^{13}C NMR) of synthetic (−)-lepadiformine C hydrochloride salt **71** were identical to those of the authentic sample.[3,4m] But the optical rotations of our and Rychnovsky's synthetic **71**, $[\alpha]_D^{24}$ −13.3 (*c* 0.80, $CHCl_3$) and $[\alpha]_D^{22}$ −13.9 (*c* 0.33, $CHCl_3$),[4m] respectively, were opposite in sign to that of the natural product, $[\alpha]_D$ +11.0 (*c* 1.00, $CHCl_3$).[3] Therefore, we also synthesized (+)-lepadiformine C (*ent*-**3**), which was enantiomeric to **3**, from pyrrolidinone *ent*-**31**, iodide *ent*-**63**, and alkyne **35** by the same synthetic procedure as that of **3** (Scheme 15). The optical rotation of *ent*-**71**, $[\alpha]_D^{25}$ +13.5 (*c* 0.85, $CHCl_3$), was identical to that of the natural product.[3] Although

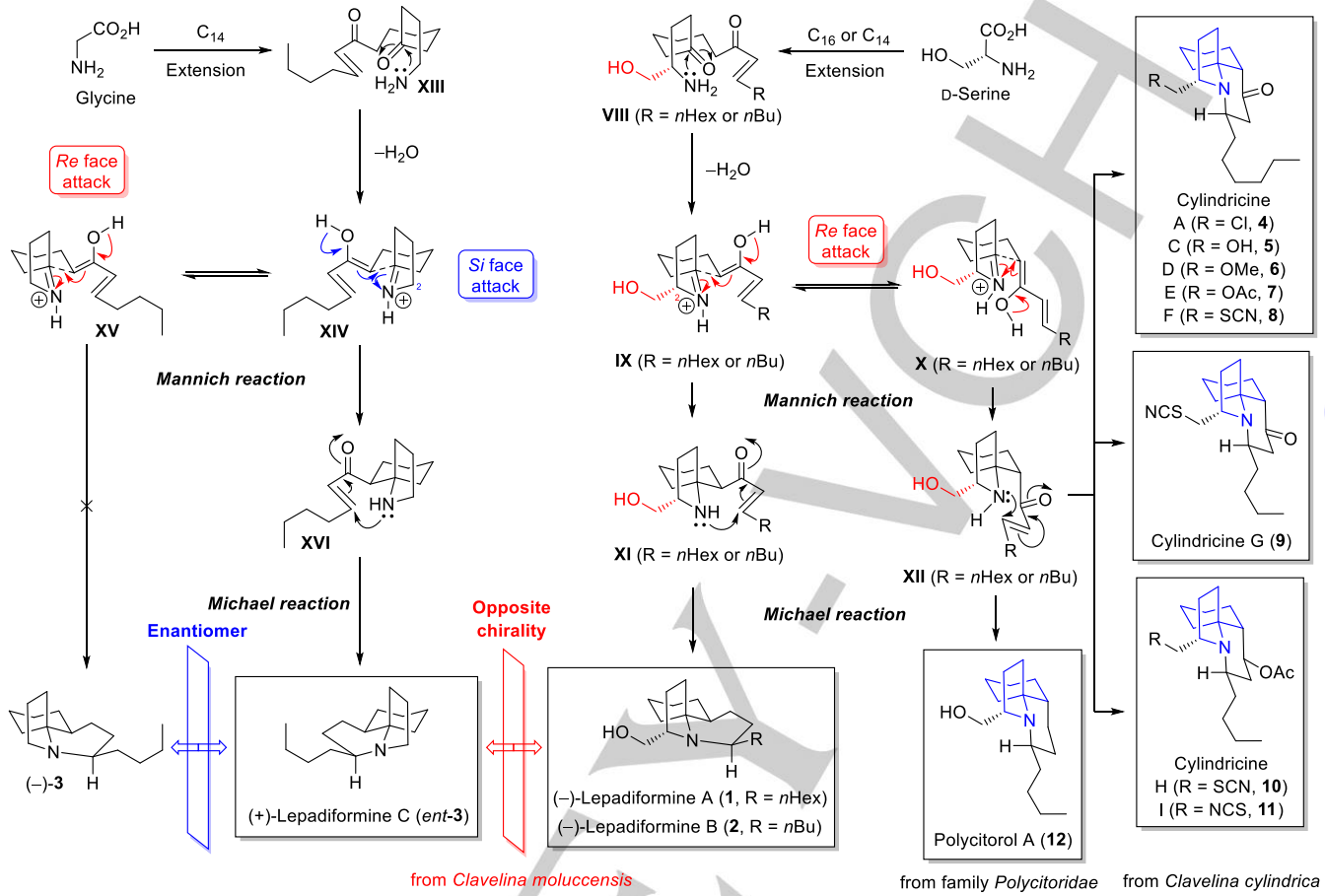


Scheme 14. Synthesis of **3**.

Rychnovsky *et al.* suggested that the optical rotation reported for the natural product, $[\alpha]_D$ +11.0 (*c* 1.00, $CHCl_3$), was that of the free base **3** and not of the HCl salt **71**,[4m] the optical rotation of our synthetic free base **3** was $[\alpha]_D^{25}$ −32.7 (*c* 0.46, $CHCl_3$) (Scheme 14). Thus, the authors suggest that the absolute configuration of natural lepadiformine C should be shown as *ent*-**3**. To further confirm our suggestion, the measurement of the optical rotation of a natural lepadiformine C free base would be necessary.

Recently, a phenomenon of enantiodivergence was uncovered as a new biosynthetic paradigm for natural products.[30] This was found in pyrrole-imidazole alkaloids isolated from different species of marine sponges. In the case of lepadiformine marine alkaloids, it is a further interesting phenomenon that lepadiformines A−C (**1**, **2**, and *ent*-**3**) have been isolated from a single species of marine tunicate, *Clavelina moluccensis*.[31] How should we consider this enantiodivergence of lepadiformines? Our hypothetical biogenesis of lepadiformines is shown in Scheme 16. We speculated the formation of an azatricyclic ring system common to lepadiformines and related marine alkaloids through (1) polyketide extension using amino acids as starter units, (2) Schiff base formation, (3) an intramolecular Mannich reaction, and (4) an intramolecular Michael reaction.[32] In lepadiformines A (**1**) and B (**2**) with a hydroxymethyl group at C2, an intramolecular Mannich reaction would proceed from the *Re* face of an iminium ion in chair-like transition state **IX** with an enol moiety in an equatorial disposition. At that time, cylindricines **4**−**11** from a different species and polycitorol A (**12**) from a different family would be produced *via* the same *Re* face attack on chair-like transition state **X** with an enol moiety in an axial disposition. On the other hand, in lepadiformine C (*ent*-**3**) without a hydroxymethyl group at C2, the *Si* face attack would predominate in transition state **XIV** due to interaction with an enzyme.

10.1002/chem.201701475



Scheme 16. Hypothetical biogenesis of lepadiformine alkaloids.

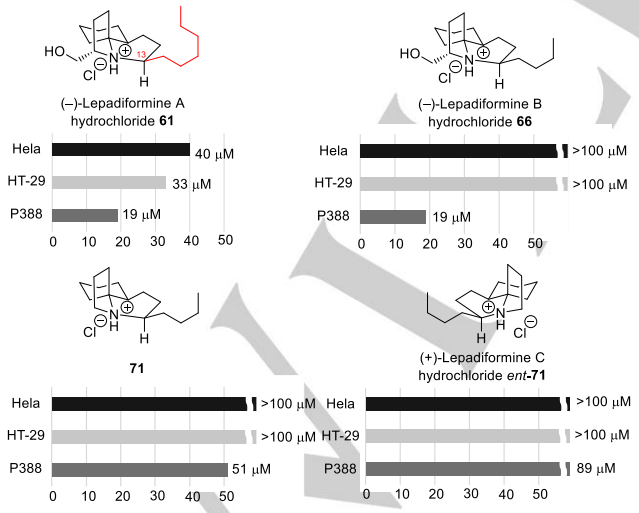


Figure 3. Cytotoxic activities of lepadiformine hydrochloride salts (**61**, **66**, **71**, and *ent*-**71**).

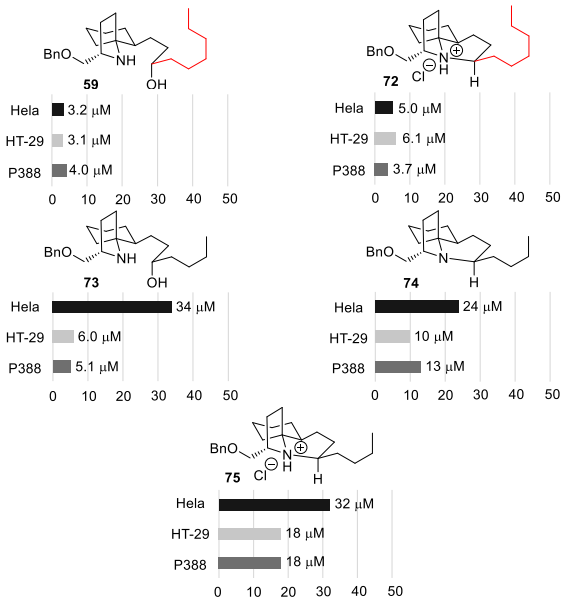


Figure 4. Cytotoxic activities of synthetic intermediates (**59** and **72**–**75**).

With these synthetic lepadiformine hydrochloride salts **61**, **66**, **71**, and *ent*-**71** in hand, we evaluated their cytotoxic activities along with those of the synthetic intermediates **59**, **73**, **74**, and hydrochloride salts **72** and **75**. The biological activities were evaluated, in terms of IC_{50} (half maximal (50%) inhibitory concentration) values against Hela, HT-29, and P388 cell lines exposed to each compound for 72 h. These results are shown in Figures 3 and 4. The (−)-lepadiformine A hydrochloride salt **61** inhibited P388 cells at 19 μM, which was similar to the value (9.4 μM, 3.10 μg mL^{-1}) reported by Biard *et al.* (Figure 3).[1a] But the cytotoxic activity of **61** against HT-29 cells (33 μM) was about ten times lower than indicated by the previous data (2.3 μM, 0.75 μg mL^{-1}).[1a] In addition, **61** showed inhibitory activity against Hela cells at 40 μM and (−)-lepadiformine B hydrochloride salt **66**, **71**, and (+)-lepadiformine C hydrochloride salt *ent*-**71** inhibited P388 cells at 19 μM, 51 μM, and 89 μM, respectively, which indicated similar activity to **61**. However, **66**, **71**, and *ent*-**71** did not show any activity against Hela and HT-29. These experimental results suggested that a hexyl side chain at C13 is important in increasing the cytotoxicity against Hela and HT-29 cells. In addition, the cytotoxic activities of **71** and *ent*-**71** against all three lines were about the same, suggesting that the absolute configuration of lepadiformine C hydrochloride salt plays a minor role in the cytotoxic activity. Interestingly, the synthetic intermediates for (−)-lepadiformine A, such as amino alcohol **59** and hydrochloride salt **72**, were more potent than **61** with cytotoxic activities against all three cell lines (3.1–6.1 μM). This may be due to hydrophobic groups (benzyl group) increasing cell permeability and cytotoxicity. The synthetic intermediates for lepadiformine B, such as amino alcohol **73**, benzyl ether **74**, and the hydrochloride salt **75**, showed similar levels of cytotoxic activities against HT-29 and P388 cells to **59** and **72**, although the activity of **75** was slightly less than that of **72**. But **73**, **74**, and **75** showed lower activities against Hela cells than **59** and **72**, indicating that the shortening of the aliphatic side chain from an *n*-hexyl group to an *n*-butyl group decreased the potency of the inhibitory activity against Hela cells. Lepadiformine alkaloids have been reported to exhibit cardiovascular effects and are expected to lead to the development of antiarrhythmic drugs.[1b,3] These fundamental findings with respect to cytotoxicity may be useful for further exploitation of lepadiformine alkaloids.

Conclusions

In conclusion, we have developed a novel method for the construction of a 1-azaspiro[4.5]decane skeleton, which is embedded in a number of complex alkaloids, from acyclic amino ynone substrates by using an $Hg(OTf)_2$-catalyzed cycloisomerization reaction. The efficient total syntheses of lepadiformines A (**1**) and B (**2**) have been accomplished by utilizing the cycloisomerization reaction as a key step with 28% and 21% overall yields, respectively, and 16 steps based on the known hemiacetal **45**. The total syntheses of (+)- and (−)-lepadiformine C have also been achieved and it has been disclosed that the absolute configuration of lepadiformine C should be shown as *ent*-**3** in its enantiomeric relationship with lepadiformines A (**1**) and B (**2**). This enantiodivergent phenomenon is of great interest with respect to the isolation of lepadiformines A−C from a single species of marine tunicate *Clavelina moluccensis*, because the first occurrence of enantiodivergence was found in natural products isolated from different species.[30a] We evaluated the cytotoxic activities of hydrochloride salts of lepadiformine alkaloids and some synthetic intermediates against Hela, HT-29, and P388 cell lines and revealed that hydrophobic factors such as the alkyl chain length and benzyl protection increase the cytotoxic activities. These findings, coupled with the development of a short and high yielding synthetic route to lepadiformine alkaloids, lay the groundwork for further investigation of biological properties.

Experimental Section

Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra are available in the SI.

Acknowledgements

This work was financially supported by the Astellas Foundation and the JGC-S Scholarship Foundation (Nikki Saneyoshi Scholarship). We particularly thank Prof. Dr. Keiji Okada for providing a medium-pressure mercury lamp. We also thank Dr. Matsumi Doe for NMR analysis of synthetic compounds.

Keywords: natural products • total synthesis • alkaloids • spiro compound • cytotoxicity

[1] a) J.-F. Biard, S. Guyot, C. Roussakis, J. F. Verbist, J. Vercauteren, J. F. Weber, K. Boukef, *Tetrahedron Lett.* **1994**, *35*, 2691−2694; b) M. Jugé, N. Grimaud, J.-F. Biard, M.-P. Sauviat, M. Nabil, J. F. Verbist, J. Y. Petit, *Toxicon* **2001**, *39*, 1231−1237.

[2] a) For a review, see: S. M. Weinreb, *Chem. Rev.* **2006**, *106*, 2531−2549; b) K. M. Werner, J. M. de los Santos, S. M. Weinreb, M. Shang, *J. Org. Chem.* **1999**, *64*, 686−687; c) W. H. Pearson, Y. Ren, *J. Org. Chem.* **1999** *64*, 688−689; d) K. M. Werner, J. M. de los Santos, S. M. Weinreb, M. Shang, *J. Org. Chem.* **1999**, *64*, 4865−4873; e) H. Abe, S. Aoyagi, C. Kibayashi, *Tetrahedron Lett.* **2000**, *41*, 1205–1208; f) H. Abe, S. Aoyagi, C. Kibayashi, *J. Am. Chem. Soc.* **2000**, *122*, 4583−4592; g) P. Sun, C. Sun, S. M. Weinreb, *Org. Lett.* **2001**, *3*, 3507−3510; h) P. Sun, C. Sun, S. M. Weinreb, *J. Org. Chem.* **2002**, *67*, 4337−4345; i) H. Abe, S. Aoyagi, C. Kibayashi, *Angew. Chem. Int. Ed.* **2002**, *41*, 3017−3020; *Angew. Chem.* **2002**, *114*, 3143−3146.

[3] M.-P. Sauviat, J. Vercauteren, N. Grimaud, M. Jugé, M. Nabil, J.-Y. Petit, J.-F. Biard, *J. Nat. Prod.* **2006**, *69*, 558−562.

[4] a) T. J. Greshock, R. L. Funk, *Org. Lett.* **2001**, *3*, 3511−3514; b) J. Liu, R. P. Hsung, S. D. Peters, *Org. Lett.* **2004**, *6*, 3989−3992; c) H. Abe, S. Aoyagi, C. Kibayashi, *J. Am. Chem. Soc.* **2005**, *127*, 1473−1480; d) M. Lee, T. Lee, E.-Y. Kim, H. Ko, D. Kim, S. Kim, *Org. Lett.* **2006**, *8*, 745−748; e) P. Schär, P. Renaud, *Org. Lett.* **2006**, *8*, 1569−1571; f) J. J. Caldwell, D. Craig, *Angew. Chem. Int. Ed.* **2007**, *46*, 2631−2634; *Angew. Chem.* **2007**, *119*, 2685−2688; g) H. Mihara, T. Shibuguchi, A. Kuramochi, T. Ohshima, M. Shibasaki, *Heterocycles* **2007**, *72*, 421−438; h) M. Fujitani, M. Tsuchiya, K. Okano, K. Takasu, M. Ihara, H. Tokuyama, *Synlett* **2010**, 822−826; i) A. M. Meyer, C. E. Katz, S.-W. Li, D. V. Velde, J. Aubé, *Org. Lett.* **2010**, *12*, 1244−1247; j) S.-L. Mei, G. Zhao, *Eur. J. Org. Chem.* **2010**,

1660−1668; k) K. Weidner, A. Giroult, P. Panchaud, P. Renaud, *J. Am. Chem. Soc.* **2010**, *132*, 17511–17515; l) M. A. Perry, M. D. Morin, B. W. Slafer, S. A. Wolckenhauer, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2010**, *132*, 9591–9593; m) M. A. Perry, M. D. Morin, B. W. Slafer, S. D. Rychnovsky, *J. Org. Chem.* **2012**, *77*, 3390−3400; n) J. In,; S. Lee, Y. Kwon, S. Kim, *Chem. Eur. J.* **2014**, *20*, 17433−17442; o) G. Pandey, V. Janakiram, *Chem. Eur. J.* **2015**, *21*, 13120−13126; p) M. G. Tabor, R. A. Shenvi, *Org. Lett.* **2015**, *17*, 5776−5779; q) S. V. Tsukanov, L. R. Marks, D. L. Comins, *J. Org. Chem.* **2016**, *81*, 10433−10443; r) S. Lee, M. Bae, J. In, J. H. Kim, S. Kim, *Org. Lett.* **2017**, *19*, 254−257.

[5] K. Nishikawa, S. Kikuchi, S. Ezaki, T. Koyama, H. Nokubo, T. Kodama, Y. Tachi, Y. Morimoto, *Org. Lett.* **2015**, *17*, 5772−5775.

[6] C. P. Li, A. J. Blackman, *Aust. J. Chem.* **1995**, *48*, 955−965.

[7] H. H. Issa, J. Tanaka, R. Rachmat, A. Setiawan, A. Trianto, T. Higa, *Mar. Drugs* **2005**, *3*, 78−83.

[8] K. Sakamoto, E. Tsujii, F. Abe, T. Nakanishi, M. Yamashita, N. Shigematsu, S. Izumi, M. Okuhara, *J. Antibiot.* **1996**, *49*, 37−44.

[9] T. S. Kam, K. H. Lim, In *The Alkaloids*, *Vol. 66* (Ed.: G. A. Cordell), Academic Press, Amsterdam, **2008**, pp. 1−111.

[10] a) R. J. Ferrier, *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455−1458; b) N. Chida, M. Ohtsuka, K. Ogura, S. Ogawa, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2118−2121; c) N. A. Petasis, S.-P. Lu, *Tetrahedron Lett.* **1996**, *37*, 141−144.

[11] a) For a review, see: D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395−403; b) Y. Liu, M. Liu, S. Guo, H. Tu, Y. Zhou, H. Gao, *Org. Lett.* **2006**, *8*, 3445−3448; c) B. V. S. Reddy, M. R. Reddy, S. Yarlagadda, C. R. Reddy, G. R. Kumar, J. S. Yadav, B. Sridhar, *J. Org. Chem.* **2015**, *80*, 8807−8814.

[12] N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133−4136.

[13] For a similar catalysis with gold(I) catalysts, see: a) W. Zi, F. D. Toste, *J. Am. Chem. Soc.* **2013**, *135*, 12600−12603; b) H. Kim, Y. H. Rhee, *J. Am. Chem. Soc.* **2012**, *134*, 4011−4014.

[14] a) A. Diéguez-Vázquez, C. C. Tzschucke, W. Y. Lam, S. V. Ley, *Angew. Chem. Int. Ed.* **2008**, *47*, 209–212; *Angew. Chem.* **2008**, *120*, 216–219; b) S. Bhuvaneswari, M. Jeganmohan, C.-H. Cheng, *Chem. Eur. J.* **2007**, *13*, 8285–8293; c) C. Liu, C. F. Bender, X. Han, R. A. Widenhoefer, *Chem. Commun.* **2007**, 3607–3618.

[15] T. Pei, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2001**, *123*, 11290–11291.

[16] a) For a review, see: M. Nishizawa, H. Imagawa, H. Yamamoto, *Org. Biomol. Chem.* **2010**, *8*, 511−521; b) M. Nishizawa, H. Takao, V. K. Yadav, H. Imagawa, T. Sugihara, *Org. Lett.* **2003**, *5*, 4563−4565; c) H. Yamamoto, I. Sasaki, H. Imagawa, M. Nishizawa, *Org. Lett.* **2007**, *9*, 1399−1402; d) K. Namba, H. Yamamoto, I. Sasaki, K. Mori, H. Imagawa, M. Nishizawa, *Org. Lett.* **2008**, *10*, 1767−1770.

[17] E. Genin, S. Antoniotti, V. Michelet, J.-P. Genêt, *Angew. Chem. Int. Ed.* **2005**, *44*, 4949–4953; *Angew. Chem.* **2005**, *117*, 5029–5033.

[18] D. Shikanai, H. Murase, T. Hata, H. Urabe, *J. Am. Chem. Soc.* **2009**, *131*, 3166–3167.

[19] T. Katoh, Y. Nagata, Y. Kobayashi, K. Arai, J. Minami, S. Terashima, *Tetrahedron* **1994**, *50*, 6221−6238.

[20] R. C. Clark, S. Y. Lee, D. L. Boger, *J. Am. Chem. Soc.* **2008**, *130*, 12355−12369.

[21] G. A. Molander, G. Hahn, *J. Org. Chem.* **1986**, *51*, 1135−1138.

[22] H. O. House, R. A. Auerbach, M. Gall, N. P. Peet, *J. Org. Chem.* **1973**, *38*, 514−522.

[23] D. F. Taber, Y. Wang, T. F. Pahutski, Jr., *J. Org. Chem.* **2000**, *65*, 3861−3863.

[24] a) J. D. White, P. Hrnciar, *J. Org. Chem.* **2000**, *65*, 9129−9142; b) S. E. Denmark, S.-M. Yang, *J. Am. Chem. Soc.* **2004**, *126*, 12432−12440; c) M. Prévost, O. St-Jean, Y. Guindon, *J. Am. Chem. Soc.* **2010**, *132*, 12433−12439.

[25] S. BouzBouz, J. Cossy, *Org. Lett.* **2004**, *6*, 3469−3472.

[26] a) K. Lam, I. E. Markó, *Org. Lett.* **2008**, *10*, 2773−2776; b) K. Lam, I. E. Markó, *Org. Lett.* **2009**, *11*, 2752−2755; c) K. Lam, I. E. Markó, *Tetrahedron* **2009**, *65*, 10930–10940; d) K. Lam, I. E. Markó, *Chem. Commun.* **2009**, 95–97.

[27] D. H. R. Barton, S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585.

[28] D. J. Chritcher, S. Connolly, M. Wills, *Tetrahedron Lett.* **1995**, *36*, 3763−3766.

[29] K. Okada, K. Okubo, M. Oda, *J. Photochem. Photobiol. A: Chem.* **1991**, 57, 265−277.

[30] a) Z. Ma, X. Wang, X. Wang, R. A. Rodriguez, C. E. Moore, S. Gao, X. Tan, Y. Ma, A. L. Rheingold, P. S. Baran, C. Chen, *Science* **2014**, *346*, 219–224; b) A. Hoshino, H. Nakai, M. Morino, K. Nishikawa, T. Kodama, K. Nishikibe, Y. Morimoto, *Angew. Chem. Int. Ed.* **2017**, *56*, 3064–3068; *Angew. Chem.* **2017**, *129*, 3110–3114.

[31] J. M. Finefield, D. H. Sherman, M. Kreitman, R. M. Williams, *Angew. Chem. Int. Ed.* **2012**, *51*, 4802–4836; *Angew. Chem.* **2012**, *124*, 4886–4920.

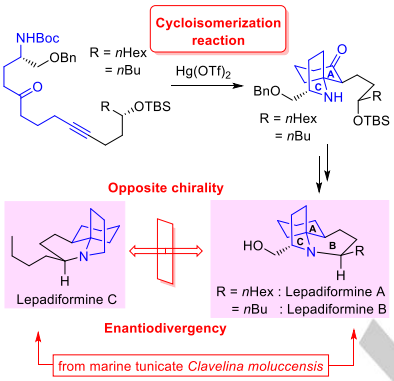
[32] For a review, see: R. B. Herbert, *Nat. Prod. Rep.* **2003**, *20*, 494–508.

10.1002/chem.201701475

WILEY-VCH

FULL PAPER

A phenomenon of enantiodivergence was found in lepadiformine alkaloids isolated from a single species marine tunicate *Clavelina moluccensis* through their syntheses. The enantioselective total syntheses have been achieved by a key mercury(II) triflate-catalyzed cycloisomerization reaction developed in our laboratory (see Scheme), and cytotoxic activities of synthesized compounds were also evaluated.



*K. Nishikawa, K. Yamauchi, S. Kikuchi, S. Ezaki, T. Koyama, H. Nokubo, K. Matsumura, T. Kodama, M. Kumagai, Y. Morimoto**

Page No. – Page No.

Total Syntheses of Lepadiformine Marine Alkaloids with Enantiodivergency, Utilizing $Hg(OTf)_2$-Catalyzed Cycloisomerization Reaction and Their Cytotoxic Activities