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Divergent Total Synthesis of the Tricyclic Marine Alkaloids Lepadiformine, Fasicularin, and Isomers of Polycitorols by Reagent-Controlled Diastereoselective Reductive Amination

Jinkyung In, Seokwoo Lee, Yongseok Kwon, and Sanghee Kim*[a]

Abstract: We describe a flexible and divergent route to the pyrrolo-/pyrido[1,2-*j*]quinoline frameworks of tricyclic marine alkaloids via a common intermediate formed by the ester–enolate Claisen rearrangement of a cyclic amino acid allylic ester. We have synthesized the proposed structure of polycitorols and demonstrated that the structure of these alkaloids requires revision. In addition to asymmetric formal syntheses, stereoselective and concise total syntheses of (−)-lepadiformine and (−)-fasicularin were also accomplished from simple, commercially available starting materials in a completely substrate-controlled manner. The key step in these total syntheses was the reagent-dependent stereoselective reductive amination of the common intermediate to yield either indolizidines **55a** or **55b**. Aziridinium-mediated carbon homologation of the hindered C-10 group to the homoallylic group facilitated the synthesis.

Introduction

There has been considerable interest in the synthesis of tricyclic marine alkaloids with a perhydropyrrolo[1,2-*j*]quinoline or perhydropyrido[2,1-*j*]quinoline ring system. The first members of this structurally unique natural product family were the cylindricines (**1**, Figure 1), which were isolated from the ascidian *Clavelina cylindrica* in the early 1990s.[1] Interestingly, pyrroloquinoline cylindricine A (**1a**) and pyridoquinoline cylindricine B (**1b**) can interconvert, presumably via aziridinium intermediate **2**. Another notable alkaloid of this general class is lepadiformine (**3a**). This marine alkaloid, which is now known as lepadiformine A, was isolated from the tunicate *Clavelina lepadiformis* in 1994 and exhibits strong cardiovascular effects as well as moderate cytotoxicity.[2] The originally proposed structure for lepadiformine A has been shown to be incorrect, and the correct relative and absolute stereochemistries were determined by its total synthesis.[3] The revised structure of lepadiformine includes a *trans*-1-azadecalin A/B ring system instead of the *cis*-1-azadecalin framework of cylindricines. X-ray crystallographic analysis of the hydrochloride salt of synthetic **3a** indicated that its B-ring exists in an unusual twist-boat form, as shown in Figure 1.[3a]

Since the isolation of cylindricines and lepadiformine A, a number of their congeners have been identified. A marine alkaloid that is very closely related to lepadiformine A is lepadiformine B (**3b**), which bears a butyl instead of a hexyl appendage at C-2. Lepadiformine C (**3c**) is another congener and lacks the hydroxymethyl group at C-13.[4] In 1997, fasicularin (**4**) was isolated from the ascidian *Neptheis fasicularis*.[5] This alkaloid exhibits modest cytotoxic activity against Vero cells and selective activity against a DNA repair-deficient yeast.[5] The structural features of fasicularin are similar to those of cylindricine B (**1b**), but the A/B ring system is a *trans*-1-azadecalin similar to that of lepadiformines. In addition, unlike most cylindricines, this alkaloid lacks the carbonyl group at C-4. More recently, two new tricyclic alkaloids were isolated from a marine ascidian of the family Polycitoridae and named polycitorols A and B by Tanaka and co-workers.[6] Based on spectral analysis, the structures of the polycitorols were proposed to be those

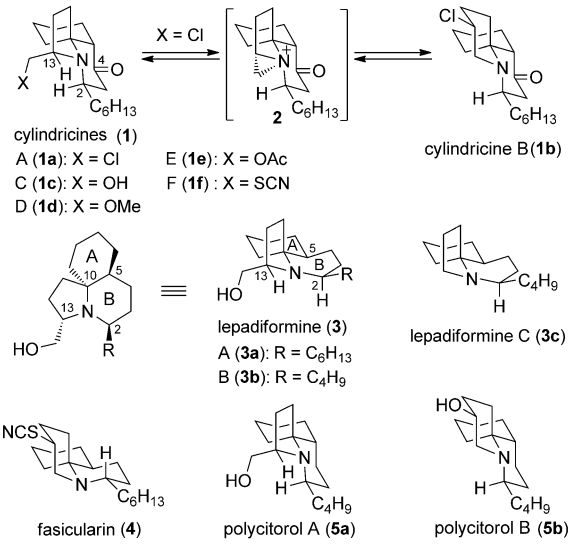

Figure 1. Structures of tricyclic marine alkaloids.

[a] *J. In, S. Lee, Y. Kwon, Prof. S. Kim*
College of Pharmacy
Seoul National University
San 56-1, Shilim, Kwanak, Seoul, 151-742 (Korea)
E-mail: pennkim@snu.ac.kr

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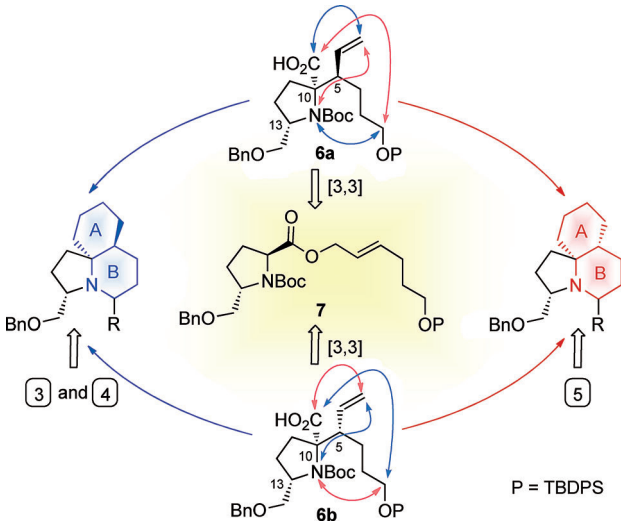
shown in **5a** and **5b**. The proposed structures of the polycitorols are similar to those of the cylindricines, but they have a butyl group rather than a hexyl group at C-2 and lack the C-4 oxygenation found in most cylindricines.

Due to their bioactivities and structural features, these tricyclic marine alkaloids have been the subject of numerous synthetic studies.[7,8] In this context, we have previously reported a formal synthesis of lepadiformine A.[9] Herein, we describe the full details of synthetic work that includes the substrate-controlled total syntheses of (−)-lepadiformine A (**3a**) and (−)-fasicularin (**4**) via a common intermediate as well as the synthesis of the proposed structure of the polycitorols (**5**). One of the key features of these total syntheses was the reagent-dependent reversal of diastereofacial selectivity in the B-ring formation of the tricyclic marine alkaloids. This key step as well as the appropriate combination of functional groups in the A/B ring formation enabled us to selectively synthesize the above-mentioned alkaloids from the same intermediate.

General synthetic strategy

The main structural difference between tricyclic marine alkaloids **3**–**5** was the stereochemistry of the A/B ring fusion. To synthesize these alkaloids, we adopted a flexible approach that could be amended to prepare both *cis* and *trans*-1-azadecalin A/B ring systems. We envisioned that either cyclic amino acid **6a** or its C-5 epimer **6b** (Scheme 1) could potentially lead to



Scheme 1. General retrosynthetic analysis. Boc = *tert*-butoxycarbonyl. TBDPS = *tert*-butyldiphenylsilyl.

both *cis* and *trans*-1-azadecalin A/B ring systems by the appropriate combination of functional groups. For example, a *trans*-1-azadecalin A/B ring system of **3** and **4** could be constructed from cyclic amino acid **6a** through a ring closure involving the formation of a bond between the C-5 vinyl group (natural product numbering) and the C-10 carboxylic group along with the formation of the piperidine B-ring by joining the nitrogen function to the C-5 propanol moiety. Alternatively, ring closure by annulation of the C-10 carboxylic group with the C-5 propanol moiety and piperidine B ring formation involving the nitrogen and C-5 vinyl group would lead to the formation of the *cis*-fused A/B ring system of the polycitorols (**5**). With cyclic amino acid **6b**, a *trans*-fused A/B ring system would be obtained by ring closure through annulation of the C-10 carboxylic group with the C-5 propanol moiety and piperidine ring formation involving the nitrogen and the C-5 vinyl group.

The ester–enolate Claisen rearrangement of amino acid allylic ester **7** was envisioned to deliver the densely functionalized cyclic amino acids **6a** or **6b**. The stereochemical outcome of the Claisen rearrangement of **7** can be determined from the enolate geometry and transition-state geometry. The Claisen rearrangement proceeds via a chairlike transition state.[10] However, at the beginning of our studies, there were no examples in the literature describing the control of the ester–enolate geometry in cyclic α-amino acid ester compounds possessing an exocyclic *N*-carbonyl group such as **7**.[11] Therefore, we were uncertain about the stereochemistry of the major product formed from the rearrangement of **7**. However, the stereochemical outcome was not a concern if high selectivity was achieved because both C-5 epimer **6a** and **6b** could be transformed to either the *cis*- or *trans*-1-azadecalin A/B ring as stated above.

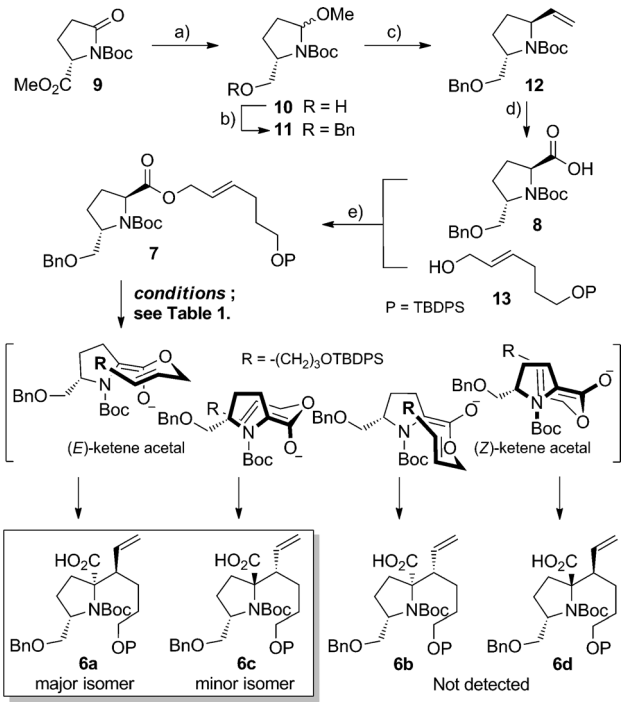
Results and Discussion

Synthesis of key intermediate 6

As per the general synthetic plan, our synthesis started with the preparation of protected cyclic amino acid **8** as a synthetic precursor for Claisen rearrangement substrate **7** (Scheme 2). Cyclic amino acid **8** was envisioned to be derived from commercially available (*S*)-methyl-*N*-Boc-pyroglutamate (**9**), which was the only source of chirality in our synthesis.

Although the stereochemistry at the α-position of the carbonyl group of **8** would be destroyed upon deprotonation during the ester–enolate Claisen rearrangement, it was prepared as a single configuration product from *N*-Boc-pyroglutamate (**9**). The DIBAL-H reduction of **9** was followed by in situ treatment with acidic methanol, affording aminal **10**. The hydroxyl group of **10** was protected as its benzyl ether to yield known compound **11**.[12] The nucleophilic addition of a vinyl group to the *N*-acyliminium ion generated in situ from **11** was achieved selectively by employing a Grignard-derived vinylcopper reagent to produce **12** as the only detectable isomer in 92% yield. The vinyl moiety of **12** was transformed to a carboxylic acid group by ruthenium tetraoxide-mediated oxidative cleavage to yield amino acid **8** in 83% yield.[13] Esterification of acid **8** with known allylic alcohol **13**[14] under Steglich's DCC coupling[15] conditions provided the desired allylic ester **7** in high yield.

With multigram quantities of **7** in hand, we explored the ester–enolate Claisen rearrangement. As mentioned earlier, either rearrangement product **6a** or **6b** could be used for the total synthesis if high selectivity was achieved in the reaction. We surveyed a series of reaction conditions involving changes



Scheme 2. Synthesis of key intermediate **6a** by an ester–enolate Claisen rearrangement: a) DIBAL-H, CH_2Cl_2, −78 °C to RT, then 2.0 M HCl (aq.), MeOH, 0 °C, 70%; b) NaH, BnBr, DMF, 0 °C to RT, 85%; c) CuI, vinylmagnesium bromide, $BF_3{\cdot}OEt_2$, THF, −78 °C to RT, 92%; d) $NaIO_4$, $RuCl{\cdot}H_2O$, CH_2Cl_2, CH_3CN, H_2O, RT, 83%; e) DCC, DMAP, CH_2Cl_2, RT, 88%; DIBAL-H = diisobutylaluminum hydride, DMF = dimethylformamide, DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine.

Table 1. Reaction conditions for the rearrangement of **7**.

Entry	Base (3 equiv)	Additive (1.5 equiv)	Solvent	Yield [%],[a] **6a**/**6c**[b]
1[c]	LiHMDS	–	THF	90, 10:1
2[c]	KHMDS	–	THF	80, 3:1
3[c]	LDA	–	THF	60, 3:1
4[c]	LiHMDS	–	THF/HMPA	60, 5:1
5[c]	LDA	–	THF/HMPA	40, 3:1
6[d]	LiHMDS	TBSCl	THF	88, 8:1
7[d]	NaHMDS	TBSCl	THF	85, 4:1
8[d]	KHMDS	TBSCl	THF	70, 5:1
9[d]	LDA	TBSCl	THF	50, 2:1

[a] Isolated yields. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Substrate was added to a solution of base at −78 °C. Solvent (0.05 M). [d] Base was added to a solution of substrate and additive at −78 °C. Solvent (0.02 M). LiHMDS = lithium bis(trimethylsilyl)amide, KHMDS = potassium bis(trimethylsilyl)amide, LDA = lithium diisopropylamide, HMPA = hexamethylphosphoramide, TBSCl = *tert*-butyldimethylsilyl chloride.

in base, additive, temperature, and solvent to achieve high stereoselectivity by selective enolization. Some typical results are summarized in Table 1.

Under all the reaction conditions tested, the major product was rearrangement product **6a**, and the minor one was **6c**. The other two possible isomers (**6b** and **6d**) were not detected, even in the reactions with HMPA (Table 1, entries 4 and 5). Due to the clear predominance of the chair conformation in the transition state of the Claisen rearrangement, the outcome of **6a** and **6c** indicated the exclusive formation of the (*E*)-ketene acetal as an intermediate during the reaction. This selective enolization might be due to the unfavorable steric interaction between the bulky *N*-Boc group and the alkyl group of the ester moiety in the transition state leading to the (*Z*)-ketene acetal.[16] Another plausible explanation for this selectivity is chelation control between the (*E*)-ester enolate oxygen atom and the heteroatom of the *N*-Boc group.[17]

The stereochemistry of rearrangement product **6a** was established by its conversion to the final natural product (vide infra), and the stereochemistry of **6c** was determined by NOE experiments after derivatization to a rigid bicyclic compound.[18] The major product **6a** resulted from rearrangement on the less-hindered face opposite the C-13 substituent. The facial selectivity of this process was dependent on the nature of the bases. LiHMDS yielded better results as the base than LDA (Table 1, entry 1 vs. 3 and 6 vs. 9). The reactions conducted with LiHMDS occurred with higher selectivity than those conducted with NaHMDS or KHMDS (entry 6 vs. entries 7 and 8). The reasons for this selectivity are not yet clear.

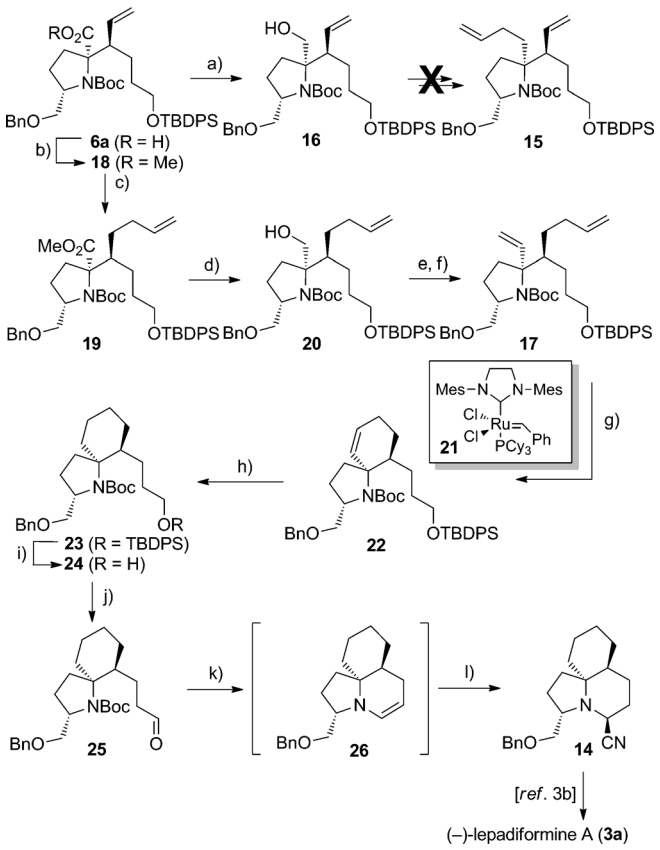
The best reaction conditions in terms of both yield and selectivity were as follows. When substrate **7** was added to a solution of LiHMDS in THF at −78 °C and gradually warmed to room temperature, a very high diastereofacial selectivity was achieved in the rearrangement to afford **6a** and **6c** in a 10:1 ratio and 90% combined yield (Table 1, entry 1). Similarly high yields and selectivity were obtained when the mixture of **7** and TBSCl was treated with LiHMDS in THF at −78 °C followed by gradual warming to room temperature (entry 6).

Formal synthesis of (−)-lepadiformine A with rearrangement product 6a

The tricyclic amino nitrile **14** (Scheme 3) was a key advanced intermediate in Weinreb's total synthesis of lepadiformine A.[3b] We envisioned that this intermediate could be readily synthesized from the functionalized cyclic amino acid **6a**, which is the major product of the Claisen rearrangement of **7**. As previously mentioned, ring closure by bonding between the C-5 vinyl group and the C-10 carboxylic group of **6a** would yield the desired *trans*-fused A/B ring system of the lepadiformines. We planned to use a ring-closing metathesis (RCM) reaction[19] for this ring closure.

To prepare the metathesis precursor, we first focused on conversion of the carboxylic acid group of **6a** into a homoallyl group in **15**. To this end, carboxylic acid **6a** was reduced with $LiAlH_4$ to the corresponding primary alcohol **16** (94%). Unfortunately, all of our attempts to convert the primary alcohol group in **16** to the homoallyl group in **15** were unsuccessful, most likely due to a high degree of steric hindrance.

The above failure forced us to devise an alternative RCM substrate. We envisioned that two-carbon-atom-homologation of the C-5 vinyl group of **6a** and conversion of a C-10 carbonyl function to a carbon–carbon double bond would provide the appropriate RCM substrate, such as diene **17**. The successful



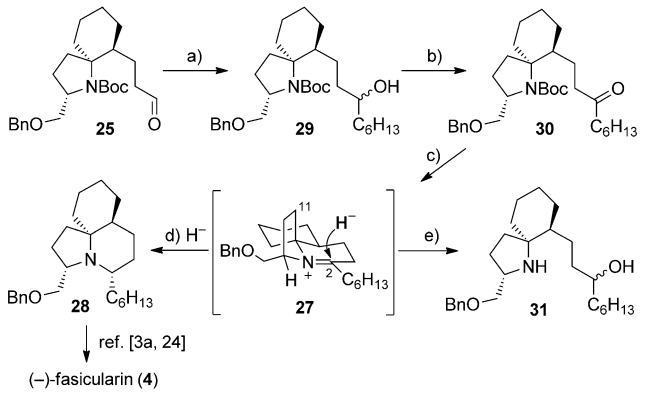
Scheme 3. Formal synthesis of (−)-lepadiformine A (**3a**): a) $LiAlH_4$, THF, 0 °C, 94%; b) MeI, K_2CO_3, acetone, reflux, 93%; c) i) 9-BBN, TlOEt, THF, 50 °C; ii) vinyl bromide, [$PdCl_2$(dppf)], $AsPh_3$, THF/DMF, 40 °C, 73%; d) $LiAlH_4$, THF, 0 °C, 91%; e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 0 °C; f) $(CH_3Ph_3P)^+I^-$, *n*BuLi, THF, 84% (over two steps); g) **21**, CH_2Cl_2, 40 °C, 98%; h) H_2, Pd/C, Et_3N, MeOH, RT, 95%; i) TBAF, THF, RT; j) Dess–Martin periodinane, CH_2Cl_2, RT, 95% (over 2 steps); k) *p*-TsOH, acetone/H_2O, reflux; l) KCN, 1 N HCl, acetone/H_2O, RT, 70% (over 2 steps). 9-BBN = 9-borabicyclo[3.3.1]nonane, TBAF = tetrabutylammonium fluoride, Dess–Martin periodinane = 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)one, *p*-TsOH = *p*-toluenesulfonic acid.

route to revised RCM substrate **17** began with methylation of the carboxylic acid moiety of Claisen rearrangement product **6a** to afford ester **18**. A one-pot tandem sequence involving regioselective hydroboration of the terminal olefin in **18** with 9-BBN followed by coupling of the resulting borane under Suzuki–Miyaura conditions ([$PdCl_2$(dppf)], $AsPh_3$) (dppf = 1,1′-bis(diphenylphosphino)ferrocene) with vinyl bromide yielded **19** in 73% overall yield.[20] Treatment of **19** with $LiAlH_4$ effected reduction of the ester to afford alcohol **20** in 91% yield. Swern oxidation of **20** followed by a Wittig reaction of the resulting hindered aldehyde successfully provided the desired RCM substrate **17** in 84% two-step yield. The RCM of diene **17** was successfully performed with second-generation Grubbs' catalyst **21**[21] in CH_2Cl_2 at 40 °C, yielding the desired azaspiro-cyclohexene derivative **22** in excellent yield (98%). Hydrogenation of the olefinic bond of **22** using H_2 and 10% Pd/C in the presence of Et_3N as a catalyst poison afforded **23** without effecting hydrogenolysis of the *O*-benzyl protecting group.[22]

After achieving carbocyclic A-ring formation, we directed our efforts toward the construction of the cyano-group-functionalized lepadiformine B-ring to complete the formal synthesis. Deprotection of silyl ether **23** with TBAF followed by oxidation of resultant alcohol **24** with Dess–Martin periodinane[23] yielded aldehyde **25** in 95% overall yield. Treatment of **25** with *p*-TsOH in aqueous acetone under reflux led to the removal of the *N*-Boc protecting group and subsequent cyclization to the unstable tricyclic enamine **26**, which has been previously reported by the Weinreb group.[3b] Under conditions analogous to those used by Weinreb, enamine **26** was converted in situ to the more stable α-amino nitrile **14** in 70% overall yield. Our spectroscopic data for **14** were identical to those previously reported. Therefore, we have accomplished the formal synthesis of (−)-lepadiformine A and can confirm the relative stereochemistry of **6a**.

Formal synthesis of (−)-fasicularin

Next, we focused our attention on the synthesis of (−)-fasicularin (**4**) from aldehyde **25**. We envisioned that the reduction of iminium species **27** (Scheme 4) from the stereoelectronically



Scheme 4. Formal synthesis of (−)-fasicularin: a) $C_6H_{13}MgBr$, THF, −78 °C, 92%; b) Dess–Martin periodinane, CH_2Cl_2, RT, 93%; c) TFA/CH_2Cl_2 (3:5), 0 °C to RT; d) $NaCNBH_3$, MeOH, −40 °C, 85% from **30** e) L-Selectride, THF, −78 °C, 80% from **30**; TFA = trifluoroacetic acid, DEAD = diethyl azodicarboxylate, L-Selectride = lithium tri-*sec*-butylborohydride.

preferred face would yield the C-2 stereochemistry of fasicularin. The expected product **28** has been converted into pyridoquinoline alkaloid **4** by Kibayashi and co-workers.[3a,24]

To continue the synthesis of (−)-fasicularin (**4**) from aldehyde **25**, the hexyl group was first introduced using hexylmagnesium bromide to afford alcohol **29** as a 1:1 mixture of diastereomers in 92% yield. Secondary alcohol **29** was oxidized with the Dess–Martin periodinane to yield ketone **30** (93%). For annulation of the B-ring by reductive amination, the *N*-Boc protecting group of **30** was removed with TFA to afford iminium salt **27**, and the resultant salt was treated with $NaCNBH_3$ in MeOH at −40 °C to give **28** as the only isomer in high overall yield. Preference for the formation of **28** could be rationalized by Stevens' stereoelectronic principle,[25] The spectroscopic data for compound **28** synthesized by this route were identical to those previously reported.[24] The remaining steps to complete the synthesis were accomplished by employing the same reac-

tion conditions as those previously described in the literature.[24]

Because the C-2 epimer of **28** could be converted to lepadiformine A in a single step, attempts were made to invert the diastereoselectivity to develop a new selective route to lepadiformine A. We envisioned that a bulky reducing agent would invert the selectivity because the reduction of iminium ion **27** by a bulky reducing agent could occur through a twisted-boat conformation (equatorial attack) to avoid the severe 1,3-diaxial interactions between the bridge carbon atom (C-11) and the incoming agent. However, after attempts with various hydride reagents, the diastereofacial preference of the reductive amination of iminium salt **27** could not be reversed. When the reduction was performed with H_2 and Pd/C in the presence of Et_3N, the diastereoselectivity was reduced to 3:1 but not inverted. When iminium salt **27** was treated with the bulky L-Selectride, the reduction product was not the product of reductive amination but secondary alcohol **31** (ca. 1:1 mixture).

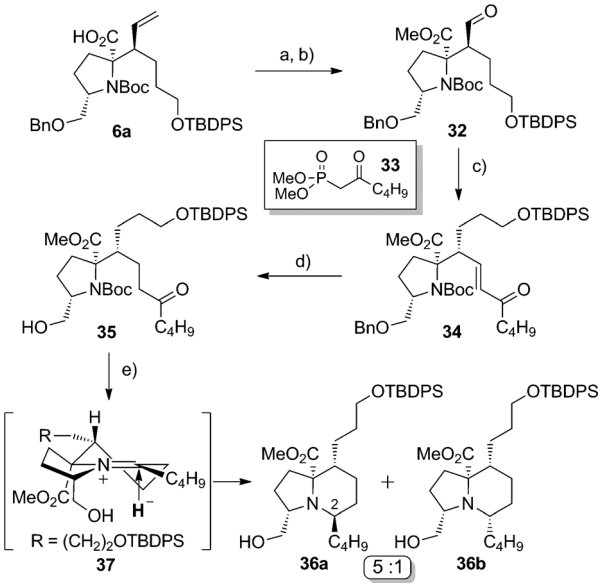
Synthesis of the proposed structure of polycitorols with rearrangement product 6a

The total synthesis of the proposed structure of polycitorols has not been previously reported. The A/B ring fusion of polycitorols was proposed to be *cis*, similar to that of cylindricines. As mentioned above, the *cis*-1-azadecalin A/B ring system of **5** would be accessible from the major rearrangement product (**6a**, Scheme 5) by a ring-closing annulation of the carboxylic group with the C-5 propanol moiety and piperidine B-ring formation involving the nitrogen and vinyl group. The formation of the B ring was expected to be produced by a reductive amination of the appropriate carbonyl group derived from the vinyl group of **6a**. Unlike the cascade sequence for the formal synthesis of lepadiformine and fasicularin, we planned to construct the piperidine B ring prior to the A ring.

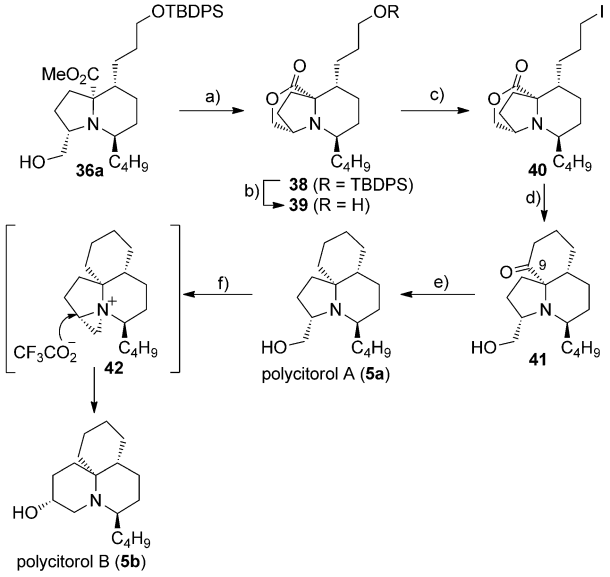
To this end, we first masked the carboxylic acid moiety of Claisen rearrangement product **6a**, and the vinyl group was converted to the corresponding aldehyde by ozonolysis. Resultant aldehyde **32** was subjected to a Horner–Emmons olefination[26] with **33** to yield α,β-unsaturated carbonyl compound **34** in 70% yield. Catalytic hydrogenation of **34** over Pd/C resulted in the reduction of the double bond and simultaneous *O*-benzyl group cleavage to afford reductive amination substrate **35** (85%).

For the intramolecular reductive amination, the *N*-Boc protecting group of **35** was removed with TFA, and the crude compound was subjected to typical reductive amination conditions. The reaction with $NaCNBH_3$/AcOH in CH_3CN at −78 °C resulted in good diastereoselectivity to yield indolizidines **36a** and **36b** in a ratio of 5:1. In other solvents, such as MeOH, THF, and CH_2Cl_2, the selectivity decreased to approximately 3:1. The C-2 stereochemistry of the two diastereomers was determined by NOESY analysis.[18] The preference for the formation of **36a** can be rationalized by Stevens' stereoelectronic principle[25] and/or substituent-directing effects. Intermediate iminium salt **37** would exist predominantly in the half-chair conformation as shown in Scheme 5. The preferred axial attack by the hydride reagent is validated by Stevens' stereoelectronic principle. In addition, in this case, the hydride donor might be delivered to the stereoelectronically preferred face by a nearby directing group, such as a hydroxyl group.

Next, we focused our efforts on the construction of the A ring with the C-10 carboxylic group and the C-5 propanol moiety of **36a**. First, the hydroxyl group of **36a** was internally protected as the lactone by treatment with NaH (Scheme 6).



Scheme 5. Synthesis of reductive amination product **36**: a) MeI, K_2CO_3, acetone, reflux; b) O_3, MeOH/CH_2Cl_2, −78 °C, then Ph_3P, 0 °C, 81% (over two steps); c) **33**, NaH, THF, 0 °C to RT, 70%; d) H_2, Pd/C, MeOH, RT, 85%; e) i) TFA/CH_2Cl_2 (3:5), 0 °C to RT; ii) $NaCNBH_3$, AcOH, CH_3CN, −78 °C, 60%.



Scheme 6. Synthesis of polycitorol A and B: a) NaH, DMF, 0 °C to RT, 90%; b) TBAF, THF, 0 °C, 88%; c) Ph_3P, I_2, imidazole, CH_2Cl_2, 0 °C, 97%; d) *t*BuLi, Et_2O, −100 °C, 60%; e) hydrazine hydrate, KOH, ethylene glycol, 160 °C, 1 h, then 210 °C, 5 h, 65%; f) TFAA, THF, 120 °C, sealed tube, 90% brsm; TFAA = trifluoroacetic anhydride.

Deprotection of silyl ether **38** followed by Appel reaction of the resultant alcohol **39** yielded iodide **40**, which was subjected to halogen–metal exchange to effect anionic cyclization.[27] Treatment of **40** with *t*BuLi at very low temperature produced the desired tricyclic product **41** in 60% yield. Finally, compound **41** was converted to the proposed structure (i.e., polycitorol A (**5a**)) by Wolff–Kishner–Huang reduction[28] of its hindered carbonyl group at C-9. The transformation of the obtained compound **5a** into the polycitorol B (**5b**) proposed structure was realized using the protocol developed by Cossy and Pardo.[29] When **5a** was heated in a sealed tube with a catalytic amount of TFAA in THF, ring-expanded product **5b** was formed presumably via aziridinium intermediate **42**. In this reaction, only one stereoisomer was observed as the final product. The spectral data for **5a** and **5b** were in good agreement with the assigned structures. The identity of synthetic compound **5a** was further confirmed by comparison of the ^{1}H NMR spectra of its hydrochloride salt with the literature spectra of the hydrochloride salt of **43**[30] (Figure 2), which differ only in the length of the alkyl chain (i.e., hexyl vs. butyl).[18]

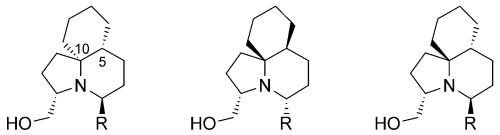


Figure 2. Structures of compounds **5a′**–**a″** and **43**–**45**.

However, the spectroscopic data for synthetic compounds **5a** and **5b** did not match those reported for the natural products.[6] These observations implied that the structures of the natural polycitorols had been assigned incorrectly. We envisioned that the stereochemical identity of natural polycitorol A could be deduced by comparison of its NMR spectral data with those for the diastereomers of lepadiformine A because the pattern of the NMR spectra of the butyl group is similar to that of the hexyl group. Thus, we compared the NMR spectroscopic data for polycitorol A with those for the reported isomers of lepadiformine A (**3a**). Of the eight possible diastereomers of **3a**, six have been synthesized and disclosed by several groups as part of their efforts toward the structural revision of the originally proposed lepadiformine A structure. Only two diastereomers (i.e., **44** and **45** in Figure 2) have not been reported. A thorough examination of the reported data of the six isomers with those of polycitorol A revealed only the differences. This implied that the configuration of one of the two previously unreported isomers is most likely that of natural polycitorol A. Our speculated structures of natural polycitorol A (i.e., **5a′** and **5a″**) might be assembled from Claisen rearrangement product **6c** by the appropriate combination of functional groups at C-10 and C-5. However, compound **6c** was the minor product of the reaction. Unfortunately, we were unable to reverse the diastereoselectivity. Therefore, our synthetic work toward elucidating the correct structure of the polycitorols was temporarily suspended.

Revised synthetic approach to (−)-lepadiformine and (−)-fasicularin

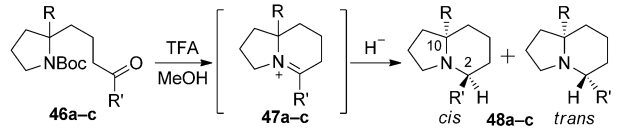
The ultimate goal of the second round of synthesis was to develop a more concise and selective synthesis of both (−)-lepadiformine A (**3a**) and (−)-fasicularin (**4**) from the same intermediate. In our preceding synthesis, the reductive amination of tricyclic substrate **29** resulted in the predominant formation of pyrroloquinoline **27b** (Scheme 4). Based on these results, we concluded that formation of the azaspirocyclic skeleton prior to the annulation of the B-ring by reductive amination does not appear to be an adequate synthetic route for controlling the C-2 stereochemistry of both epimers. Therefore, in the new approach, the formation of the A-ring was postponed until the B-ring of the tricyclic alkaloid was constructed by reductive amination.

Model system for a unified route to both (−)-lepadiformine (3a) and (−)-fasicularin (4)

Before starting the second round of total synthesis, an appropriate model system was developed to determine if the revised sequence would provide adequate control of the stereochemistry at C-2. Therefore, we chose pyrrolidine derivatives **46a**–**c**[18] (Table 2) as the reductive amination/cyclization precursors. The first model compound, **46a**, has no substituent at C-10 (lepadiformine numbering), while the second one, **46b**, has an ester substituent, similar to the real system. Compound **46c** has a hydroxyl methyl group protected with a nonchelating bulky silyl group at the C-10 position.

For the intramolecular reductive amination, the *N*-Boc protecting groups of the model compounds were removed with TFA to afford iminium salt **47**, and the resulting salt was subjected to various reduction conditions to yield indolizidines **48**. The results are summarized in Table 2. Regardless of the nature of the reducing agent, compound **46a**, which has no substituent at C-10, led to the exclusive formation of *cis*-**48a**, in which the C-10 and C-2 hydrogen atoms have a *cis* arrangement (Table 2, entries 1–5). However, when the reduction was performed with **46b**, which has a substituent at C-10, reagent-dependent stereoselectivity was observed. For example, upon addition of $NaCNBH_3$ at room temperature, indolizidine *cis*-**48b** was obtained as the major reductive amination product (entry 6). Higher selectivity was obtained at lower temperatures (entries 7 and 8). Reduction in THF yielded a higher selectivity than that in MeOH (entries 8 vs. 9). When $NaBH_4$ and $Na(OAc)_3BH$ were employed as the reducing agent, a high diastereofacial selectivity for *cis*-**48b** was also observed (entries 10 and 11). However, when iminium salt **47b** was treated with the bulky reducing agent L-Selectride, the diastereofacial selectivity was completely reversed (entry 12). Under these reduction conditions, indolizidine *trans*-**48b** was the major isomer and was obtained in a ratio of 1:11 with a combined yield of 75%. The reductive amination under catalytic hydrogenation condi-

Table 2. Model systems for reductive amination.



a : R = H, R' = C_6H_{13} **c** : R = $CH_2OTBDPS$, R' = CH_3

b : R = CO_2Me, R' = CH_3

Entry	Substrate	Reducing agent	Solvent	T [°C]	Yield [%],[a] *cis*/*trans*
1	**46a**	$NaCNBH_3$	MeOH	−40	78, 1:0
2	**46a**	$NaBH_4$	MeOH	−40	85, 1:0
3	**46a**	$Na(OAc)_3BH$	MeOH	−40	85, 1:0
4	**46a**	L-Selectride	THF	−78	80, 1:0
5	**46a**	Pd/C	MeOH	RT	90, 1:0
6	**46b**	$NaCNBH_3$	MeOH	RT	83, 5:1
7	**46b**	$NaCNBH_3$	MeOH	0	80, 7:1
8	**46b**	$NaCNBH_3$	MeOH	−40	92, 20:1
9	**46b**	$NaCNBH_3$	THF	−40	76%, 74:1
10	**46b**	$NaBH_4$	MeOH	−40	80, 9.4:1
11	**46b**	$Na(OAc)_3BH$	MeOH	−40	85, 7.3:1
12	**46b**	L-Selectride	THF	−78	75, 1:11
13	**46b**	Pd/C	MeOH	RT	73, 1:13
14	**46b**	$LiEt_3BH$	THF	−78	95, 1:2.4
15	**46c**	$NaCNBH_3$	MeOH	−40	89, 2.8:1
16	**46c**	$NaBH_4$	MeOH	−40	91, 5:1
17	**46c**	$Na(OAc)_3BH$	MeOH	−40	89, 2.4:1
18	**46c**	L-Selectride	THF	−78	80, 1:7.1
19	**46c**	$LiEt_3BH$	THF	−78	90, 1:2
20	**46c**	Pd/C	MeOH	RT	93, 1:22

[a] Yields and ratio were determined by GC analysis.

tions also yielded *trans*-**48b** as a major isomer with high selectivity (entry 13), while the reaction with $LiEt_3BH$ afforded low diastereoselectivity (entry 14). Substrate **46c** also exhibited reagent-dependent stereoselectivity (entries 15–20), and the diastereofacial selectivity pattern was the same as that observed for **46b**. However, the level of selectivity was generally lower, most likely due to the difference in the nature of the C-10 substituents, with the exception of the reaction involving catalytic hydrogenation (entry 20). This hydride reagent-dependent reversal of diastereofacial selectivity in the formation of indolizidine and similar ring systems has not been previously reported in the literature. This complete reversal of stereochemistry in the reductive amination reaction could be explained by both steric and stereoelectronic factors. Iminium salt **47** could exist in one of two half-chair conformations, **47A** and **47′B**, as shown in Figure 3. Our theoretical calculations predicted that **47A** was more stable than **47′B** regardless of the substituent at C-10.[31] Therefore, we expected that iminium salt **47** would exist predominantly in conformation **47A** at reaction temperature. According to the stereoelectronic principles delineated by Stevens,[25] the addition of the hydride reagent to the iminium moiety should occur from the stereoelectronically preferred face of **47A** (Figure 3, path a) via a chairlike transition state to yield *cis*-**48**. However, in the case of a bulky reducing agent, "axial attack" (Figure 3, path a) would be disfavored due to severe steric interactions between the incoming bulky reagent and the C-10 substituent group. Therefore, "equatorial attack"

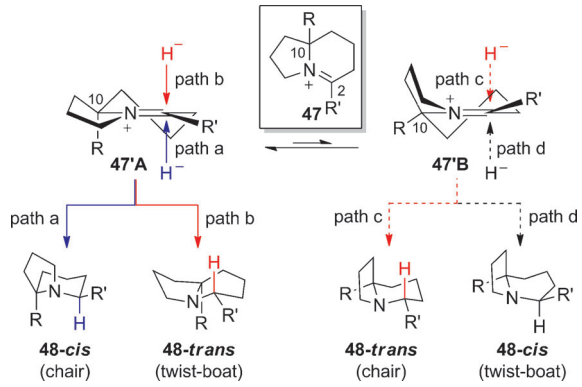


Figure 3. Two half-chair conformations of iminium salt **47** and reaction pathways to **48**.

(Figure 3, path b) through a twisted-boat conformation, which would lead to the formation of *trans*-**48**, might be more sterically favored in the case of a bulky hydride donor and C-10 substituted substrate.

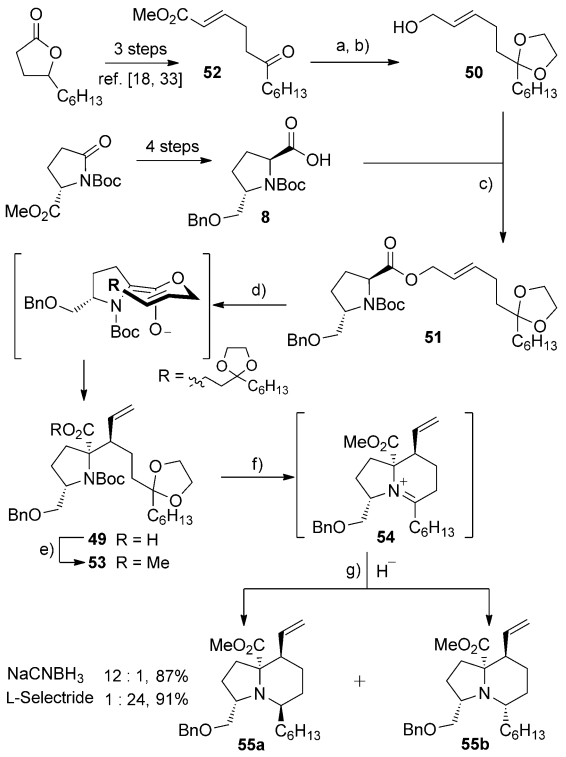
Another possible mechanistic path via the less stable conformer **47′B** cannot be completely ruled out. If the reaction rate through conformer **47A** is considerably slower than the interconversion rate of the two conformers, the reduction of the iminium ion by the bulky reducing agent would occur from the less stable conformer **47′B**, as stated by the Curtin–Hammett principle.[32] Therefore, it is not unreasonable to postulate that reduction by L-Selectride can also occur from the stereoelectronically preferred face of conformer **47′B** (Figure 3, path c) to yield indolizidine *trans*-**48**.

Synthesis of the B/C ring system of (−)-lepadiformine and (−)-fasicularin

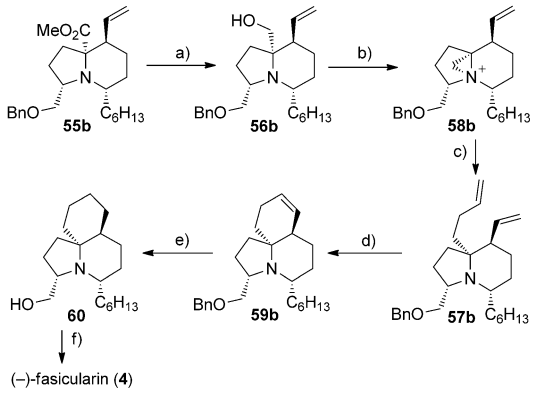
With the opportunity to access both C-2 epimers, we initiated the second round of total synthesis. In our new synthesis, instead of utilizing Claisen rearrangement product **6a**, a more elaborate rearrangement product **49** (Scheme 7) was devised for the concise synthesis. Therefore, our synthesis began with the preparation of allylic alcohol **50** for the new Claisen rearrangement substrate **51**. For the synthesis of **51**, we utilized known ketone **52**,[33] which was readily synthesized in three steps from commercially available γ-decanolactone. The ketone group of **52** was protected as the ethylene ketal, and the ester group was then reduced with DIBAL-H to provide allylic alcohol **50** in 77% overall yield.

Esterification of acid **8** with allylic alcohol **50** provided allylic ester **51** (88%). The ester–enolate Claisen rearrangement was accomplished using the previously described reaction conditions. Treatment of **51** with LiHMDS in THF at −78 °C and gradual warming to room temperature afforded, after esterification with $TMSCHN_2$, the desired rearrangement product **53** and a minor amount of its stereoisomer in 88% combined yield and 10:1 diastereoselectivity.

For the intramolecular reductive amination, the *N*-Boc and ketal protecting groups of **53** were simultaneously removed with TFA to yield iminium salt **54**. In light of the model system



Scheme 7. Synthesis of indolizidines **55a** and **55b** by using the ester–enolate Claisen rearrangement and reductive amination: a) ethylene glycol, PPTS, toluene, reflux; b) DIBAL-H, THF, −78 °C, 77% (over two steps); c) EDCI, DMAP, CH_2Cl_2, RT, 88%; d) LiHMDS, TBSCl, THF, −78 °C to RT; e) $TMSCHN_2$, MeOH, RT, 88% from **51**; f) TFA/CH_2Cl_2 (3:5), 0 °C to RT; g) conditions A: $NaCNBH_3$, MeOH, −78 °C, 87% from **53**, **55a**/**55b** = 12:1; conditions B: L-Selectride, THF, −78 °C, 91% from **53**, **55a**/**55b** = 1:24. PPTS = pyridinium *p*-toluenesulfonate, EDCI = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride, $TMSCHN_2$ = (trimethylsilyl)diazomethane.



Scheme 8. Completion of the synthesis of (−)-fasicularin: a) $LiAlH_4$, THF, −78 to 0 °C, 96%; b) MsCl, Et_3N, Et_2O, 0 °C; c) allylmagnesium bromide, CuI, THF, −78 °C to RT, 60% from **56b**; d) Grubbs II catalyst **21**, CH_2Cl_2, reflux, 90%; e) H_2, Pd/C, MeOH, RT, 92%; f) NH_4SCN, DEAD, Ph_3P, CH_2Cl_2, RT, 88%. MsCl = methanesulfonyl chloride.

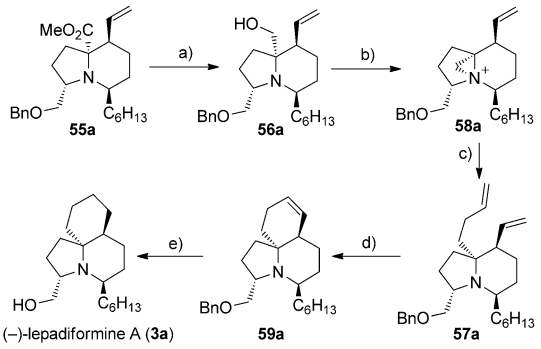
study, the resultant salt was treated with hydride reagents. When the reduction was performed with $NaCNBH_3$ at −78 °C, reductive amination product **55a** was obtained along with a minor amount of its stereoisomer **55b** in 87% combined yield and high diastereoselectivity (12:1).[34] When iminium salt **54** was treated with L-Selectride at −78 °C, the diastereofacial selectivity was completely inverted, which afforded indolizidine **55b** as the major isomer in a ratio of 1:24 and 91% combined yield.

Total synthesis of (−)-lepadiformine and (−)-fasicularin

After accomplishing the stereoselective formation of diastereoisomers **55a** and **55b**, we focused our efforts on the construction of the A-ring through an RCM reaction to complete the synthesis. For the total synthesis of (−)-fasicularin (**4**), the ester of **55b** was reduced with $LiAlH_4$ to the corresponding primary alcohol, **56b**, in 96% yield (Scheme 8). Despite considerable steric hindrance, we successfully converted the hydroxymethyl group of **56b** to the homoallyl group in **57b** with the assistance of the tertiary amine within the molecule. Treatment of **56b** with MsCl in the presence of Et_3N resulted in the unstable aziridinium salt **58b**, which was treated with allyl cuprate derived from allylmagnesium bromide and CuI. The allyl cuprate regioselectively attacked the reactive aziridinium ion at the methylene carbon atom to form desired RCM substrate **57b** in 60% yield over two steps. Although aziridinium ions are well-established intermediates,[35] their reactions with a carbon nucleophile are much less general and have been less widely applied in synthesis.[36] Therefore, we believe that this successful aziridinium-mediated carbon homologation at a sterically hindered position will increase the utility of the aziridinium ion in the synthesis of complex nitrogen-containing compounds.

The RCM of diene **57b** was successfully performed, furnishing the desired tricyclic compound **59b** in high yield (90%). Catalytic hydrogenation of **59b** over Pd/C resulted in the reduction of the olefinic bond and removal of the benzyl protecting group to yield tricyclic compound **60** in 92% yield. The spectroscopic data for compound **60** synthesized by this route were identical to those previously reported.[24] Completion of the synthesis was accomplished by employing the same reaction conditions as those previously described in the literature.[24] The spectral and optical rotation data for synthetic (−)-fasicularin (**4**) were in good agreement with the reported values.[5,24]

With the synthesis of (−)-fasicularin (**4**) accomplished, we next turned to the synthesis of (−)-lepadiformine A (**3a**) from indolizidine **55a** (Scheme 9). To construct the A-ring, we used the same methodology as for fasicularin. Therefore, the ester of **55a** was reduced to alcohol **56a** (97%). Again, aziridinium ion-mediated allylation provided the corresponding RCM substrate, **57a**, in 65% overall yield.[37] The RCM of diene **57a** followed by hydrogenation yielded (−)-lepadiformine A (80%), the spectral data of which (^1H and ^{13}C) were in complete agreement with those reported in the literature.[2a,24] The optical rotation of synthetic lepadiformine was also in agreement with that found in the literature.



Scheme 9. Completion of the synthesis of (−)-lepadiformine: a) $LiAlH_4$, THF, −78 to 0 °C, 97%; b) MsCl, Et_3N, Et_2O, 0 °C; c) allylmagnesium bromide, CuI, THF, −78 °C to RT, 65% from **56a**; d) Grubbs II catalyst **21**, CH_2Cl_2, reflux, 90%; e) H_2, Pd/C, MeOH, RT, 89%.

Conclusion

The planning and implementation of flexible, divergent total syntheses of pyrrolo-/pyrido[1,2-*j*]quinoline tricyclic marine alkaloids is presented. A functionally and stereochemically enriched intermediate was concisely and stereoselectively assembled by employing an ester–enolate Claisen rearrangement reaction of the cyclic amino acid allylic ester possessing an exocyclic *N*-carbonyl group. This common intermediate was readily converted to (−)-lepadiformine A, (−)-fasicularin, and the proposed structure of polycitorols A and B in a substrate-controlled manner. In these studies, we have demonstrated that the structure of polycitorols requires revision. With the more elaborate ester–enolate Claisen rearrangement product, the more concise and selective synthesis of both lepadiformine A and fasicularin was also achieved in a substrate- and reagent-controlled manner. One of the key features employed in these total syntheses was a hydride reagent-dependent reversal of diastereofacial selectivity in the formation of the indolizidine, which we believe is the first example of this occurrence. In addition, aziridinium-mediated carbon homologation of the hindered C-10 group into a homoallylic group greatly facilitated the synthesis.

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Keywords: aziridinium · diastereoselectivity · reductive amination · substrate and reagent control · total synthesis

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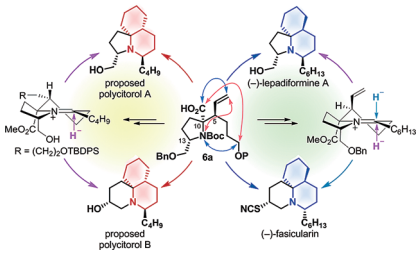
FULL PAPER

From one to four: The title marine natural products were synthesized in a completely substrate-controlled manner via a common intermediate derived from the amino acid ester–enolate Claisen rearrangement. The key step involves a reagent-dependent stereoselective reductive amination (see scheme).



Organic Chemistry

*J. In, S. Lee, Y. Kwon, S. Kim**

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Divergent Total Synthesis of the Tricyclic Marine Alkaloids Lepadiformine, Fasicularin, and Isomers of Polycitorols by Reagent-Controlled Diastereoselective Reductive Amination