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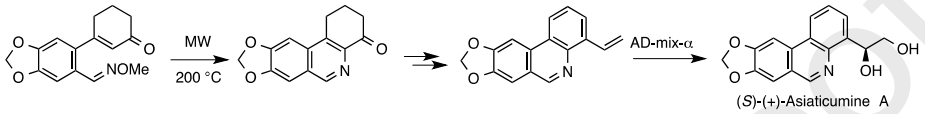

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First asymmetric enantioselective total synthesis of phenanthridine alkaloid, (*S*)-(+)-asiaticumine and its enantiomer

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ABSTRACT

In this study, the first asymmetric enantioselective total syntheses of (+)-asiaticumine A (**2**) and its enantiomer were accomplished through a seven-step sequence using the bond formation between the C4a and N5 positions of the phenanthridine framework based on the microwave-assisted electrocyclization of cyclohexenylbenzaldoxime methyl ether as an aza 6π-hexatriene system followed by the Sharpless asymmetric dihydroxylation as the key step. In addition, the absolute configuration of natural (+)-**2** was determined to be *S* by Mosher's method.

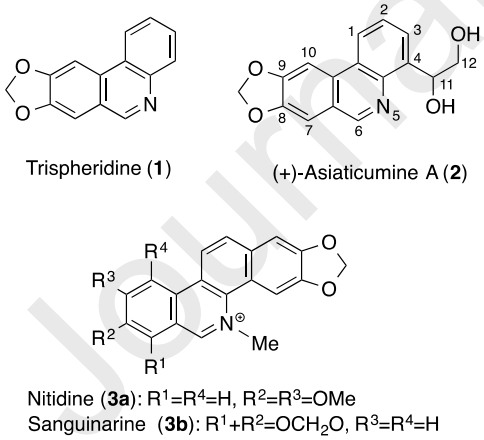

Fig. 1. Phenanthridine alkaloids.

Phenanthridines, represented by trispheridine (**1**), constitute an important moiety found in natural products and biologically active molecules (Fig. 1). In particular, among benzo[*c*]phenanthridines, nitidine (**3a**) [1] exhibits potential antileukemic activity through the inhibition of topoisomerases, while sanguinarine (**3b**) [2] has been reported to exhibit antibacterial and antifungal activities. A series of aforementioned benzo[*c*]phenanthridines have been reported to show various pharmacological properties including antitumor activity [3].

Owing to their unique structures and characteristic biological activities, the development of a convenient and efficient synthetic route to phenanthridine and benzo[*c*]phenanthridine alkaloids has attracted considerable attention from synthetic and medicinal chemists [4]. Several groups have successively reported their efforts to synthesize phenanthridine derivatives using biphenyl imidoyl radical intermediates, which are formed by the addition of various radicals to 2-isocyanobiphenyls [5]. For example, Chatani et al. demonstrated a Mn(III)-mediated annulation of 2-isocyanobiphenyls using boronic acid.[5a] Furthermore, Walton et al. demonstrated phenanthridine synthesis via the cyclization of imidyl radicals, which were generated from *O*-phenyl oxime under microwave (MW) irradiation [6].

We have performed the synthetic studies of fused pyridine ring systems via the electrocyclization of an aza 6π-hexatriene system [7]. To date, we have reported the construction of several fused pyridine ring systems, such as furo[3,2-*h*]isoquinoline [8], azaanthraquinone [9], β-carboline alkaloids [10], and azafluorenone [11], using the MW-assisted electrocyclization of a 1-aza 6π-hexatriene system. Furthermore, we have reported the total synthesis of a phenanthridine alkaloid (trispheridine **1**) [12] and benzo[*c*]phenanthridine alkaloids (nitidine **3a**, sanguinarine **3b**, chelerythrine, and broussonpapyrine) [13] using the similarly method.

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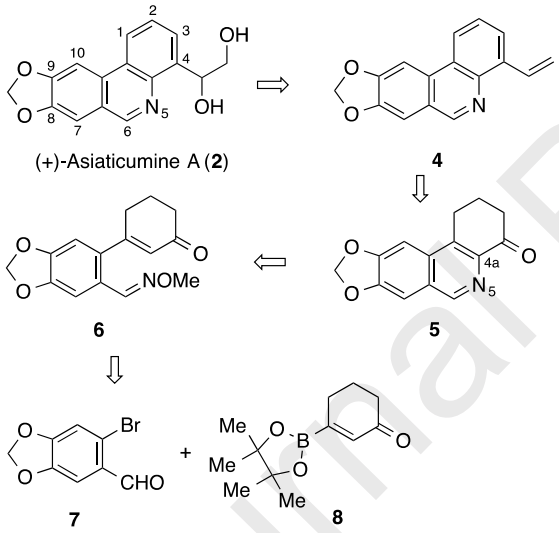
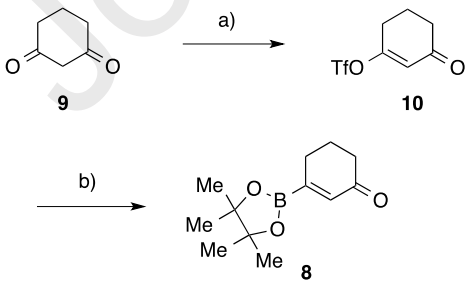
as illustrated in Fig. 1, was isolated from *Crinum asiaticum* L. var. *sinicum* Baker with asiaticumine B and 21 known compounds by Zhang et al. in 2009 [14]. Its structure was elucidated to be (+)-4-(1,2-dihydroxyethyl)-8,9-methylenedioxyphenanthridine via spectroscopic and chemical analyses. However, the absolute configuration at the C-11 position is undetermined as yet.

Herein, we have described the details of the first asymmetric enantioselective total syntheses of (+)-asiaticumine A (**2**) using the application of pyrido-annulation via electrocyclization of an aza 6π-hexatriene system followed by the Sharpless asymmetric dihydroxylation as the key step.

As shown in the retrosynthetic analysis (Scheme 1), we aimed to synthesize (+)-asiaticumine A (**2**) from 4-vinylphenanthridine **4** through Sharpless asymmetric dihydroxylation. 4-Vinylphenanthridine **4** can be obtained from dihydrophenanthridinone **5** in a few steps. Moreover, dihydrophenanthridinone **5** can be derived via the MW-assisted electrocyclization of cyclohexenylbenzaldoxime methyl ether **6** using the bond formation between the C4a and N5 positions of the phenanthridine framework. Cyclohexenylbenzaldoxime methyl ether **6** can be synthesized from 6-bromopiperonal (**7**) and 3-cyclohexenylboronic acid pinacol ester **8** by the Suzuki–Miyaura reaction.



Scheme 1. Retrosynthetic analysis of (+)-asiaticumine A (**2**).

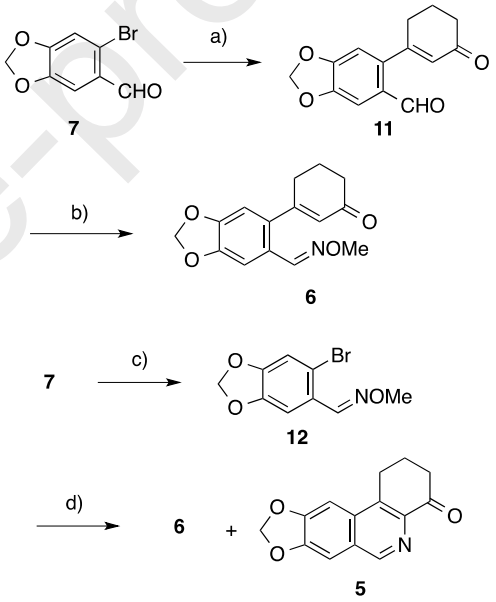


Scheme 2. Synthesis of pinacol borate **8.** Reagents and conditions: a) Tf_2O, pyridine, CH_2Cl_2, −78 °C → rt, 12 h, 98%; b) bis(pinacolato)diboron, AcOK, $PdCl_2$(dppf), dioxane, 80 °C, 1 h, **8** was used without purification.

1,3-dione (**9**) with trifluoromethanesulfonic anhydride (Tf_2O) and pyridine afforded triflate **10** [15], which was treated with bis(pinacolato)diboron in the presence of $PdCl_2$(dppf) to yield pinacol borate **8** (Scheme 2) [16].

To synthesize dihydrophenanthridinone **5**, oxime ether **6** was prepared as a precursor of **5**. The Suzuki–Miyaura reaction of the readily available 2-bromopiperonal (**7**) with cyclohexenylboronic acid pinacol ester **8** was performed in the presence of $PdCl_2$(dppf) and Na_2CO_3 in toluene at 110 °C for 1.5 h to afford cyclohexenylbenzaldehyde **11** in 67% yield. The subsequent treatment of aldehyde **11** with NH_2OMe afforded oxime ether **6** in 99% yield (Scheme 3).

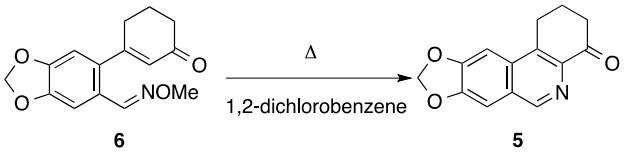
Furthermore, we examined the synthesis of oxime ether **6** via a reverse route. The treatment of 2-bromopiperonal (**7**) with NH_2OMe afforded oxime ether **12** in a 90% yield. Subsequently, the reaction of **12** with pinacol borate **8** yielded the cyclization product dihydrophenanthridinone **5** (14%) along with oxime ether **6** (69%). Thus, the first route is considered to be efficient owing to the easy product purification of the product in each step.



Scheme 3. Synthesis of oxime ether **6.** Reagents and conditions: a) **8**, 2 M Na_2CO_3, $PdCl_2(PPh_3)_2$, toluene, 110 °C, 1.5 h, 67%; b) NH_2OMe·HCl, AcONa, EtOH, 80 °C, 0.5 h, 99%; c) NH_2OMe·HCl, AcONa, EtOH, 80 °C, 10 min, 90%; d) **8**, 2 M Na_2CO_3, $PdCl_2(PPh_3)_2$, toluene, 110 °C, 1.5 h, **6** (69%), **5** (14%).

Next, oxime ether **6** was subjected to thermal electrocyclization at 180 °C in 1,2-dichlorobenzene under both MW-assisted and conventional conditions. As shown in Table 1, by comparing the cyclization reactions under both conditions, the MW-assisted conditions were observed to significantly reduce the reaction time and increase the yield (runs 1 and 2). Furthermore, when the reaction temperature was increased to 200 °C under MW-assisted conditions, dihydrophenanthridinone **5** was obtained in 91% yield (run 3). In addition, when the reaction time was longer than that of run 3 under the same conditions, the yield decreased because product **5** decomposed. Thus, it was determined that the yield and reaction rate of this type of thermal electrocyclization were promoted by MW irradiation.

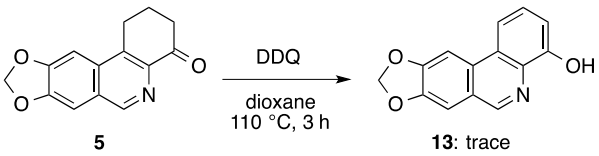
Tab % electrocyclization.[a]



Run	MW	Time (h)	Temp (°C)	Yield (%) of **5**
1	−	24	180	15
2	+	5	180	76
3	+	2	200	91
4	+	5	200	56

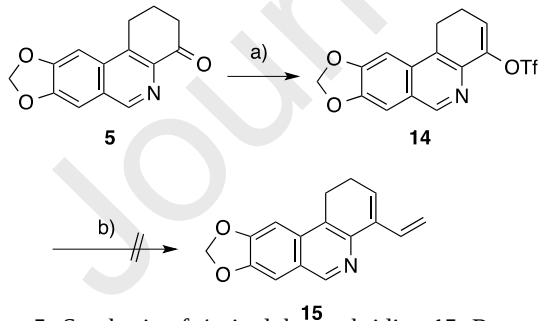
[a] A solution of oxime ether **6** in 1,2-dichlorobenzene was heated with MW irradiation or without MW irradiation under N_2 atmosphere.

A direct conversion of dihydrophenanthridinone **5** to phenanthridine **13** was attempted (Scheme 4). As a method to obtain the desired phenanthridine **13**, heating of **5** in the presence of Pd–C [13c] was ineffective. Subsequently, the oxidation of **5** with DDQ was performed to obtain a small amount of **13**.



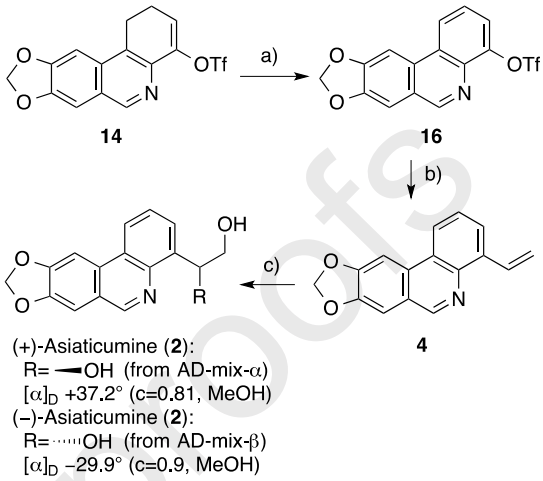
Scheme 4. Dehydrogenation of dihydrophenanthridinone **5**

Therefore, **5** was treated with *N*-phenylbis(trifluoromethanesulfonamide) (Tf_2NPh) and LDA to afford triflate **14** in 60% yield (Scheme 5). To obtain 4-vinylphenanthridine **15**, the Stille reaction between triflate **14** and vinyltributyltin in the presence of $PdCl_2(PPh_3)_2$ was conducted. However, the desired product, namely **15**, could not obtained.



Scheme 5. Synthesis of 4-vinylphenanthridine **15**. Reagents and conditions: a) LDA, Tf_2NPh, THF, −78 °C → rt, 4 h, 60%; b) vinyltributyltin, Et_4NCl, $PdCl_2(PPh_3)_2$, DMF, 80 °C, 1 h.

However, the oxidation of triflate **14** with DDQ in dioxane produced the expected phenanthridine **16** in 88% yield (Scheme 6). The Stille reaction of **16** with vinyltributyltin in the presence of $PdCl_2(PPh_3)_2$ produced 4-vinylphenanthridine **4** in 89% yield. Finally, the Sharpless asymmetric dihydroxylation [17] of 4-vinylphenanthridine **4** was investigated as follows. The reaction yield ($[\alpha]_D$ +37.2°, *c* = 0.81, MeOH). However, the reaction of **4** with AD-mix-β afforded (−)-**2** in 70% yield ($[\alpha]_D$ −29.9°, *c* = 0.9, MeOH). The specific rotation of the former (+)-**2** approximately corresponded to that reported for natural (+)-**2** ($[\alpha]_D$ +6°, *c* = 0.29, MeOH [14]), but the reason for the large difference of specific rotation is not clear. The spectroscopic data for (+)-**2** and (−)-**2** were identical to those of natural **2** in all aspects.



Scheme 6. Synthesis of asiaticumine A (**2**). Reagents and conditions: a) DDQ, dioxane, rt, 3 h, 88%; b) vinyltributyltin, Et_4NCl, $PdCl_2(PPh_3)_2$, DMF, 80 °C, 1 h, 89%; c) AD-mix-α or AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, rt, 24 h, (+)-**2** (98%), (−)-**2** (70%).

The enantiomeric excesses of (+)-**2** and (−)-**2** were analyzed based on the ^1H NMR spectra of appropriate (*S*)-MTPA ester [18], which was prepared via the selective protection of its C-12 primary hydroxyl group by the TBDMS group, followed by the esterification of its C-11 secondary hydroxyl group by (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPACl). Thus, the enantiomeric excesses of (+)-**2** and (−)-**2** were 91 and 84%ee, respectively.

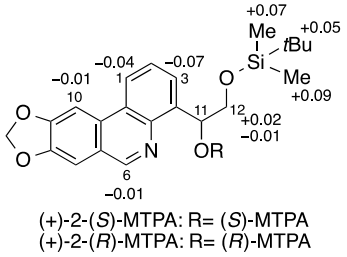


Fig. 2. Δδ (δ_S-δ_R) values for (*S*)- and (*R*)-MTPA esters of (+)-**2**.

To determin the absolute configuration of (+)-**2**, similarly the (+)-**2**-(*R*)-MTPA ester was prepared from (+)-**2** by treatment with (*S*)-MTPACl. The Δδ (δ_S-δ_R) values of protons obtained by ^1H NMR analyses of (+)-**2**-(*S*)-MTPA and (+)-**2**-(*R*)-MTPA measured in $CDCl_3$ are depicted in Fig. 2. The negative sign of the Δδ value of phenanthridine moiety (H-1, H-3, H-6, H-10) and the positive sign of the protons of TBDMS group indicates. Therefore, the absolute configurations of (+)-**2** and (−)-**2** were determined to be *S* and *R*, respectively, by the Mosher's method [19].

In conclusion, the first enantioselective total syntheses of (+)-asiaticumine A (**2**) and its enantiomer were achieved through a seven-step sequence via the construction of a phenanthridine

6π-hexatriene system followed by the Sharpless asymmetric dihydroxylation as the key step. Furthermore, the absolute configuration of natural (+)-asiaticumine A **(2)** was determined to be *S*. In addition, the biological activities of (+)-**2**, its enantiomer, and their derivatives are under evaluation.

Acknowledgments

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[18] **(+)-2-(*S*)-MTPA ester** [(+)-1-(8,9-methylenedioxyphenanthridin-4-yl)-2-(*tert*-butyldimethylsilyloxy)ethyl (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetate]: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 3.68 (s, 3H), 3.94 (dd, *J* = 7.8, 11.5 Hz, 1H), 4.18 (dd, *J* = 2.5, 11.5 Hz, 1H), 6.18 (s, 2H), 7.36 (s, 3H), 7.37–7.51 (m, 5H), 7.64 (d, *J* = 7.0 Hz, 2H), 7.91 (s, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 9.11 (s, 1H).
(+)-2-(*R*)-MTPA ester [(+)-1-(8,9-methylenedioxyphenanthridin-4-yl)-2-(*tert*-butyldimethylsilyloxy)ethyl (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetate]:^{1}H-NMR (300 MHz, $CDCl_3$) δ −0.08 (s, 3H), 0.01 (s, 3H), 0.83 (s, 9H), 3.59 (s, 3H), 3.95 (dd, *J* = 7.0, 11.1 Hz, 1H), 4.16 (dd, *J* = 3.0, 11.1 Hz, 1H), 6.18 (s, 2H), 7.35–7.41 (m, 3H), 7.50–7.61 (m, 4H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.92 (s, 1H), 8.36 (d, *J* = 7.8 Hz, 1H), 9.12 (s, 1H).
(–)-2-(*S*)-MTPA ester [(–)-1-(8,9-methylenedioxyphenanthridin-4-yl)-2-(*tert*-butyldimethylsilyloxy)ethyl (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetate]:^{1}H-NMR (300 MHz, $CDCl_3$) δ −0.08 (s, 3H), 0.01 (s, 3H), 0.83 (s, 9H), 3.59 (s, 3H), 3.95 (dd, *J* = 7.0, 11.1 Hz, 1H), 4.16 (dd, *J* = 3.0, 11.1 Hz, 1H), 6.18 (s, 2H), 7.35–7.43 (m, 3H), 7.51–7.62 (m, 4H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.92 (s, 1H), 8.36 (d, *J* = 7.8 Hz, 1H), 9.12 (s, 1H).

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Supplementary dada

Supplementary data to this article can be found online at https://.....

♦T
asiaticumine A has been accomplished.
♦The construction of phenanthridine framework by MW-assisted electrocyclization.
♦The synthesis of 1,2-dihydroxyethyl moiety by Sharpless asymmetric dihydroxylation.
♦Its absolute configuration was determined to be *S* by Mosher's method.