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Asymmetric Total Synthesis of (-)-Stemonamine and its Stereochemical Stability

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Key Words: Alkaloids; Asymmetric synthesis; Total synthesis; Ynolate; Dieckmann condensation

Abstract: The first asymmetric total synthesis of (-)-stemonamine is described. The key reactions included intramolecular acylation to construct the seven-membered ring and a tandem [2+2] cycloaddition-Dieckmann condensation reaction using an ynolate to form the fully substituted cyclopentenone moiety. Racemization and epimerization of the natural product were first experimentally demonstrated.

Natural products are usually produced in an optically pure form of only one enantiomer, because the stereochemistry of natural products is strictly controlled during biosynthesis processes.[1] It is also well known that both enantiomers of natural products can be produced in different organisms.[2] However, the production of a racemic or a scalemic mixture from a single organism only occurs in rare cases.[3] For example, some natural products have optically unstable structures. Thus, racemization can occur both in nature and during isolation of compounds even if the compounds are produced in their optically pure forms.[4]

Optically unstable natural products have attracted much interest, in particular, stemonamine (**1**),[5] which has interesting structural features such as sterically hindered consecutive spiro-quaternary centers and a fused ring system containing a fully substituted cyclopentanone (A ring), a pyrrolidine (B ring), an azepane (C ring), and a butenolide (D ring). Stemonamine is one of the *Stemona* alkaloids,[6] which can be isolated from plants belonging to the Stemonaceae family. These alkaloids consist of more than 140 compounds that can be classified into eight structural groups based on the connection and the number of rings and side chains.[6b] Stemonamine group, one of

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these groups, includes stemonamine (**1**), isostemonamine (**2**),[5] stemonamide (**3**),[5b] maistemonine (**4**),[5b,7] and other related compounds (Figure 1).[8] Intriguingly, although alkaloids **1–4** were isolated from the root of *Stemona japonica Miq.,* which has been used as traditional Chinese medicine for curing respiratory diseases and infections with worms, only stemonamine and its diastereomer, isostemonamine have been isolated as racemates.[5] Therefore, it was anticipated that these two alkaloids could have both a racemic and an epimeric pathway from one to the other via a retro-Mannich/Mannich type intermediate **5**.[5a] Although the total synthesis of racemic stemonamine has been reported by Tu/Zhang et al. and Ishibashi et al.,[9] no subsequent work has been carried out to explore the stereochemical stability of stemonamine. Ishibashi et al. have reported that both stemonamine and isostemonamine were obtained from a single synthetic intermediate, which has an identical stereochemistry to isostemonamine.[9d] This supports the fact that stemonamine can be epimerized to isostemonamine, but there are still questions regarding its stereochemical stability, including the kinetics of the interconversion process. Moreover, since nonracemic stemonamine has not yet been obtained, the racemization of stemonamine is yet to be demonstrated experimentally.

Thus, the complex structure and unexplored stereochemical stability of stemonamine prompted an investigation into its asymmetric synthesis. This was anticipated to be challenging because of the possibility of the racemization of synthetic intermediates and the product itself, and also because this would provide information about the fundamental physical properties of stemonamine such as specific optical rotation, which is otherwise difficult to obtain. Herein, we report the first total synthesis of (-)-stemonamine using an intermolecular acylation and an ynolate-initiated tandem reaction. Furthermore, the study provides a better understanding of the stereochemical stability of stemonamine and the kinetics of its interconversion between enantiomeric and diastereomeric forms.

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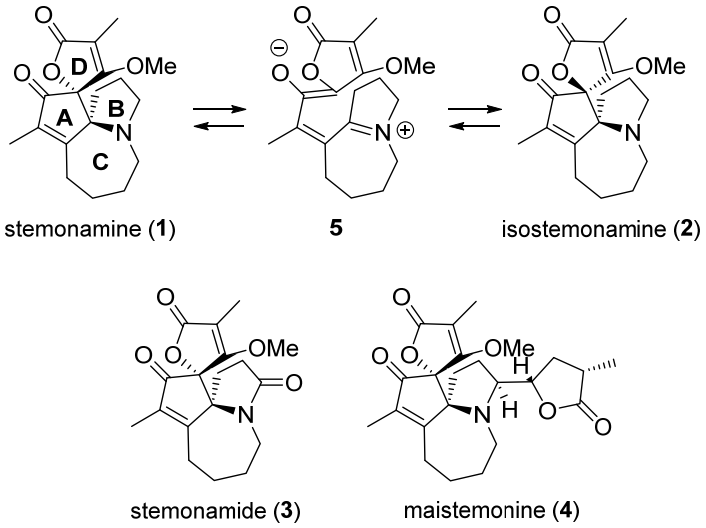

Figure 1. *Stemona* alkaloids and the proposed interconversion mechanism between stemonamine (**1**) and isostemonamine (**2**).

The retrosynthetic pathway to stemonamine (**1**) is shown in Scheme 1. The D-ring was constructed using a modified version of the procedure reported by Tu and Zhang.[10] To obtain the key intermediate **6**, we utilized two unique reactions developed by our group. The cyclopentenone moiety (A ring) could be formed by an ynolate (**8**)-initiated tandem [2+2] cycloaddition-Dieckmann condensation reaction[11] of ketoester **7**. This reaction is regarded as a formal [4+1]-type annulation, which is generally suitable for the synthesis of sterically crowded, multisubstituted cycloalkenones. Since seven membered rings are not always synthesized in high yield,[12] we decided to use an intramolecular acylation of iodide **9** for construction of the seven membered ring of **7**. This approach was derived from an analogous reaction used to construct the seven membered ring in our total synthesis of sundiversifolide.[13] Iodide **9** could be prepared from proline derivative **10** and hydroxylactone **11**, both of which are readily available as an optically active form.

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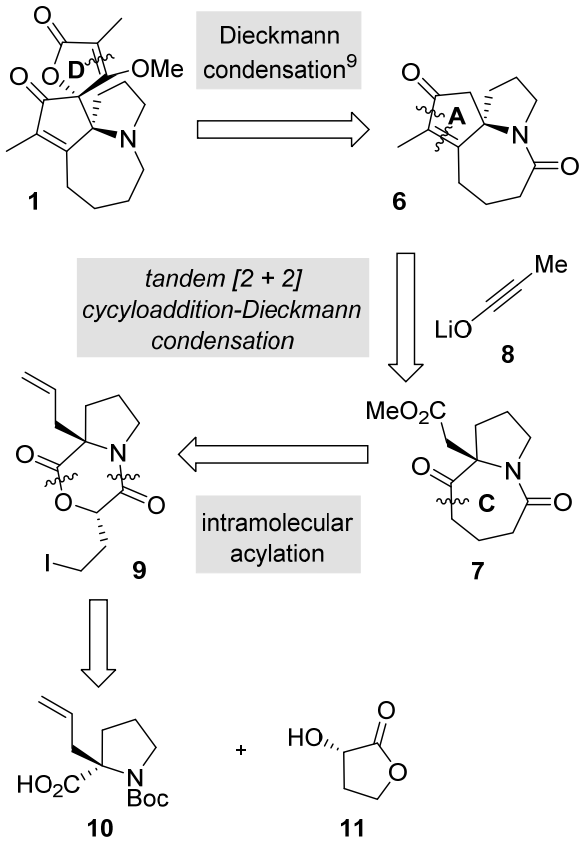

Scheme 1. Retrosynthetic analysis of (-)-stemonamine (**1**)

The first step of the synthesis is a condensation reaction of proline derivative **10** with hydroxylactone **11**, both of which are easily prepared from *L*-proline[14] and *L*-malic acid,[15] respectively (Scheme 2). The sequential removal of the Boc group of ester **12** and the subsequent lactamization afforded lactam **13** in high yield. After several attempts to directly transform alcohol **13** into the corresponding iodide **9**, the method developed by Khazdooz (using P_2O_5 and KI)[16] was found to be suitable as it could be scaled up easily, affording good yield and easy purification.

Next, the first key reaction was carried out. The intramolecular acylation of iodide **9** via lithiated intermediate **14** (formed using *t*BuLi at -78 °C), successfully provided seven-membered hemiacetal **15**. Optimization of the reaction conditions afforded the product in 91% yield, even on over 10 mmol scales.

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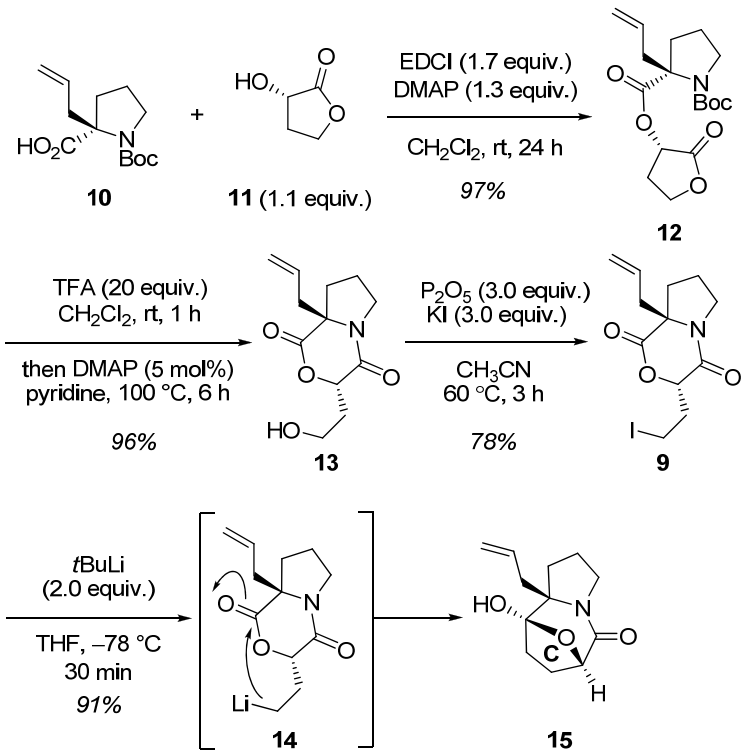

Scheme 2. Synthesis of hemiacetal intermediate **15**.

The next step involved the reductive removal of the α-oxygen atom adjacent to the carbonyl group of lactam **15** (Scheme 3). Interestingly, the equilibrium between the hemiacetal and the ketol forms of 1**5** emphatically favored the hemiacetal form, resulting in **15**, which shows a low propensity for acetal-opening reactions. After numerous attempts, the Appel reaction[17] followed by the reductive removal of the iodo group provided compound **17** in high yield (see Scheme 3). The terminal olefin **17** was subjected to oxidative cleavage, followed by methylation using $TMSCHN_2$ to form ketoester **7**.

In an effort to construct the cyclopentenone moiety (A ring), an ynolate-initiated tandem reaction was investigated as the second key reaction (Scheme 3). Ketoester **7** was subjected to a tandem reaction initiated by ynolate **8**, generated from α,α-dibromoester **18**[18] using the procedure developed by our group.[19] Without purification, the resulting *β*-lactone **19** was further treated with silica gel (pH = 6.0 ± 1.0) to facilitate decarboxylation, which afforded tricyclic intermediate **6** in 88% yield over two steps. It is noteworthy that the ynolate was able to react with the sterically hindered ketone moiety (adjacent to a quaternary carbon) even at temperatures as low as

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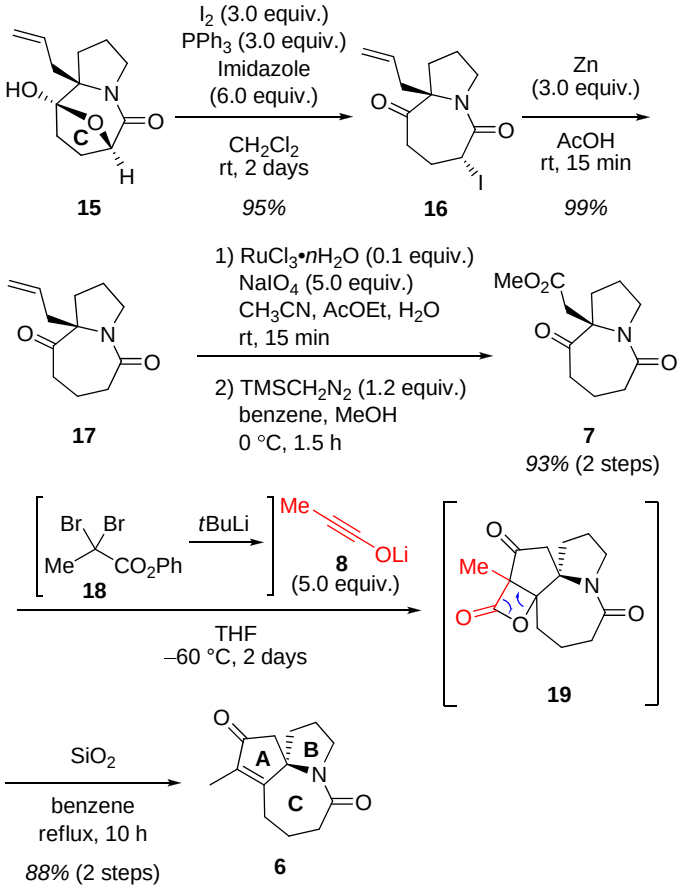
-60 °C, demonstrating the high reactivity of ynolates.



Scheme 3. Synthesis of key intermediate **6**.

With key intermediate **6** in hand, construction of the butenolide moiety (D ring) was attempted, based on the work carried out by Tu and Zhang[10] (Scheme 4). An aldol reaction of **6** with propanal using LiHMDS diastereoselectively formed alcohol **20**. A Dess-Martin oxidation afforded 1,3-diketone **21**, which was treated with cerium trichloride under an oxygen atmosphere[20] to form α-oxidized products **22** and **23** in 4:1 d.r., along with unidentified chlorinated products **24**. Compound **22**, with the desired stereochemistry, was then converted into carbonate **25** using ethyl chloroformate and DMAP.[21] A Dieckmann condensation reaction of **25** using KHMDS followed by methylation afforded the tetracyclic product **26** in 62% yield over two steps; however, an enantiomeric excess of 61% was obtained for **26**. The optical purity of **25** could not be verified;[22] it is possible that the racemization process may initiate over the course of the synthesis, and/or that the basic conditions used for the Dieckmann condensation reaction may cause racemization through the ring-opening process (see the

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Supplementary Information). Thiolactamization of **26** using Lawesson's reagent followed by recrystallization provided thioamide **27** in 80% ee. As the final step, reduction of the thiocarbonyl group using Raney Ni afforded stemonamine (**1**). However, work-up under room temperature conditions and purification with silica gel column chromatography gave a completely racemic mixture of stemonamine, along with significant amounts of isostemonamine (combined yield: 89%). HPLC analysis of the products using a chiral column (CHIRALPAK AD) revealed that stemonamine easily racemizes and epimerizes during the chromatography process; this is likely due to the acidity of silica gel, and furthermore the compound has a tendency to racemize gradually in solution at room temperature (*vide infra*). Therefore, following the reduction using Raney Ni, a rapid work-up was carried out under low-temperature conditions, which afforded optically active (-)-stemonamine (**1**) with a significant specific optical rotation ($[\alpha]^{23}_{D}$ = -47) and optical purity (58% ee), although with the co-occurrence of (-)-isostemonamine (**2**, 2%,[23] 55% ee). The HPLC separation of the product using a chiral column (CHIRALPAK AD-H) provided more optically active (-)-stemonamine, with 98% ee and $[\alpha]^{23}_{D}$ = -75.

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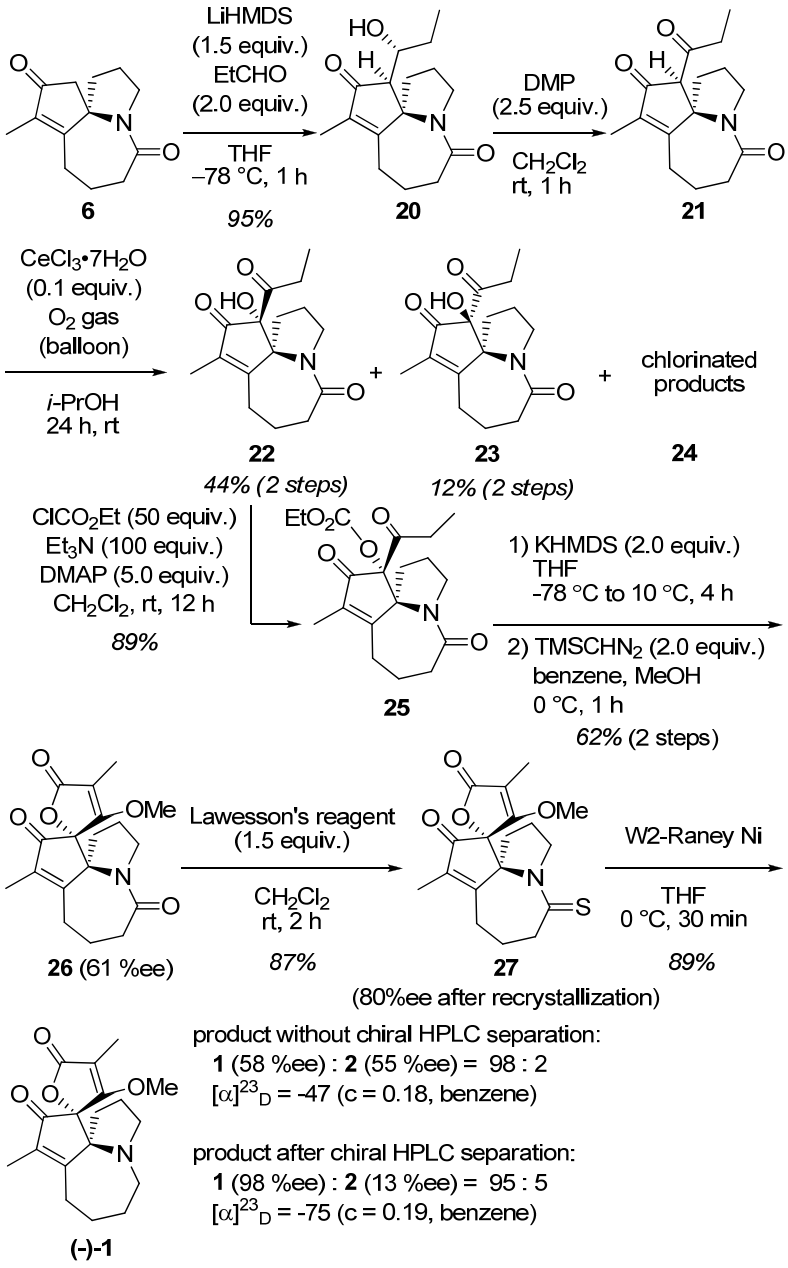

Scheme 4. Synthetic route to (-)-stemonamine.

The "apparent" rate constants and half-lives of the racemization and epimerization reactions[24] were determined under several conditions (Tables 1). It was found that (-)-stemonamine racemizes faster in protic solvents than in aprotic solvents (entries 1-7), and the process in 20% isopropanol/hexane speeds up higher temperature (entries 1, 3, 4 and 5). Moreover, the epimerization to (±)-isostemonamine was found to proceed much slower than the racemization (entries 1, 3 and 4). This is reasonable because the epimerization via intermediate **5** requires rotation of bond *A*, which has more

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double-bond character, while racemization requires rotation around bond *B*, which has more single-bond character (Scheme 5). In addition, the steric effect of the B ring is expected to affect the rotation of bond *B* more than that of bond *A*. The equilibrium ratio of stemonamine and isostemonamine (80 °C, in isopropanol) was also revealed to be 2:1 (equilibrium constant: K_c = 0.50), which indicates that stemonamine is more thermodynamically stable than isostemonamine.

Table 1. Rate constants and half-lives of racemization (ee) of (-)-**1** and epimerization of (±)-**1** into (±)-**2**.

			racemization		epimerization	
entry	solvent	temp.	k (10^{-4} s^{-1})	half-life	k (10^{-4} s^{-1})	half-life
1	20% isopropanol in hexane	60 °C	0.74	2.6 h	0.026	74 h
2	isopropanol	25 °C	0.54	3.6 h	-[a]	-[a]
3	20% isopropanol in hexane	45 °C	0.22	9.0 h	0.0071	270 h
4	20% isopropanol in hexane	25 °C	0.035	55 h	<0.0015	>1000 h
5	20% isopropanol in hexane	10 °C	0.0097	200 h	-[a]	-[a]
6	toluene	25 °C	0.0078	250 h	-[a]	-[a]
7	$CHCl_3$	25 °C	0.0072	270 h	-[a]	-[a]

[a] not determined.

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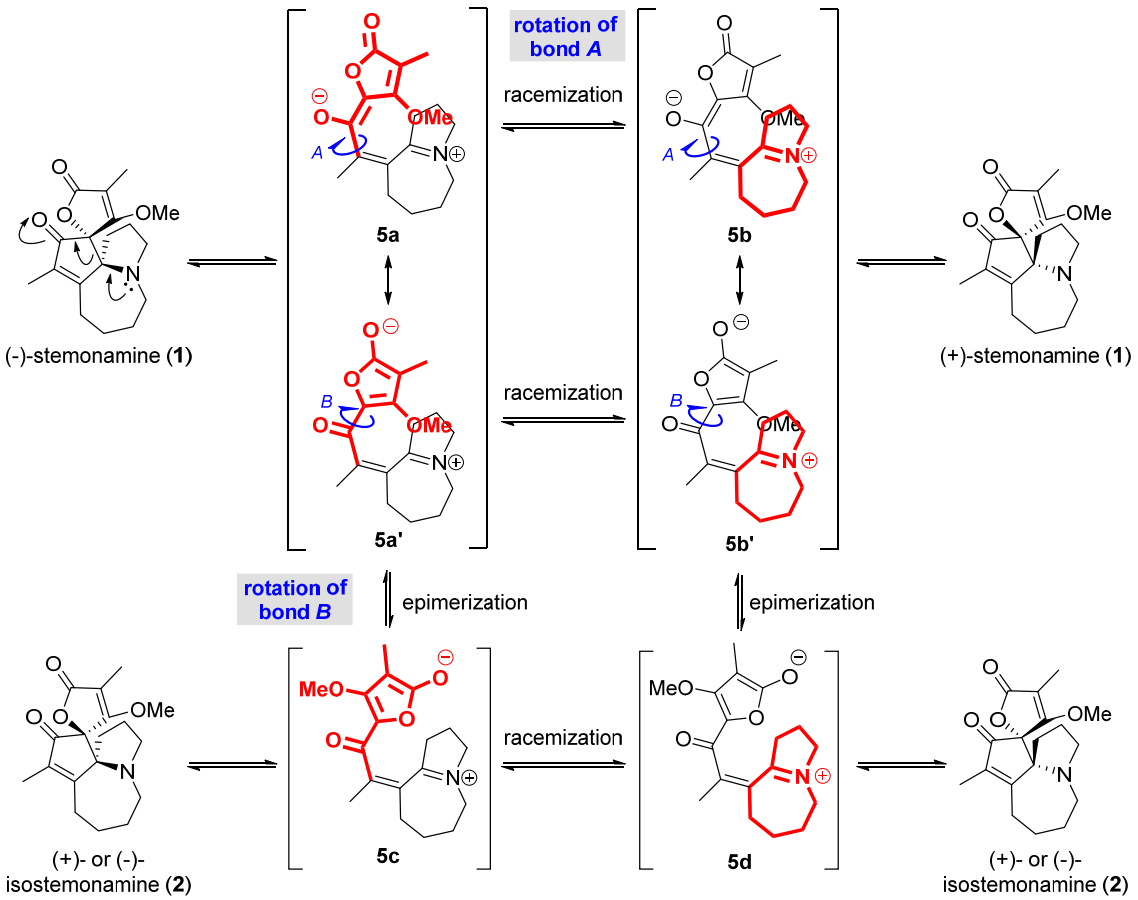

Scheme 5. Proposed mechanisms for racemization and epimerization.

In conclusion, the first total synthesis of nonracemic (-)-stemonamine is achieved in 17 steps from known compounds. Key reactions included the intramolecular acylation reactionand the ynolate-initiated tandem [2+2] cycloaddition-Dieckmann condensation reaction,. Although the obtained natural product stemonamine **1** was not enantiopure because it is optically unstable, racemization and epimerization of stemonamine were verified experimentally, and the half-lives of the constituent processes were successfully determined. The optical rotation of the enantio-enriched natural product was also demonstrated, and thus the absolute configuration was assigned. The investigation of the biological activity of stemonamine is under progress and the results will be reported in due course.

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Research Promotion Program for Agriculture, Forestry, Fisheries and Food industry (M.S.) and the MEXT Project of "Integrated Research Consortium on Chemical Sciences" (T.I.). This work was performed under the Cooperative Research Program of "Network Joint Research Center for Materials and Devices." We thank Mr. T. Matsumoto at Kyushu University for the X-ray crystal structure analyses. We are grateful to Prof. K. Tomooka, and Dr. K. Igawa at Kyushu University for instruction in the chiral HPLC analysis and determination of half-lives.

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[21] This reaction was accelerated when solvent amount of ethyl chloroformate and trimethylamine were used.

[22] Chiral HPLC analysis of **20**, **21**, **22**, **23**, and **25** was attempted to determine their optical purity, but only a single peak was detected under all conditions.

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[23] The yield was estimated by chiral HPLC analysis.
[24] The rate constants and the half-lives shown in this report are not real values because the racemization and the epimerization occur at the same time.