Organic LETTERS

Letter

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Asymmetric Total Synthesis of Lepadiformine C Using Memory of Chirality in an Intramolecular Ester Enolate Michael Addition

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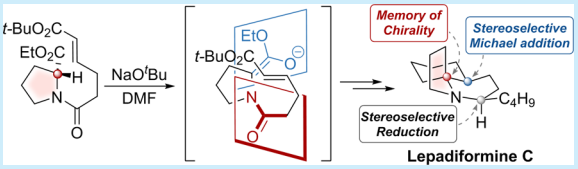
Supporting Information

ABSTRACT: The asymmetric synthesis of lepadiformine C was achieved using D-proline as the only chiral source. The synthetic strategy features the use of the principle of "memory of chirality" in an intramolecular Michael addition to construct the bicyclic intermediate without the aid of external chiral sources. A brief mechanistic rationale is presented to account for the stereochemical outcome.



Lepadiformine C (**1**, Figure 1) is a tricyclic marine alkaloid with a perhydropyrrolo[1,2-*j*]quinoline ring system. This

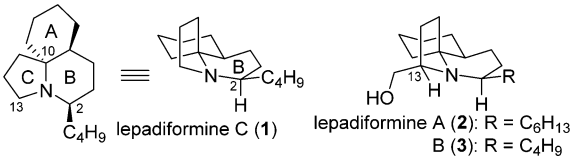


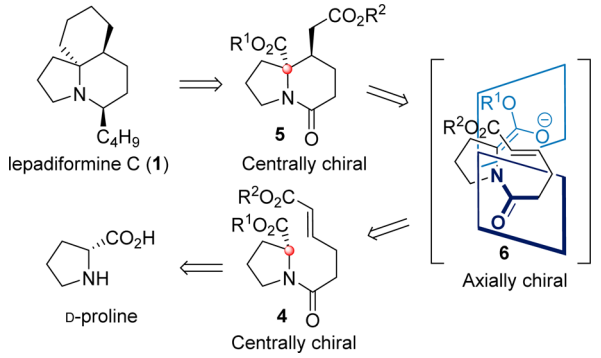
Figure 1. Structures of lepadiformines (**1**–**3**).

alkaloid was isolated from the tunicate *Clavelina moluccensis* together with its congeners, lepadiformine A (**2**) and B (**3**), each of which has a hydroxymethyl group at C-13.[1] Despite only a few reported biological effects,[1b,c] these tricyclic alkaloids have been the subject of extensive synthetic studies due to their intriguing structural features.[2−4] The construction of the tricycle framework characterized by the *trans*-1-azadecalin A/B ring and the AC spiro-cyclic ring system is the primary synthetic challenge posed by the lepadiformines. While the total synthesis of lepadiformine A has been published numerous times,[3] only a few total syntheses have been reported for lepadiformine C.[4] In this paper, we report the stereoselective asymmetric synthesis of lepadiformine C (**1**) using the amino acid D-proline as the only chiral source.

As outlined in Scheme 1, we envisioned that the intramolecular Michael addition[5] of proline ester **4** would provide bicyclic compound **5**, putting in place the substituents necessary for the formation of the A ring of lepadiformine C (**1**). If the central chirality in the proline moiety of **4** was transformed into the axial chirality in the enolate intermediate **6**, and the transient axial chirality was transferred back to central chirality in product **5**, the asymmetric synthesis could be achieved from D-proline without the aid of external chiral sources.

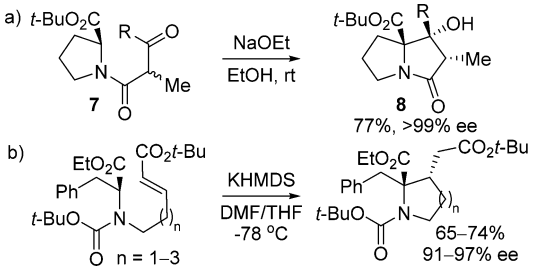
The use of "memory of chirality" (MOC) is an attractive strategy for asymmetric synthesis.[6,7] However, MOC has thus far found limited applications in total synthesis.[8] Recently, we

Scheme 1. Retrosynthetic Analysis of Lepadiformine C (1)



have reported the total synthesis of (−)-penibruguieramine A using the MOC phenomenon.[8b] MOC was utilized during the intramolecular aldol reaction of proline ester **7** to afford the bicyclic product **8** with the correct absolute and relative configuration required to proceed to the natural product (Scheme 2a). Successful examples of MOC in the intramolecular Michael addition of *α*-amino ester enolates have been reported by Kawabata, in which a bulky *N*-*tert*-butoxycarbonyl (Boc) group is essential for the generation of

Scheme 2. Previously Reported Related MOC Phenomena



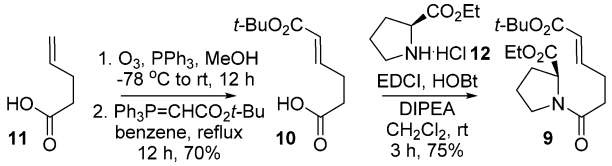
Received: November 28, 2016

DOI: 10.1021/acs.orglett.6b03550
Org. Lett. XXXX, XXX, XXX−XXX

the axial chirality in the enolate intermediate (Scheme 2b).[9] Based on these precedents, we anticipated a successful MOC in the intramolecular Michael reaction of proline ester **4**.

Another concern for this MOC-Michael reaction strategy is the resulting diastereoselectivity. A computational study indicated that the desired *trans*-Michael adduct **5** is not thermodynamically favored over the *cis*-isomer (see Supporting Information (SI)), which suggested that the reaction should be carried out under kinetic control for the formation of the *trans* isomer. We postulated kinetically relevant transition states for this reaction (*vide infra*) and eventually designed the Michael substrate **9** (Scheme 3).

Scheme 3. Synthesis of Michael Substrate 9



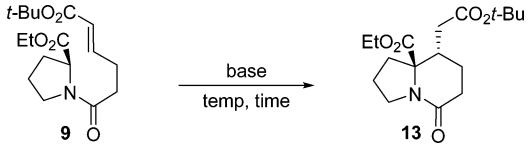
Our study commenced with the preparation of substrate **9** for the key Michael reaction. The known acid **10**[10] with a *tert*-butyl enoate group was readily prepared from commercial γ,δ-unsaturated acid **11** via sequential ozonolysis and Wittig olefination. The obtained acid **10** was condensed with L-proline ethyl ester (**12**) instead of the less common D-enantiomer. The HOBt/EDCI-mediated coupling afforded **9** without erosion of enantiomeric purity.

With compound **9** in hand, we investigated the intramolecular Michael reaction with the aim of obtaining of the desired diastereo- and enantioselective outcome. In addition to the envisioned intramolecular Michael reaction, **9** can also undergo other competitive intra- and intermolecular side reactions, including Dieckmann-type condensations,[11] due to the presence of multiple enolizable carbonyl groups. Thus, a judicious choice of base and reaction conditions was necessary to obtain the desired product.

Various bases and conditions were screened; the results are listed in Table 1. A promising result was obtained when substrate **9** was treated with *tert*-butoxide as a base. The reaction with 1.1 equiv of NaO^{t}Bu at rt in DMF rapidly yielded the bicyclic compound **13** as a single diastereomer in 82% yield (entry 1). The reaction took place also when KO^{t}Bu was used as a base (entry 2), but the yield of **13** was significantly lower because of the formation of substantial amounts of polar side products which were difficult to characterize. When LiO^{t}Bu was used, no reaction occurred and only starting material was recovered (entry 3). These results indicated the marked influence of the countercation on the success of intramolecular Michael reaction. This countercation effect may be due to the subtle difference in basicity between alkali metal *tert*-butoxides.[12] The *trans* relative stereochemistry of **13** was determined by 2D NMR analysis (see SI). The enantiomeric excess of **13** was determined to be 88% by chiral HPLC analysis upon conversion to a UV-active thioamide derivative (see SI and Scheme 6). This result indicated that MOC was exerted during the intramolecular Michael addition of **9**.

To enhance the degree of chirality preservation, the reaction conditions using NaO^{t}Bu were further optimized. Changing the amount of NaO^{t}Bu did not alter the enantiomeric purity of product (entries 4 and 5). Changing the solvent system from

Table 1. Reaction Conditions for Michael Addition of 9[a]



entry	base (equiv)	temp	time	yield (%)[b]	ee (%)[c]
1	NaO^{t}Bu (1.1)	rt	10 min	82	88
2	KO^{t}Bu (1.1)	rt	3 h	45	88
3	LiO^{t}Bu (1.1)	rt	12 h	0	–
4	NaO^{t}Bu (3)	rt	10 min	71	89
5	NaO^{t}Bu (0.5)	rt	2 h	69	89
6	NaO^{t}Bu (1.1)	0 °C	2 h	76	92
7	NaO^{t}Bu (1.1)	−20 °C	12 h	62	95
8	NaO^{t}Bu (1.1)	−40 °C	72 h	23	98
9	NaOEt (1.1)	rt	12 h	77	89
10[d]	NaHMDS (3)	−78 °C	1 h	48	94

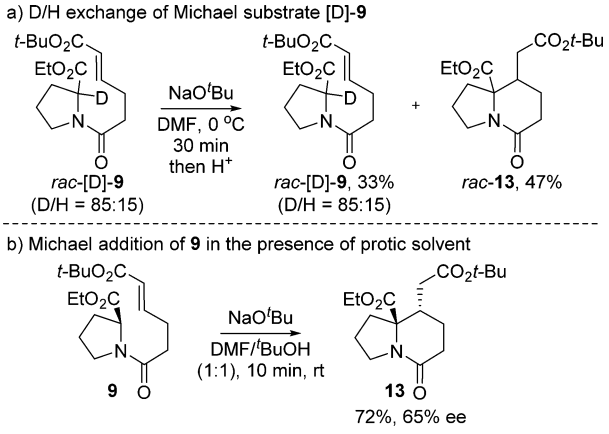
[a]Reactions were performed with **9** (50 mg, 0.15 mmol) at a substrate concentration of 0.01 M in DMF. [b]Yield was estimated from the ^{1}H analysis. [c]Enantiomeric excess was determined by chiral HPLC analysis of thioamide derivative from **13**. [d]THF was used as the reaction solvent.

DMF only led to a lower enantiomeric purity and yield (see SI). When the temperature was decreased, the enantiomeric purity of the product increased (entries 6−8), albeit to the detriment of the reaction rate and yield; the enantiomeric purity of the reaction with NaO^{t}Bu at −20 °C was greater than 95% with a yield of 62%. NaOEt also yielded the desired **13** without significant loss of yield (entry 9). On the other hand, the strong base NaHMDS resulted in an intractable mixture of side products and a low yield of product **13**, although the reaction at −78 °C delivered the product in high (94%) ee (entry 10).[13]

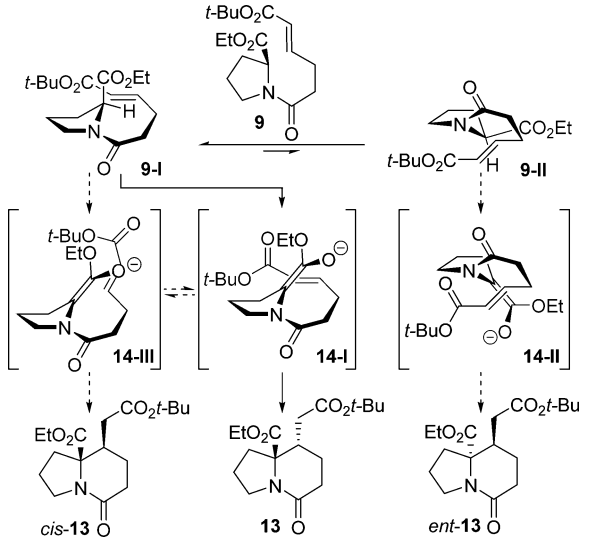
To understand the stereochemical outcome of the intramolecular Michael addition of **9**, we performed additional experiments. Resubjection of *trans* Michael product **13** to the reaction conditions resulted in no change in the product profile; the enantiomeric purity of **13** remained unchanged, and the *cis* diastereomer was not formed (see SI). This result suggested that the above Michael reaction is irreversible.[14] We analyzed the remaining substrate in the incomplete reaction mixture from the reaction of entry 6 in Table 1 and found that the proline stereocenter of the stating material was not racemized (see SI). The deuterium level at the proline stereocenter remained the same (Scheme 4a). These results suggested that any ester enolate intermediate is rapidly converted to the Michael product. When the reaction was performed in the presence of an external proton source, the enantiomeric purity of product was significantly reduced. For example, the enantiomeric purity of the product from the reaction in DMF/^{t}BuOH (1:1) at rt was only 65% (Scheme 4b). Based on these observations together with the obtained MOC results, a Michael reaction mechanism was proposed as depicted in Scheme 5. The axially chiral enolate **14-I** (with an arbitrary enolate geometry) is formed selectively over **14-II** via the favored conformer **9-I** with minimized 1,3-allylic strain. The transient ester enolate **14-I** undergoes Michael addition prior to the racemization of axial chirality. The reaction via conformer **14-III**, which leads to the formation of the *cis*-isomer, is less favorable due to steric repulsion between the proline moiety and the *tert*-butyl enoate group.

DOI: 10.1021/acs.orglett.6b03550
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Exploratory Studies To Determine the Intramolecular Michael Addition Mechanism



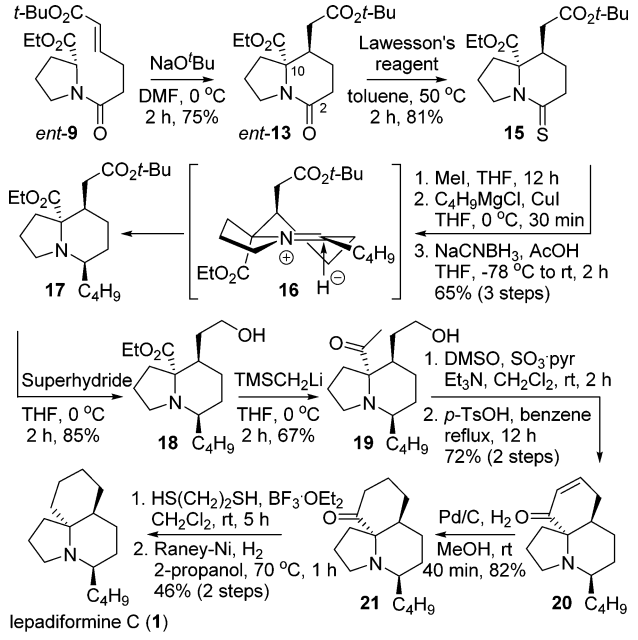
Scheme 5. Proposed Mechanistic Route for the Michael Addition



Having achieved the diastereo- and enantioselective intramolecular Michael reaction of proline ester **9**, we next focused on the total synthesis of lepadiformine C (**1**). To this end, the enantiomer of bicyclic compound **13** was prepared in 93% ee from *ent*-**9** using the conditions in entry 6 of Table 1 (Scheme 6). For the introduction of the butyl group at C-2 (natural product numbering), the amide group of *ent*-**13** was first converted to the thioamide with Lawesson's reagent. Methylation of thioamide **15** and treatment of the resulting thioiminium salt with *n*-butyl cuprate, followed by reduction of iminium intermediate **16** with $NaCNBH_3$, afforded indolizidine **17** as a single diastereomer in 62% yield over three steps.[15] The diastereofacial selectivity is a consequence of the preferred axial attack of the hydride on the half-chair iminium intermediate **16**.[16]

The A ring was constructed from the two ester groups on **17**. The *tert*-butyl ester group was reduced with Superhydride to the corresponding primary alcohol **18**, and the sterically hindered C-10 ester group was converted to a methyl ketone group with (trimethylsilyl)methyllithium to give **19**.[17] A Parikh–Doering oxidation of the primary alcohol in **19**, followed by an acid-catalyzed intramolecular aldol condensation, afforded the desired tricyclic product **20** in good overall

Scheme 6. Total Synthesis of Lepadiformine C (1)



yield. The final task in completing the synthesis was the removal of the enone functionality in the A ring. This was accomplished expediently via three steps that included the double bond hydrogenation of the enone, thioketalization, and reduction of the thioketal with Raney nickel.[18] The spectral and optical rotation data of the synthetic lepadiformine C (**1**) were in good agreement with those previously reported.[1c,4]

In this study, using the principles of "memory of chirality" (MOC), we successfully achieved a concise asymmetric total synthesis of lepadiformine C (**1**). Proline was the only chiral source, and all stereocenters were established without the aid of an external chiral influence. The key synthetic sequence was the intramolecular Michael reaction of proline-amide **9**, which proceeded with a high level of chirality preservation and with complete diastereoselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03550.

Copies of ^{1}H and ^{13}C NMR spectra of all new compounds and preparation of starting materials (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Mid-Career Researcher Program (NRF-2016R1A2A1A05005375) of the National

DOI: 10.1021/acs.orglett.6b03550
Org. Lett. XXXX, XXX, XXX−XXX

Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP). This work was also supported by Basic Science Research Program (NRF-2016R1A6A3A01013304) through the NRF funded by the Ministry of Education.

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DOI: 10.1021/acs.orglett.6b03550
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