

HETEROCYCLES, Vol. 97, No. 2, 2018, pp. 712 - 718. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 16th February, 2018, Accepted, 16th March, 2018, Published online, 29th March, 2018
DOI: 10.3987/COM-18-S(T)71

FIRST ASYMMETRIC TOTAL SYNTHESIS OF (–)-ISOSTEMONAMINE AND KINETIC ANALYSIS OF ITS ISOMERIZATIONS

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Dedicated to Professor Kiyoshi Tomioka on the occasion of his 70th birthday

Abstract – The first asymmetric total synthesis of (–)-isostemonamine is reported herein. The key reactions include the regioselective oxidation of the diketone, which is reported to be an intermediate in our synthesis of (–)-stemonamine. The chiral high-performance liquid chromatography (HPLC) analysis of the racemization and epimerization of (–)-isostemonamine revealed that isostemonamine isomerizes significantly faster than stemonamine.

Racemic natural products isolated from single organisms are relatively rare because their stereochemistry is strictly controlled in a biosynthesis process.¹ However, several natural products are known to be racemized.² We are interested in these class of natural products, particularly, two of the stemona alkaloids.

Over 140 stemona alkaloids have been isolated from plants belonging to the Stemonaceae family. These plants are used as traditional Chinese medicine for treating respiratory diseases and infections with worms.³ The alkaloids have a pyrrolo[1,2-*a*]azepine core as a common scaffold and are classified into eight groups according to their structural features. Among these, the stemonamine group^{4,5} includes the representative alkaloid, stemonamine (**1**, Figure 1), which has a complex structure including consecutive quaternary centers and tetracyclic skeleton such as a fully substituted cyclopentenone (A ring), pyrrolidine (B ring), azepane (C ring), and butenolide (D ring).⁴ The other alkaloid, isostemonamine (**2**), is a diastereomer of stemonamine, having a different stereochemistry at the D ring.⁴ These two alkaloids were expected to racemize and epimerize to each other on the basis of the fact that both are isolated from the root of *Stemona japonica* Miq. as racemates.⁴

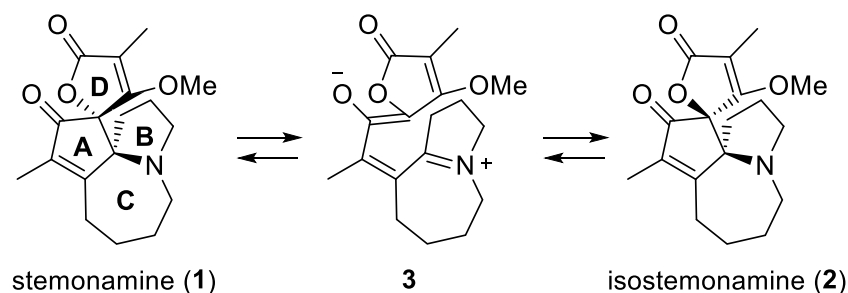
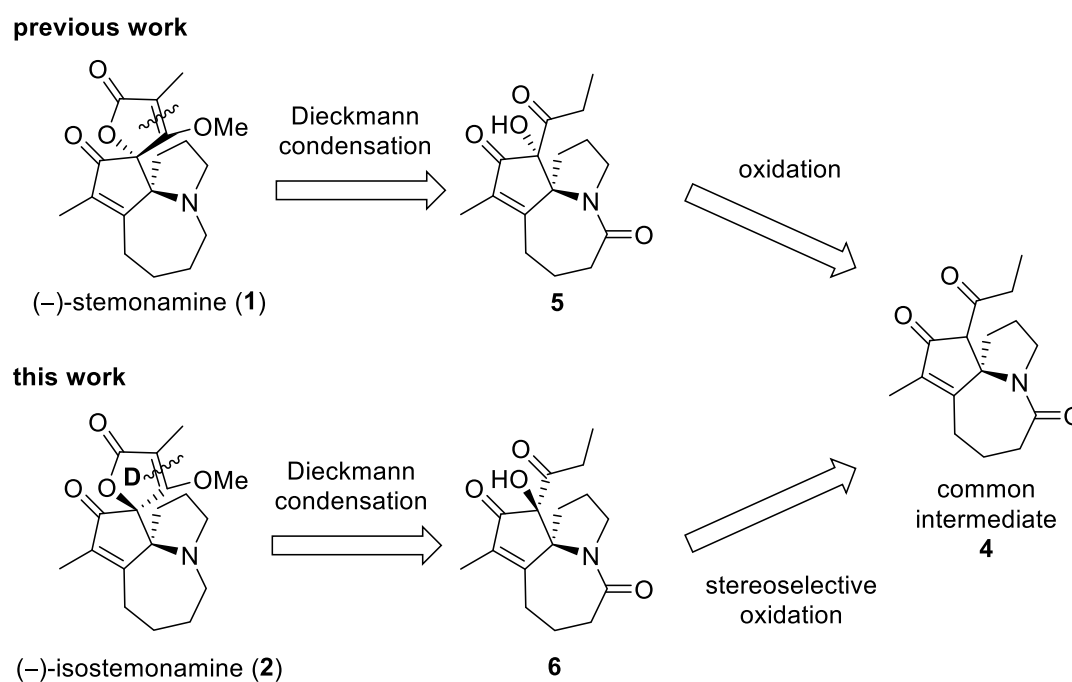


Figure 1. Stemonamine and isostemonamine

Recently, we have reported the first asymmetric total synthesis of (–)-stemonamine and experimentally verified the racemization and epimerization of this natural product (Scheme 1).⁶ In this study, we prepared a diketone intermediate **4** utilizing our original reactions as key reactions: an intramolecular acylation⁷ to construct the seven-membered ring (C ring), and a ynolate-initiated tandem [4+2] cycloaddition/Dieckmann condensation⁸ to develop the cyclopentenone moiety (A ring). (–)-Stemonamine was successfully obtained from compound **4** using a modified method reported by Zu and Zhang.⁹ The chiral HPLC analysis of (–)-stemonamine revealed that racemization occurs faster than epimerization.

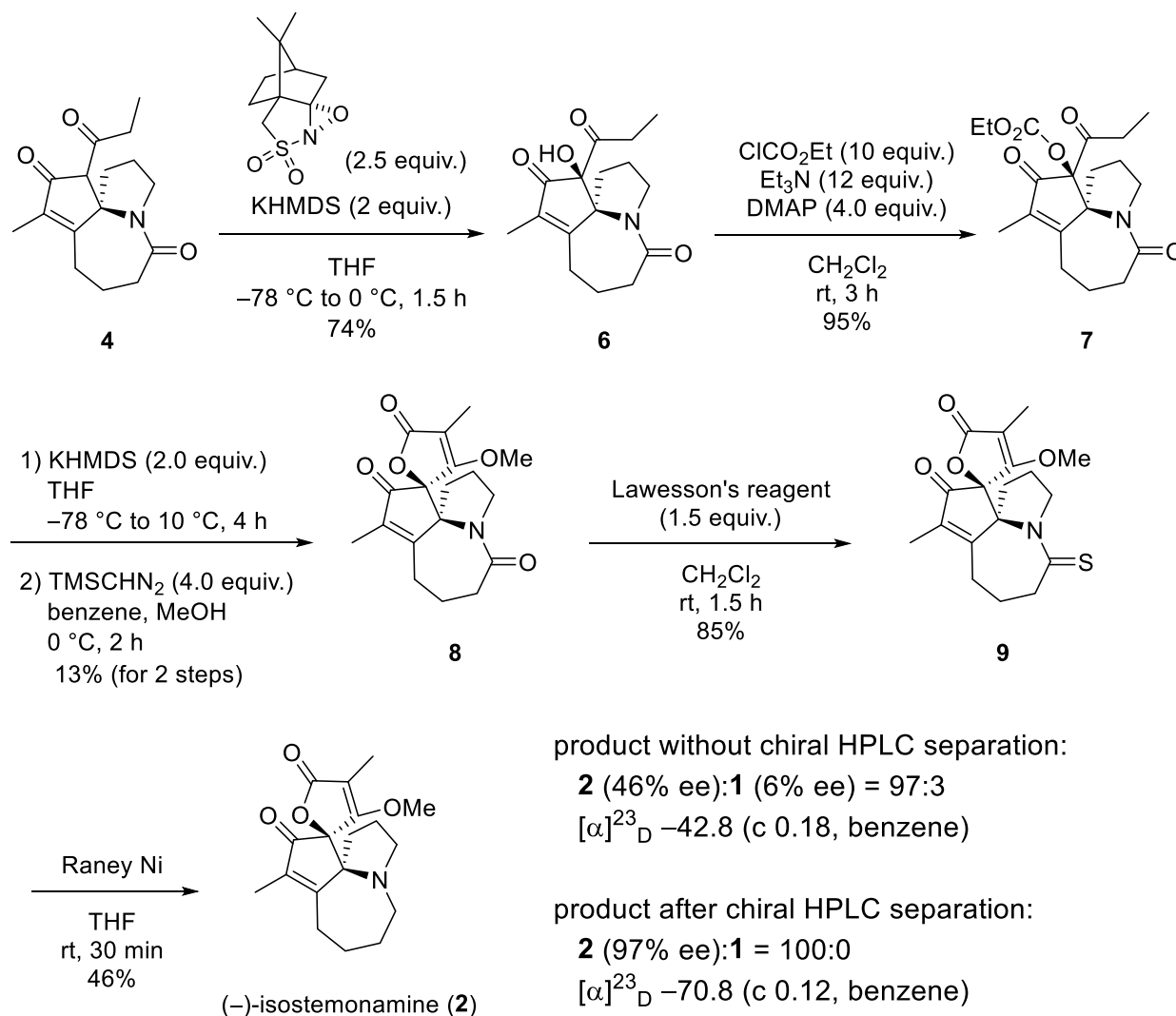
Herein, we report the first total synthesis of (–)-isostemonamine using the regioselective oxidation of diketone **4** as a key step. Furthermore, the kinetic analysis of isomerizations of (–)-isostemonamine revealed a different stereochemical stability from that of stemonamine.



Scheme 1. Synthetic scheme of (–)-stemonamine and retrosynthetic analysis of isostemonamine

Our retro-synthetic analysis of (–)-isostemonamine (**2**) is depicted in Scheme 1. The D ring could be constructed using the Dieckmann condensation reaction, which was used in our synthesis of (–)-stemonamine.^{6a} The precursor of the reaction, alcohol **6**, was obtained from the regioselective oxidation of diketone **4**. Accordingly, the synthetic plan uses diketone **4** as a common intermediate for the synthesis of both stemonamine and isostemonamine.

Our synthesis of isostemonamine commenced with the regioselective oxidation of a common intermediate **4** (Scheme 2). Oxaziridines were chosen as regioselective oxidants because of availability.¹⁰ Although racemic Davis' oxaziridine (3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine)¹¹ gave a trace amount of oxidized product, (+)-camphorylsulfonyloxaziridine¹² regioselectively provided the oxidized product **6** with desired stereochemistry. Conversion of the alcohol **6** to isostemonamine was examined based on the method for our total synthesis of (–)-stemonamine.^{6a} Treatment of **6** with ethyl chloroformate provided



Scheme 2. Total synthesis of (–)-isostemonamine

carbonate **7** with 95% yield. A Dieckmann condensation reaction of **7** using KHMDS, followed by methylation using TMS-diazomethane, afforded the product with D ring in 13% yield over 2 steps. Our synthesis of stemonamine revealed that the product after the Dieckmann condensation process had a reduced enantiomeric excess.^{6a} Accordingly, this process should also provide a product with reduced enantiomeric excess in the synthesis of isostemonamine. However, HPLC analysis using chiral columns such as CHIRALPAK AD, AD-H, and OD-H did not detect peaks of enantio-pair of **8**. Therefore, the enantiomeric excess of **8** was not determined. The thioamidation of **8** using Lawesson's reagent smoothly produced **9** in high yield. Finally, thioamide **9** was treated with W2 Raney Ni to yield isostemonamine (**2**) along with small amount of stemonamine (**1**) (combined chemical yield: 46%). Since our previous study revealed that isostemonamine easily racemizes and epimerizes even at room temperature,^{6a} the work-up operation of this step was carried out under cooling conditions using ice bath (see Experimental section for details). The obtained natural product showed a moderate enantiomeric excess (46% ee) and specific optical rotation ($[\alpha]^{23}_{\text{D}} -42.8$, c 0.18, benzene). The HPLC separation of the product using chiral column (CHIRALPAK AD-H) produced a more optically pure (–)-isostemonamine with 97% ee and $[\alpha]^{23}_{\text{D}} -70.8$ (c 0.12, benzene).

The stereochemical stability of (–)-isostemonamine was analyzed using chiral HPLC. The conditions for analysis were based on the one established in our previous study (CHIRALPAK AD-H, 20% isopropanol in hexane).^{6a} Table 1 shows the “apparent” rate constants and half-lives of the racemization and epimerization of (–)-isostemonamine under varying conditions.¹³ Results show that the racemization of (–)-isostemonamine is faster in protic solvents than in aprotic solvents and accelerates at higher

Table 1. Rate constants and half-lives of racemization and epimerization of (–)-isostemonamine (**2**)

entry	solvent	temp. (°C)	(–)-isostemonamine				(–)-stemonamine ^{6a}			
			racemization		epimerization		racemization		epimerization	
			k^a	$t_{1/2}$ (h)	k^a	$t_{1/2}$ (h)	k^a	$t_{1/2}$ (h)	k^a	$t_{1/2}$ (h)
1	20% <i>i</i> -PrOH in hexane	60	11	0.18	0.066	29	0.74	2.6	0.026	74
2	20% <i>i</i> -PrOH in hexane	45	2.9	0.67	0.010	190	0.22	9.0	0.0071	270
3	20% <i>i</i> -PrOH in hexane	25	0.53	3.6	<0.001	>1000	0.035	55	<0.001	>1000
4	20% <i>i</i> -PrOH in hexane	10	0.11	18	- ^b	- ^b	0.0097	200	- ^b	- ^b
5	CHCl ₃	25	0.16	12	- ^b	- ^b	0.0072	270	- ^b	- ^b

^a rate constants ($\times 10^{-4} \text{s}^{-1}$). ^b not determined.

temperature, while the epimerization to (\pm)-stemonamine is slower than the racemization. This behavior was also observed in the isomerization of (–)-stemonamine and can be explained in the same way as that of stemonamine.^{6a} In addition, both the process involving (–)-isostemonamine was found to be much faster than those of (–)-stemonamine.^{6a} One conceivable reason for this is the difference in steric hindrance in bond rotations of intermediate **3** (Figure 2). The racemization and epimerization of stemonamine requires rotation around bonds A and B in both intermediates **3a** and **3b**, where the methoxy group on D ring hinders the rotation on one direction due to steric repulsion between the methoxy group and B ring. On the other hand, the racemization and epimerization of isostemonamine requires rotation around bonds A and B in both intermediates **3c** and **3d**, where steric repulsion between the D and B rings should be less than those in **3a** and **3b** due to the methoxy group being located opposite to the B ring.

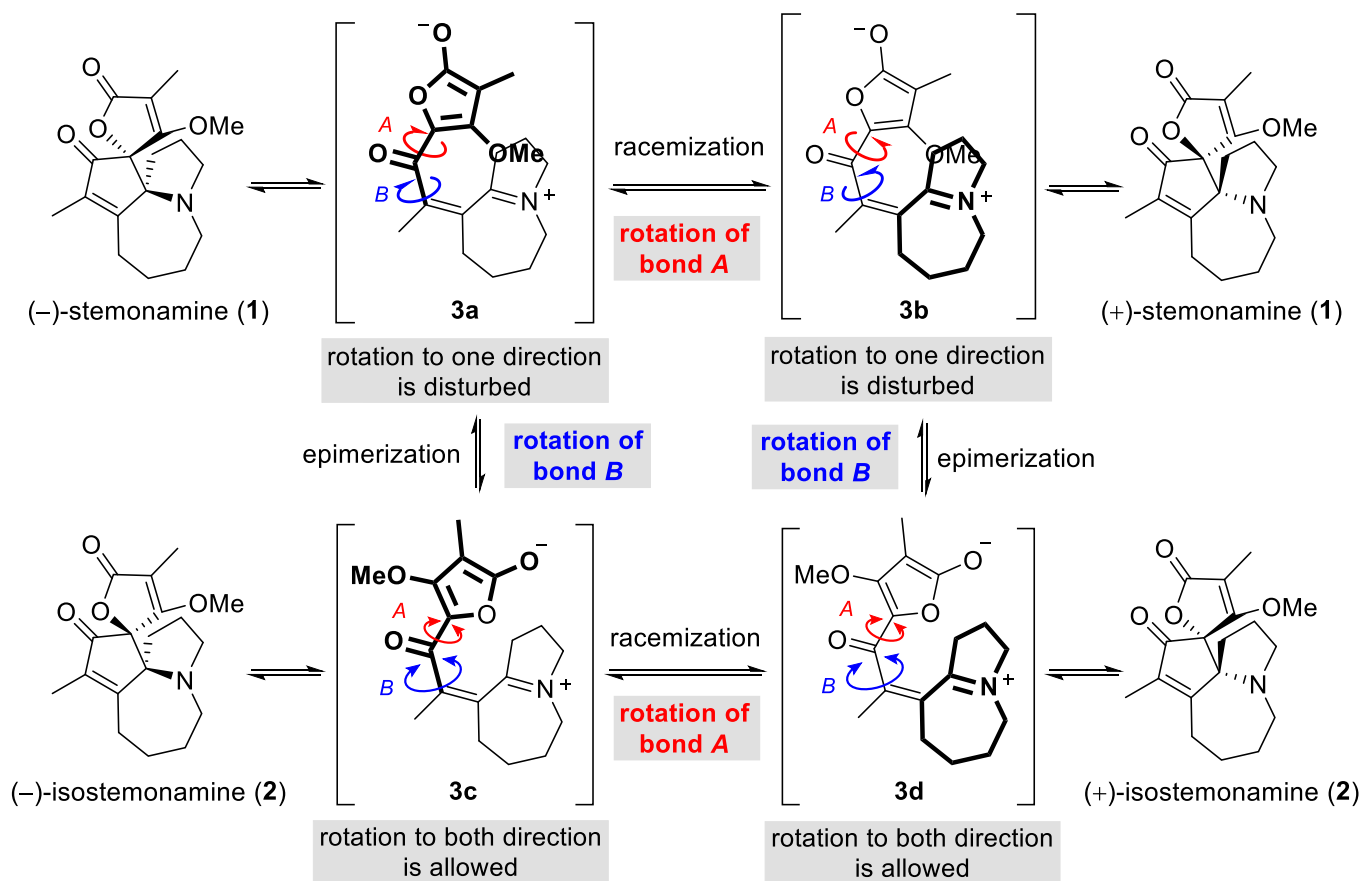


Figure 2. Plausible difference among isomerizations of stemonamine and isostemonamine

In conclusion, the first total synthesis of (–)-isostemonamine was achieved from the diketone intermediate. The oxidation of this compound using chiral oxaziridine diastereoselectively produced an alcohol with desired stereochemistry. It also provided the transformations used in our synthesis of

(-)-stemonamine, which successfully yielded (-)-isostemonamine with 97% ee. Furthermore, the racemization and epimerization of (-)-isostemonamine were found to be faster than those of (-)-stemonamine. The investigation of the biological activity of stemonamine and isostemonamine is undergoing, and the results will be reported in due course.

ACKNOWLEDGEMENTS

This work was partially supported by JSPS KAKENHI Grant Number (No. JP22390002, JP24106731, JP16H01157, JP26293004, JP17K14449), Science and Technology 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 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. We thank Dr. K. Nishikawa for early investigation of the key oxidation step.

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